CV Complications of Hypoglycemia

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Table 1. Symptoms of Hypoglycemia

Autonomic	Neuroglycopenic
Palpitations	Difficulty concentrating
Sweating	Confusion
Anxiety	Weakness
Hunger	Drowsiness
Nausea	Vision changes
	Difficulty speaking
	Headache
	Dizziness

Table 3. Risk Factors for Severe Hypoglycemia

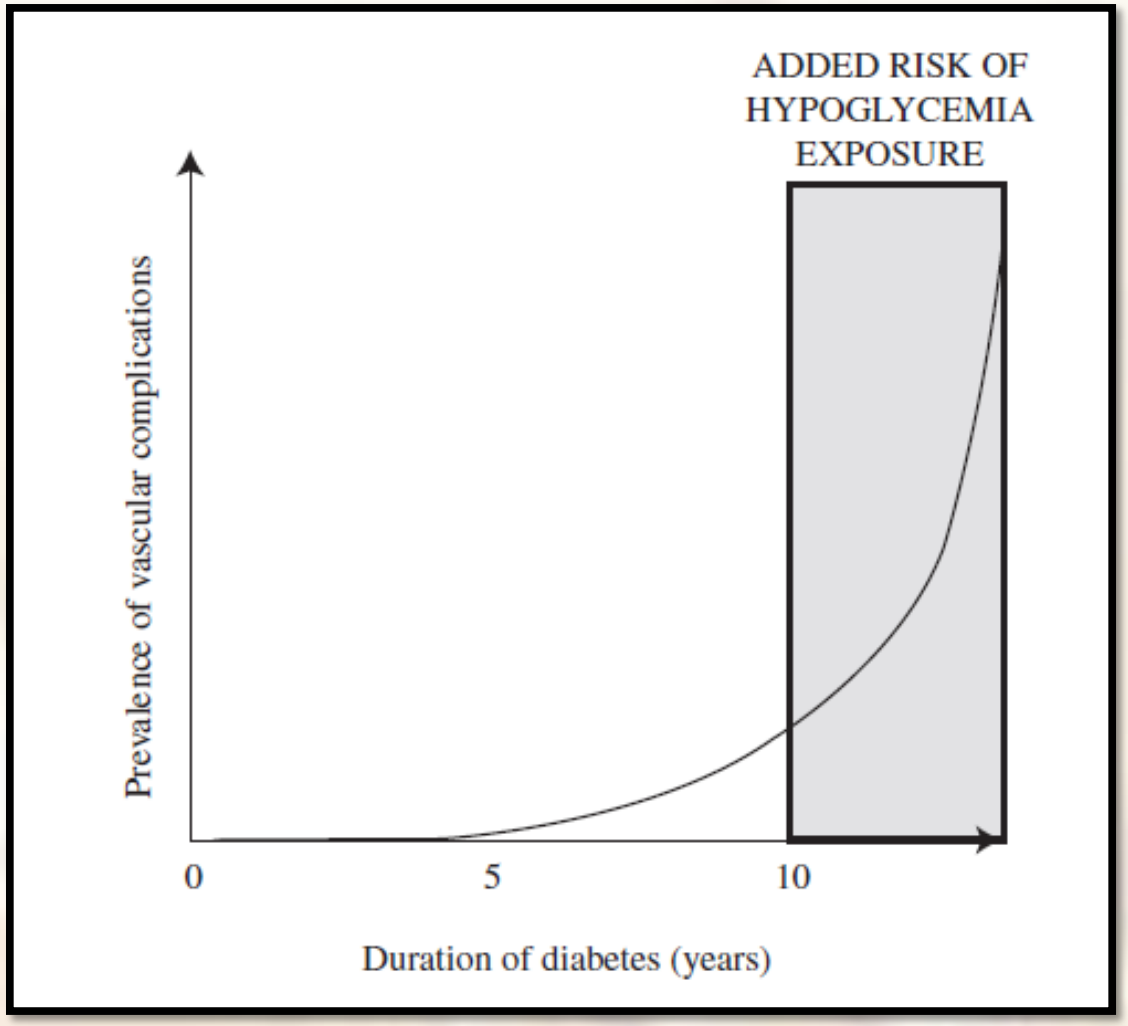
Hemoglobin A1c <6%
Hypoglycemic unawareness
Autonomic neuropathy
Cognitive impairment
Renal dysfunction
Insulin therapy
Sulfonylurea therapy
Previous episodes of severe hypoglycemia
Missed meals

Table 4. Rates of Hypoglycemia and Change in HbA1c With Current Antihyperglycemic Agents

	Change in HbA1c, %	Hypoglycemia, Odds Ratio
Sulfonylureas	–0.82*	8.86*
Meglitinides	–0.71*	10.51*
DPP-4 inhibitors	–0.69*	1.13
GLP-1 receptor agonists	–1.02*	0.92
Basal insulin	–0.88*	4.77*
Premixed insulin	–1.07*	17.78*

DPP-4 indicates dipeptidyl peptidase 4; GLP-1, glucagon-like peptide-1; and HbA1c, hemoglobin A1c

Risks of hypoglycemia on the vasculature:



Diabetes subjects with normal glycosylated hemoglobin (5.6%) but significant glycemic excursions and hypoglycemic (time spent hypoglycemic [< 70 mg/dL] = 22%).

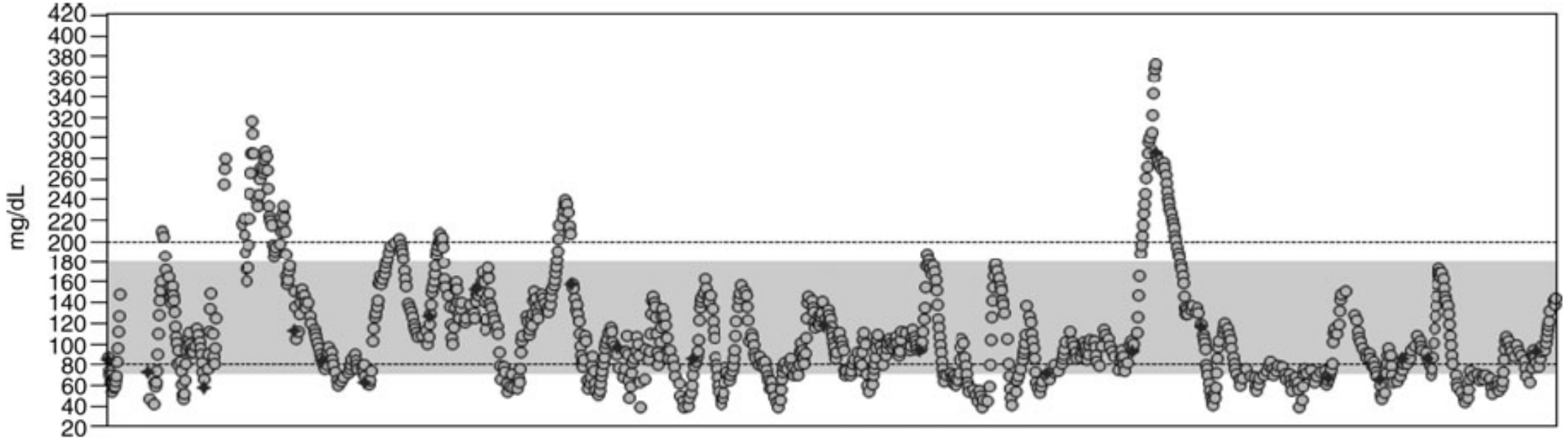
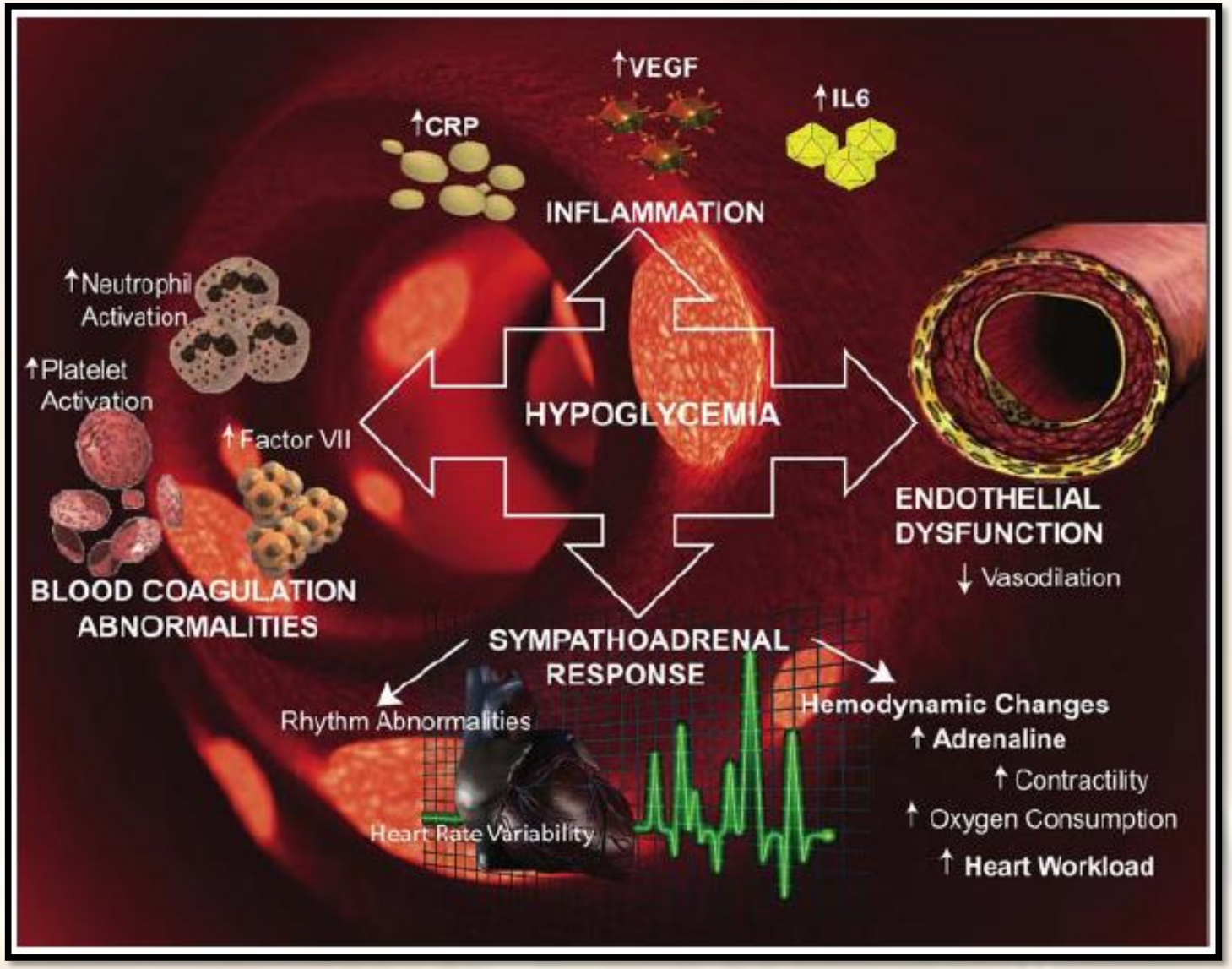


FIG. 2. Example of a diabetes subjects with normal glycosylated hemoglobin (5.6%) but significant glycemic excursions and hypoglycemic (time spent hypoglycemic [<70 mg/dL]=22%).

Mechanisms by which hypoglycemia may affect cardiovascular events



“Dead in Bed” Syndrome

Link between overnight low blood glucose levels and abnormal heart rates that disturb the flow of blood to the heart.

Table 2. Rates of Hypoglycemia in the ACCORD, VADT, and ADVANCE Clinical Trials

	Standard Glucose Control Arm, %	Intensive Glucose Control Arm, %	*P* Value
ACCORD	5.1	16.2	<0.001
ADVANCE	1.5	2.7	<0.001
VADT	9.9	21.2	<0.001

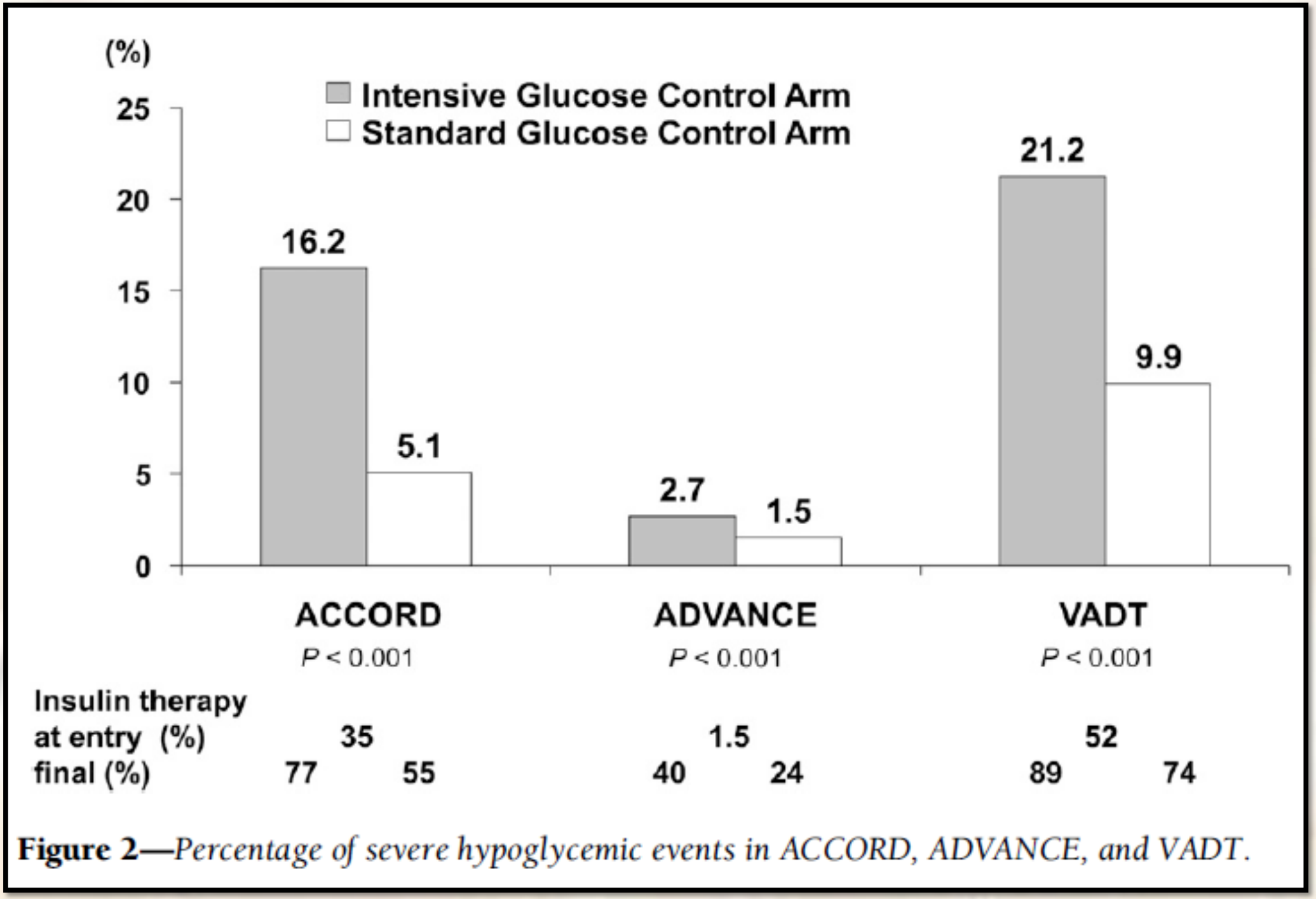


Figure 2—*Percentage of severe hypoglycemic events in ACCORD, ADVANCE, and VADT.*

systematic review and meta-analysis with bias analysis

- Six eligible studies with 9,03,510 participants were identified.
- Severe hypoglycemia was strongly associated with a higher risk of cardiovascular disease (relative risk 2.05, 95 confidence interval 1.74 to 2.42; P<0.001).
- Excess fraction of cardiovascular disease incidence that was attributable to severe hypoglycemia (the population attributable fraction) was 1.56% (95% confidence interval 1.32% to 1.81%; P<0.001).
- Severe hypoglycemia is associated with a higher risk of cardiovascular disease
- Avoiding severe hypoglycemia may be important to prevent cardiovascular disease in people with type 2 diabetes.

Data on Hypoglycemia and Cardiovascular Disease from Clinical Trials

Study	*Description*	*Population*	*Treatments*	*Outcome*
DCCT/ EDIC[5]	Effect of intensive vs. conventional treatment on micro- and macrovascular complications	1,441 T1D adolescents and adults (13–39 years old) with diabetes duration of 1–15 years	Intensive treatment (multiple injections or pump) vs. standard therapy	Reduced CVD by 54%, but only evident after long-term (>12-year) follow-up
UKPDS[45]	Randomized control trial of intensive therapy to reduce complications of T2D	5,102 newly diagnosed T2D adults	Two intensive treatment arms (insulin/ sulfonylurea or metformin) vs. conventional therapy	No difference in CVD outcomes after trial, but 10-year follow-up revealed a modest reduction in CVD
ACCORD[46]	Randomized control trial of excellent HbA1c (<6%) vs. 7.0–7.9%	10,251 T2D patients, 40–79 years of age with CVD or 55–79 years of age with atherosclerosis or ≥ two risk factors	Combinations of all available treatments to achieve goal HbA1c	Study stopped 3.5 years early because of increased overall and CVD mortality
ADVANCE[47]	Test if glucose lowering decreased risk of CVD in T2D patients with at least one risk factor	11,140 patients with T2D in 20 countries, ≥55 years of age and ≥30 years of age at diagnosis	Intensive glucose lowering (≤6.5%) vs. standard treatment	No difference in CVD end point by treatment group
VADT[48]	Determine effect of intensive glycemic control on CVD risk	1,791 patients with T2D on insulin or maximal-dose oral agents	Intensive treatment (<6.0%) vs. standard treatment	No difference in CVD end point by treatment group

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 14, Supplement 1, 2012

Hypoglycemia in Diabetes Mellitus as a Coronary Artery Disease Risk Factor in Patients at Elevated Vascular Risk

Table 1. Baseline Characteristics Stratified by Hypoglycemia

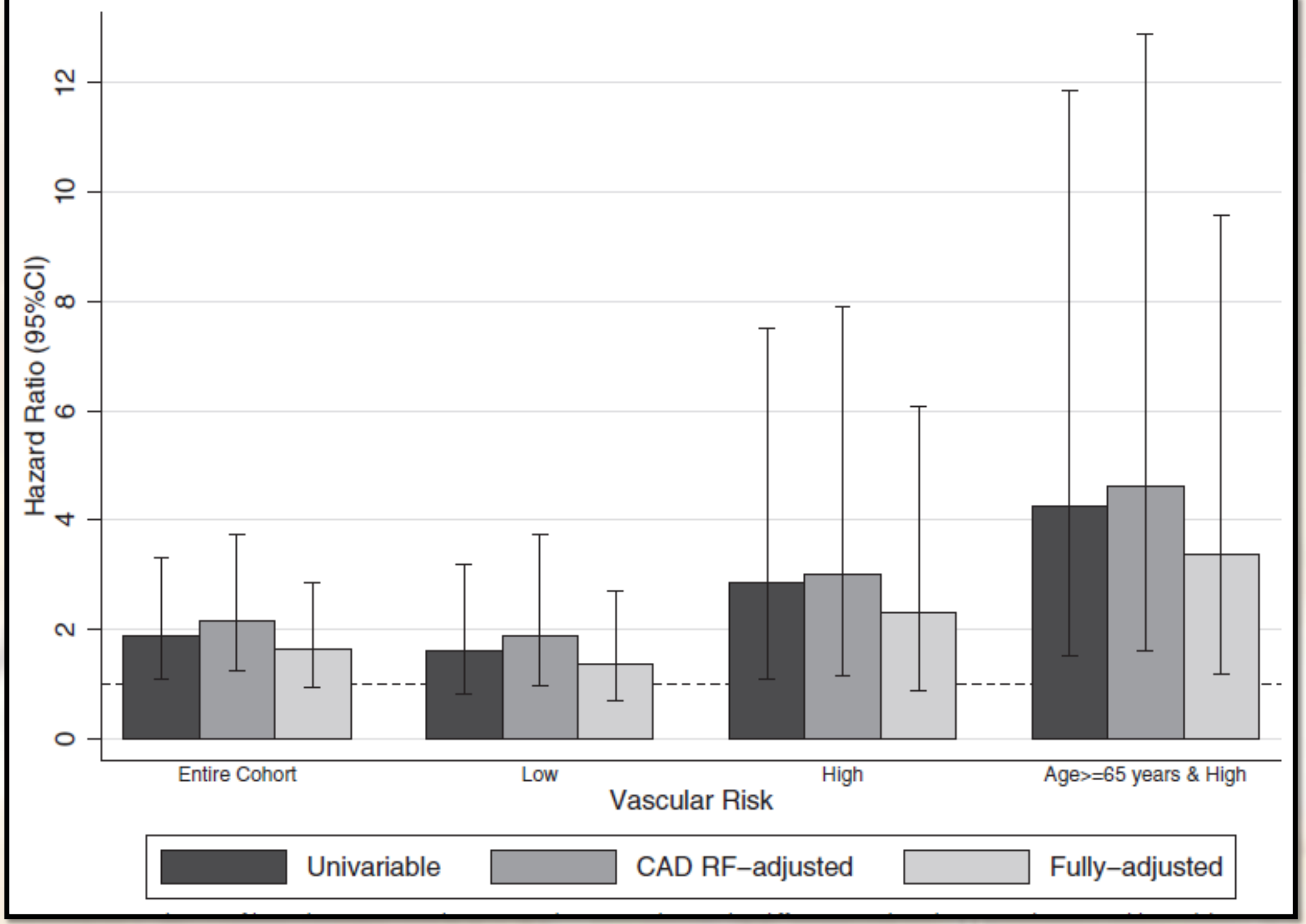
Baseline Characteristics	No Hypoglycemia (n = 8888)		Hypoglycemia (n = 285)		*P* Value
Age (y), median/mean (SD)	60.63/60.67	(14.30)	59.40/58.76	(15.50)	.03
Women, n (%)	4565	(51.36)	170	(59.65)	.01
Non-White race/ethnicity, n (%)	2605	(29.55)	102	(35.92)	.02
< High school education, n (%)	1267	(18.52)	39	(18.84)	.91
Diabetes duration, median/mean years (SD)	3.70/3.30	(1.82)	4.57/3.94	(1.60)	<.001
Hypertension, n (%)	5030	(56.59)	144	(50.53)	.04
Dyslipidemia, n (%)	5557	(62.52)	157	(55.09)	.01
Microvascular disease, n (%)	1583	(17.81)	133	(46.67)	<.001
Renal failure, n (%)	452	(5.09)	49	(15.79)	<.001
Neuropathy, n (%)	1221	(13.74)	106	(37.19)	<.001
Retinopathy, n (%)	440	(4.95)	61	(21.40)	<.001
Dysrhythmia, n (%)	1541	(17.34)	63	(22.11)	.04
Cerebrovascular disease, n (%)	371	(4.17)	15	(5.26)	.37
Peripheral vascular disease, n (%)	317	(3.57)	11	(3.86)	.79
Cancer, n (%)	459	(5.16)	22	(7.72)	.06
Dementia, n (%)	370	(4.16)	15	(5.26)	.36
Insulin, n (%)	2361	(26.56)	166	(58.25)	<.001
Sulfonylurea, n (%)	2979	(33.52)	94	(32.98)	.85
≥3 noninsulin antidiabetic agents, n (%)	593	(6.67)	24	(8.42)	.25
Medication count, median/mean (SD)	6.00/7.24	(6.24)	8.00/9.59	(7.81)	<.001
BMI (kg/m^2), median/mean (SD)	30.61/31.82	(7.51)	28.58/30.39	(7.89)	.004
eGFR (mL/min per 1.73 m^2), median/mean (SD)	74.69/74.25	(24.33)	71.98/69.62	(27.32)	.002
LDL (mg/dL), median/mean (SD)	88.00/92.06	(33.52)	78.00/83.20	(31.35)	<.001
HDL (mg/dL), median/mean (SD)	49.00/51.29	(15.77)	53.00/57.44	(20.08)	<.001
HbA1c (%), median/mean (SD)	7.20/7.66	(1.62)	7.50/7.95	(1.89)	.01
Hospitalization, n (%)	1691	(19.03)	85	(29.82)	<.001
≥5% weight loss within a year	494	(10.21)	21	(11.89)	.476
≥2 HbA1c measurements/year, n (%)	4573	(52.22)	182	(64.08)	<.001

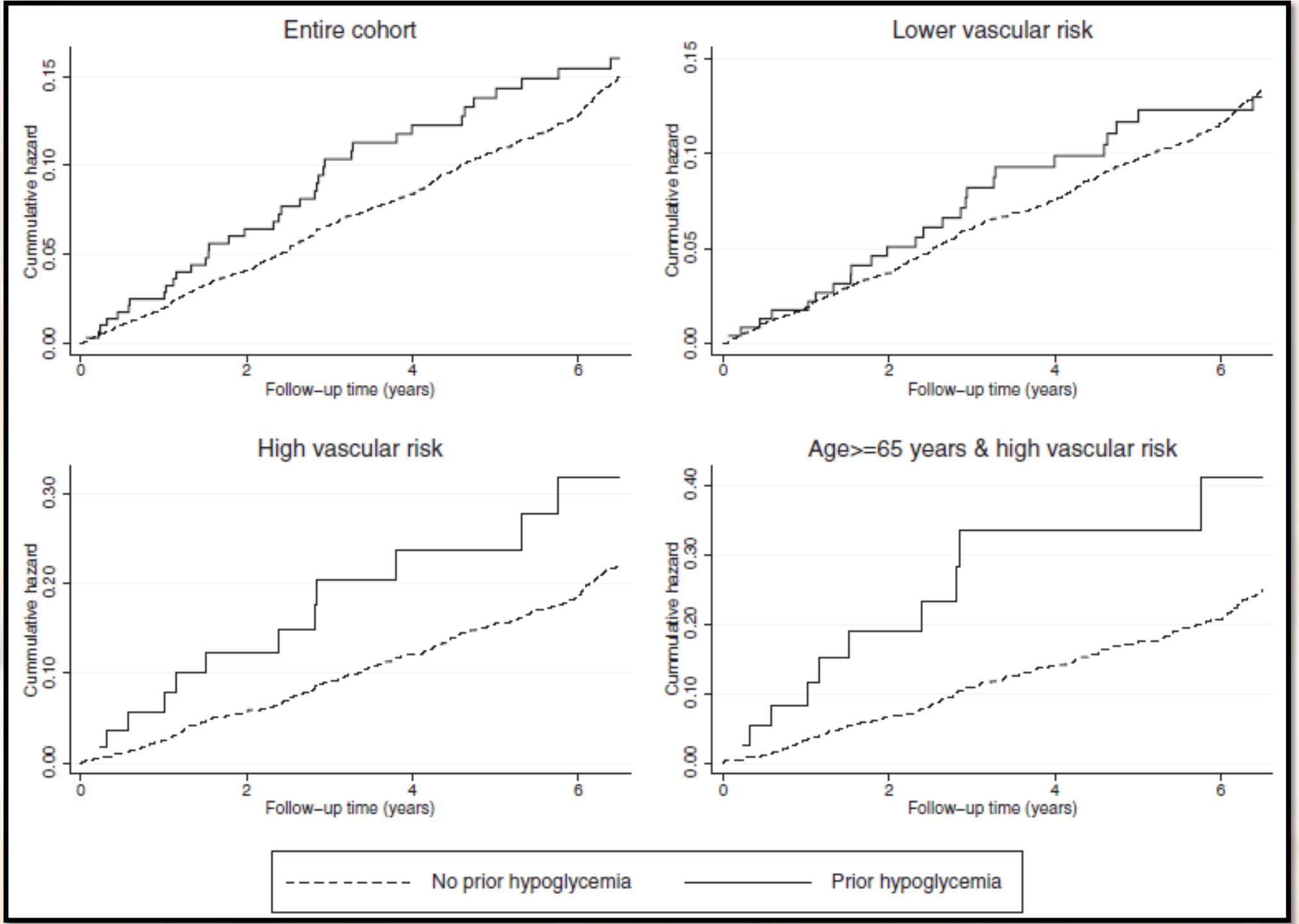
J Clin Endocrinol Metab, February 2016, 101(2):659–668

Table 2. Association Between Hypoglycemia and Incident CAD With Time Interaction in the Entire Cohort and Subgroups of Different Vascular Risk

	Entire Cohort (n = 9173)			Low Vascular Risk (n = 7350)			High Vascular Risk (n = 1823)			Age ≥65 Years and High Risk (n = 996)		
Hypoglycemia, n (%)	**285 (3.11)**			**230 (3.13)**			**55 (3.02)**			**38 (3.82)**		
	HR	**95%CI**	***P* Value**	**HR**	**95%CI**	***P* Value**	**HR**	**95%CI**	***P* Value**	**HR**	**95%CI**	***P* Value**
Hypoglycemia (univariable model)												
Main effect	1.90	(1.09–3.31)	.023	1.61	(0.82–3.18)	.168	2.86	(1.09–7.50)	.033	4.27	(1.53–11.86)	.003
TVC	0.83	(0.69–0.99)	.044	0.85	(0.68–1.05)	.133	0.81	(0.58–1.13)	.210	0.73	(0.48–1.11)	.140
1 year	1.58	(1.03–2.42)	.034	1.37	(0.81–2.31)	.235	2.31	(1.11–4.79)	.024	3.13	(1.48–6.61)	.003
2 years	1.31	(0.94–1.85)	.115	1.17	(0.77–1.77)	.469	1.87	(1.04–3.38)	.037	2.29	(1.20–4.37)	.012
3 years	1.09	(0.78–1.54)	.609	0.99	(0.66–1.49)	.970	1.52	(0.82–2.82)	.186	1.68	(0.77–3.68)	.197
Hypoglycemia (CAD risk factor adjusted multivariable model)												
Main effect	2.15	(1.24–3.74)	.007	1.90	(0.97–3.75)	.063	3.01	(1.15–7.91)	.025	4.62	(1.65–12.90)	.004
TVC	0.84	(0.71–1.01)	.061	0.86	(0.69–1.06)	.159	0.81	(0.57–1.13)	.136	0.75	(0.50–1.13)	.173
1 year	1.82	(1.19–2.78)	.006	1.63	(0.97–2.75)	.066	2.46	(1.18–5.10)	.016	3.46	(1.63–7.37)	.001
2 years	1.53	(1.09–2.16)	.014	1.40	(0.92–2.13)	.115	2.00	(1.11–3.62)	.022	2.60	(1.35–4.99)	.004
3 years	1.29	(0.92–1.82)	.142	1.20	(0.80–1.81)	.384	1.63	(0.88–3.03)	.122	1.95	(0.88–4.30)	.099
Hypoglycemia (fully adjusted multivariable model)												
Main effect	1.65	(0.95–2.87)	.078	1.37	(0.69–2.72)	.365	2.32	(0.88–6.09)	.089	3.37	(1.19–9.57)	.022
TVC	0.84	(0.70–1.01)	.057	0.85	(0.69–1.06)	.143	0.83	(0.60–1.15)	.268	0.79	(0.53–1.19)	.255
1 year	1.39	(0.90–2.13)	.134	1.17	(0.69–1.99)	.562	1.93	(0.92–4.04)	.082	2.67	(1.22–5.82)	.014
2 years	1.17	(0.82–1.65)	.382	0.97	(0.65–1.53)	.989	1.60	(0.88–2.94)	.126	2.10	(1.07–4.15)	.032
3 years	0.98	(0.69–1.39)	.922	0.85	(0.56–1.30)	.450	1.34	(0.71–2.51)	.369	1.80	(0.80–4.01)	.153

TVC, time varying covariate, time interaction with hypoglycemia. Main effect: effect estimate of hypoglycemia after accounting for time


Hazard Ratio (95%CI)
0
2
4
6
8
10
12
Entire Cohort
Low
High
Age>=65 years & High
Vascular Risk
Univariable
CAD RF–adjusted
Fully–adjusted


Entire cohort
Cummulative hazard
0.00
0.05
0.10
0.15
0
2
4
6
Follow–up time (years)
Lower vascular risk
Cummulative hazard
0.00
0.05
0.10
0.15
0
2
4
6
Follow–up time (years)
High vascular risk
Cummulative hazard
0.00
0.10
0.20
0.30
0
2
4
6
Follow–up time (years)
Age>=65 years & high vascular risk
Cummulative hazard
0.00
0.10
0.20
0.30
0.40
0
2
4
6
Follow–up time (years)
No prior hypoglycemia
Prior hypoglycemia

Result of logistic regression analysis of the case-control study within the EURODIAB PCS.

	All complications		CVD	
	OR (95% CI)	OR (95% CI)*	OR (95% CI)	OR (95% CI)*
Duration of diabetes (1 year)	1.13 (1.08–1.19)	1.13 (1.08–1.19)	1.12 (1.06–1.19)	1.13 (1.07–1.20)
Systolic blood pressure (1 mmHg)	1.01 (0.99–1.03)	1.02 (1.00–1.04)	1.02 (1.00–1.04)	1.02 (1.00–1.04)
Log AER	2.84 (1.99–4.03)	2.40 (1.70–3.40)	2.65 (1.66–4.23)	2.03 (1.26–3.25)
LDL cholesterol (1 mmol/L)	1.03 (0.76–1.40)	0.97 (0.71–1.32)	0.91 (0.63–1.31)	0.85 (0.58–1.23)
Smoke	1.44 (1.05–1.95)	1.45 (1.05–2.01)	1.60 (1.09–2.35)	1.70 (1.14–2.53)
Log TNF-α	7.12 (3.24–15.65)	6.06 (2.69–13.62)	5.63 (2.30–13.77)	4.78 (1.90–12.0)
Severe hypoglycemia (yes vs. no)	0.46 (0.26–0.84)	0.62 (0.33–1.17)	0.47 (0.23–0.93)	0.61 (0.28–1.30)
Nonsevere hypoglycemia (*n*)				
≤2	1.00	1.00	1.00	1.00
3–5	0.80 (0.41–1.57)	0.90 (0.45–1.79)	1.01 (0.44–2.29)	1.09 (0.47–2.57)
>5	1.03 (0.53–2.02)	1.11 (0.56–2.20)	1.15 (0.50–2.65)	1.24 (0.53–2.90)
HbA_{1c} (1%)		1.57 (1.25–1.97)		1.60 (1.21–2.11)

ORs are adjusted for age, sex, diabetes duration, systolic blood pressure, log AER, LDL cholesterol, smoke, and log TNF-α. *ORs are further adjusted for HbA_{1c}.

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Variables associated with severe hypoglycemia in the nested case-control study of the EURODIAB PCS.

	Number of episodes of severe hypoglycemia in the past year			
	0	1–2	3+	*P* value
All subjects	359	100	72	0.50
Age (years)	39.2 ± 9.7	39.4 ± 10.9	42.0 ± 10.7	0.09
Males	175 (48.7%)	58 (58.0%)	39 (54.2%)	0.23
Diabetes duration (years)	21.0 ± 9.4	22.0 ± 9.7	23.7 ± 9.6	0.08
HbA_{1c} (%)	8.7 ± 1.6	8.3 ± 1.6	8.0 ± 1.6	0.001
Case subjects (*n* = 363)	251	64	48	
CRP (mg/L)	1.25 (0.48–2.69)	1.20 (0.45–2.69)	1.17 (0.42–3.23)	0.92
IL-6 (pg/mL)	2.53 (1.36–4.01)	2.41 (1.44–4.75)	2.36 (1.43–3.43)	0.86
TNF-α (pg/mL)	3.08 (2.23–3.98)	3.72 (2.39–4.60)	3.40 (2.03–4.24)	0.0009
E-selectin (ng/mL)	33 (25–41)	36 (26–46)	30 (19–40)	0.08
sVCAM (ng/mL)	406 (335–490)	408 (336–468)	449 (336–563)	0.08
HSP27 (pg/mL)	638.0 (276.7–1,305.0)	687.6 (274.7–1,286.0)	728.7 (342.9–1,693.5)	0.74
Anti-HSP60 (μg/mL)	21.14 (11.23–37.00)	22.28 (12.11–40.74)	21.65 (12.15–37.47)	0.91
Anti-HSP70 (μg/mL)	153.7 (102.4–215.1)	154.2 (94.7–250.0)	148.0 (102.1–217.4)	0.92
Control subjects (*n* = 168)	108	36	24	
CRP (mg/L)	0.78 (0.36–1.80)	0.84 (0.43–2.01)	0.54 (0.28–1.44)	0.39
IL-6 (pg/mL)	1.73 (1.06–2.11)	1.72 (0.99–1.91)	1.59 (0.99–2.74)	0.87
TNF-α (pg/mL)	2.11 (1.67–2.89)	2.29 (1.81–3.24)	2.03 (1.93–2.90)	0.41
E-selectin (ng/mL)	28 (24–40)	30 (28–43)	26 (19–36)	0.33
sVCAM (ng/mL)	371 (322–439)	356 (312–393)	372 (363–427)	0.63
HSP27 (pg/mL)	549.0 (209.9–1,173.0)	464.6 (219.2–1,013.0)	890.0 (230.6–1,062.5)	0.09
Anti-HSP60 (μg/mL)	21.38 (10.20–29.98)	19.62 (11.65–23.78)	20.11 (12.59–29.12)	0.88
Anti-HSP70 (μg/mL)	174.3 (121.5–247.0)	150.8 (113.2–235.9)	193.3 (141.0–247.5)	0.33

Data are either means ± SD or geometric means (interquartile range).

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HYPOGLYCEMIA AFTER CARDIAC SURGERY

Table 1
Demographic Characteristics of Original Study Population

Variable	No hypoglycemia (n = 1,110)	Hypoglycemia (n = 215)	*P* value
Age (years)	63.8 ± 13.6	64.9 ± 13.6	.27
Body mass index (kg/m^2)	29.0 ± 6.5	26.2 ± 6.0	<.001
Female	340 (31%)	96 (45%)	<.001
Surgery type			.22
CABG	409 (37%)	66 (31%)	
Valve repair or replacement	473 (43%)	99 (45%)	
CABG and valve procedure	228 (21%)	50 (23%)	
Diabetes mellitus	277 (25%)	71 (33%)	.014
Left ventricular ejection fraction	55.2 ± 12.7	53.7 ± 13.6	.12
Hypertension	815 (73%)	146 (68%)	.10
Dyslipidemia	754 (68%)	125 (58%)	.005
Cigarette smoker	160 (14%)	38 (18%)	.22
Renal failure[a]	31 (3%)	16 (7%)	<.001
Dialysis	26 (2%)	14 (7%)	.001
Chronic lung disease	129 (12%)	30 (14%)	.78
Previous myocardial infarction	231 (21%)	48 (22%)	.62
Prior stroke	74 (5%)	25 (12%)	.011

Abbreviation: CABG = coronary artery bypass graft.
Data are expressed as n (%) or means ± SD.
[a] Creatinine on admission >2.0 mg/dL.

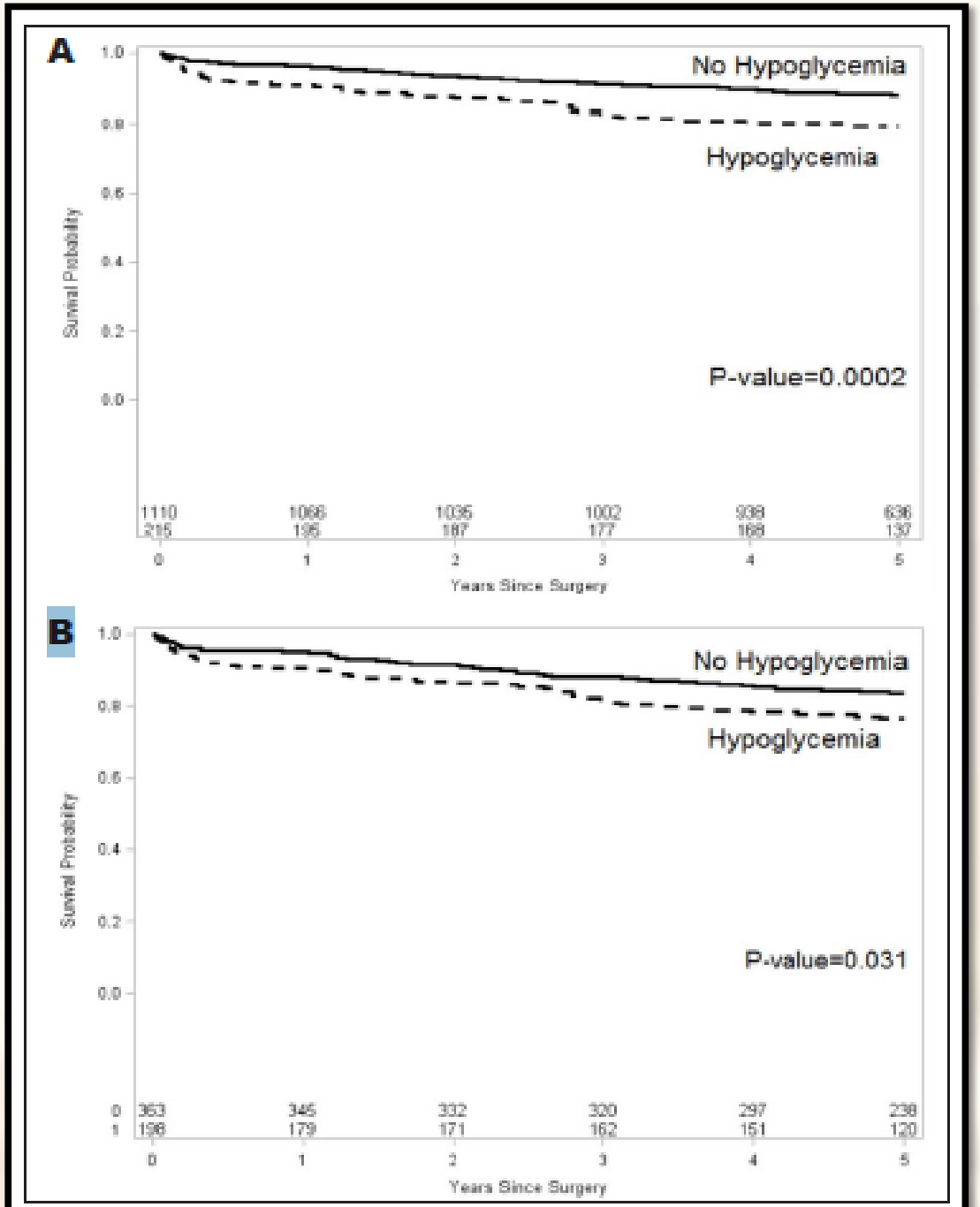


Fig. 3. Kaplan-Meier survival curves by hypoglycemia status in the original (*A*) and propensity score–matched (*B*) groups.

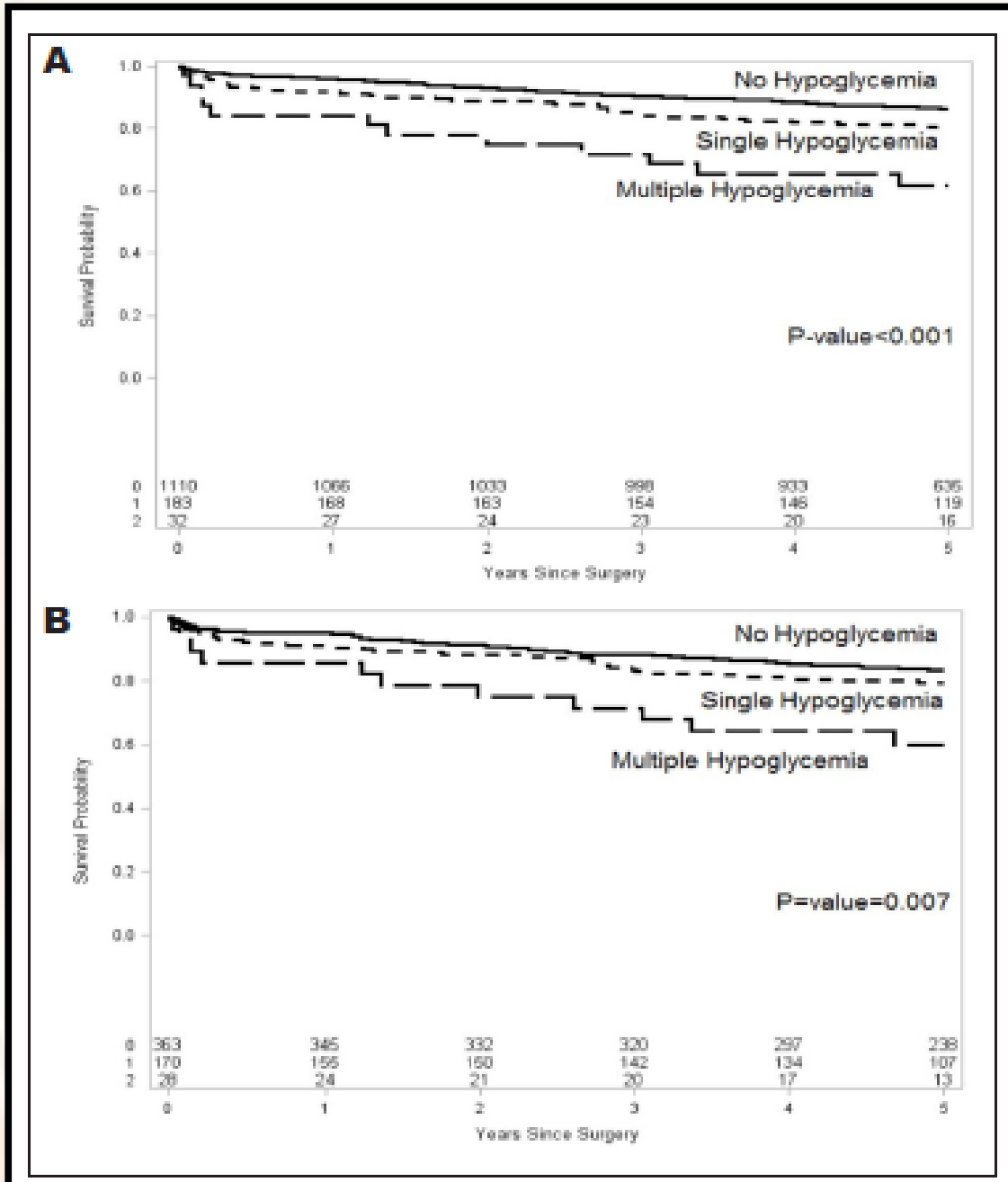


Fig. 4. Kaplan-Meier survival curves in propensity score–matched groups. Group of hypoglycemic patients was further divided into one or more than one hypoglycemic episode in the original (*A*) and propensity score–matched (*B*) groups.

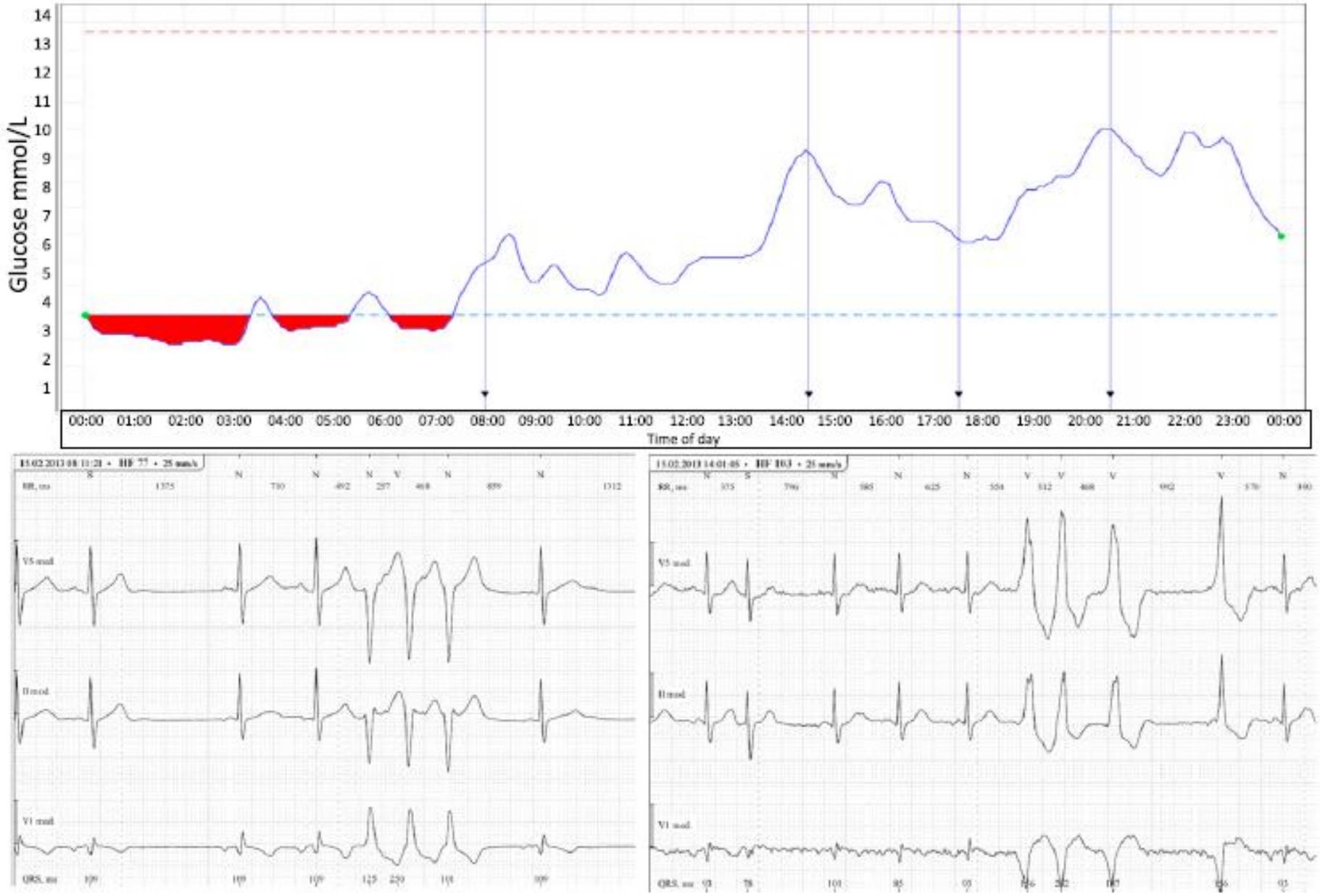


Figure 1—Case report: male 63 years old with documented stenosis of the internal cerebral artery, diabetes duration 12 years, and treatment with 22 IU insulin glargine at bedtime: parallel recording of continuous glucose monitoring system and Holter.

Table 1—Hypoglycemia-mediated effects that may contribute to cardiovascular dysfunction

Risk factor	Hypoglycemia-induced effect contributing to the risk factor
Abnormal cardiac repolarization	QT interval prolongation, increased plasma epinephrine and norepinephrine concentrations, hypokalemia
Reduced myocardial perfusion	Hemodynamic changes with increase to cardiac workload and heart rate, fall in central arterial pressure and large vessel elasticity
Atherosclerosis	Increase of endothelial dysfunction and inflammation
Prothrombotic state	Increased platelet aggregation, increased coagulation

Modified with permission from Hanefeld et al. (20).

Effect of experimental hypoglycemia on QT interval

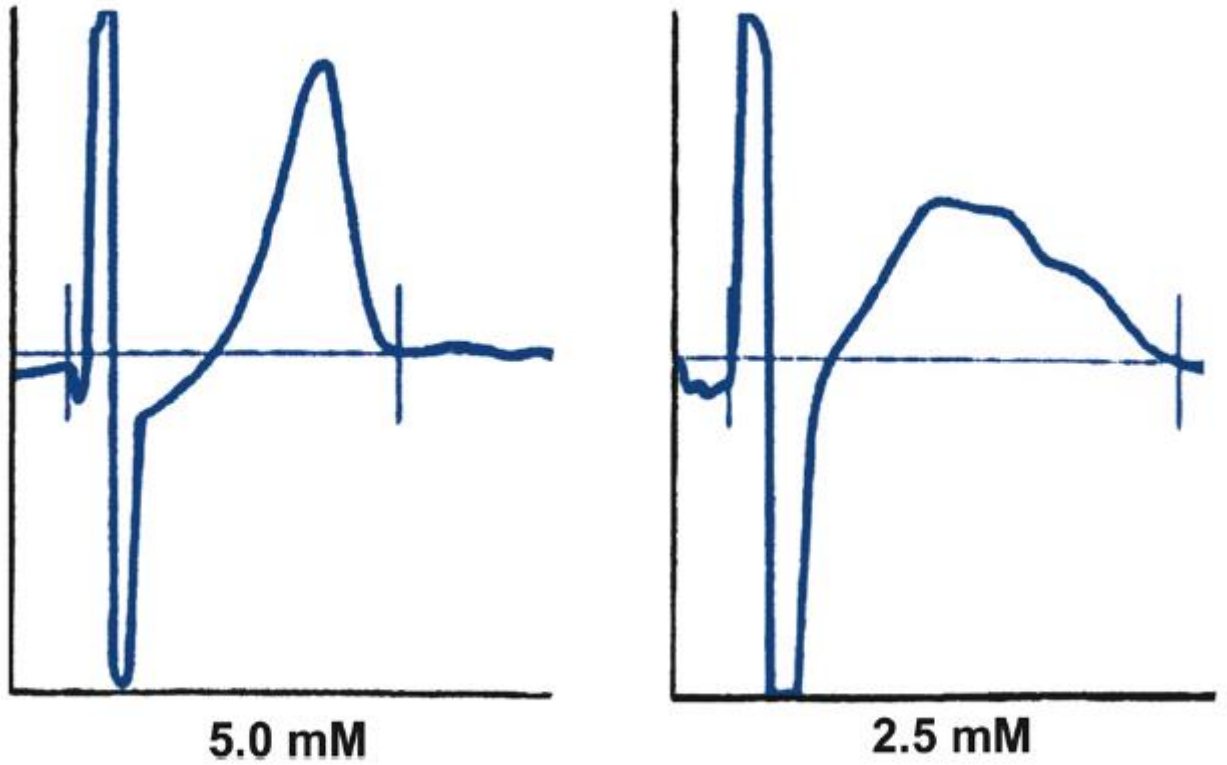
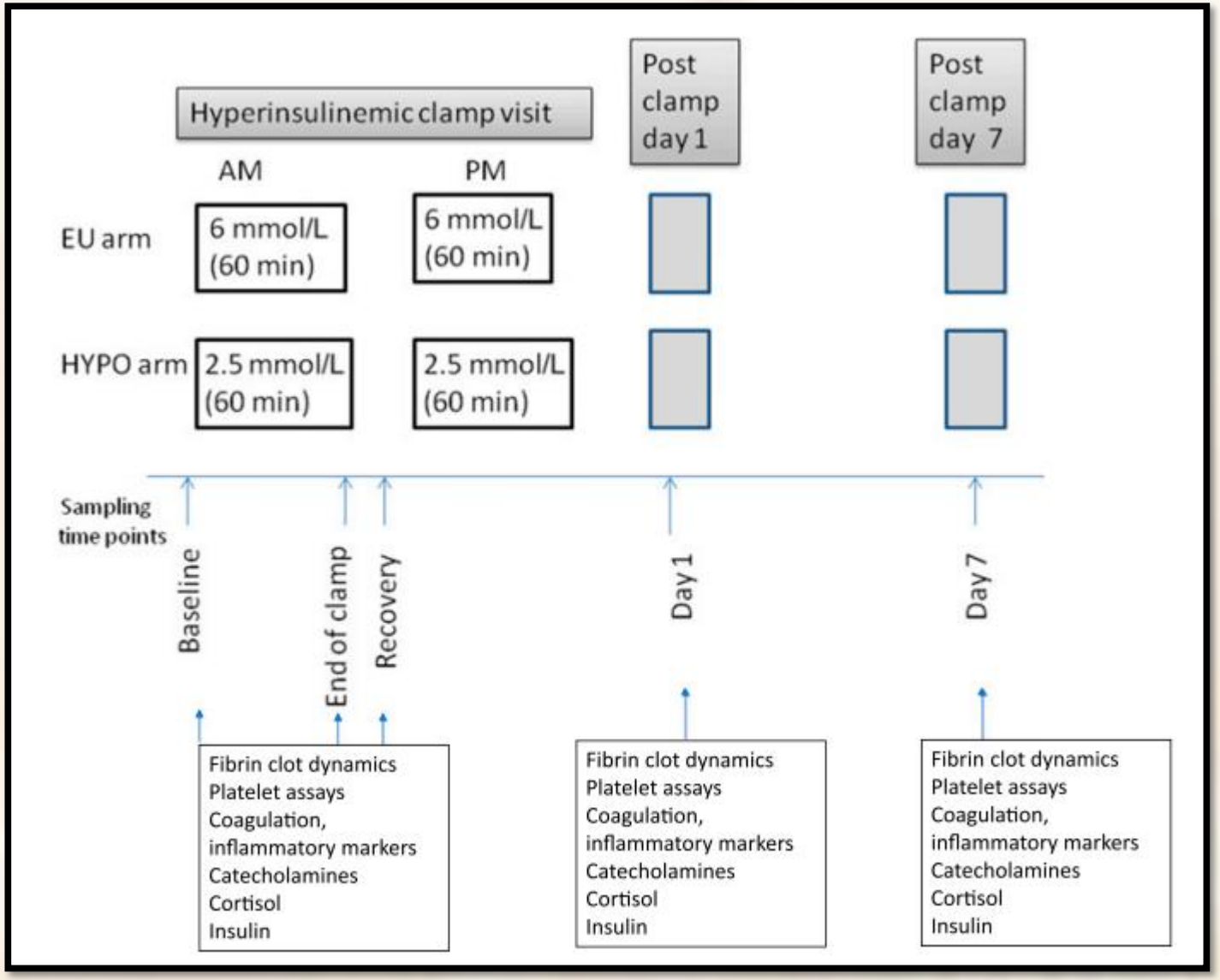
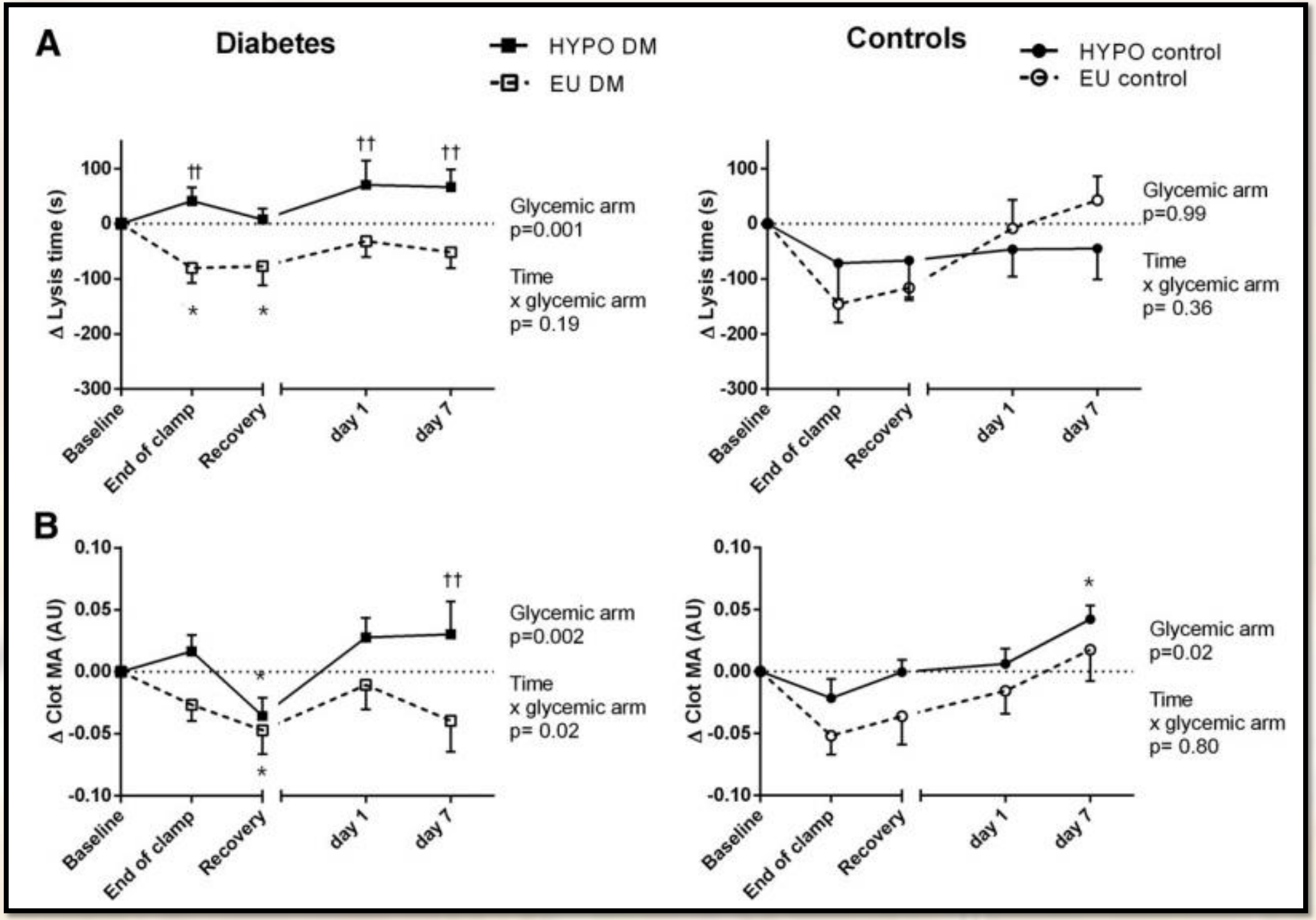
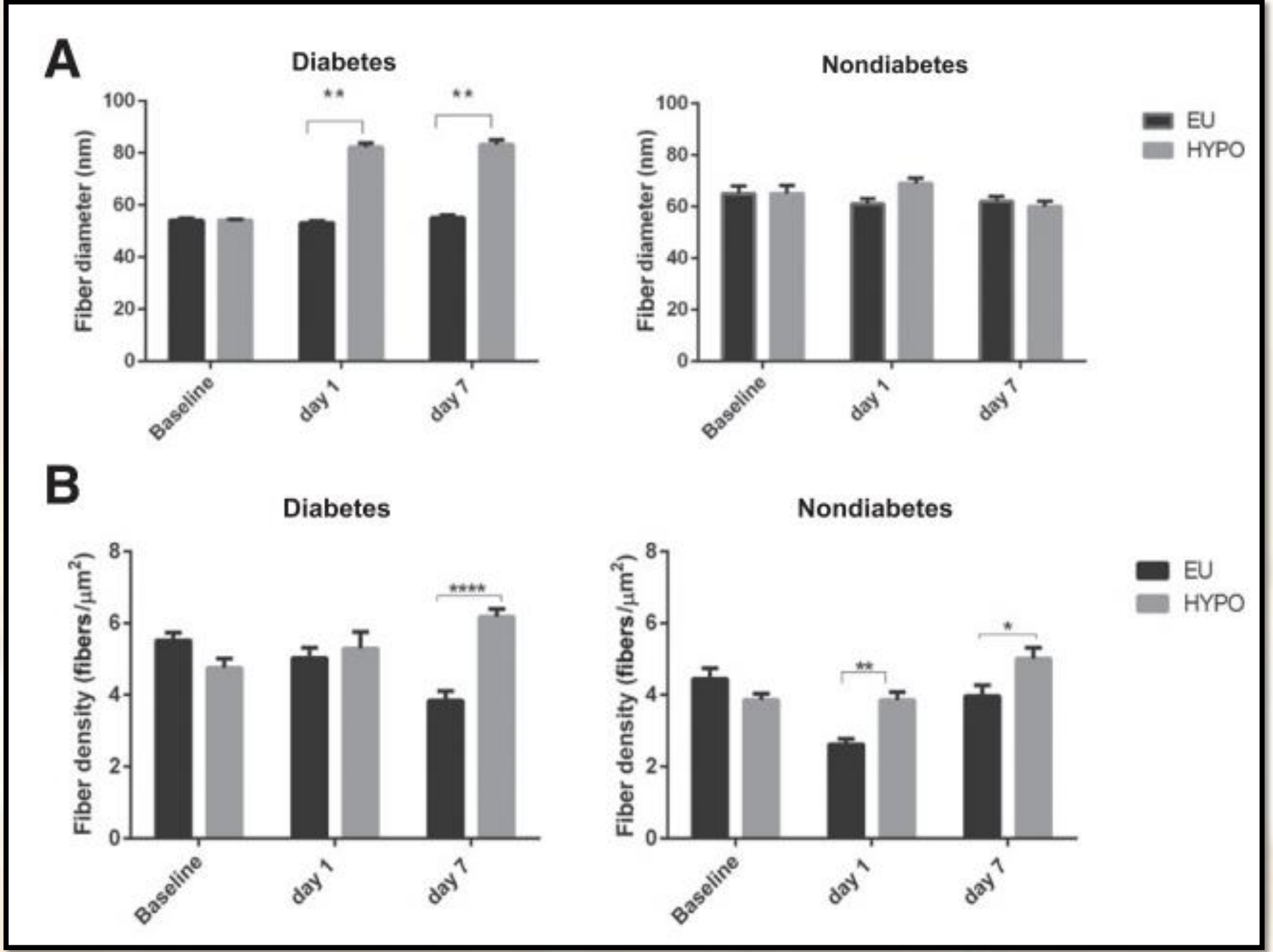


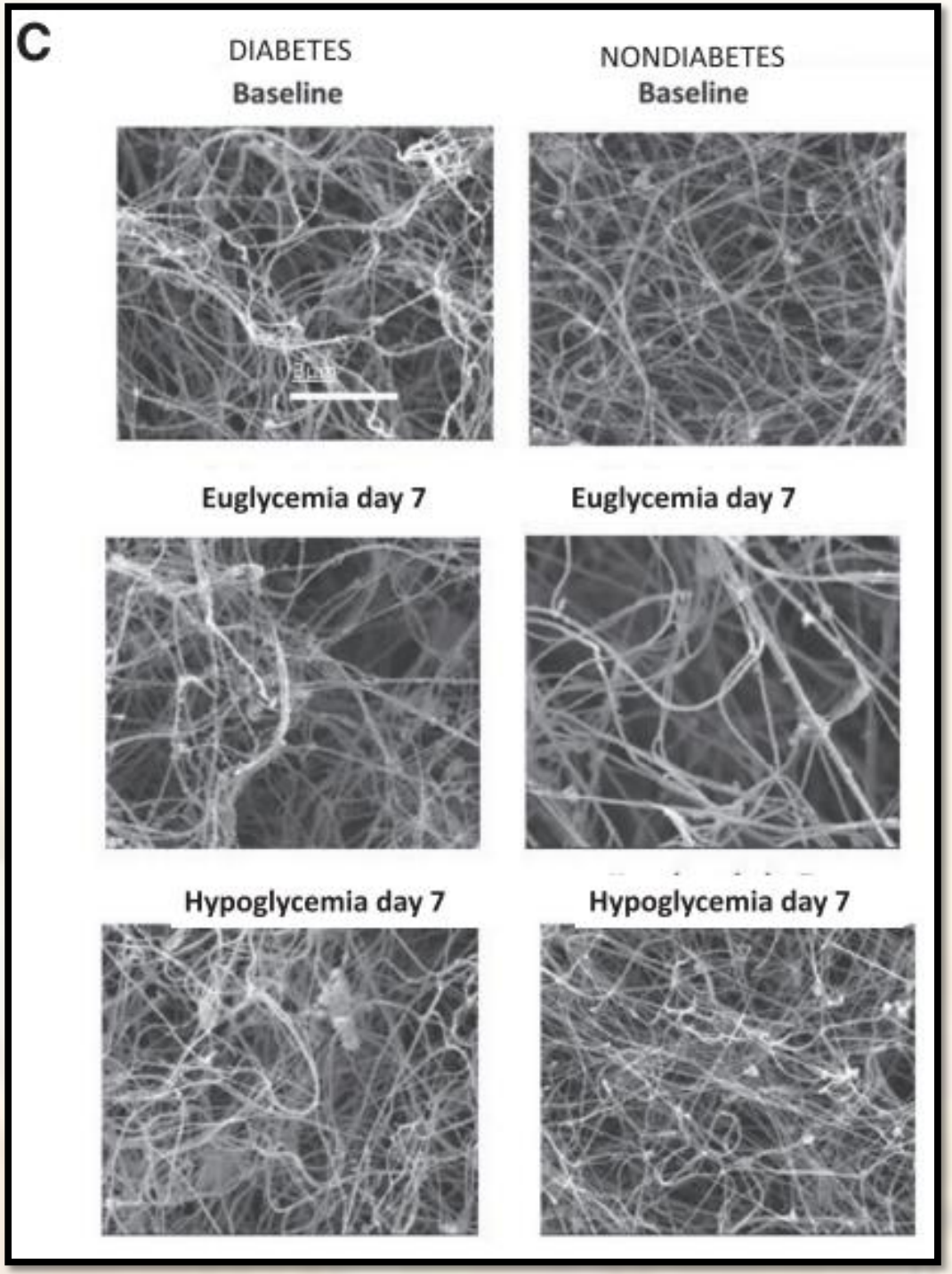
Figure 1—*Typical QT measurement with a screen cursor placement from a subject during euglycemia* (left panel), *showing a clearly defined T wave, and hypoglycemia* (right panel), *showing prolonged repolarization and a prominent U wave. Reproduced from Marques et al. (20) with permission from John Wiley & Sons.*

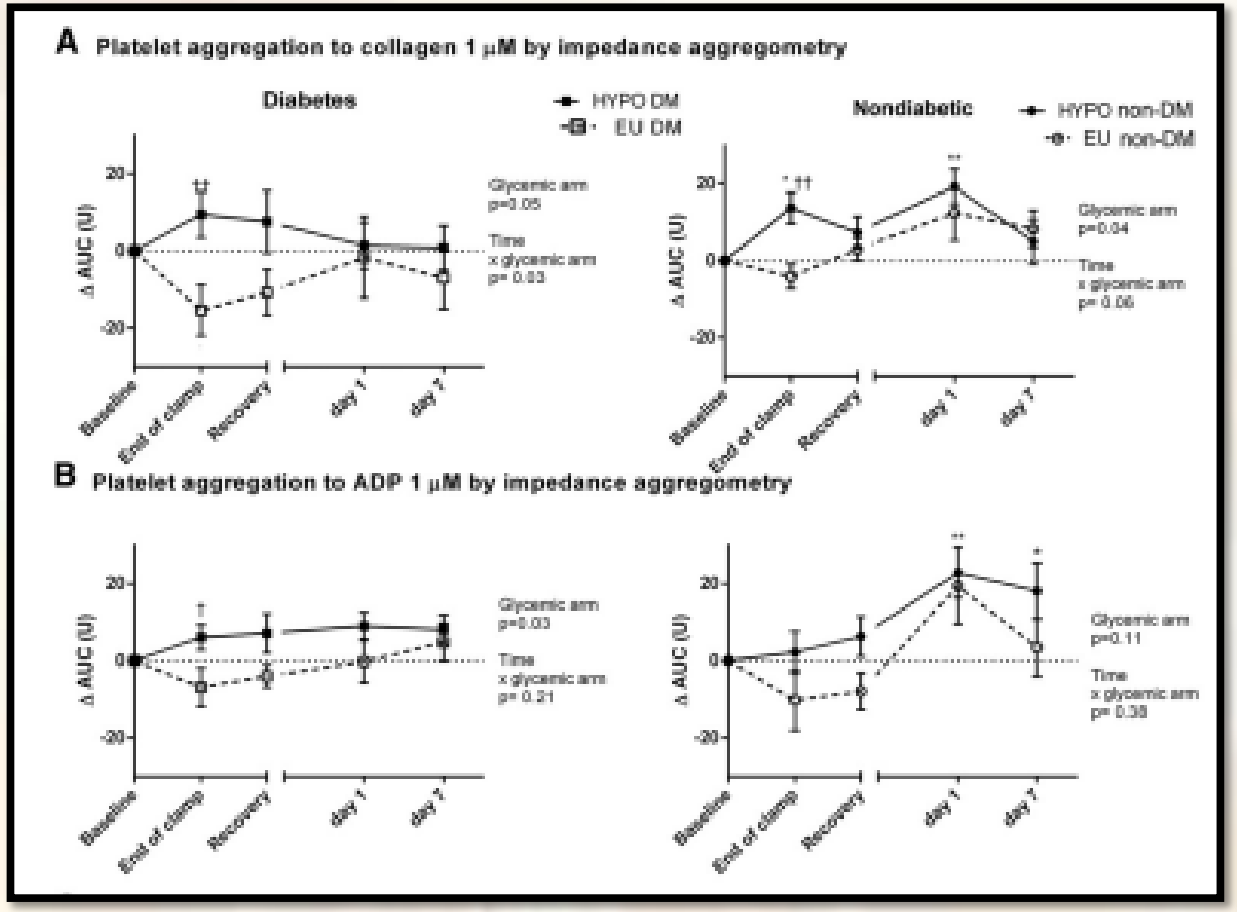
Prolonged Prothrombotic Effects of Antecedent Hypoglycemia in Individuals With Type 2 Diabetes

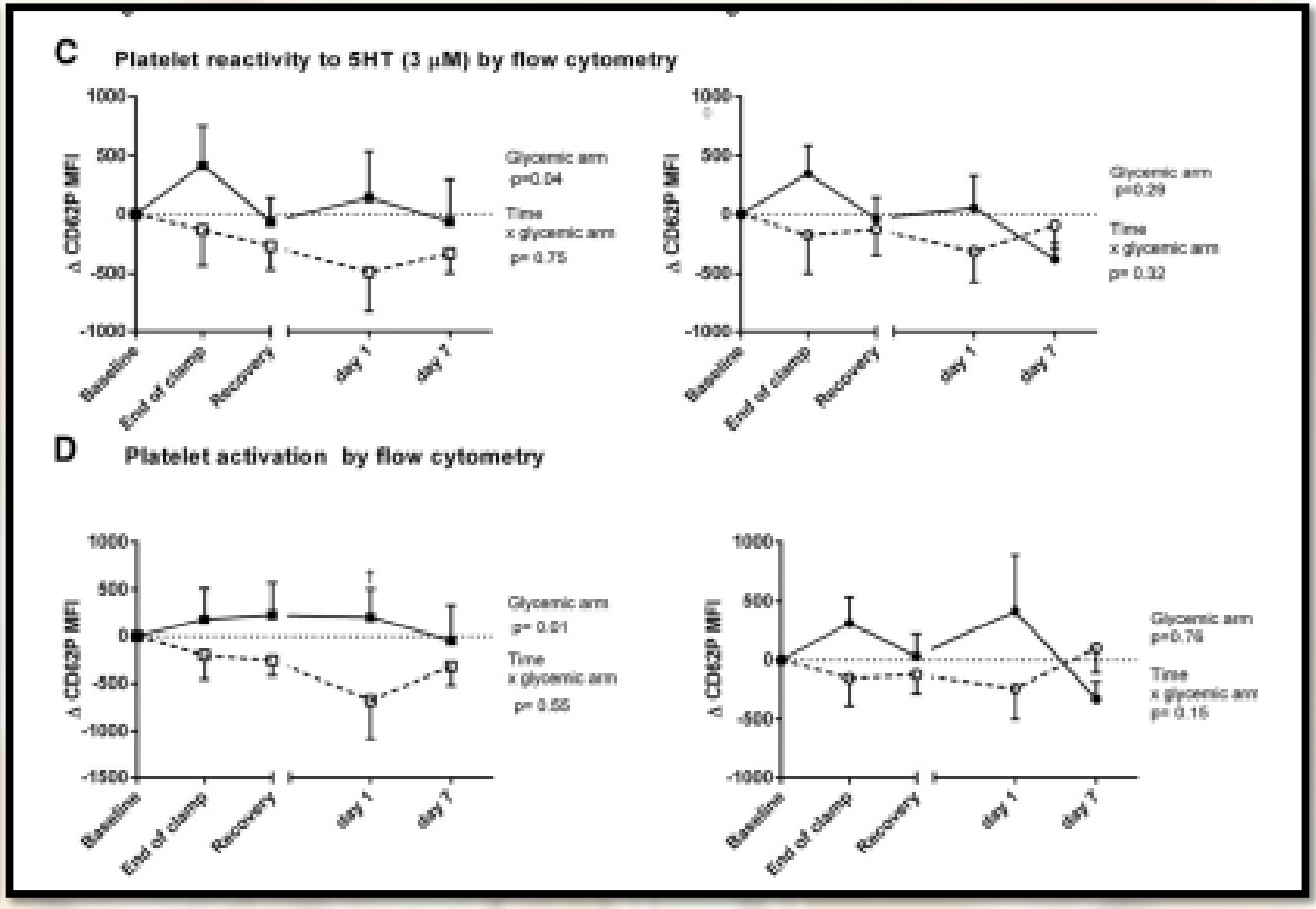



A
Diabetes
HYPO DM
EU DM
Controls
HYPO control
EU control
Δ Lysis time (s)
100
0
-100
-200
-300
††
*
Baseline
End of clamp
Recovery
day 1
day 7
Glycemic arm
p=0.001
Time
x glycemic arm
p= 0.19
Glycemic arm
p=0.99
Time
x glycemic arm
p= 0.36
B
Δ Clot MA (AU)
0.10
0.05
0.00
-0.05
-0.10
Glycemic arm
p=0.002
Time
x glycemic arm
p= 0.02
Glycemic arm
p=0.02
Time
x glycemic arm
p= 0.80


A
Diabetes
Nondiabetes
Fiber diameter (nm)
100
80
60
40
20
0
**
**
Baseline
day 1
day 7
EU
HYPO
B
Diabetes
Nondiabetes
Fiber density (fibers/μm²)
8
6
4
2
0
****
**
*
Baseline
day 1
day 7
EU
HYPO


C
DIABETES
Baseline
NONDIABETES
Baseline
Euglycemia day 7
Euglycemia day 7
Hypoglycemia day 7
Hypoglycemia day 7


A
Platelet aggregation to collagen 1 µM by impedance aggregometry
Diabetes
HYPO DM
EU DM
Nondiabetic
HYPO non-DM
EU non-DM
Δ AUC (U)
Glycemic arm p=0.05
Time x glycemic arm p= 0.03
Glycemic arm p=0.04
Time x glycemic arm p= 0.06
Baseline
End of clamp
Recovery
day 1
day 7
B
Platelet aggregation to ADP 1 µM by impedance aggregometry
Glycemic arm p=0.03
Time x glycemic arm p= 0.21
Glycemic arm p=0.11
Time x glycemic arm p= 0.38


C
Platelet reactivity to 5HT (3 µM) by flow cytometry
Δ CD62P MFI
Glycemic arm p=0.04
Time x glycemic arm p= 0.75
Glycemic arm p=0.29
Time x glycemic arm p= 0.32
D
Platelet activation by flow cytometry
Glycemic arm p= 0.01
Time x glycemic arm p= 0.55
Glycemic arm p=0.76
Time x glycemic arm p= 0.16
Baseline
End of clamp
Recovery
day 1
day 7

Relationship Between Hypoglycemic Episodes and Ventricular Arrhythmias in Patients With Type 2 Diabetes and Cardiovascular Diseases: Silent Hypoglycemias and Silent Arrhythmias

Annett Stahn,[1] Frank Pistrosch,[1,2] Xenia Ganz,[1,2] Madlen Teige,[2] Carsta Koehler,[3] Stefan Bornstein,[1] and Markolf Hanefeld[1,2]

Table 1—Baseline characteristics and parameters of glycemic control during 5 days of CGMS recording

Characteristics	Group	Mean	SD	*P* value	Range
Age (years)	1	67.6	6.4	0.540	56–80
	2	66.2	7.0		51–77
HbA_{1c} (%)	1	7.3	0.8	0.349	5.9–8.9
	2	7.6	0.7		6.6–9.0
HbA_{1c} (mmol/mol)	1	56	6.1	0.349	41–74
	2	60	5.5		51–75
Systolic BP (mmHg)	1	146.2	20.7	0.508	105–183
	2	142.0	10.1		125–155
Diastolic BP (mmHg)	1	78.8	9.2	0.528	61–98
	2	80.6	4.6		73–90
Sodium (mmol/L)	1	138.1	2.9	0.684	132.4–144
	2	137.7	3.2		132.5–143.2
Potassium (mmol/L)	1	4.42	0.36	0.727	3.6–4.9
	2	4.38	0.39		3.77–5.06
Cholesterol (mmol/L)	1	4.7	0.9	0.940	3.2–7.0
	2	4.7	1.3		2.7–6.1
HDL cholesterol (mmol/L)	1	1.2	0.3	0.180	0.7–1.8
	2	1.4	0.4		0.7–2.1
LDL cholesterol (mmol/L)	1	2.6	0.7	0.942	1.0–4.0
	2	2.5	0.9		1.3–3.6
Triglycerides (mmol/L)	1	2.4	1.7	0.052	0.4–7.9
	2	1.4	0.3		0.6–1.7
Creatinine (μmol/L)	1	82.3	21.3	0.280	68–124
	2	76.4	14.0		49–98
Mean IG	1	8.20	1.67	0.422	5.6–11.4
	2	8.63	1.15		5.9–10.3
Maximal IG (mmol/L)	1	15.7	3.3	0.578	9.5–22.2
	2	15.1	2.2		11.7–17.9
Minimal IG (mmol/L)	1	3.28	0.9	0.000	2.2–6.0
	2	5.01	1.0		3.7–6.7
SD of IG (mmol/L)	1	2.33	0.78	0.148	1.3–4.3
	2	1.97	0.55		1.2–3.0
AUC_D2 (mmol/L-1 h)	1	2,368	613	0.129	1,630–3,869
	2	2,670	438		1,714–3,479
MAGE (mmol/L)	1	4.9	1.5	0.649	2.78–9.42
	2	4.5	1.7		2.71–6.55
HEs per patient with IG <3.1 mmol/L	1	1.0	1.6	0.049	0–6
	2	0	0		0
HEs per patient with IG <3.9 mmol/L	1	2.6	3.1	0.010	0–12
	2	0.2	0.4		0–1
Time spent with IG <3.1 mmol/L (min)	1	39.5	70.5	0.008	0–240
	2	0	0		0
Time spent with IG <3.9 mmol/L (min)	1	156	255	0.047	0–996
	2	2.9	7.5		0–25
Distribution of HEs*					
Daytime (6:00 A.M.–10:00 P.M.): 11					
Nocturnal (10:00 P.M.–6:00 A.M.): 26					

Group 1, high-risk group (29 men, 1 woman); group 2, control group (9 men, 3 women). AUC_D2, AUC for glucose at recording day 2. χ^2 test for sex: $P = 0.063$. *<3.1 mmol/L for group 1.

Table 2—ECG parameters during 5 days of parallel recording

Parameters	Group	Mean	SD	*P* value	Range	Comment
Mean heart rate (bpm)	1	69.4	8.6	0.096	55–89	
	2	78.0	15.8		64–96	
Minimal heart rate (bpm)	1	53.1	8.9	0.603	43–78	
	2	54.5	3.9		46–60	
Maximal heart rate (bpm)	1	110.5	17.7	0.293	79–159	
	2	117.6	23.9		72–154	
Mean QTc (ms)	1	376.9	48.7	0.531	300–475	
	2	388.0	50.2		307–445	
SDNNs (ms)	1	121.2	36.2	0.448	55–225	
	2	112.6	22		84–184	
SVESs per patient (*n*)	1	633	1,345	0.458	6–6,938	
	2	322	764		0–2,723	
VESs per patient (*n*)	1	3,607	7,977	0.027	1–35,328	28 patients in group 1
	2	144	217		0–732	11 patients in group 2
Couplets per patient (*n*)	1	20.5	53.3	0.054	0–258	17 patients (56.7%) in group 1
	2	0.9	1.2		0–4	6 patients (50%) in group 2
Triplets per patient (*n*)	1	2.2	6.3	0.080	0–32	10 patients (33.3%) in group 1
	2	0.1	0.3		0–1	1 patient (8.3%) in group 2
VTs per patient (*n*)	1	0.5	1.3	0.05	0–5	5 patients (16.7%) in group 1
	2	0	0		0	None in group 2

Group 1, high-risk group; group 2, control group; SVES, supra-VES.

Table 3—Relationship between severe HEs and cardiac arrhythmia during 5 days of parallel recording

Outcomes	HE	Mean	SD	*P* value
VESs per patient (*n*)	Yes	3,377	7,219	0.688
	No	2,371	6,416	
Couplets per patient (*n*)	Yes	41.7	81.8	0.024
	No	5.5	16.7	
Triplets per patient (*n*)	Yes	2.36	4.3	0.597
	No	1.33	5.8	
VTs per patient (*n*)	Yes	1.0	1.9	0.017
	No	0.1	0.3	

HE "Yes," $n = 12$; HE "No," $n = 30$.

Conclusion

- Smaller observational and epidemiological studies suggest an association between hypoglycemia and cardiovascular events, there is currently no evidence for causality.
- Severe episodes of hypoglycemia are associated with an increased risk of severe ventricular arrhythmias.

Thank you