The pathophysiology and clinical implications of Hypoglycemia

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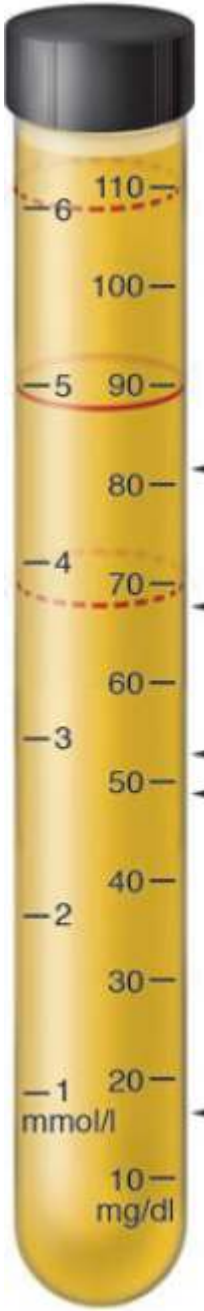
Responses to falling plasma glucose concentrations



↓ Insulin

↑ Glucagon
⇑ Epinephrine

Symptoms
↓ Cognition
Aberrant behavior
Seizeure, coma

Neuronal Death

Hormones	Baseline	Hypoglycemia (<50 mg/dL)
Epinephrine (pmol/L)	179±20	4251±568*
NE (pmol/L)	1128±124	1957±134*
Cortisol (nmol/L)	330±32	714±42*
Glucagon (ng/L)	50±6	112±17*
GH (ng/mL)	4±1.34	25±5*

Cryer PE, J Clin Invest 2007
Joy NG et al., Diabetes (in press)

Hypoglycemia

ADA and The Endocrine Society, Workgroup on Hypoglycemia in April 2012

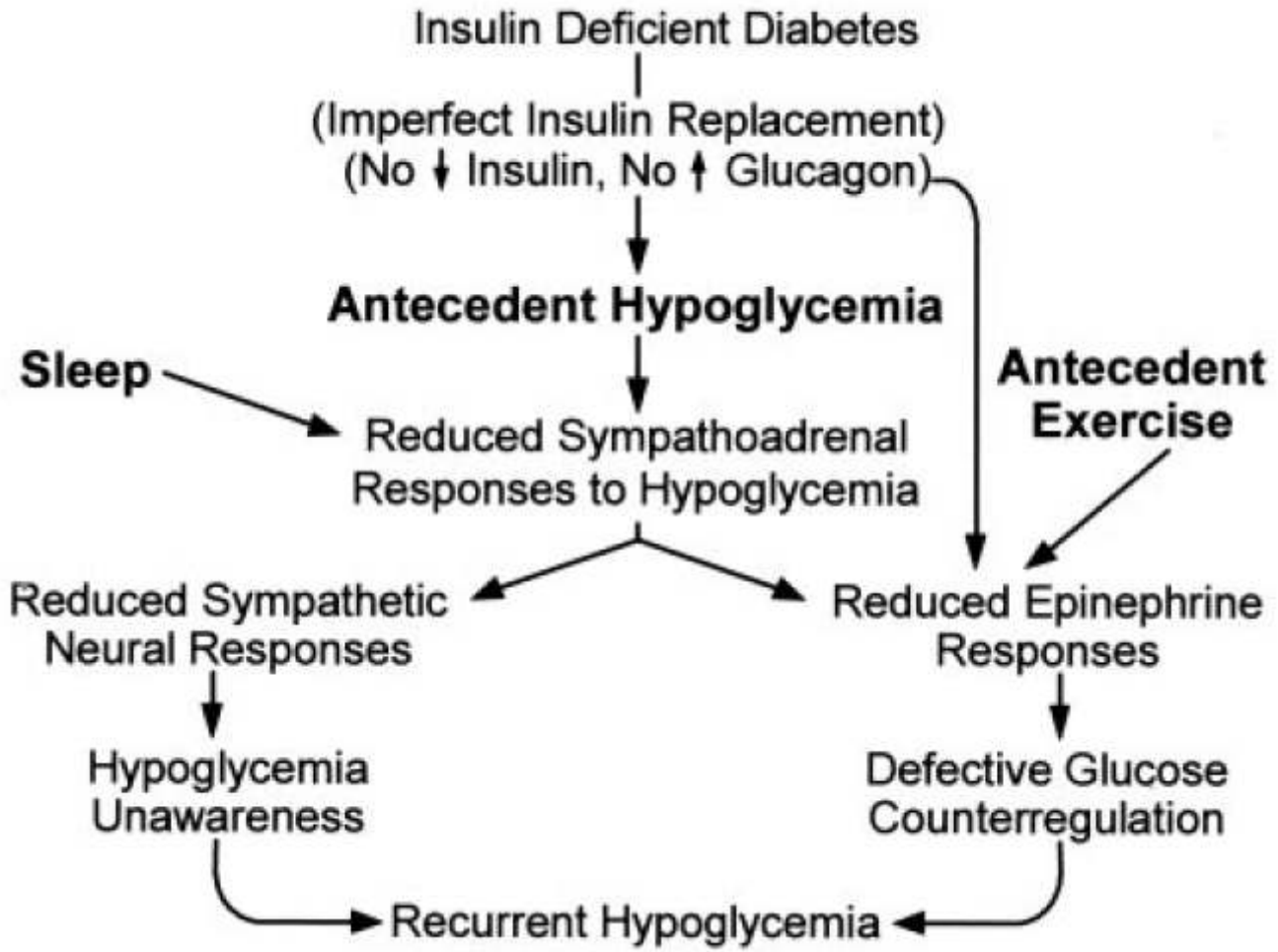
- All episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm

- Plasma glucose level $\leq$ 70 mg/dL

- ~ the lower limit of the normal postabsorptive plasma glucose concentration
- The thresholds for activation of counterregulatory systems in nondiabetic individuals
- The upper limit of plasma glucose level reported to reduce counterregulatory responses to subsequent hypoglycemia

Seaquist et al., Clin Endocrinol Metab, 2013, 98(5):1845–1859

Hypoglycemia-Associated Autonomic Failure

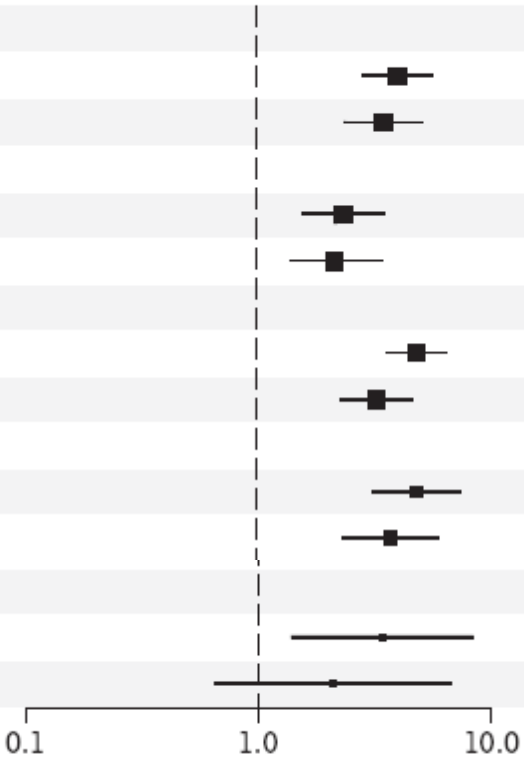


Affected patients are at 25-fold or greater increased risk for severe iatrogenic hypoglycemia during aggressive glycemic therapy

Cryer PE, Diabetes 54:3592–3601, 2005

Severe Hypoglycemia (<50 mg/dl) and Major Outcomes in ADVANCE Study

Events	Severe Hypoglycemia (N=231)	No Severe Hypoglycemia (N=10,909)	Hazard Ratio (95% CI)
	no. of patients with events (%)		
Major macrovascular events	33 (15.9)	1114 (10.2)	
Unadjusted model			4.05 (2.86–5.74)
Adjusted model			3.53 (2.41–5.17)
Major microvascular events	24 (11.5)	1107 (10.1)	
Unadjusted model			2.39 (1.60–3.59)
Adjusted model			2.19 (1.40–3.45)
Death from any cause	45 (19.5)	986 (9.0)	
Unadjusted model			4.86 (3.60–6.57)
Adjusted model			3.27 (2.29–4.65)
Cardiovascular disease	22 (9.5)	520 (4.8)	
Unadjusted model			4.87 (3.17–7.49)
Adjusted model			3.79 (2.36–6.08)
Cancer	5 (2.2)	149 (1.4)	
Unadjusted model			3.44 (1.40–8.42)
Adjusted model			2.11 (0.65–6.82)



Zoungas S et al., NEJM 2010

Severe hypoglycemia and mortality in ACCORD

Role in mortality	Total (n=431)	Intensive	Conventional
Possible	8.8%	10.2%	7.0%
Probable	0.7%	0.41%	1.1%
Definite	0.23%	0.41%	0%

Of the 74 participants who reported any severe hypoglycemia during the study and died, six (8.1%) died within 30 days of the event.

Bonds DE et al. Bmj 2010

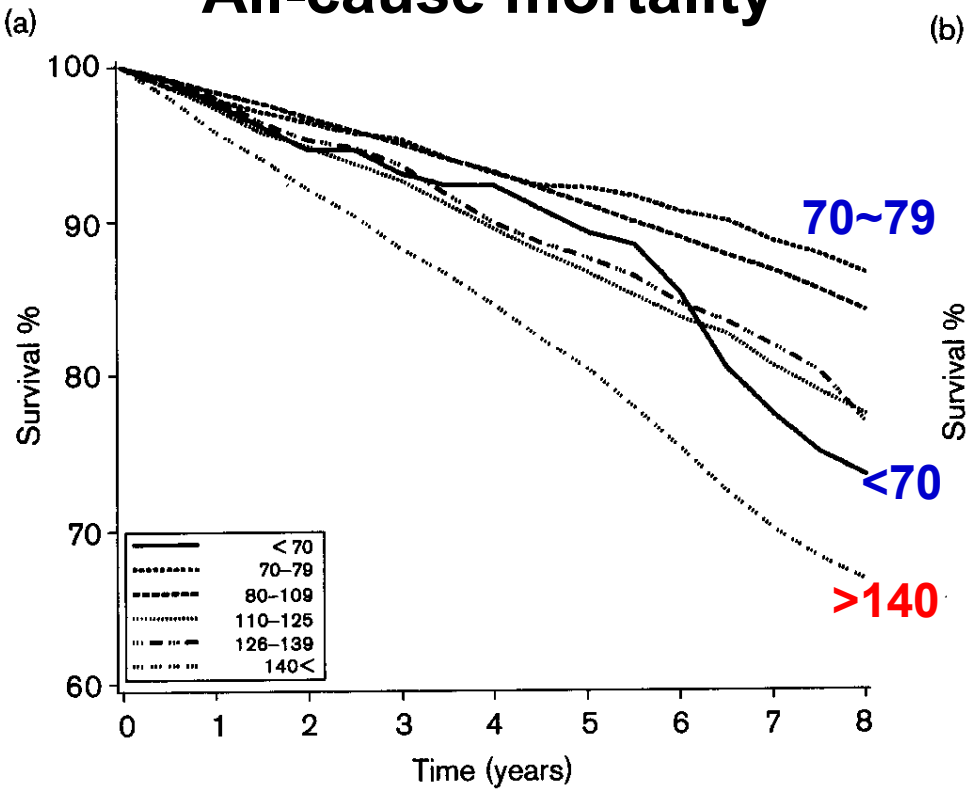
The effects of severe hypoglycemia on CV outcomes in the ORIGIN trial

Groups	Outcomes	Hazard ratio (95% CI)	*P*
Subset with severe hypoglycemia	CV death, nonfatal MI, or nonfatal stroke	1.58 (1.24–2.02)	<0.001
	Total mortality	1.74 (1.39–2.19)	<0.001
	CV death	1.71 (1.27–2.30)	<0.001
	Arrhythmic death	1.77 (1.17–2.67)	<0.001
Severe hypoglycemia in Standard vs. Glargine Group	CV death, nonfatal MI, or nonfatal stroke	1.70 (1.01–2.87)	0.047
	Total mortality	2.31 (1.47–3.64)	<0.001
	CV death	2.09 (1.15–3.82)	0.016
	Arrhythmic death	2.94 (1.29–6.70)	0.010

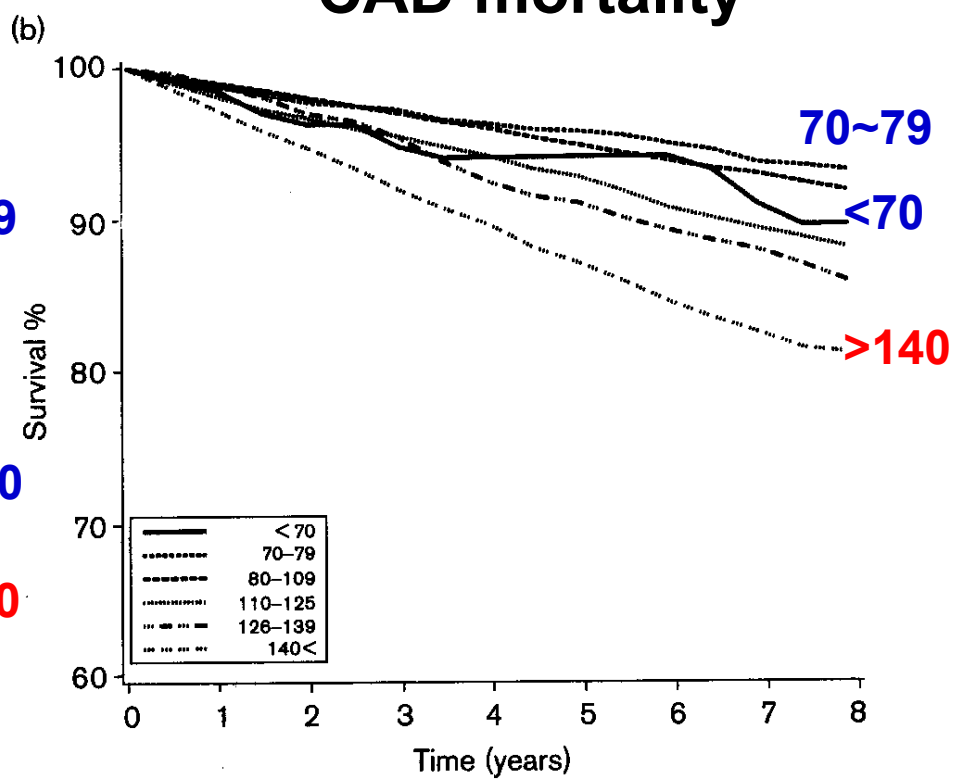
Gerstein HC et al.; ORIGIN Trial Investigators.. N Engl J Med 2012
The ORIGIN Trial Investigators. Mellbin LG et al., Eur Heart J 2013

The effect of hypoglycemia: 8-year mortality in patients with CAD

All-cause mortality



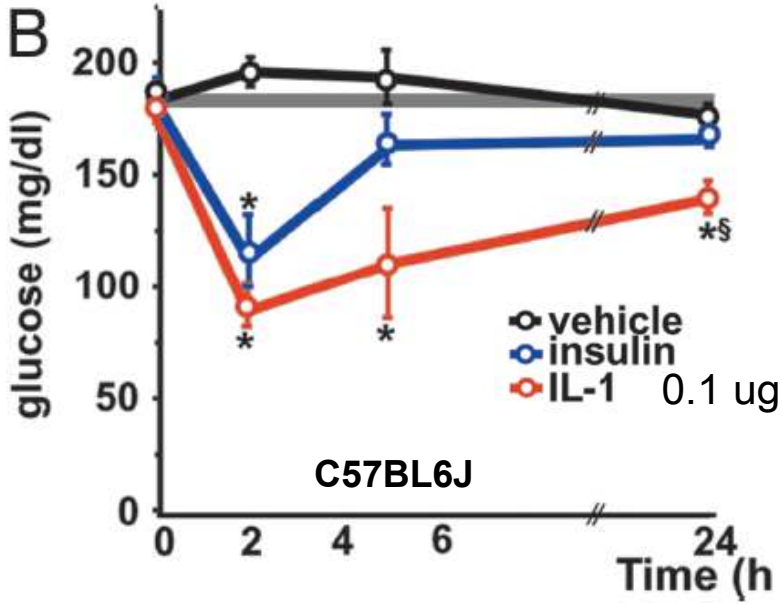
CAD mortality

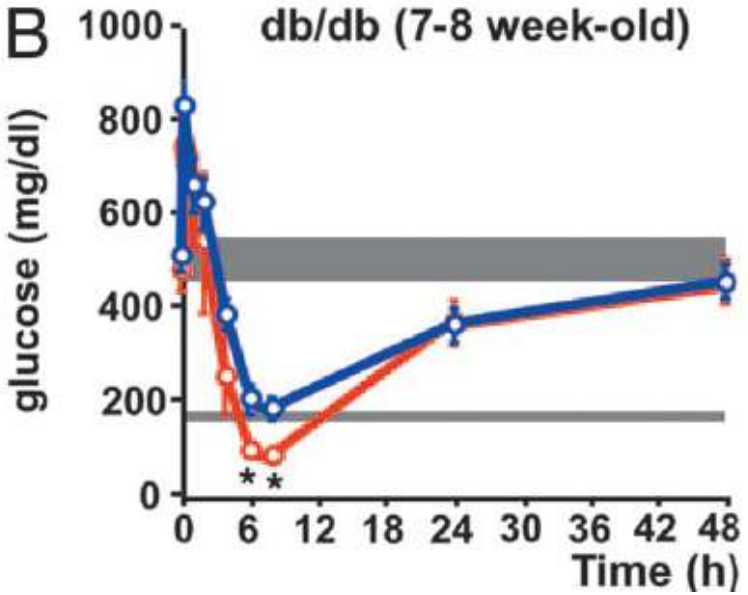


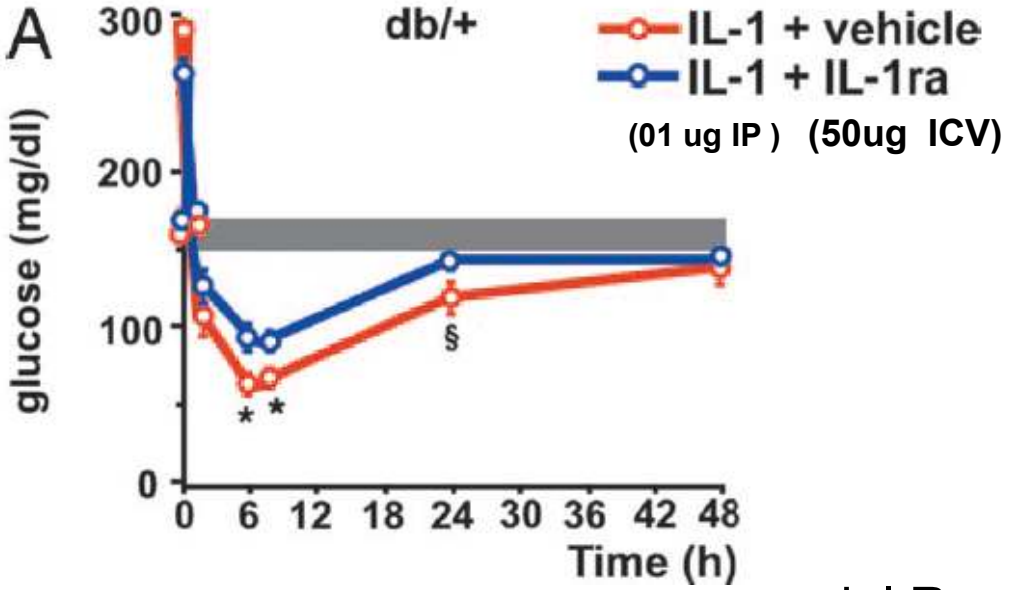
Bezafibrate Infarction Prevention study

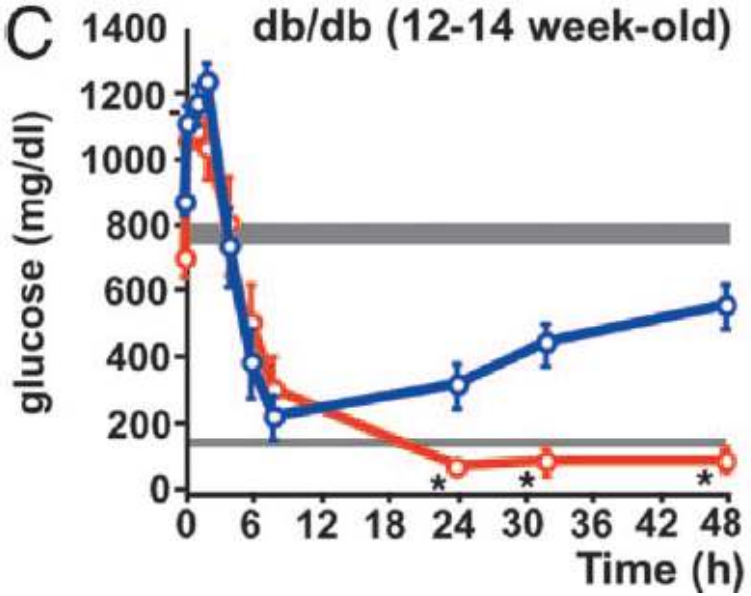
Fisman EZ et al., *Eur J Cardiovasc Prev Rehabil 11:135-143, 2004*

IL-1β induces hypoglycemia



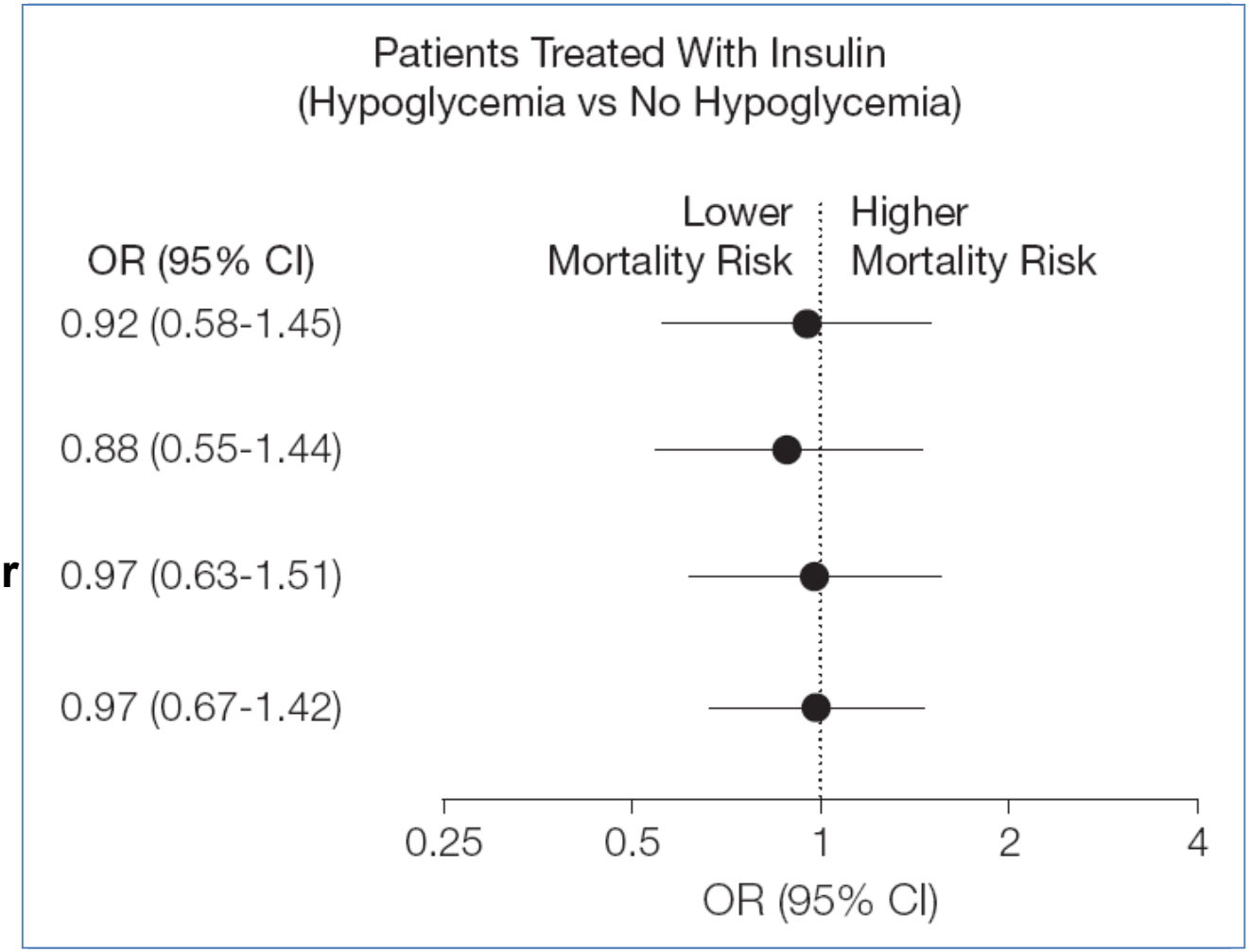




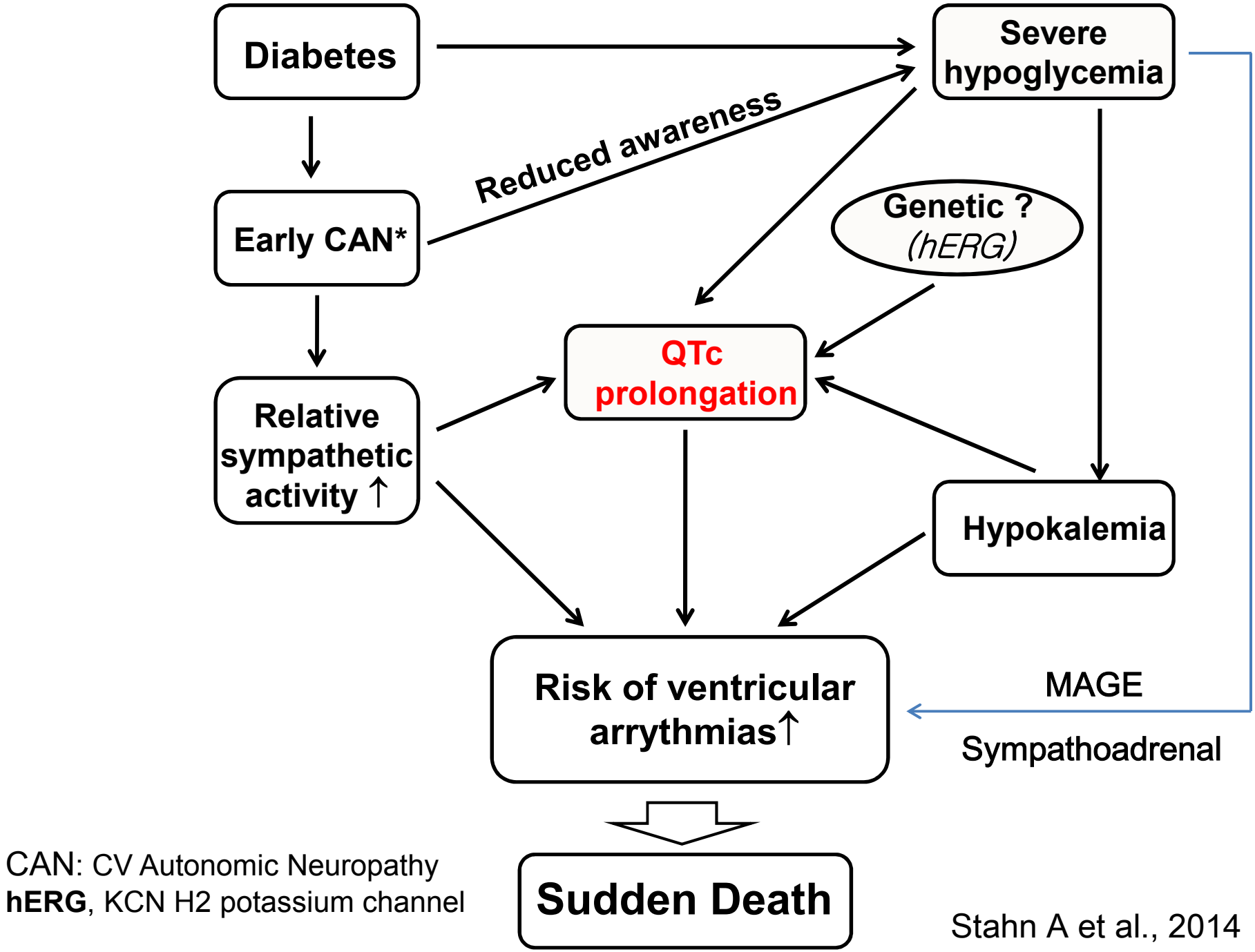


del Rey *et al. PNAS 2006*

Association Between Hypoglycemia and In-Hospital Mortality After Multivariable Adjustment

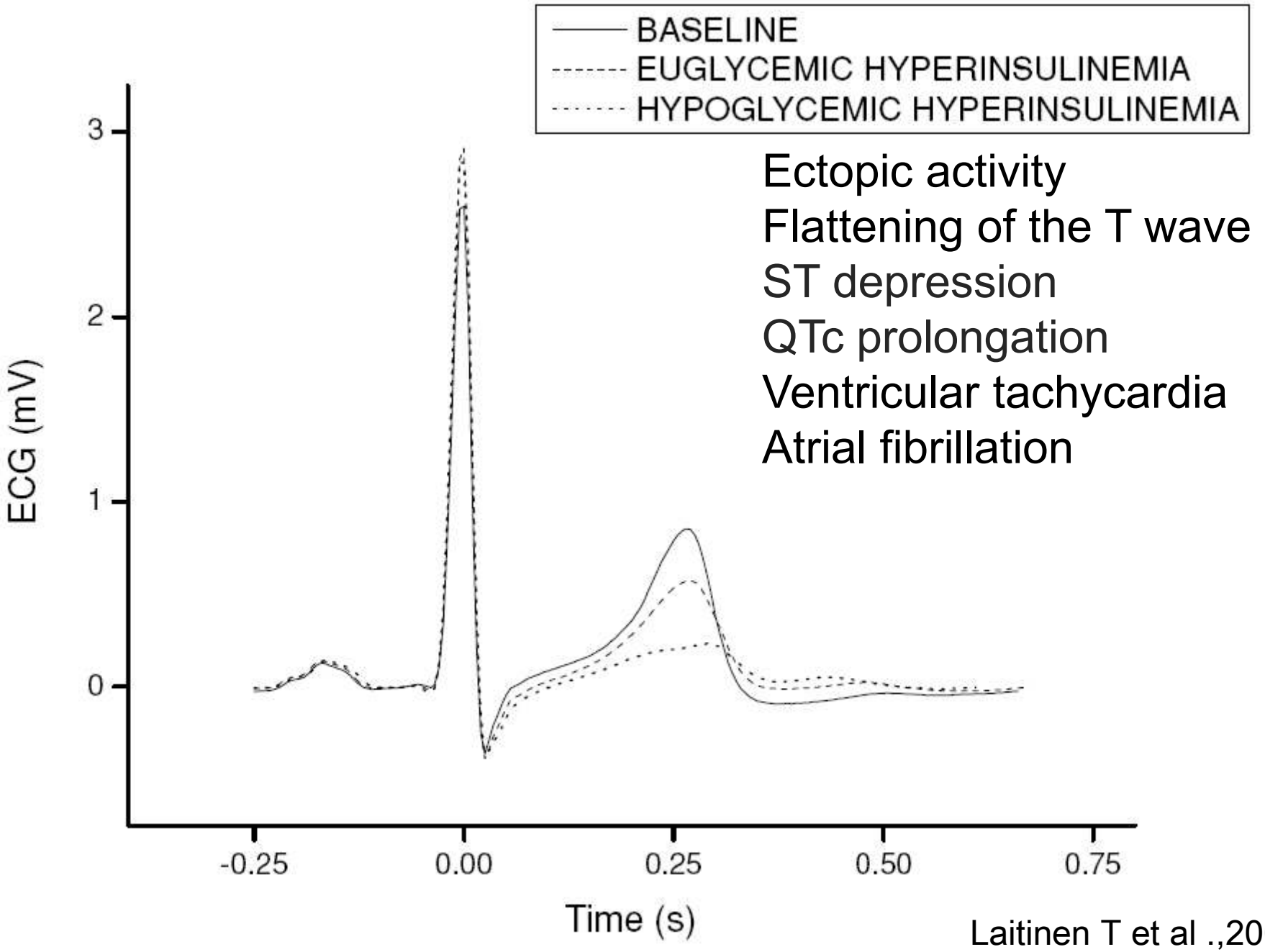


7820 AMI patients with hyperglycemia (≥140 mg/dL) on admission.
Hypoglycemia; glucose < 60 mg/dL., Kosiborod M et al, *Jama 2009*



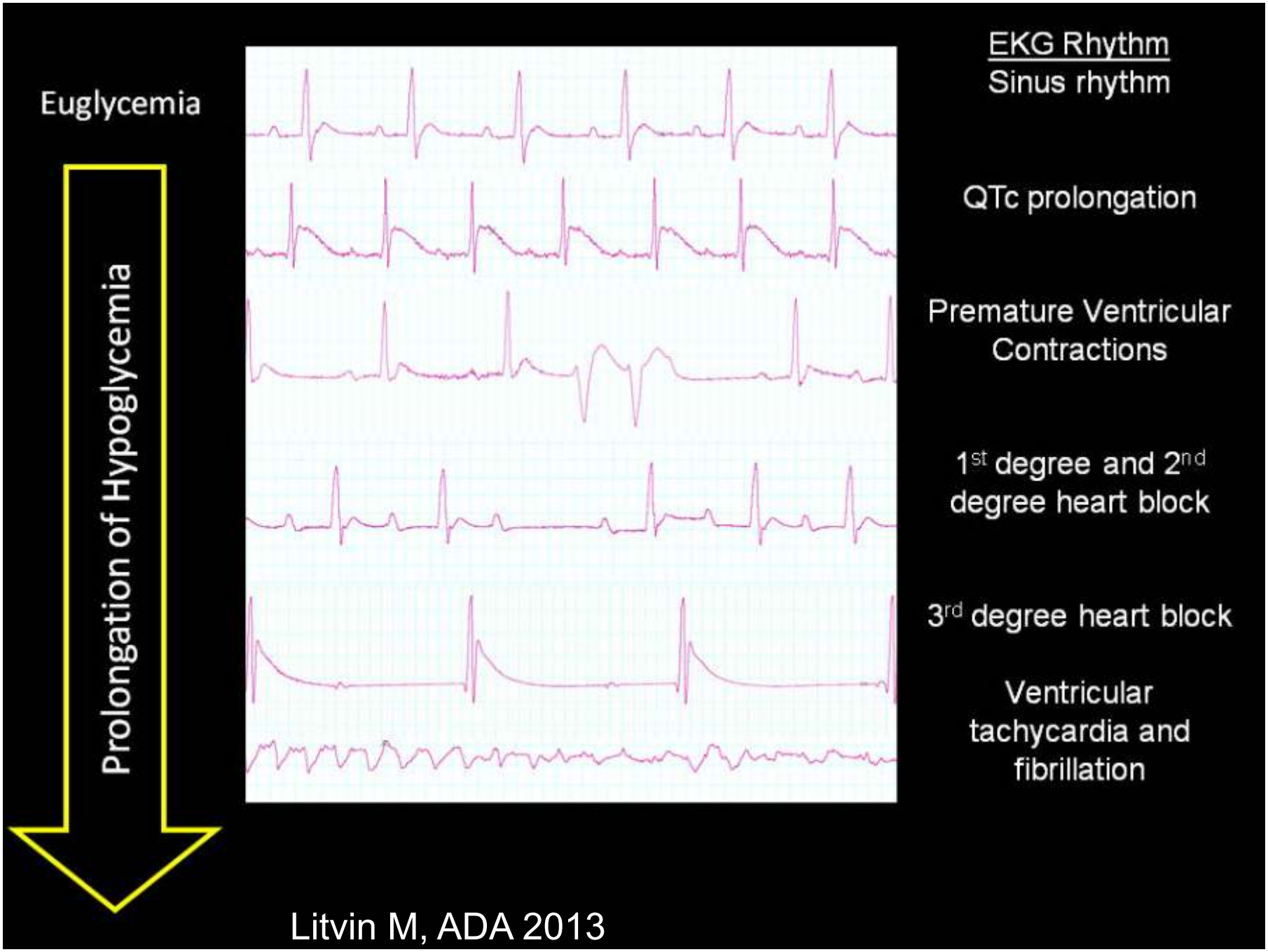
CAN: CV Autonomic Neuropathy
hERG, KCN H2 potassium channel

Stahn A et al., 2014

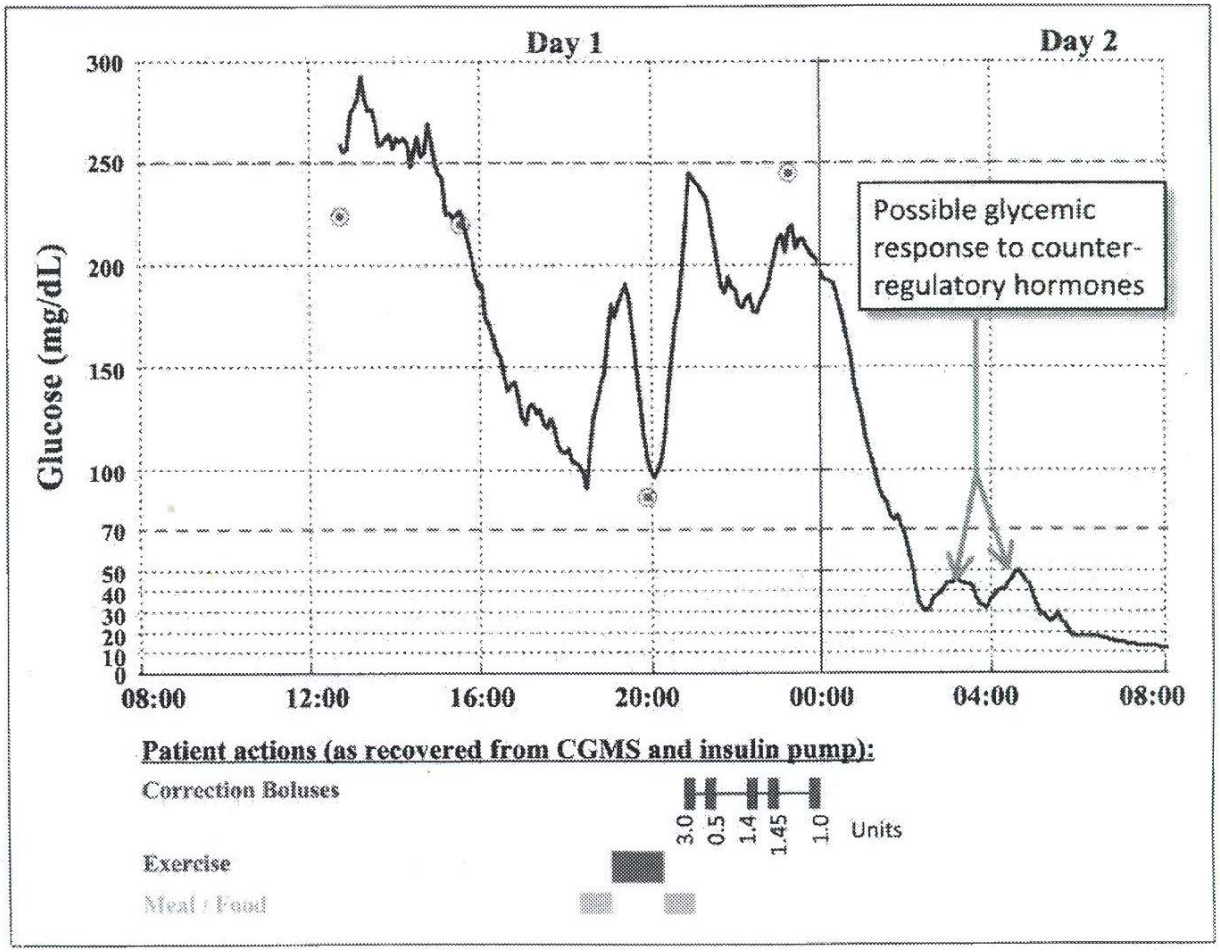


Ectopic activity
Flattening of the T wave
ST depression
QTc prolongation
Ventricular tachycardia
Atrial fibrillation

Laitinen T et al .,2008


Euglycemia
Prolongation of Hypoglycemia
EKG Rhythm
Sinus rhythm
QTc prolongation
Premature Ventricular Contractions
1st degree and 2nd degree heart block
3rd degree heart block
Ventricular tachycardia and fibrillation
Litvin M, ADA 2013

Dead-in-bed syndrome, captured by CGMS

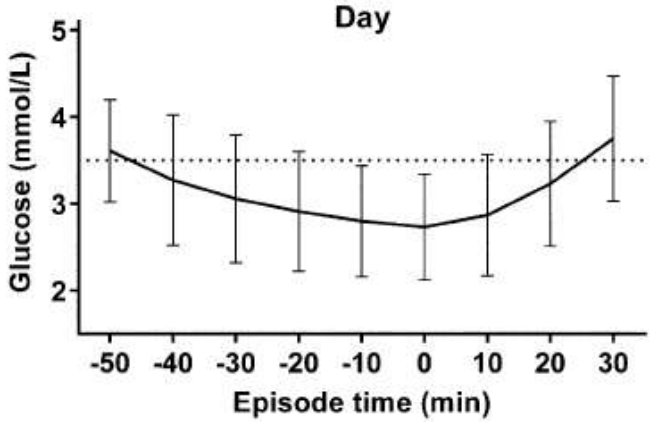


*Postmortem vitreous humor glucose **25mg/dL**; Tanenberg RG et al., 2010*

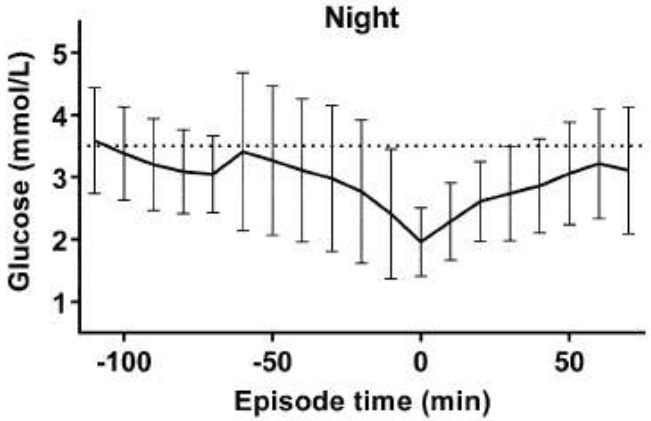
In monkeys, 5–6 hrs of blood glucose levels < 20 mg/dl were required for brain damage (average 13 mg/dl). Kahn KJ & Myers RE 1971

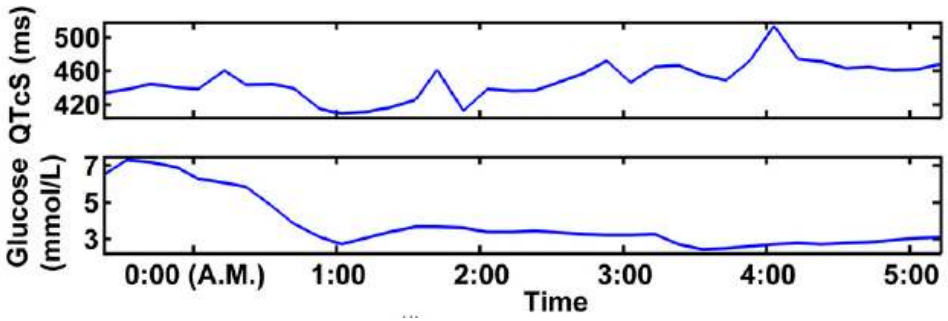
Hypoglycemia in insulin-treated high risk Type 2 DM patients

62 min

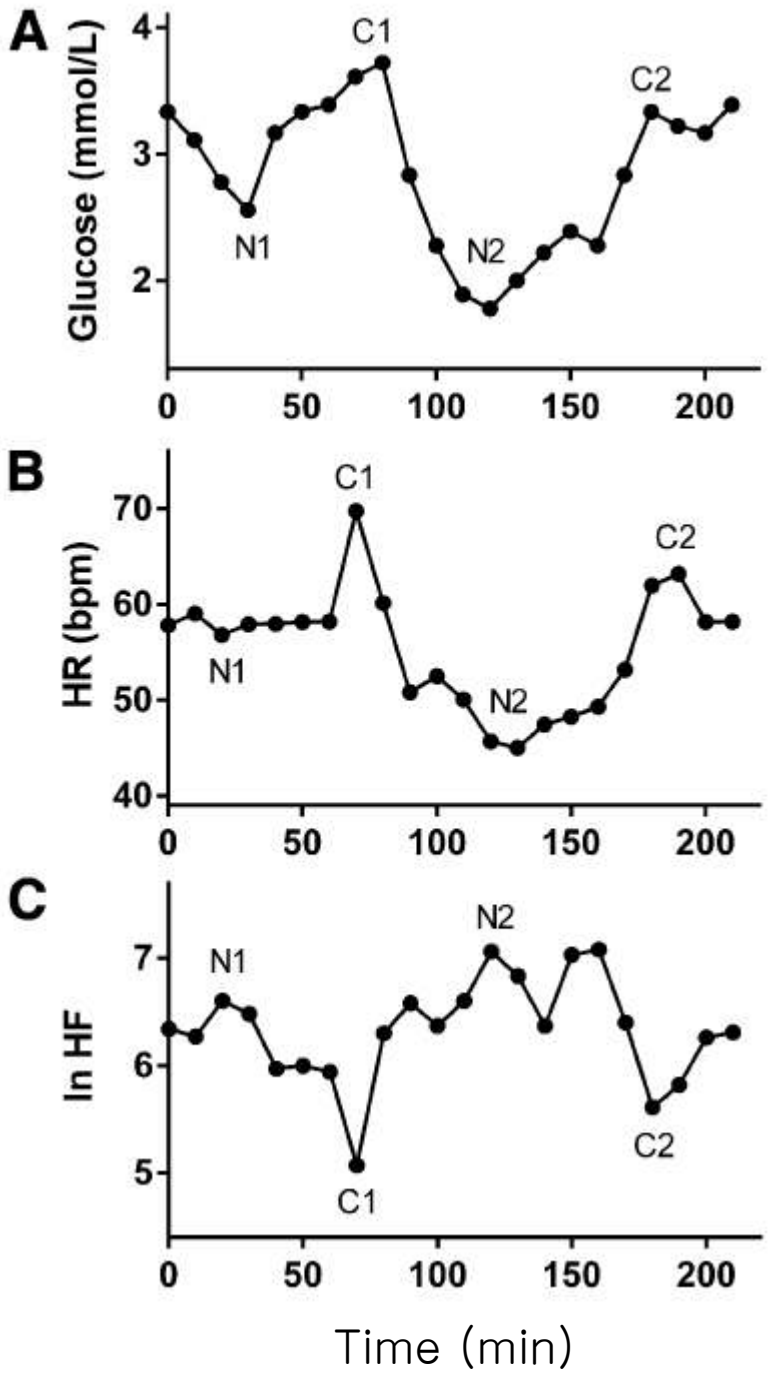


119 min





Chow E et al., Diabetes 2014



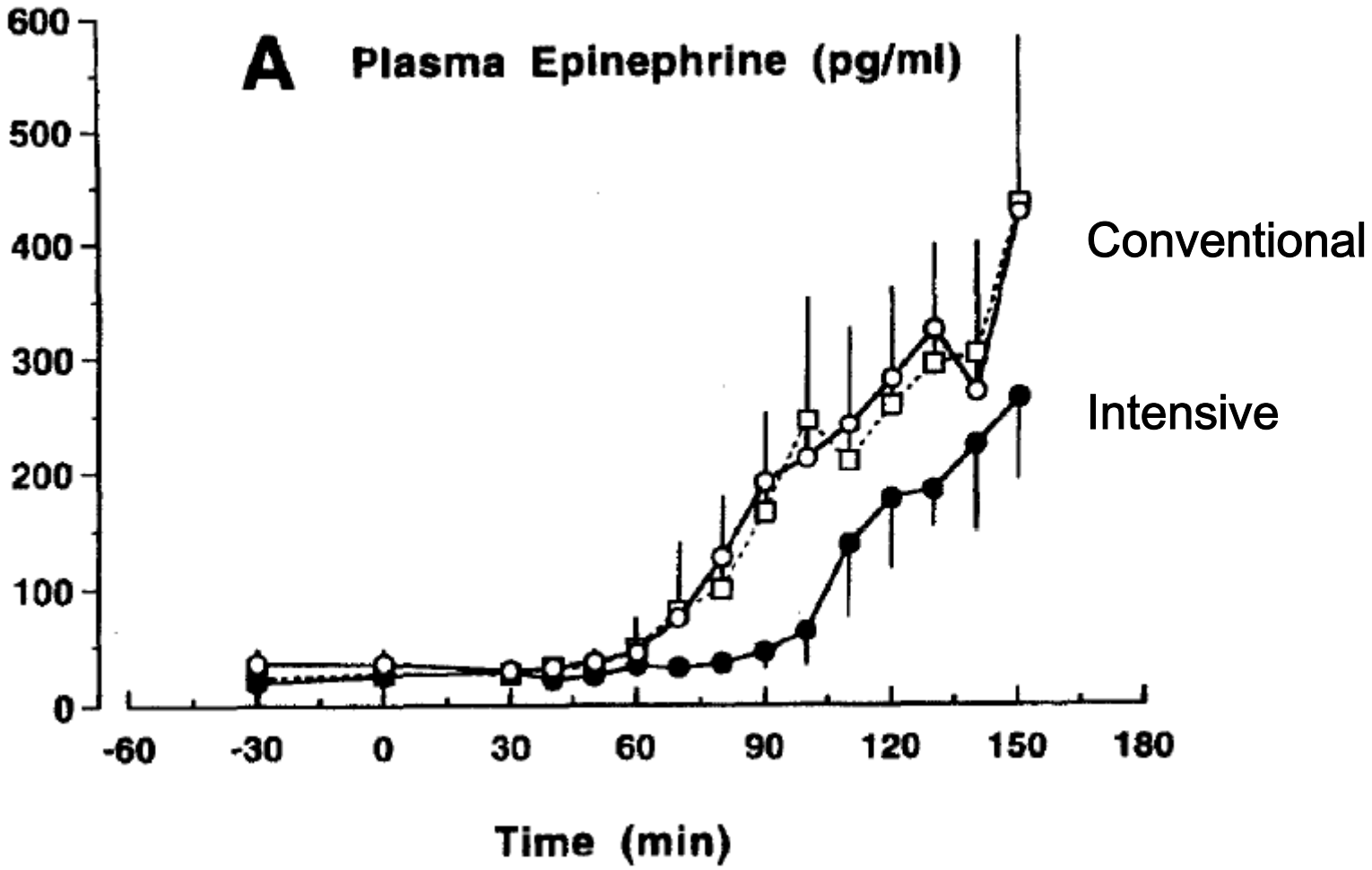
Association of Hypoglycemia and Cardiac Ischemia: CGMS and Holter monitoring

	Total Episodes	Chest pain (+)	Abnormal ECG (+)
Hypoglycemia (<70mg/dL)	54	10*	6*
Symptomatic	26	10*	4*
Asymptomatic	28	-	2
Normoglycemia w/o rapid changes	NA	0	0
Hyperglycemia	59	1	0
Rapid changes in glucose (> 100mg/dL per hr)	50	9*	2

* P < 0.01 vs. episodes during hyperglycemia and hypoglycemia

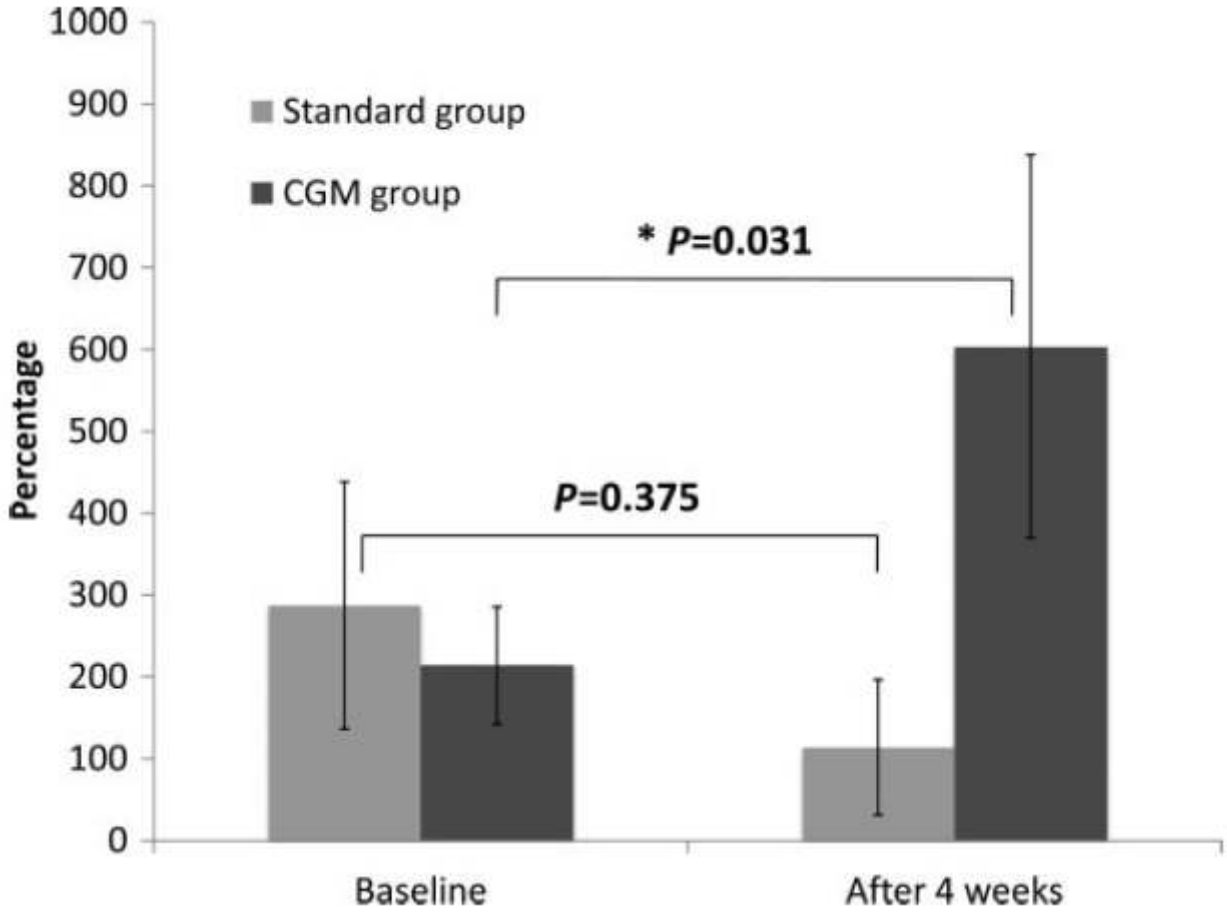
Patients (n=19) had CAD with a mean age of 58 ± 16 years: HbA1c, 7.1 ± 0.8%; DM duration, 12.9 ± 5.6 years; being treated with insulin with or without metformin. *DESOUZA C et al., DIABETES CARE 2003*

Epinephrine response to Hypoglycemia



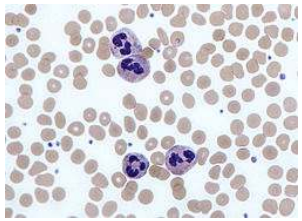
Davis M et al., Am J Med. 1994

Improved epinephrine responses in hypoglycemia unawareness with real-time CGMS monitoring in adolescents with type 1 diabetes.



Ly TT et al., Diabetes Care. 2011

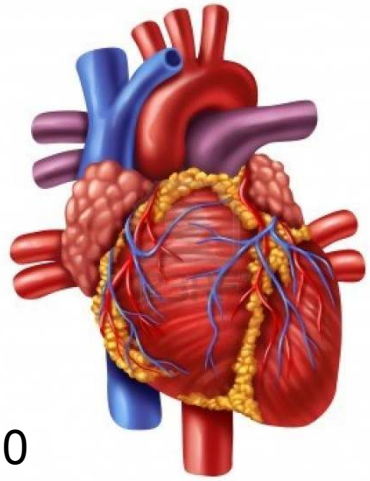
↑ PLT activation & aggregation,
↑ P-selectin
↑ vWF and factor VIII
↑ WBC and neutrophil activation
↑ Hct & Plasma viscosity
↑ PAI-1, Trombin/Anti-thrombin complex
↑ Oxidative stress markers



Endothelial dysfunction
Vasconstriction
Adhesion

↑ ET1, CRP, IL-6, IL-8, IL-1β, TNFα, ROS
VCAM-1, ICAM-1, E-selectin

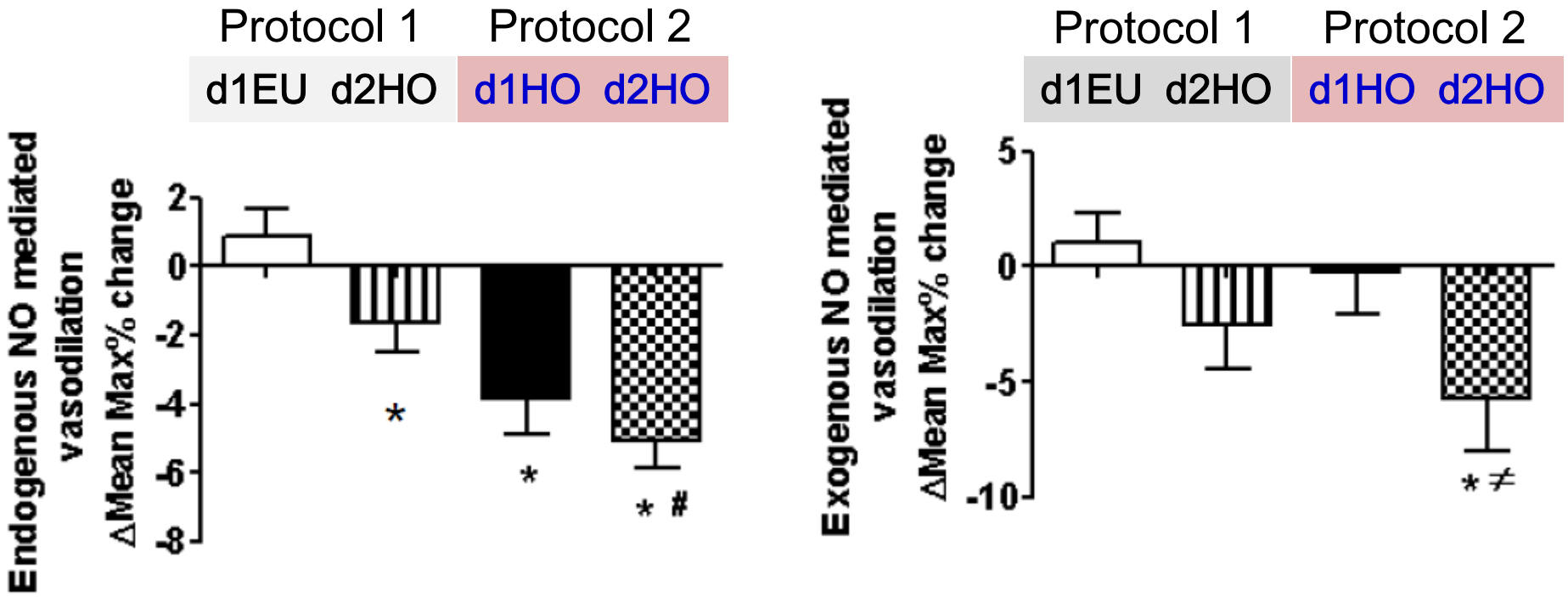
Hypoglycemia



↓ Myocardial Blood Flow Reserve
⇑ O2 demand and work load
ECG changes
Abnormal HRV

Rana OA, et al. Heart 2013
Desouza et al., Diabetes Care 2010
Joy NG et al., Diabetes (in press)

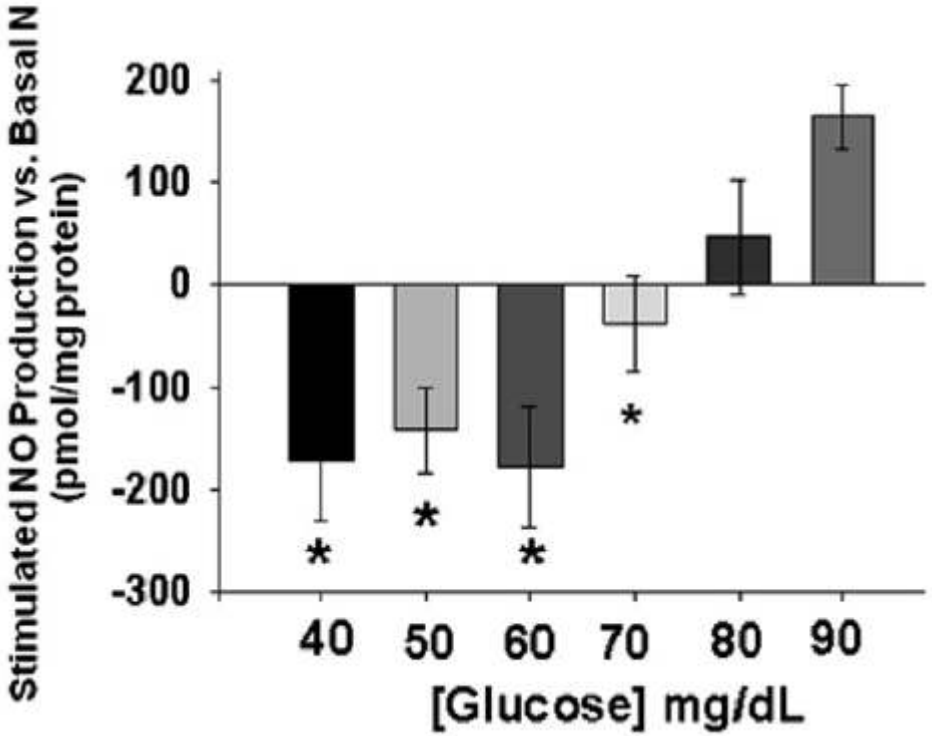
Hypoglycemia and Endothelial dysfunction

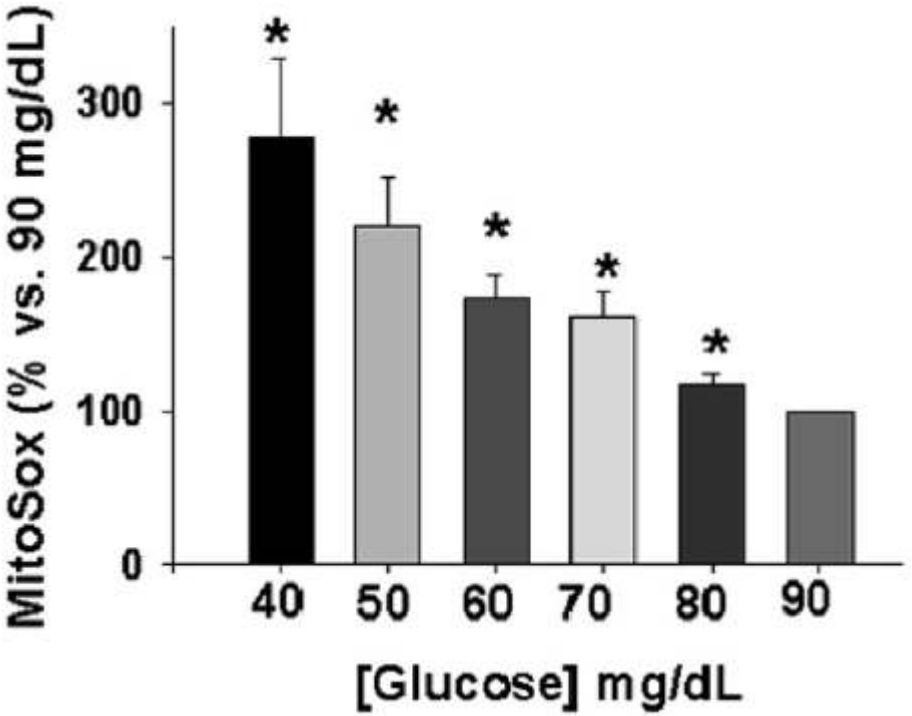


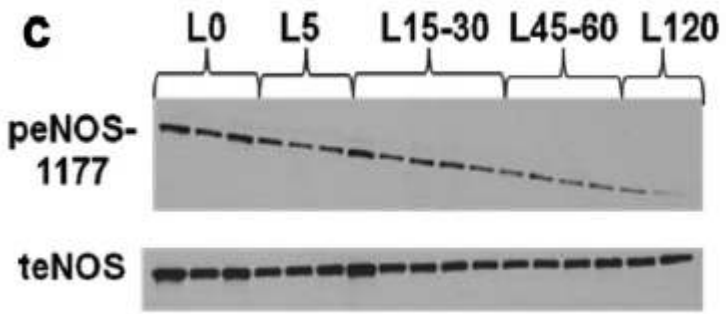
Flow mediated dilation (FMD) of the dominant brachial artery was measured using 2D Doppler ultrasound during reactive hyperemia and exogenous NTG administration

Joy NG et al., Diabetes (in press)

Effect of low glucose (LG) exposure on NO and mitochondrial superoxide production in HUVECs

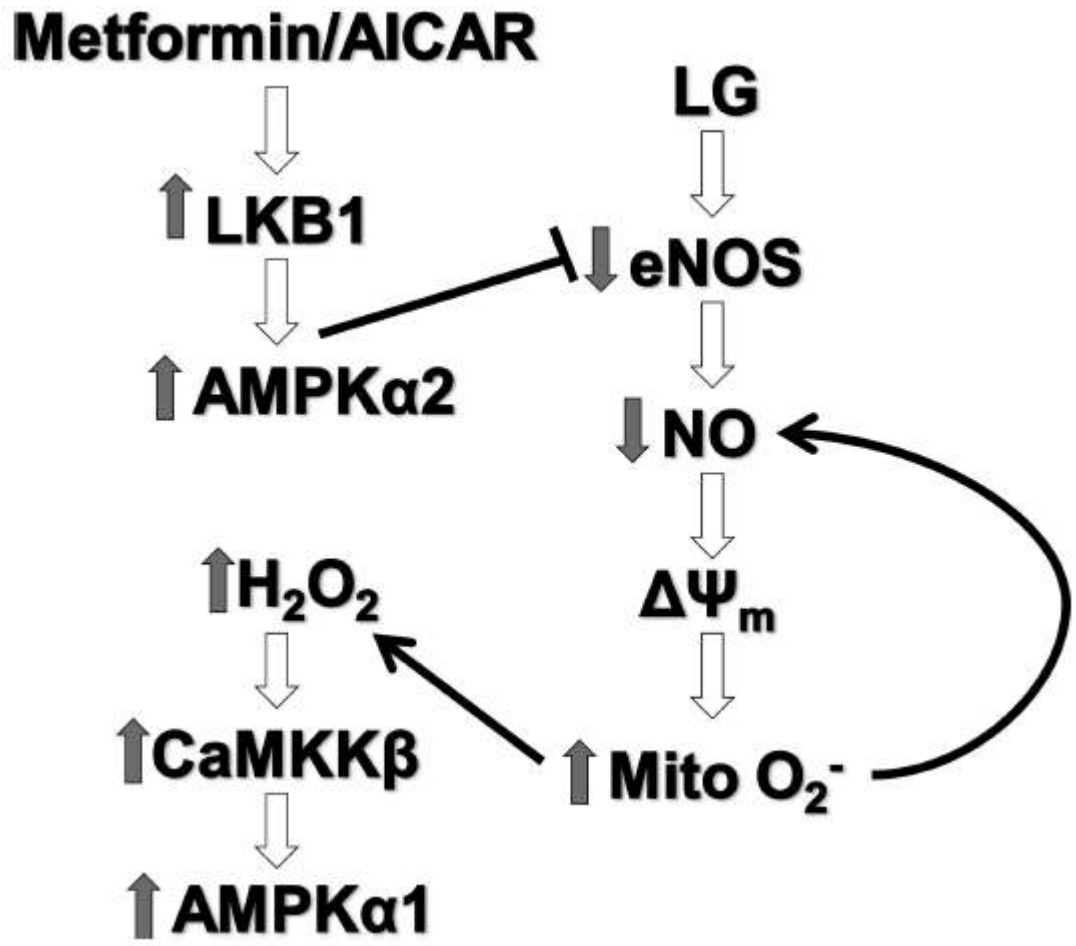






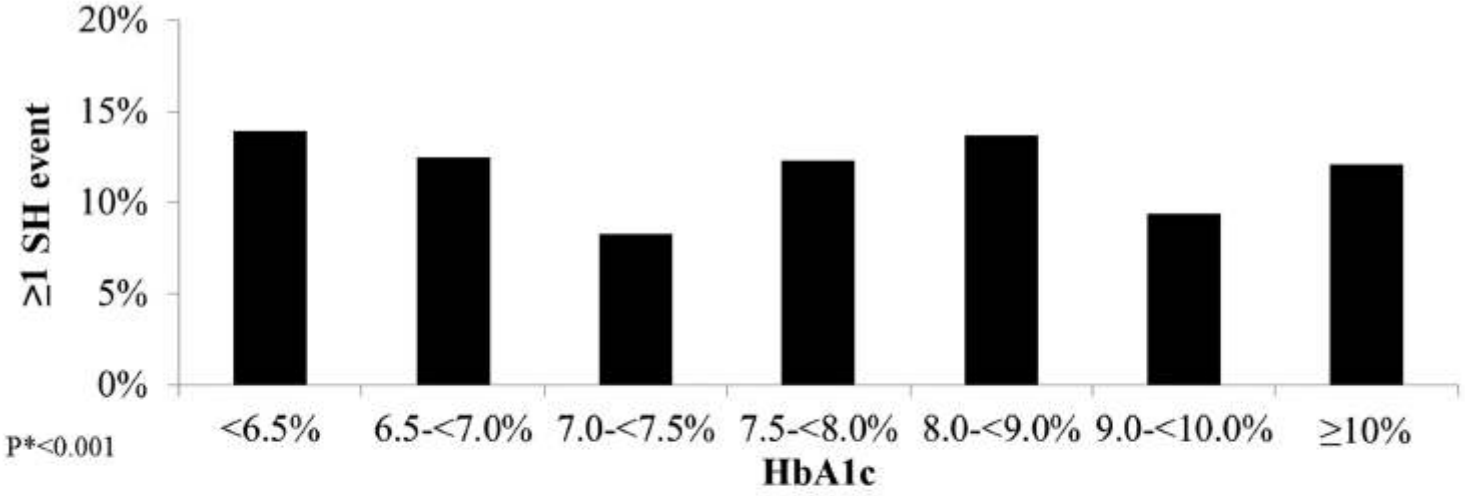
Wang J et al., Arterioscler Thromb Vasc 2012

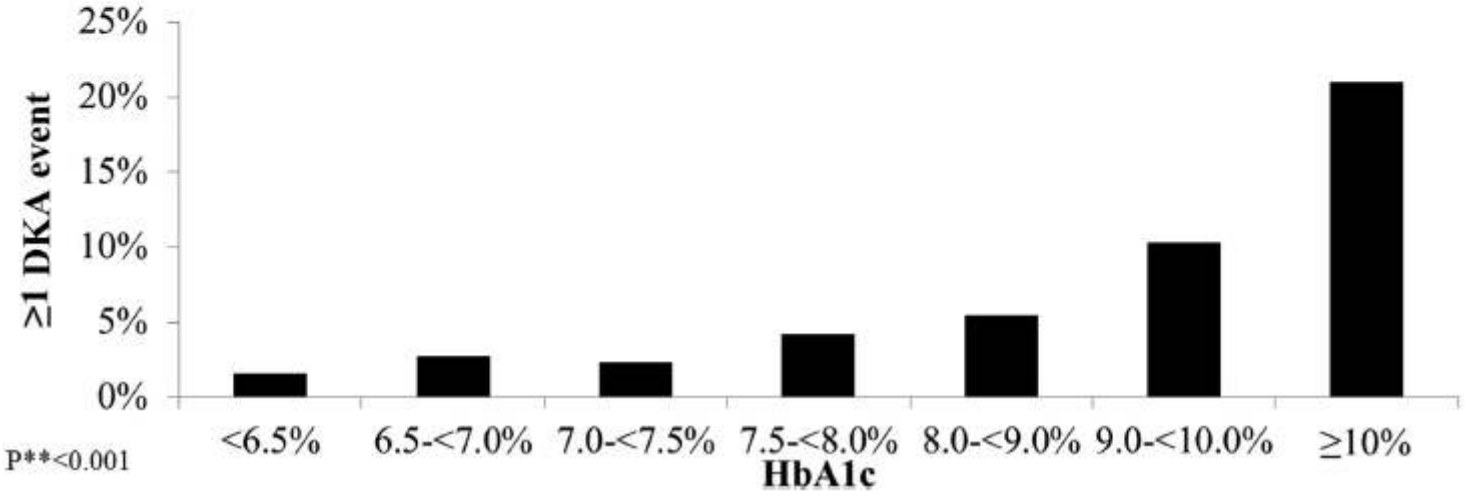
Effect of low glucose (LG) exposure on NO and mitochondrial superoxide production in HUVECs



Wang J et al., Arterioscler Thromb Vasc 2012

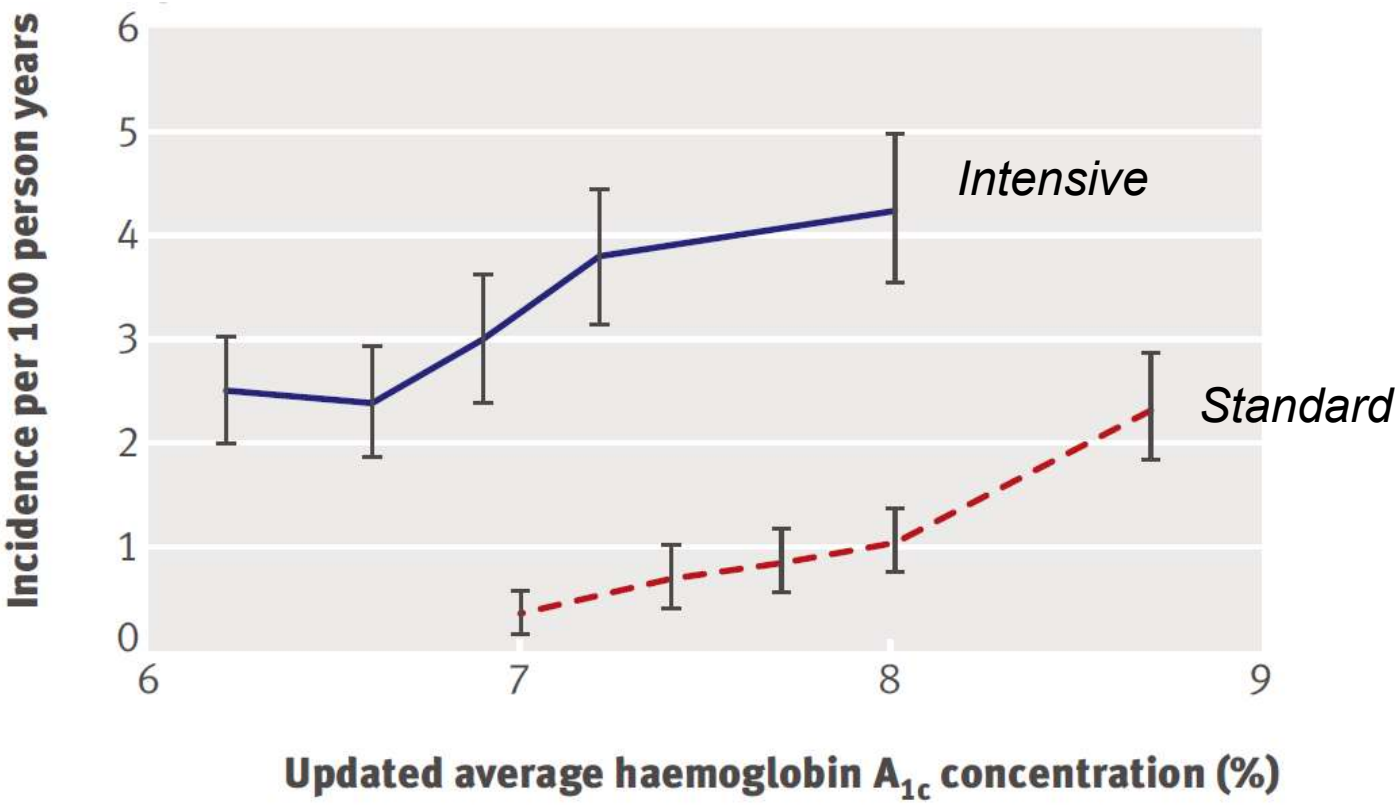
The 12-month frequency of severe HO and DKA according to HbA1c level (Adults with T1DM)





Weinstock RS 2013

Severe hypoglycemia in in ACCORD



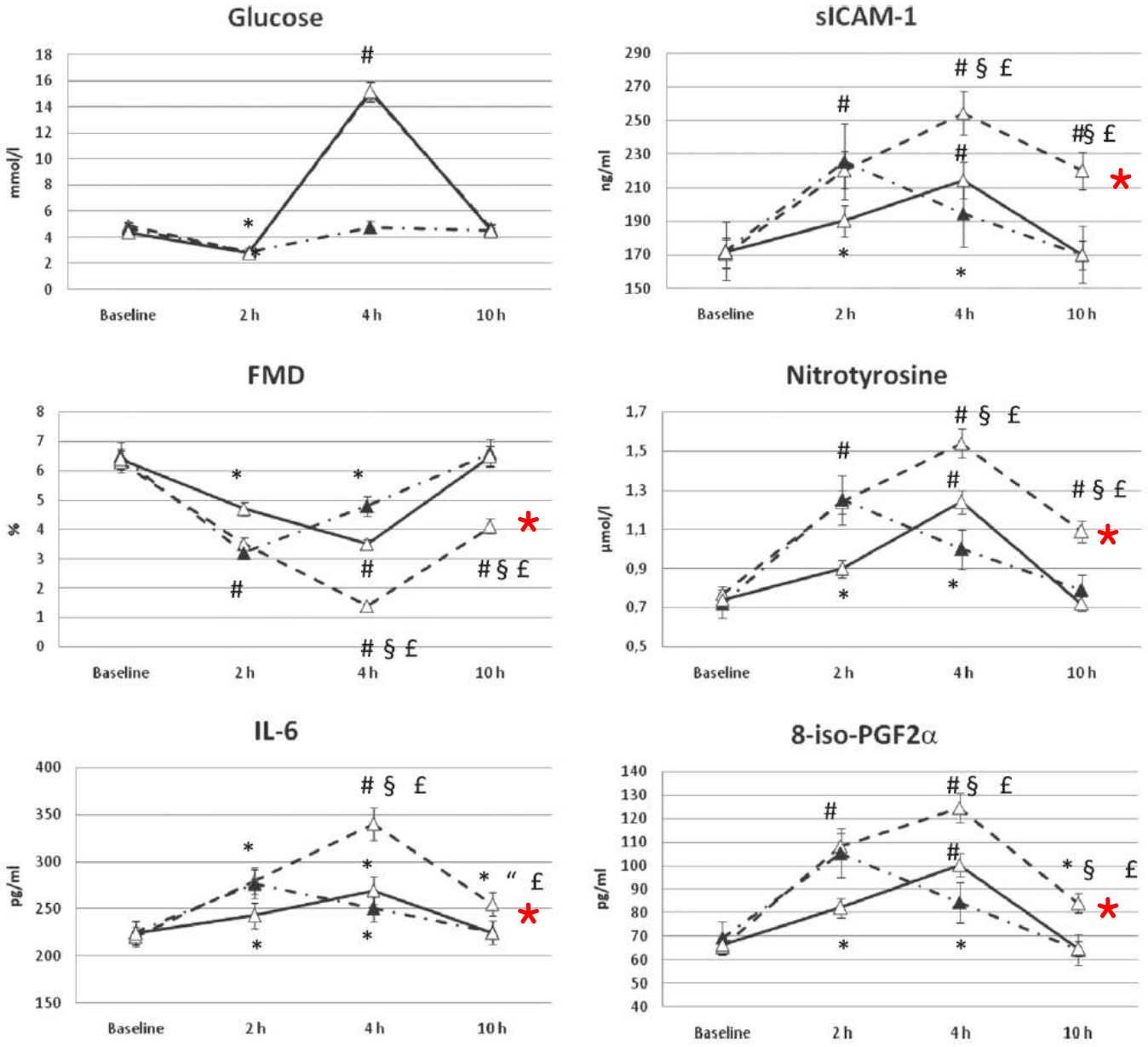
Severe hypoglycemia accompanied by an inability to achieve an HbA1c <6.0% was associated with insulin deficiency (C-peptide <0.45 ng/ml) (adjusted OR 23.2 [95% CI 9.0, 59.5], p < 0.0001) and the presence of autoantibodies (with OR range 3.9-16.7).

Miller ME *et al. BMJ 340:b5444, 2010;* Chow LS et al., Diabetologia. 2015

Hyperglycemia After Recovery From Hypoglycemia Worsens Various Parameters

In patients with T1DM

HO→ EU
HO→ HE (270 mg/dl)
HO+ VitC.→ HE+Vit.C



Ceriello A et al.,
Diabetes 2012

Hypoglycemia at Admission in Patients with Acute Myocardial Infarction Predicts a Higher 30-Day Mortality in Patients with Poorly Controlled Type 2 Diabetes Than in Well-Controlled Patients

Sang Ah Lee, Suk Ju Cho, Myung Ho Jeong, Young Jo Kim, Chong Jin Kim, Myeong Chan Cho, Hyo-Soo Kim, Youngkeun Ahn, Gwanpyo Koh, Jeong mi Lee, Seok Kyu Oh, Kyeong Ho Yun, Ha Young Kim, Chung Gu Cho, *Dae Ho Lee**, on behalf of the KAMIR/KorMI Registry

Diabetes Care 37 (8), 2014

Objectives

- To evaluate the association between admission hypoglycemia and 30-day mortality in AMI patients,
- To determine whether these associations differed according to the pre-admission diabetes control status in AMI patients with type 2 diabetes mellitus.

Diabetes Care 37 (8), 2014

Methods & Subjects

- 34,943 AMI patients with or without type 2 diabetes from two AMI registries: the Korea Acute Myocardial Infarction Registry (**KAMIR**) and the Korea Working Group on Myocardial Infarction (**KorMI**).

- Analyzed two groups, the type 2 diabetes mellitus and non-diabetic groups.

- Each group was stratified into 5 subgroups (groups 1-5) according to the serum glucose level at admission: <70 mg/dL; 70-139 mg/dL; 140-199 mg/dL; 200-259 mg/dL; and ≥260 mg/dL.

- The primary study outcome was 30-day all-cause mortality

Baseline characteristics of the study subjects (n = 34,943)

	Non-diabetic (n=14,229)	Type 2 diabetes (n=20,714)	P value
Age (years)	63.31 ± 0.47	64.09 ± 0.08	<0.001
Sex (female)	44.71%	37.25%	0.001
BMI (kg/m^2)	23.73 ± 0.03	23.89 ± 0.03	<0.001
sBP (mmHg)	128.51 ± 0.28	128.48 ± 0.26	0.910
dBP (mmHg)	78.77 ± 0.24	78.13 ± 0.23	<0.001
HbA1c (%)	5.75 ± 0.01	7.76 ± 0.02	<0.001
Glucose (mmol/L)	7.92 ± 0.04	10.52 ± 0.03	<0.001
Creatinine (µmol/L)	99.58 ± 1.36	114.72 ± 1.17	<0.001
Triglycerides (mmol/L)	1.44 ± 0.01	1.49 ± 0.01	0.001
HDL cholesterol (mmol/L)	1.16 ± 0.005	1.15 ± 0.003	0.005
LDL cholesterol (mmol/L)	3.01 ± 0.010	2.95 ± 0.009	<0.001
hsCRP (mg/L)	3.11 ± 0.06	3.78 ± 0.07	<0.001

Baseline characteristics of the study subjects (n = 34,943)

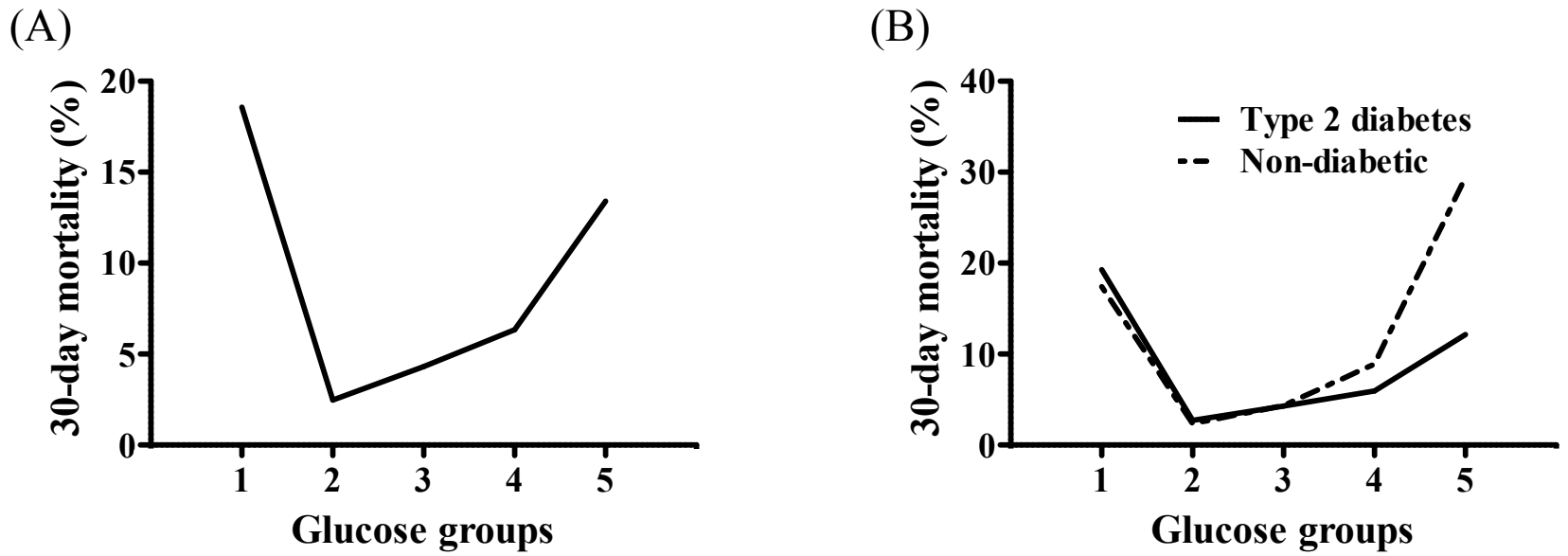
	Non-diabetic (n=14,229)	Type 2 diabetes (n=20,714)	P value
Killip class			<0.001
I	71.47%	72.81%	
II	13.49%	14.44%	
III	9.54%	7.31%	
IV	5.49%	5.44%	
Hypertension	52.23%	48.57%	<0.001
Smoking	40.68%	43.27%	<0.001
Previous MI	7.94%	6.13%	<0.001
Heart failure	2.56%	1.67%	<0.001
PAD	1.11%	0.54%	<0.001
CVA	7.62%	6.37%	<0.001

Baseline characteristics of the study subjects (n = 34,943)

	Non-diabetic (n=14,229)	Type 2 diabetes (n=20,714)	P value
Statin	65.19%	73.85%	<0.001
Aspirin	14.89%	13.40%	<0.001
Clopidogrel	4.89%	5.80%	<0.001
Hypertension treatment	89.44%	89.38%	0.478
Beta-blocker	9.07%	7.39%	<0.001
ACE inhibitor/ARB	94.085%	94.82%	0.101
CCB	10.85%	8.75%	<0.001
Nitrate	5.23%	3.42%	<0.001
Thrombolysis	3.61%	6.69%	<0.001
Primary PCI	90.26%	79.87%	<0.001

The 30-day mortality rates of the 5 glucose groups:

the total AMI patient cohort (n = 34,943) (A) and the AMI patients with (n=20,714) and without type 2 diabetes (n=14,229) (B).



The 5 glucose subgroups according to the admission serum glucose levels, as follows: group 1, <70 mg/dL; group 2, 70-139 mg/dL; group 3, 140-199 mg/dL; group 4, 200-259 mg/dL; and group 5, ≥260 mg/dL.

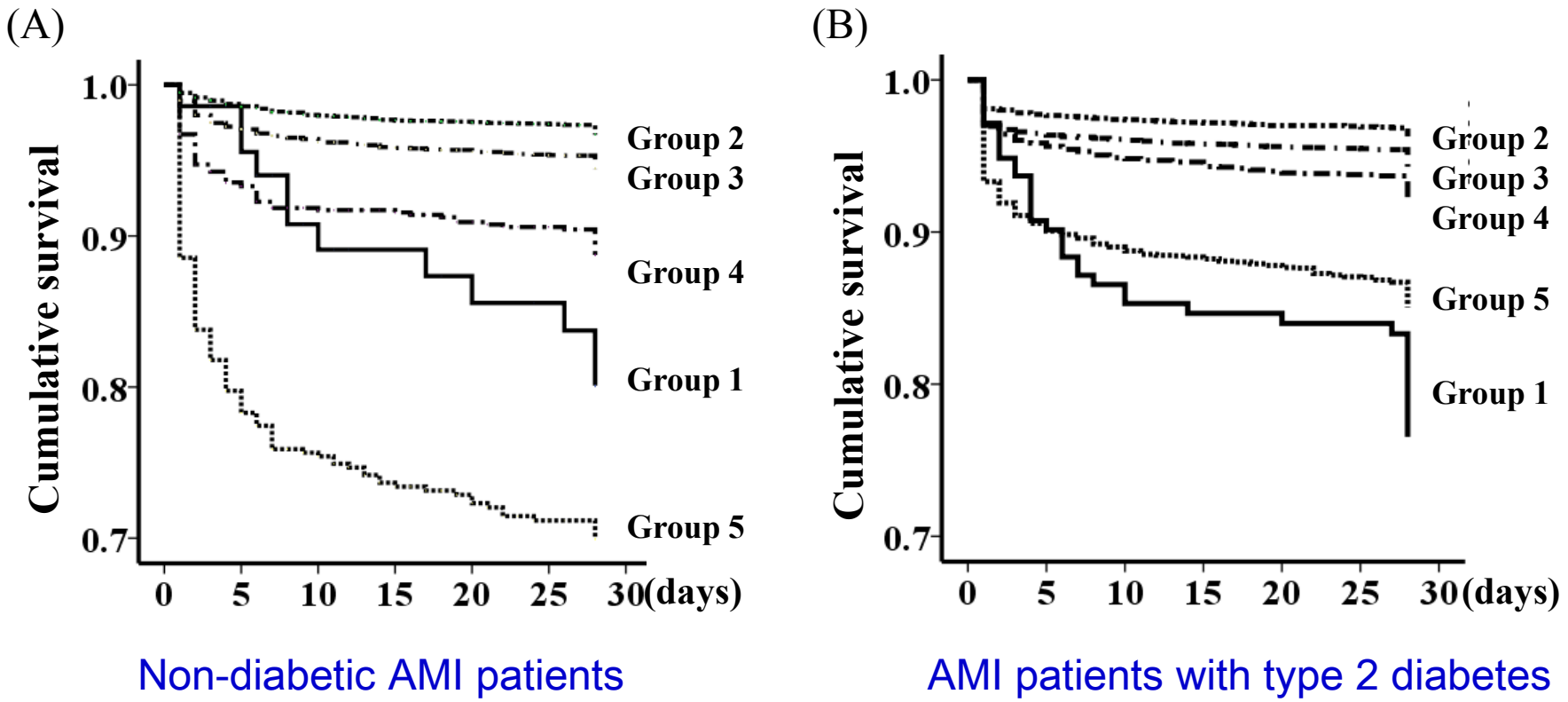
The clinical characteristics of the 5 glucose groups based on admission glucose levels in AMI patients without diabetes

Groups	Group 1 (n = 154)	Group 2 (n = 7,783)	Group 3 (n = 4,040)	Group 4 (n = 777)	Group 5 (n = 402)	P value
Age (years)	63.8±1.1	62.4±0.2	63.9±0.2	66.7±0.5	67.6±0.6	<0.001
Female (%)	26.45%	24.46%	27.25%	35.31%	40.04%	<0.001
BMI (Kg/m^2)	23.99±0.25	23.79±0.03	23.71±0.05	23.51±0.12	22.85±0.16	<0.001
sBP (mmHg)	123.2±2.26	130.2±0.29	127.5±0.42	123.8±1.07	114.6±1.65	<0.001
dBP (mmHg)	76.6±1.30	79.5±0.17	78.4±0.25	76.8±0.61	71.9±0.98	<0.001
Killip class I	70.68%	78.99%	71.63%	55.79%	33.70%	<0.001
II	11.28%	13.17%	15.50%	17.81%	13.66%	
III	9.02%	4.99%	7.05%	10.59%	17.62%	
IV	9.02%	2.84%	5.81%	15.82%	35.02%	
Glucose (mmol/l)	3.33±0.06	6.39±0.01	8.96±0.01	12.37±0.03	18.84±0.22	<0.001
HbA1c (%)	6.19±0.15	5.69±0.01	5.78±0.01	5.88±0.02	5.77±0.03	<0.001
Creatinine (μmol/L)	142.7±31.9	95.6±1.5	99.8±2.3	118.2±7.9	121.9±4.7	< 0.001
Hypertension	40.9%	43.96%	45.96%	49.36%	46.82%	<0.001
Heart failure	2.58%	1.19%	1.28%	2.89%	2.10%	<0.001

The clinical characteristics of the 5 glucose groups based on admission glucose levels in AMI patients with type 2 diabetes

Groups	Group 1 (n= 255)	Group 2 (n= 7432)	Group 3 (n= 6276)	Group 4 (n= 3396)	Group 5 (n= 3737)	P value
Age (years)	67.6±0.7	63.1±0.2	64.4±0.2	64.4±0.2	65.2±0.2	<0.001
Killip class I	59.91%	78.50%	72.13%	67.89%	55.45%	<0.001
II	16.59%	11.91%	14.95%	14.88%	15.97%	
III	14.28%	6.96%	8.27%	10.83%	16.54%	
IV	9.22%	2.63%	4.65%	6.40%	12.06%	
Glucose (mmol/l)	2.97±0.05	6.36±0.01	9.19±0.01	12.58±0.02	19.39±0.08	<0.001
HbA1c (%)	8.08±0.13	6.74±0.04	7.10±0.03	7.64±0.03	8.76±0.05	<0.001
Creatinine (μmol/L)	136.7±8.9	104.9±1.9	109.3±1.9	120.8±2.9	133.7±3.0	<0.001
hsCRP (mg/L)	14.1±2.40	8.2±0.37	8.7±0.44	10.3±0.67	11.3±0.67	<0.001
Diabetes treatment	71.24%	58.95%	67.31	62.68	74.15	<0.001
Heart failure	3.92%	1.92%	2.19%	2.74%	3.73%	<0.001
Statin use	14.11%	7.24%	8.46%	8.75%	9.15%	<0.001
Hypertension Tx	95.00%	87.52%	88.76%	91.76%	90.61%	<0.001
ARB	13.73%	6.16%	7.66%	7.77%	8.75%	<0.001

Cumulative survival curves according to the admission glucose levels



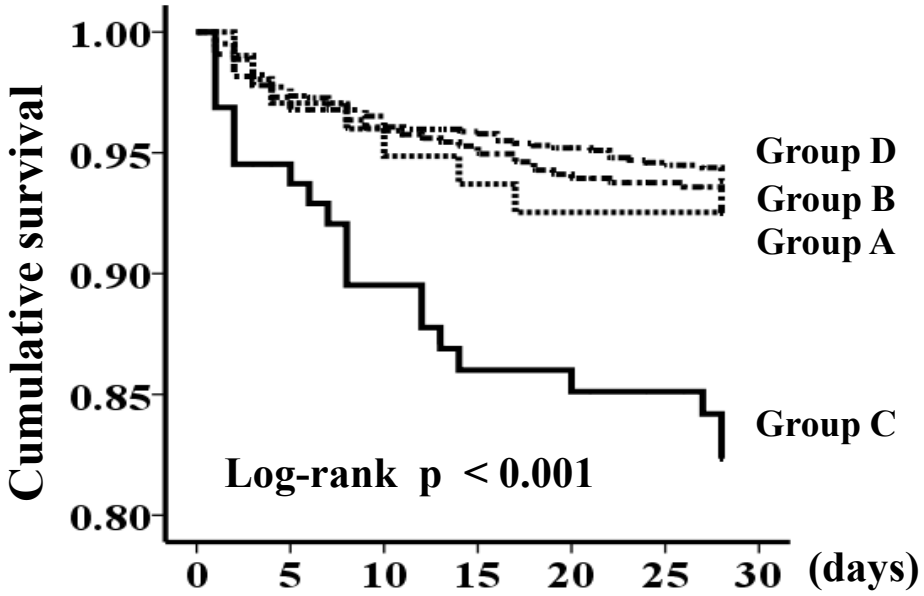
Non-diabetic AMI patients

AMI patients with type 2 diabetes

The 5 glucose subgroups according to the admission serum glucose levels, as follows: group 1, <70 mg/dL; group 2, 70-139 mg/dL; group 3, 140-199 mg/dL; group 4, 200-259 mg/dL; and group 5, ≥260 mg/dL.

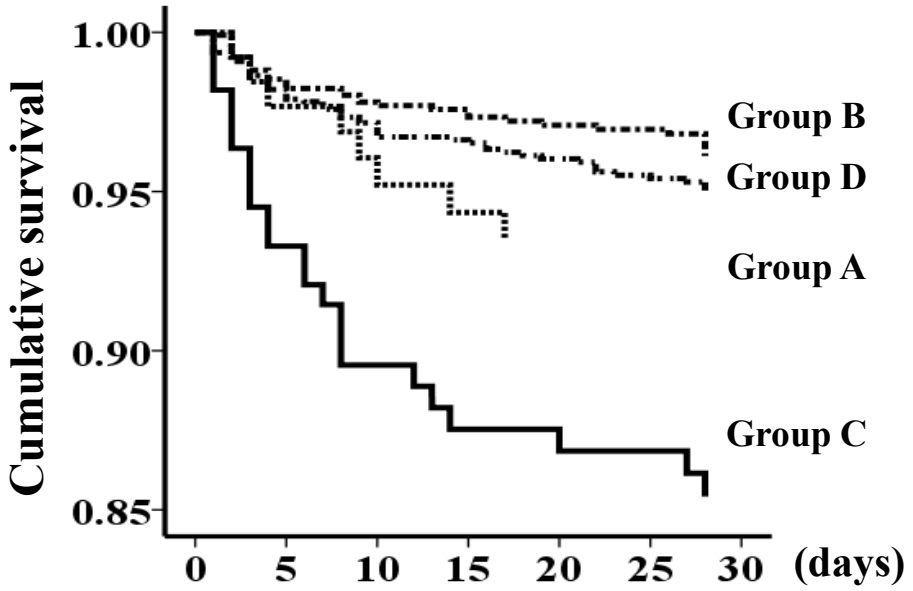
The effects of admission hypoglycemia and the pre-admission diabetes control status on 30-day cumulative survival in AMI patients with type 2 diabetes.

(A)



Kaplan-Meier survival estimates

(B)



Cox-proportional regression analysis after adjusting for multiple factors.

Group A, HbA1c <6.5% and serum glucose <70 mg/dL; group B, HbA1c <6.5% and serum glucose ≥200 mg/dL; group C, HbA1c ≥8.0% and <70 mg/dL; and group D, HbA1c ≥8.0% and serum glucose ≥200 mg/dL

Conclusions

- Hypoglycemia in AMI patients with or without type 2 diabetes is a more important factor related to 30-day mortality than was previously thought.

- Hypoglycemia in AMI patients with poorly controlled diabetes is associated with increased mortality compared with patients with well-controlled diabetes.

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