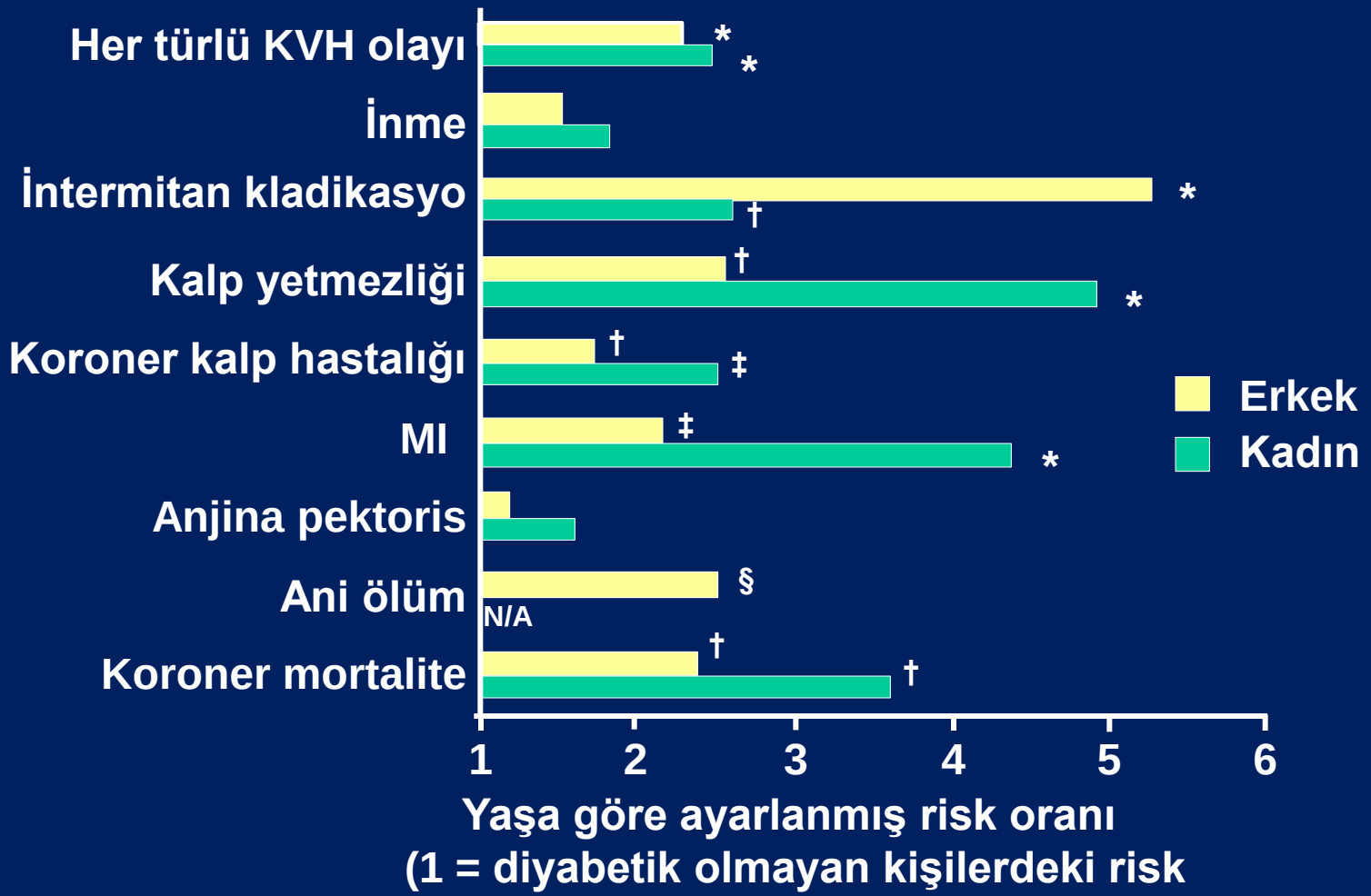
GLİSEMİK DEĞİŞKENLİK , ENDOTEL DİSFONKSİYONU VE MİKROVASKÜLER KOMPLİKASYONLAR

Prof. Dr. Mustafa KUTLU

Konuşma planı

- PPG – KV risk ve Mortalite ilişkisi
- APG, PPG ve Ortalama glukozun Fruktozamin ve A1C'ye katkısı
- Glisemik Değişkenlik parametreleri: MAGE,MPPG, Hipoglisemi ,PPG,Günlük GD
- Glisemik Değişkenlik– Mikrovasküler komplikasyonlar
- Glisemik Değişkenlik– KV risk ve Mortalite ilişkisi
- Öneriler

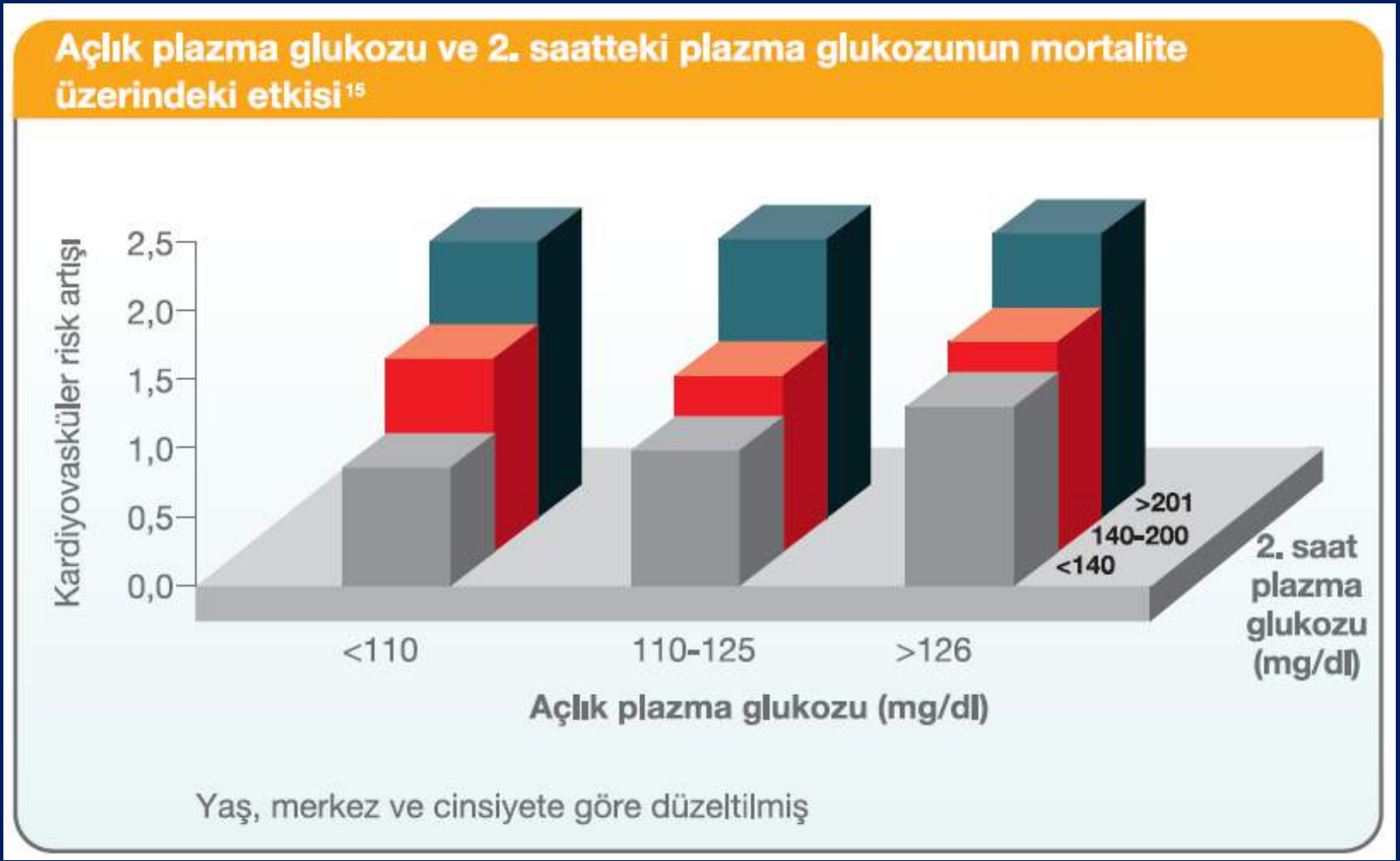
Diyabet KVH riskini arttırır



*$P < 0.001$; †$P < 0.05$; ‡$P < 0.01$; §$P < 0.1$

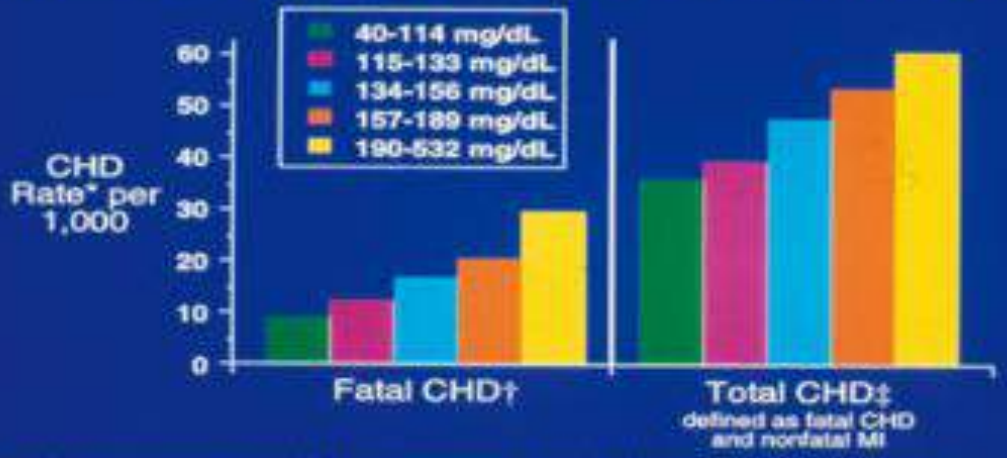
Kannel WB, *et al*. *Am Heart J* 1990; 120:672–676.'dan uyarlanmıştır

2. Saatteki Kan Glukozu, Açlık Kan Şekerinden Bağımsız Kardiyovasküler Risk Faktörüdür



DECODE Study Group. Lancet 1999;354:617–621

Honolulu Heart Study: Postchallenge Glucose Concentration and CHD



*12-year age-adjusted incidence of CHD by 1-hour postchallenge serum glucose (random 50-g dextrose load). Honolulu Heart Study (N=6,394).
†P < .001 comparing quintiles 1 and 5.
‡P < .01 comparing quintiles 1 and 5.
Donahue RP, et al. *Diabetes*. 1987;36:689-692.

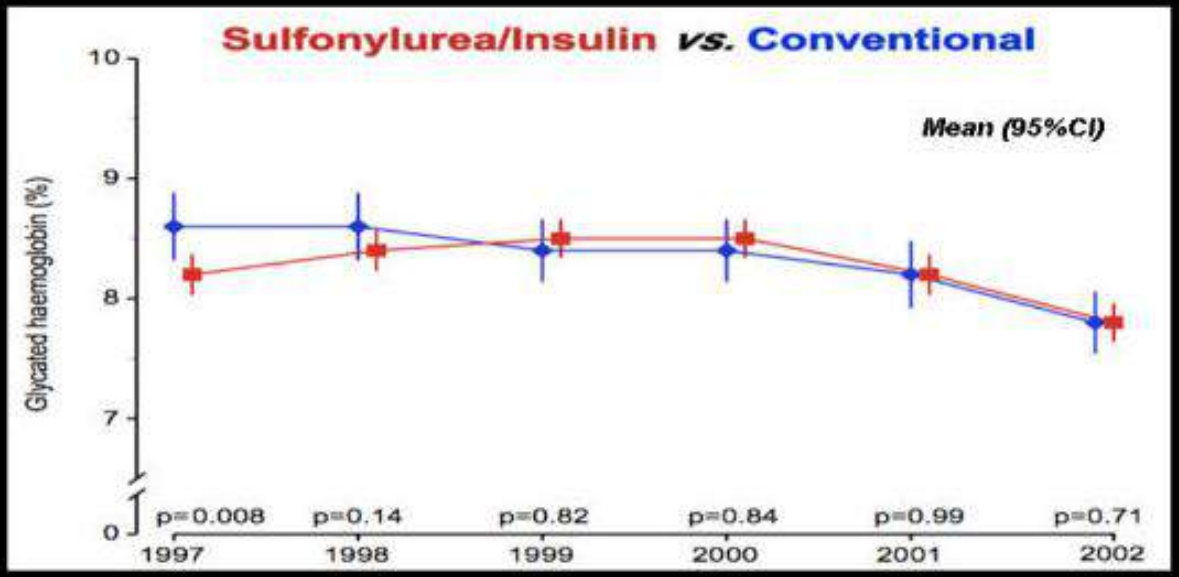
13

Relative Risk of Age-Adjusted Rate of Ischemic Heart Disease over Four Year Period in 4662 Men Aged 45-79 Years

Brit Med J 322:15,2001

*self-report

UKPDS: Post-Trial Changes in A1C



Holman RR, et al. *New England Journal of Medicine* 2008; 359:1577-1589

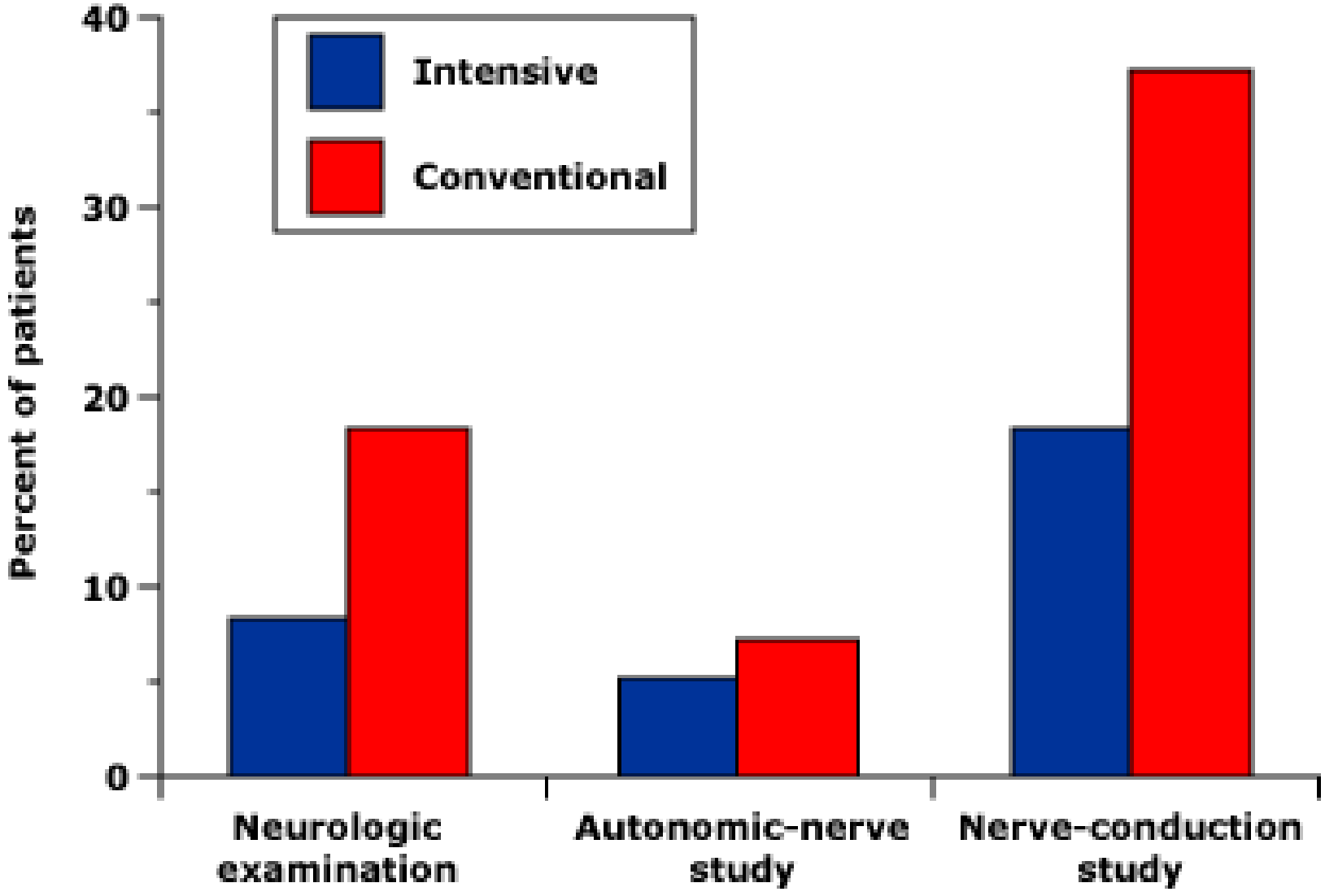
UKPDS: "Legacy Effect" of Glucose Therapy

After median 8.8 years post-trial follow-up

Aggregate Endpoint		1997	2007
Any diabetes related endpoint	*RRR:*	12%	9%
	P:	0.029	0.040
Microvascular disease	*RRR:*	25%	24%
	P:	0.009	0.001
Myocardial infarction	*RRR:*	16%	15%
	P:	0.052	0.014
All-cause mortality	*RRR:*	6%	13%
	P:	0.44	0.007

RRR = Relative Risk Reduction **P = Log Rank**

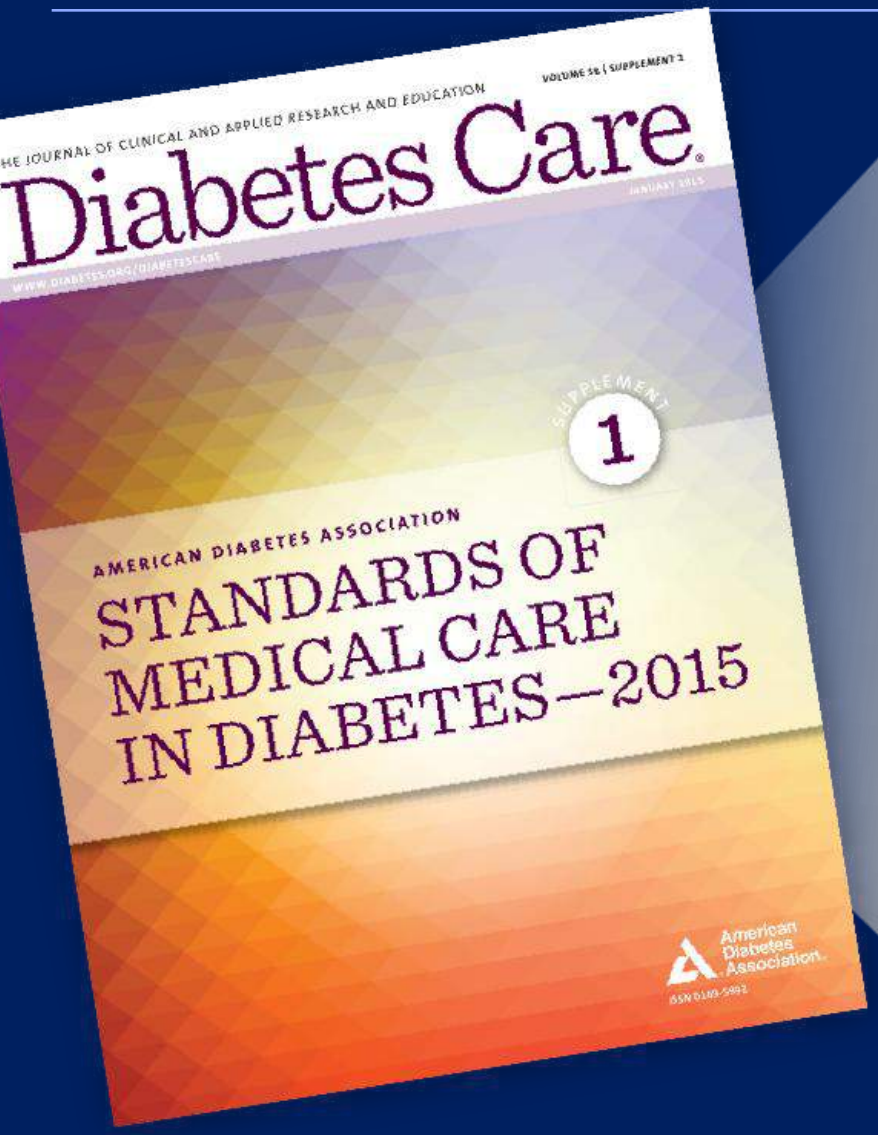
Holman RR, et al. *New England Journal of Medicine* 2008; 359:1577-1589


Intensive
Conventional
Percent of patients
40
30
20
10
0
Neurologic examination
Autonomic-nerve study
Nerve-conduction study

Glisemik kontrol parametreleri

- HbA_{1c} (A1C), Fruktozamin
- Açlık ve pre-prandiyal plazma glukoz
- Post-prandiyal plazma glukoz
- Evde kan glukoz takibi (SMBG) ve ortalama glukoz
- Kanda ve idrarda keton cisimleri,Ox stress ürünleri

ADA 2015 kılavuzu glisemik dalgalanmaların önemini vurgulamaktadır

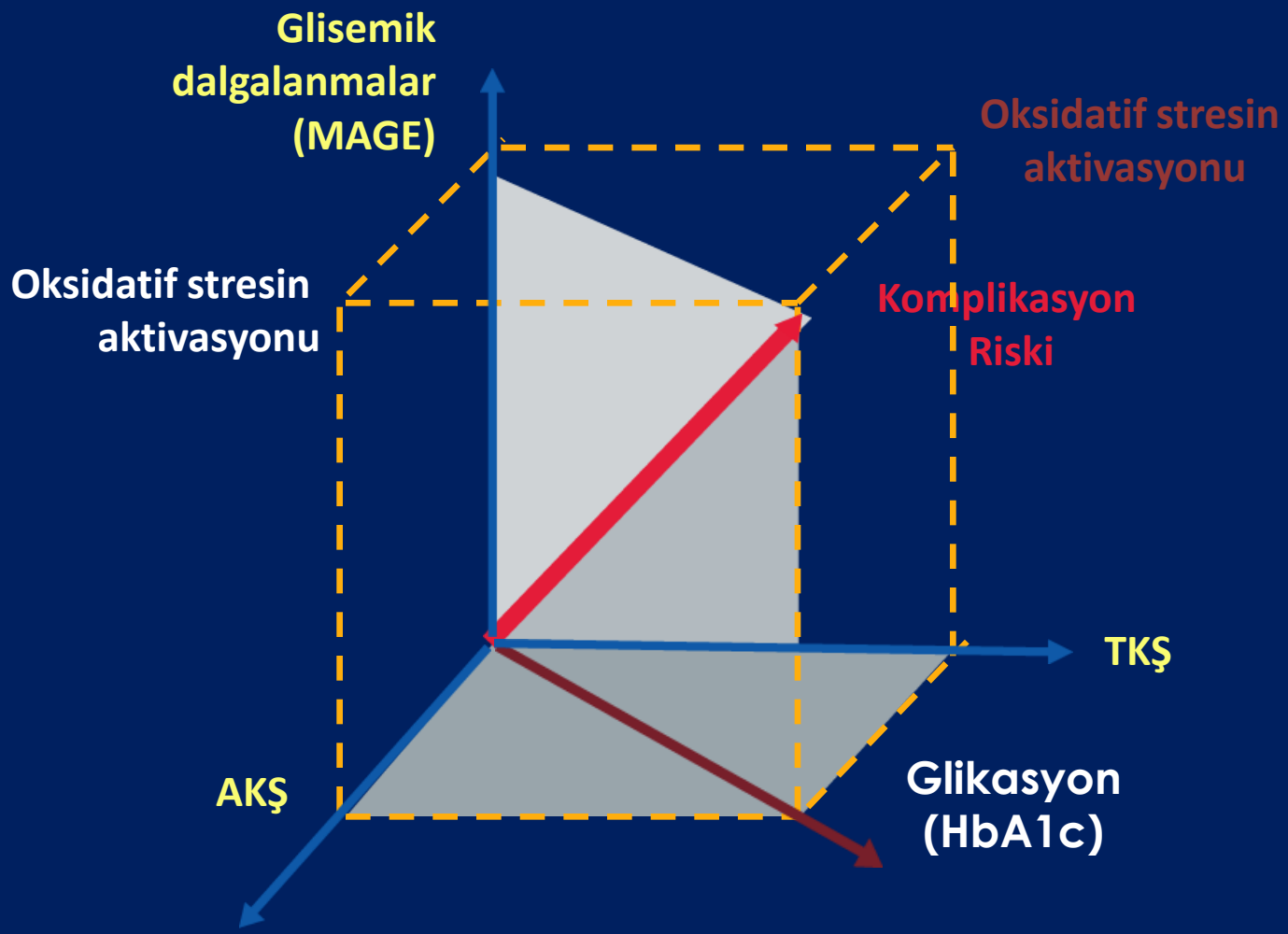


HbA1c glisemik dalgalanmalar veya hipoglisemiyi yansıtmamaktadır.

Bazı gözlemsel çalışmalar gösteriyor ki glisemik kontrol nöropati semptomlarını azaltmak için yeterli değildir aynı zamanda aşırı glisemik dalgalanmalar da önlenmelidir.

ADA standarts of medical care in diabetes. Diabetes Care 2015;38(Suppl. 1):S1–S94.

GD-HbA1c'nin ötesinde glisemik kontrol



Hiperglisemiye neden olan 3 ana glisemik bozukluk vardır

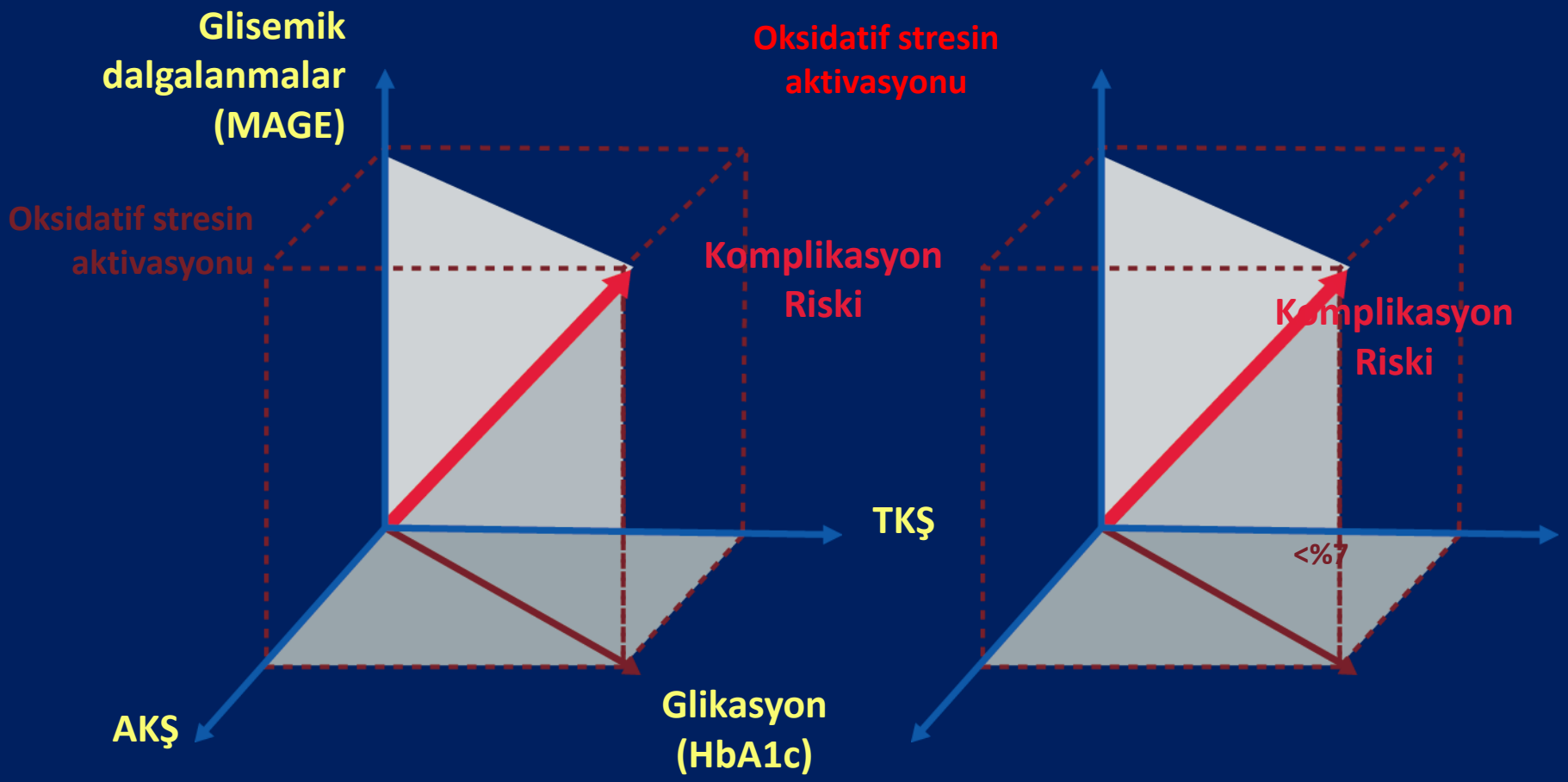
Hiperglisemi nedeniyle 2 patolojik süreç aktive olur

Sonuç olarak komplikasyon riski artar

Glisemik dalgalanmalar kan glukoz düzeyinin açlık ve toklukta normal kabul edilen değerlerin üzerinde ve altında seyretmesi olarak tanımlanmaktadır.
MAGE: Glisemik dalgalanmaların ortalama büyüklüğü.
1.Monnier L, Colette C. *Diabetes Care 2008;* 31 (Suppl. 2):S150–S154.

Komplikasyon riskini azaltmak için HbA1c'nin ötesinde tüm faktörler kontrol edilmelidir[1]

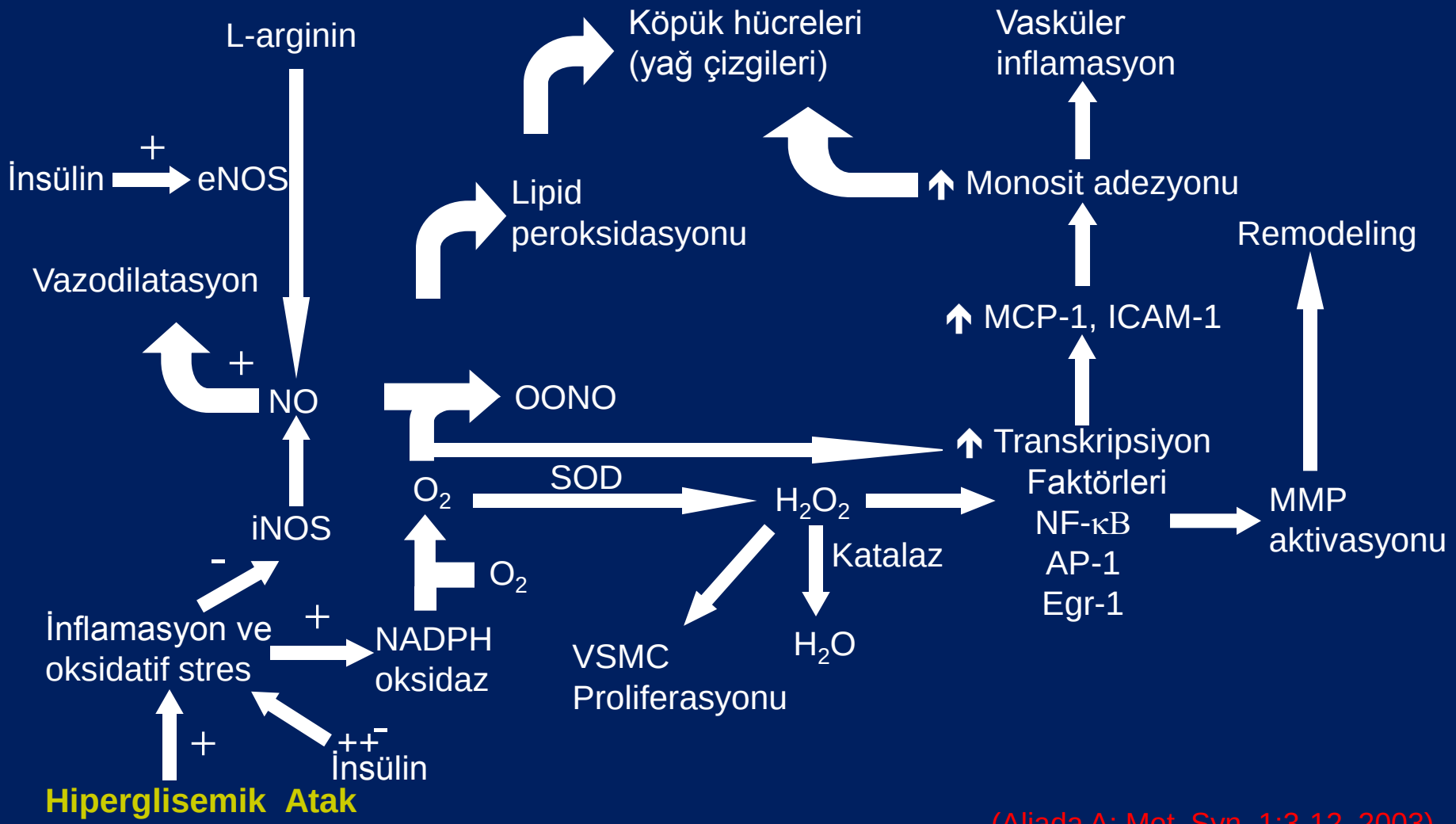
Normoglisemik aralığın dışındaki glisemik dalgalanmalar, diyabetik vasküler hasar üzerinde kronik hiperglisemiden daha fazla etkilidir[2]



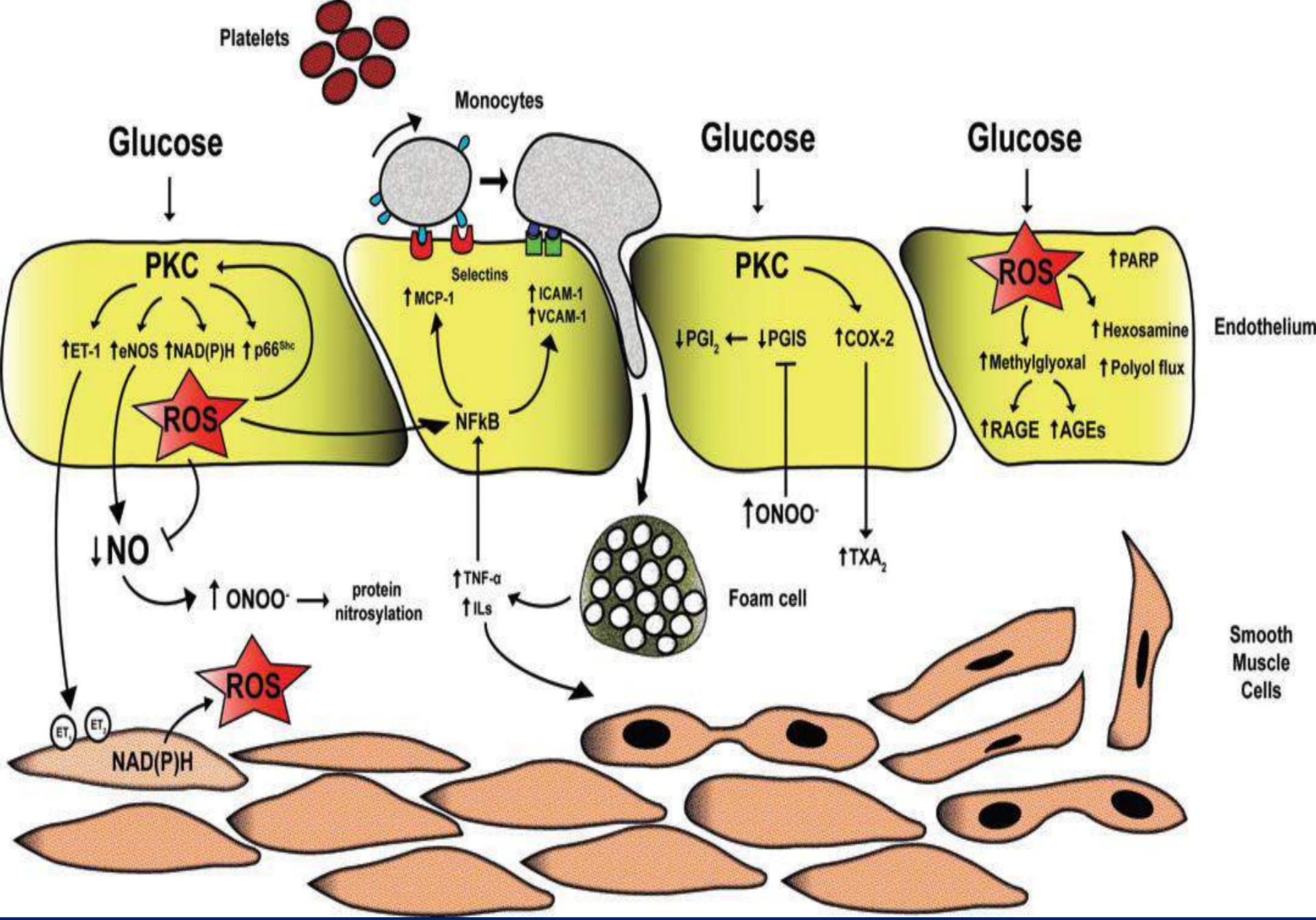
Glisemik dalgalanmalar kan glukoz düzeyinin açlık ve toklukta normal kabul edilen değerlerin üzerinde ve altında seyretmesi olarak tanımlanmaktadır.
MAGE: Glisemik dalgalanmaların ortalama büyüklüğü.

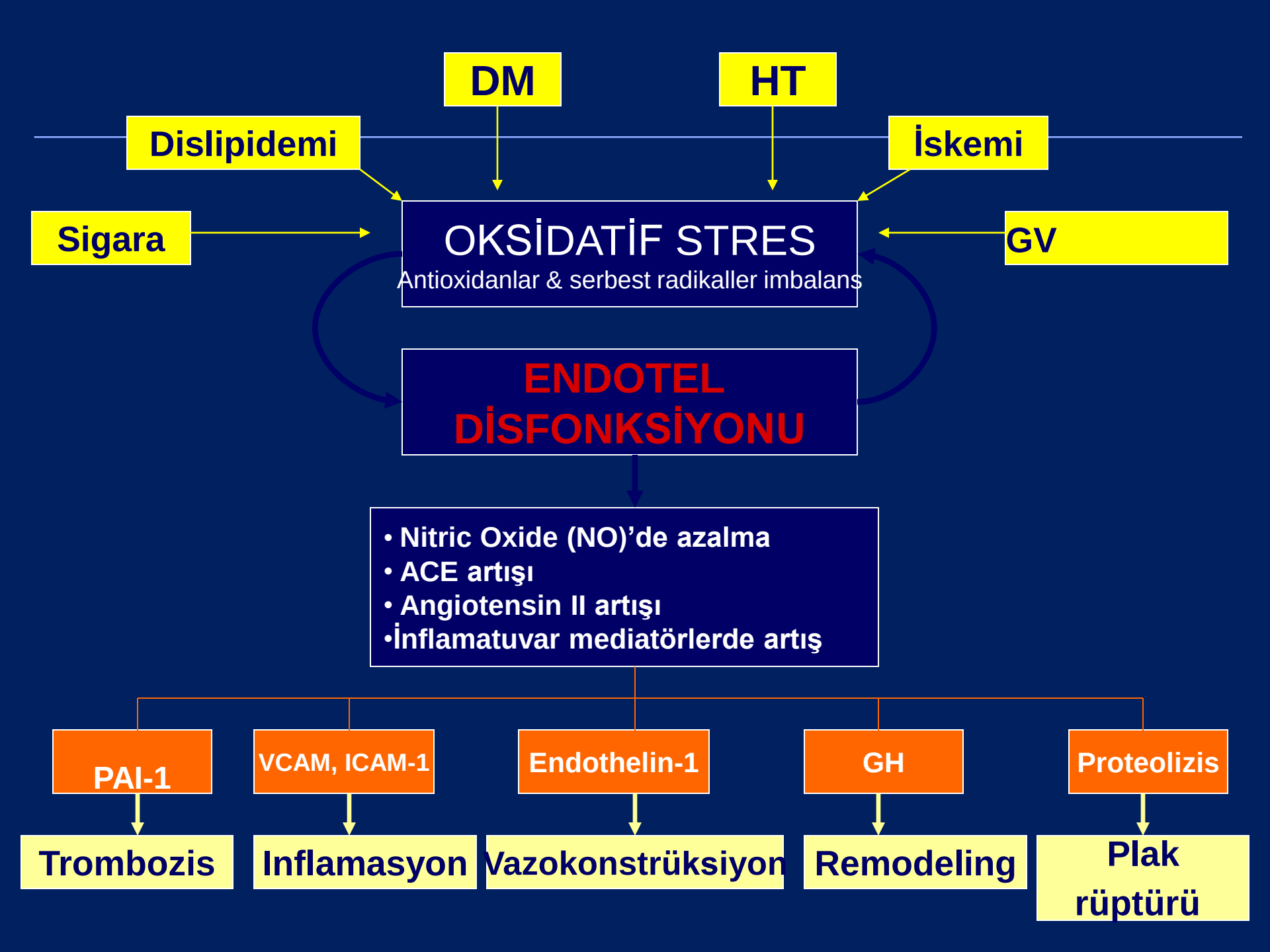
1.Monnier L, Colette C. *Diabetes Care 2008;* 31 (Suppl. 2):S150–S154. 2. Hinzmann R et al. *Int. J. Med. Sci.* 2012;9: 665-681.

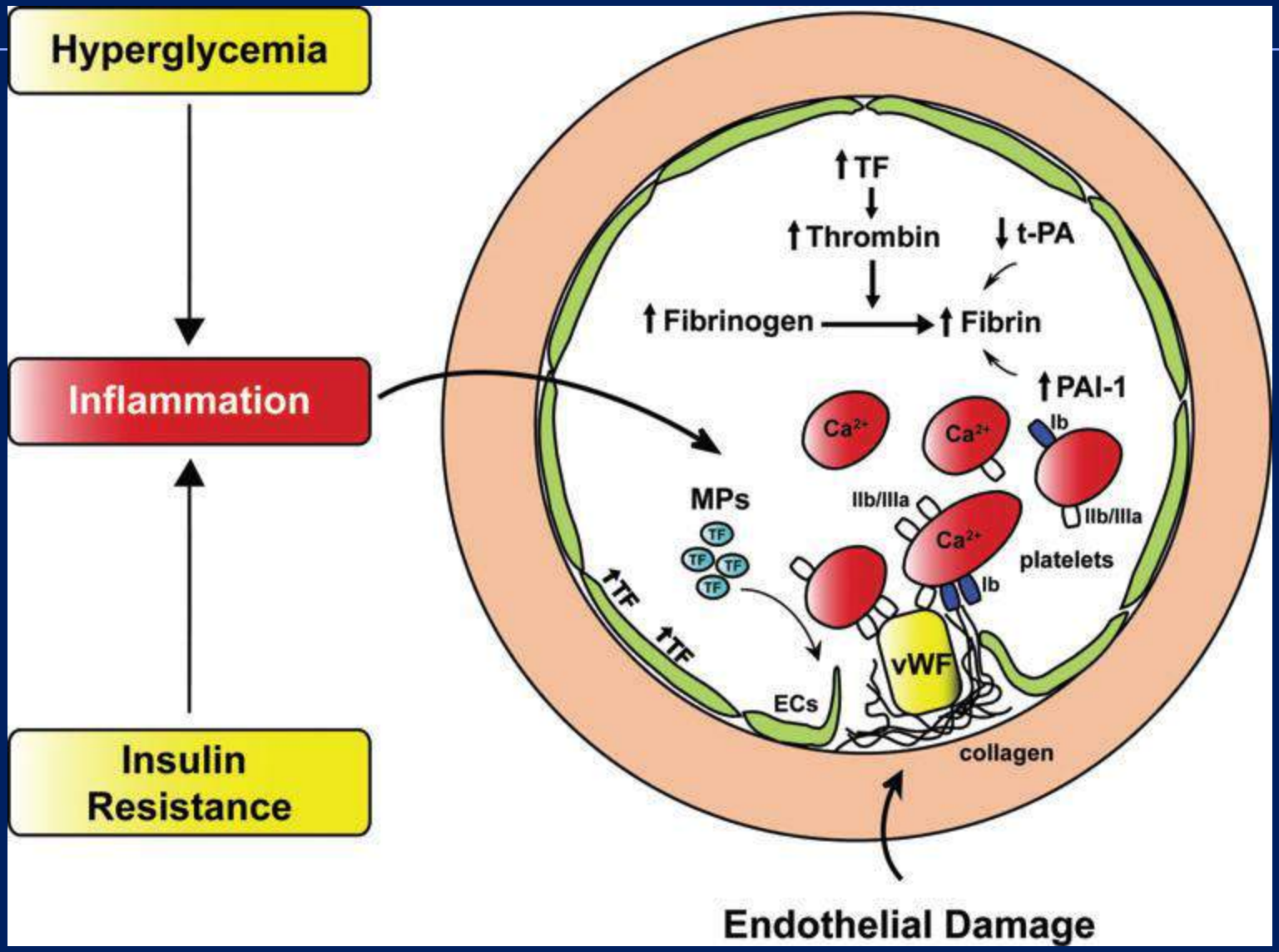
Diabetes mellitus, Mikrovasküler Komp ve KVH



(Aljada A; Met. Syn. 1:3-12, 2003)


Platelets
Monocytes
Glucose
Glucose
Glucose
PKC
↑ET-1 ↑eNOS ↑NAD(P)H ↑p66Shc
ROS
Selectins
↑MCP-1
↑ICAM-1
↑VCAM-1
NFkB
PKC
↓PGI2 ← ↓PGIS
↑COX-2
ROS
↑PARP
↑Hexosamine
↑Methylglyoxal
↑Polyol flux
↑RAGE ↑AGEs
Endothelium
↓NO
↑ ONOO- → protein nitrosylation
↑TNF-α
↑ILs
Foam cell
↑ONOO-
↑TXA2
ROS
ET1 ET2
NAD(P)H
Smooth Muscle Cells


DM
HT
Dislipidemi
İskemi
Sigara
OKSİDATİF STRES
Antioxidanlar & serbest radikaller imbalans
GV
ENDOTEL DİSFONKSİYONU
• Nitric Oxide (NO)'de azalma
• ACE artışı
• Angiotensin II artışı
•İnflamatuvar mediatörlerde artış
PAI-1
VCAM, ICAM-1
Endothelin-1
GH
Proteolizis
Trombozis
Inflamasyon
Vazokonstrüksiyon
Remodeling
Plak rüptürü


Hyperglycemia
Inflammation
Insulin Resistance
↑TF
↑Thrombin
↓t-PA
↑Fibrinogen
↑Fibrin
↑PAI-1
Ca2+
Ca2+
Ib
MPs
IIb/IIIa
Ca2+
IIb/IIIa
platelets
TF
TF
TF
TF
Ib
↑TF
↑TF
vWF
ECs
collagen
Endothelial Damage

GLİSEMİK DEĞİŞKENLİK ve Vasküler Endotel Değişiklikleri

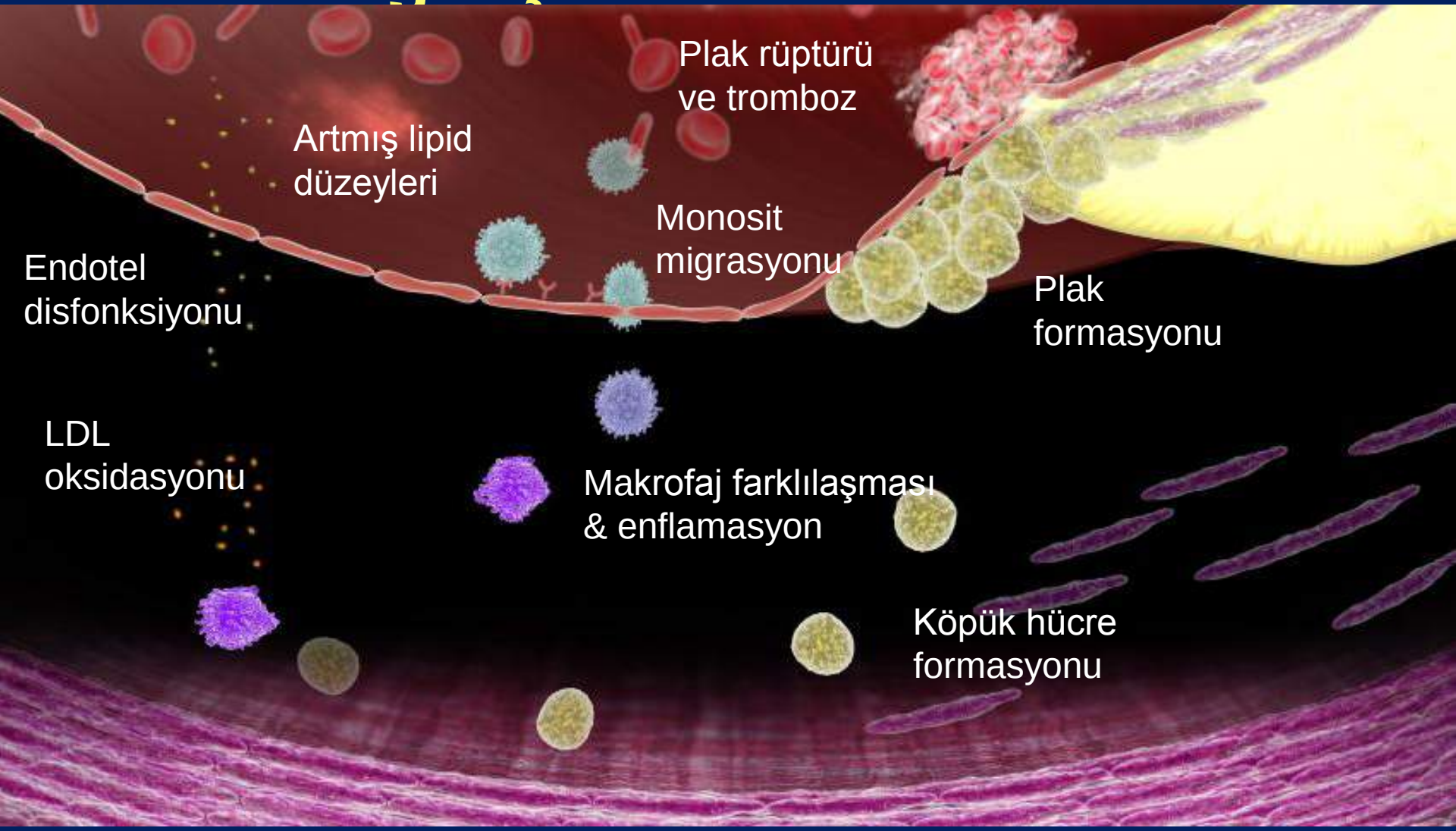
- ↓eNOS aktivitesi
- ↑Endotelin-I düzeyleri
- ↓Prostasiklin serbestleşmesi
- ↑Adezyon molekül ekspresyonu
- ↑Trombosit ve monosit adezyonu
- ↑Prokoagülan aktivitesi
- ↑İleri glikozilasyon ürünleri
- Fibrinolitik aktivitede bozulma
  - Oksidatif stres artışı,Pseudo hipoksia
  - NaK-ATPaz aktivitesinde azalma

Y.Saisho:İnt.j.Mol Sci.Oct 2014

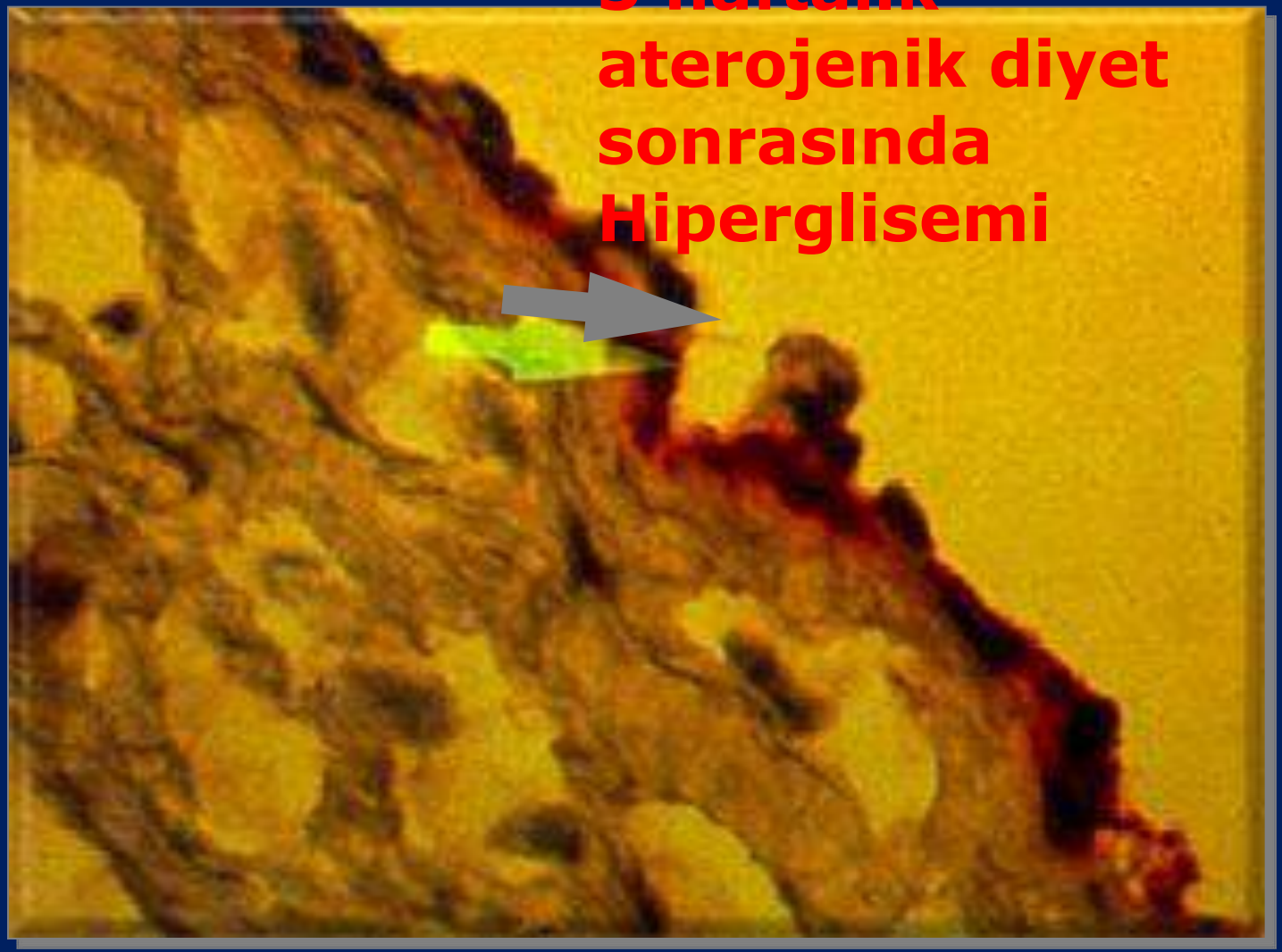
Endotel fonksiyonunun değerlendirilmesi

- İntrakoroner doppler ile kan akımının asetilkoline cevabının ölçülmesi
- Pozitron emisyon tomografisi (PET)
- İmpedans pletismografi
- Brakial USG
- Venöz çalışmalar
- Endotel kaynaklı bileşiklerin kanda tayini
  - Endotelin
  - vWF
  - Trombomodulin
  - Selektin adezyon molekülleri (VCAM, ICAM)
  - PAI-1

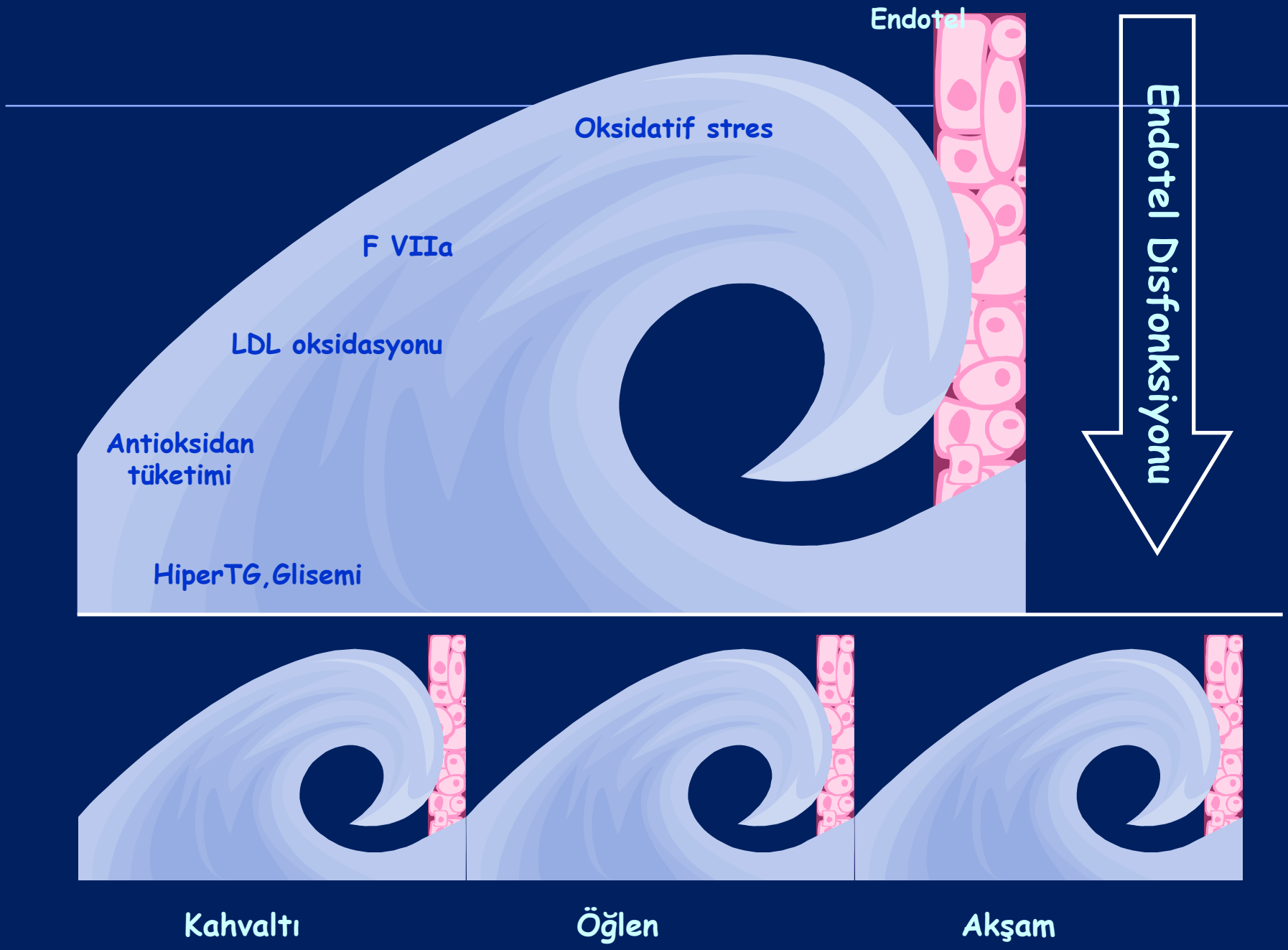
ED ve Hiperglisemik atakta rüptür sürecinin gelişimi



Tavşan Aortunda VCAM-1 Salınımı

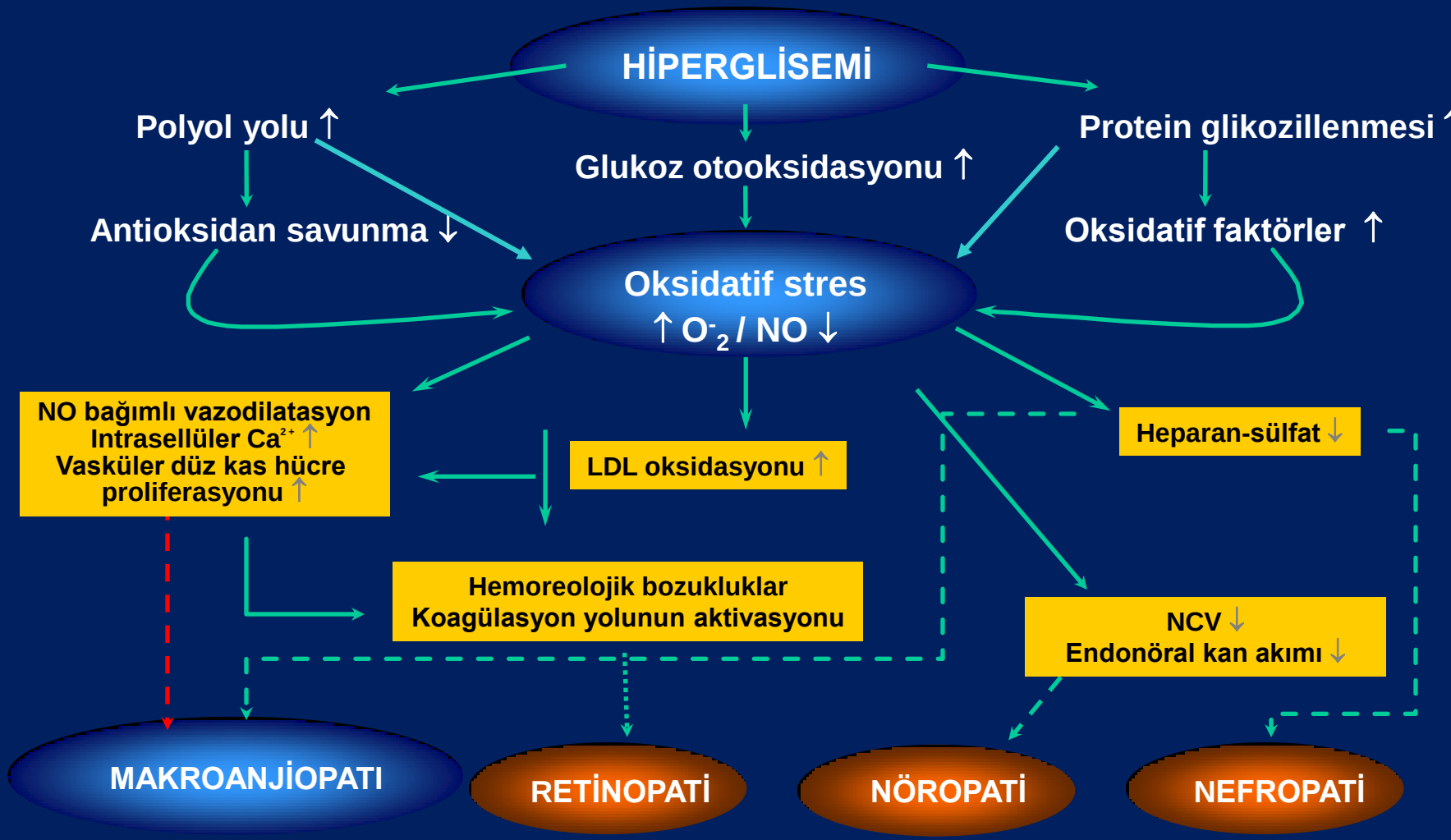


Li H et al. *Arterioscler Thromb* 1993;13:197-204.



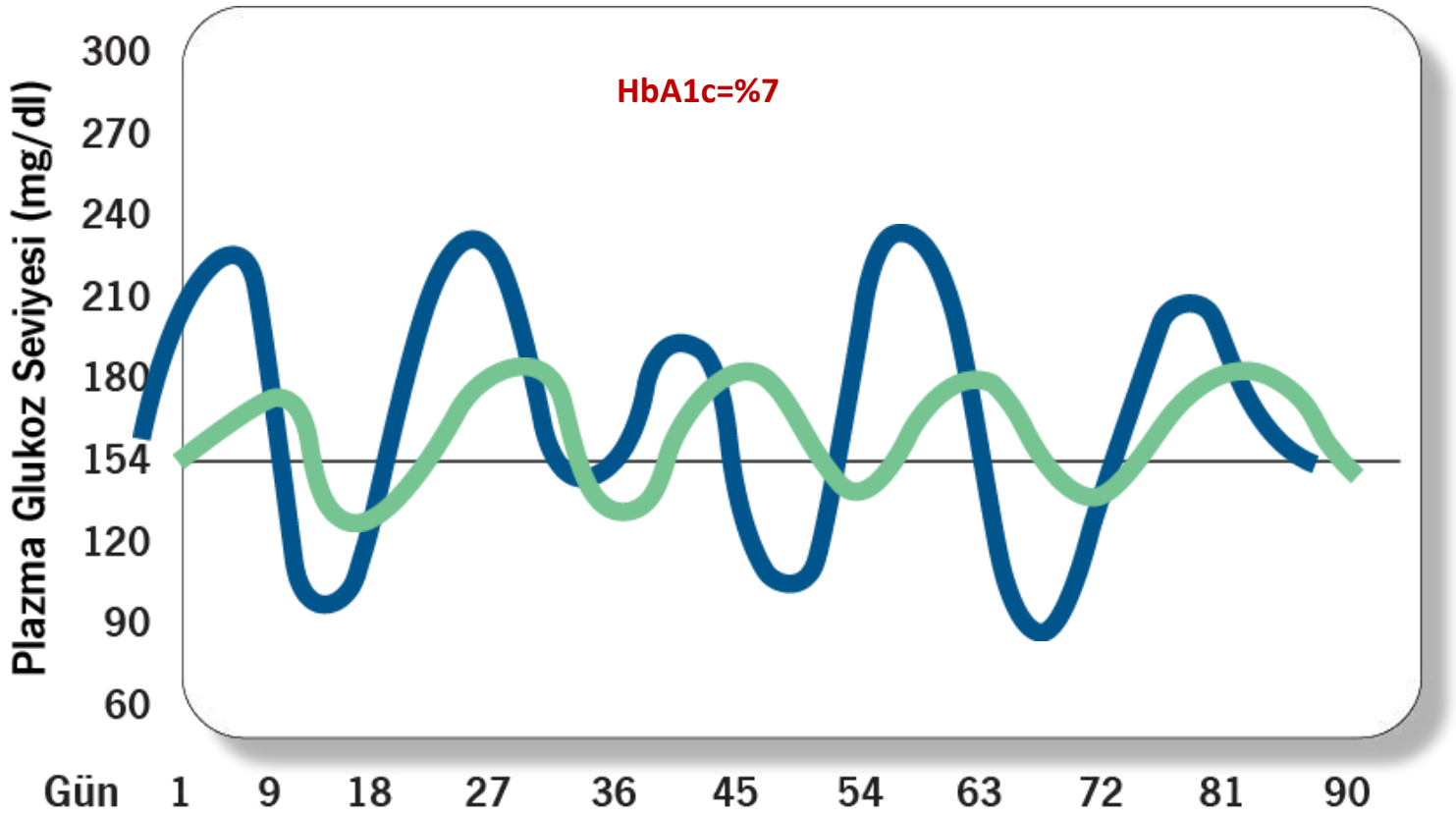
Ceriello A, 2001

Hiperglisemik piklerin diyabet komplikasyonlarına olası etkisi

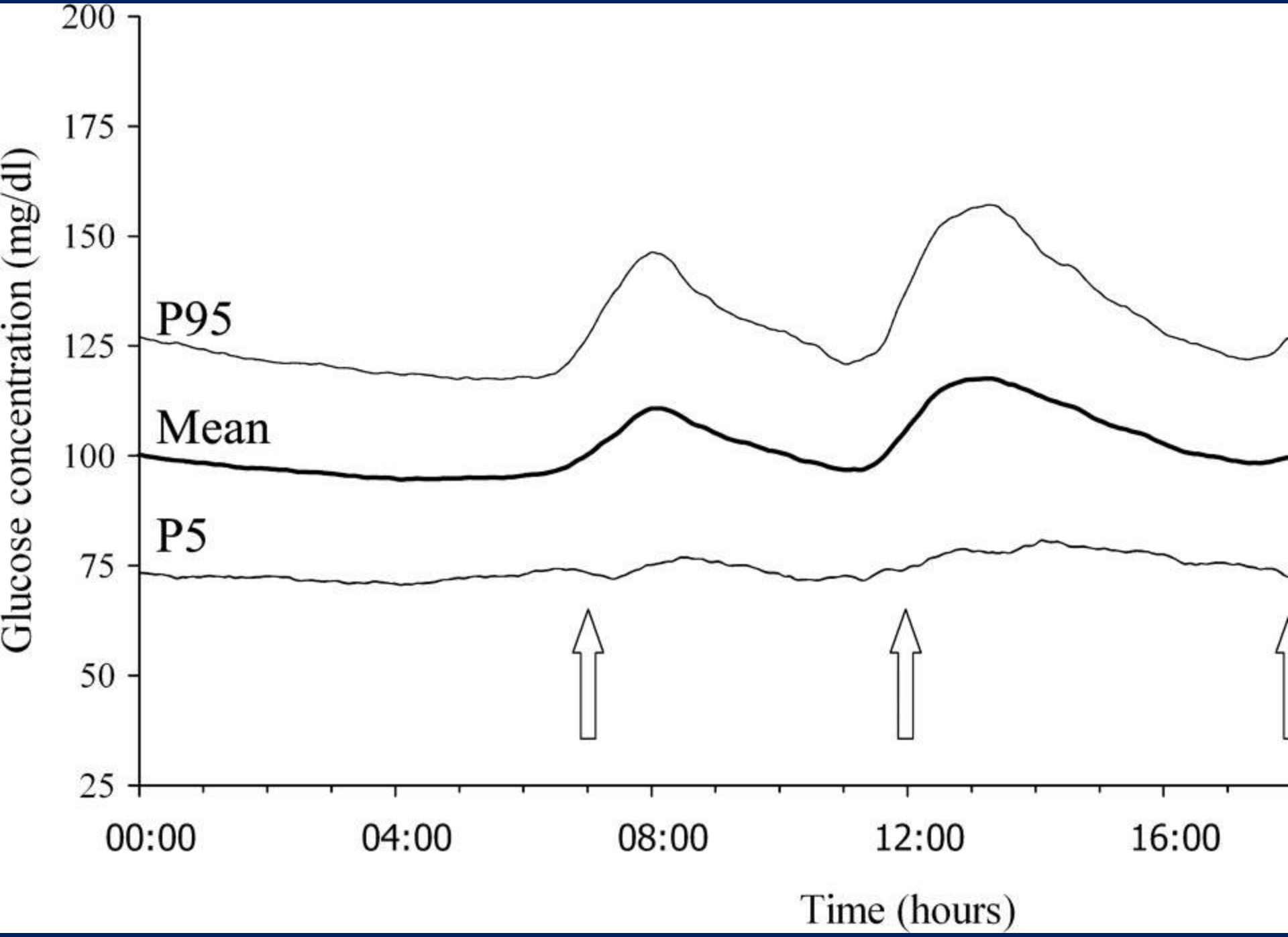


A.Ceriollo . Diab Med 27, 862-67,2010

Aynı HbA1c değerlerine sahip 2 hastada glisemik dalgalanma profilleri farklı olabilir



Monnier L, Colette C. *Diabetes Care 2008;* 31 (Suppl. 2):S150–S154.


200
175
150
125
100
75
50
25
Glucose concentration (mg/dl)
P95
Mean
P5
00:00
04:00
08:00
12:00
16:00
Time (hours)

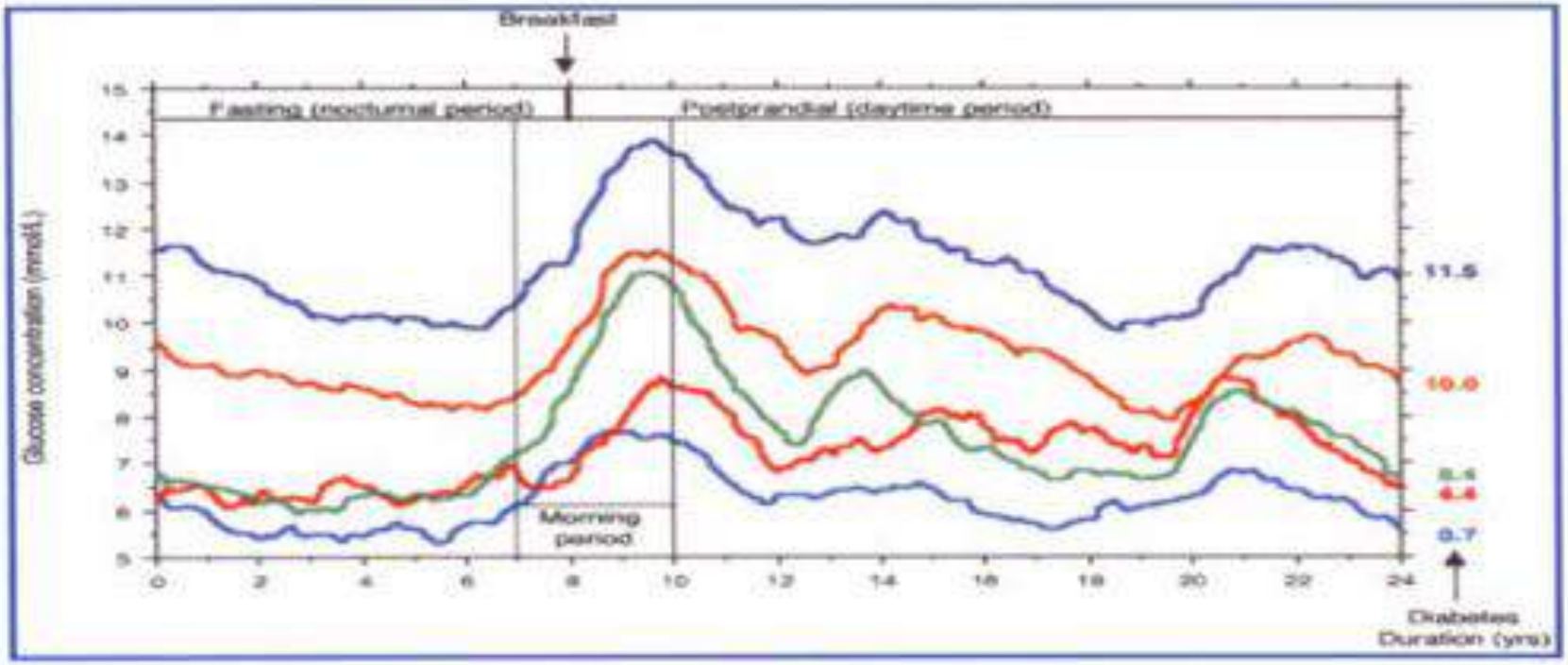
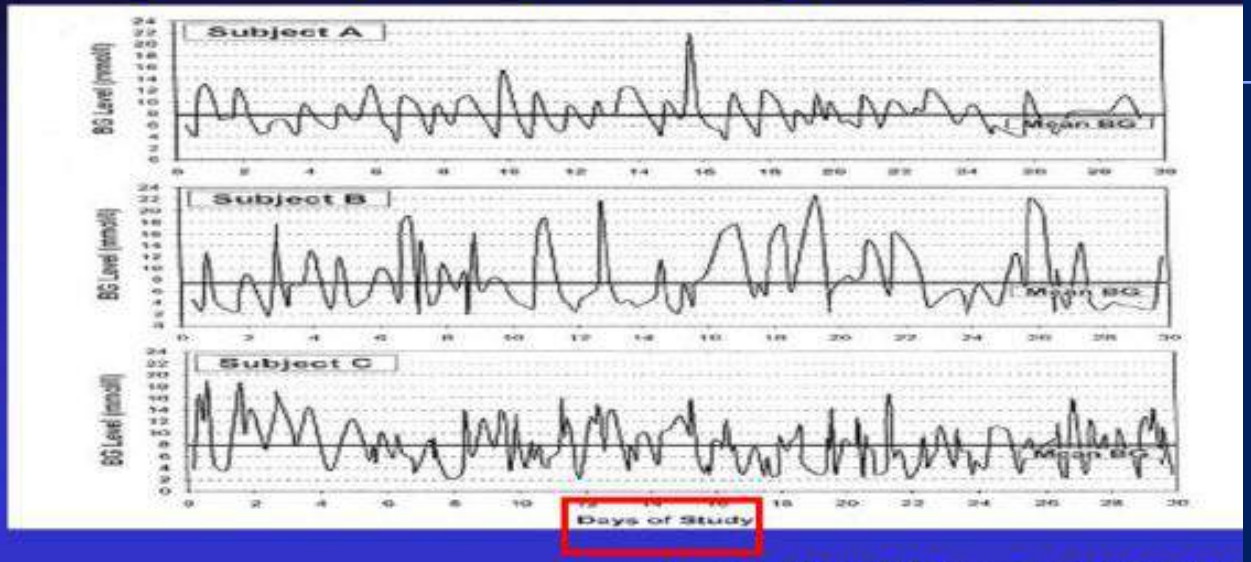


Figure 1— Twenty-four hour recordings from the CGMS in the five groups of patients with type 2 diabetes. Curve 1 (blue): A1C <6.5%; curve 2 (red): ≤ 6.5% to <7%; curve 3 (green): ≤7% to <8%; curve 4 (orange): ≤8% to 9%; curve 5 (purple): ≥9%.

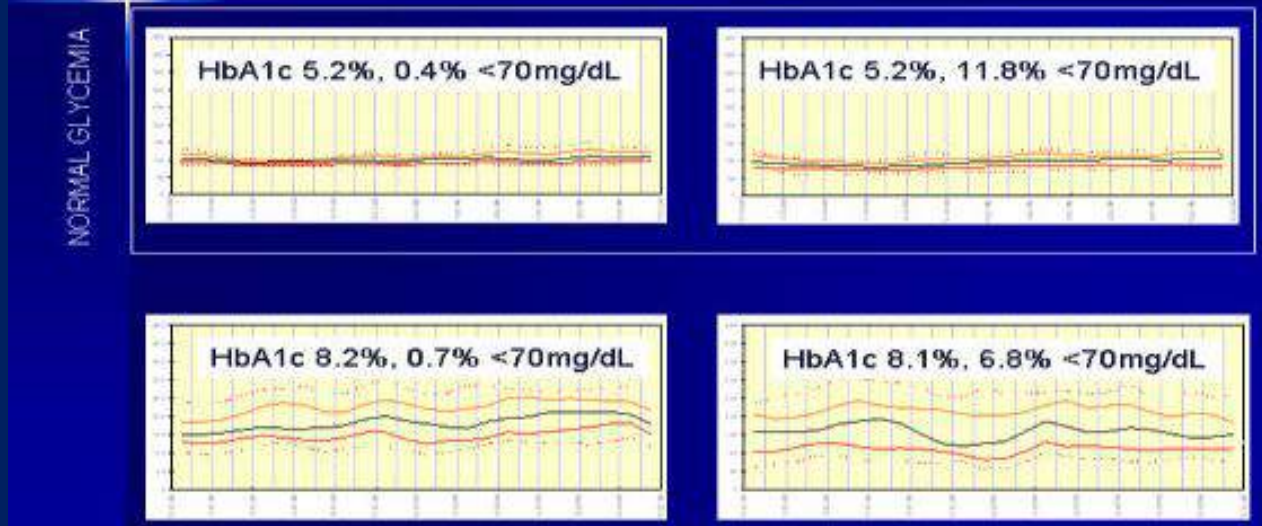
Diabetes Care 30:263, 2007

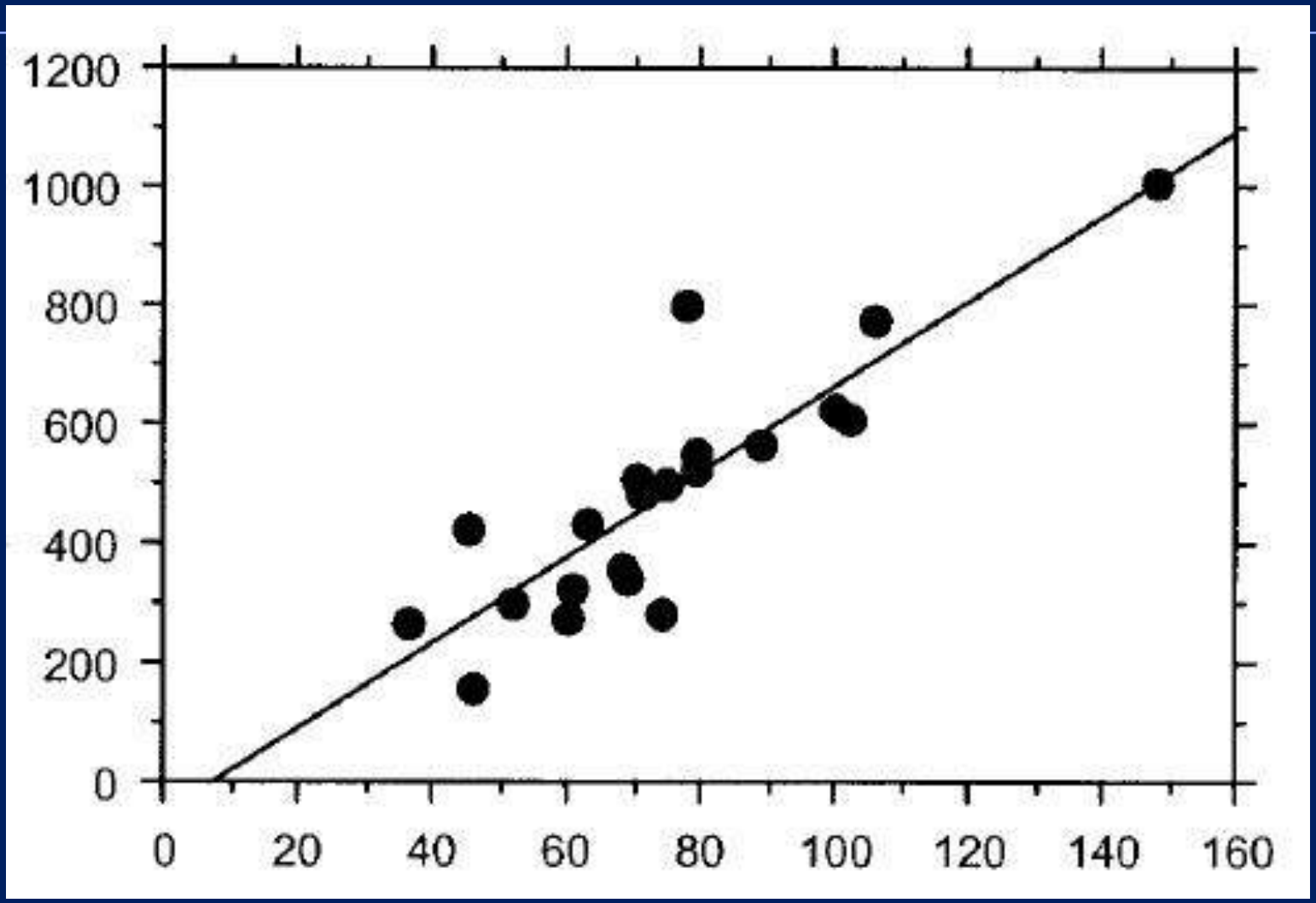
Patients with identical mean glucose values differ significantly in amplitude of glycemic spikes



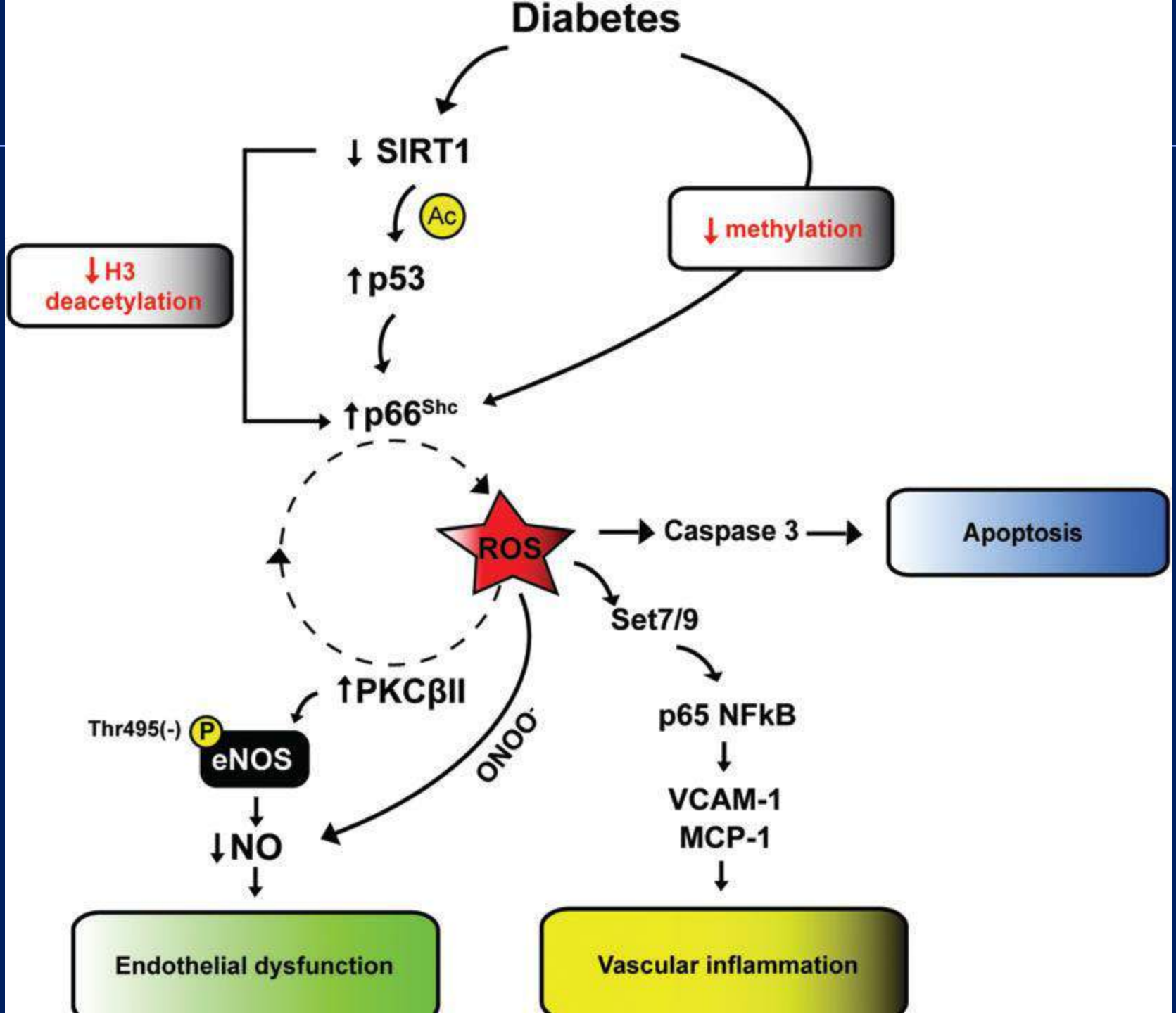
Kovatchev BP et al. *Diabetes Care*. 2006;29:2433.

Comparison of Subjects with Similar HbA1c and Varying Levels Of Hypoglycemia

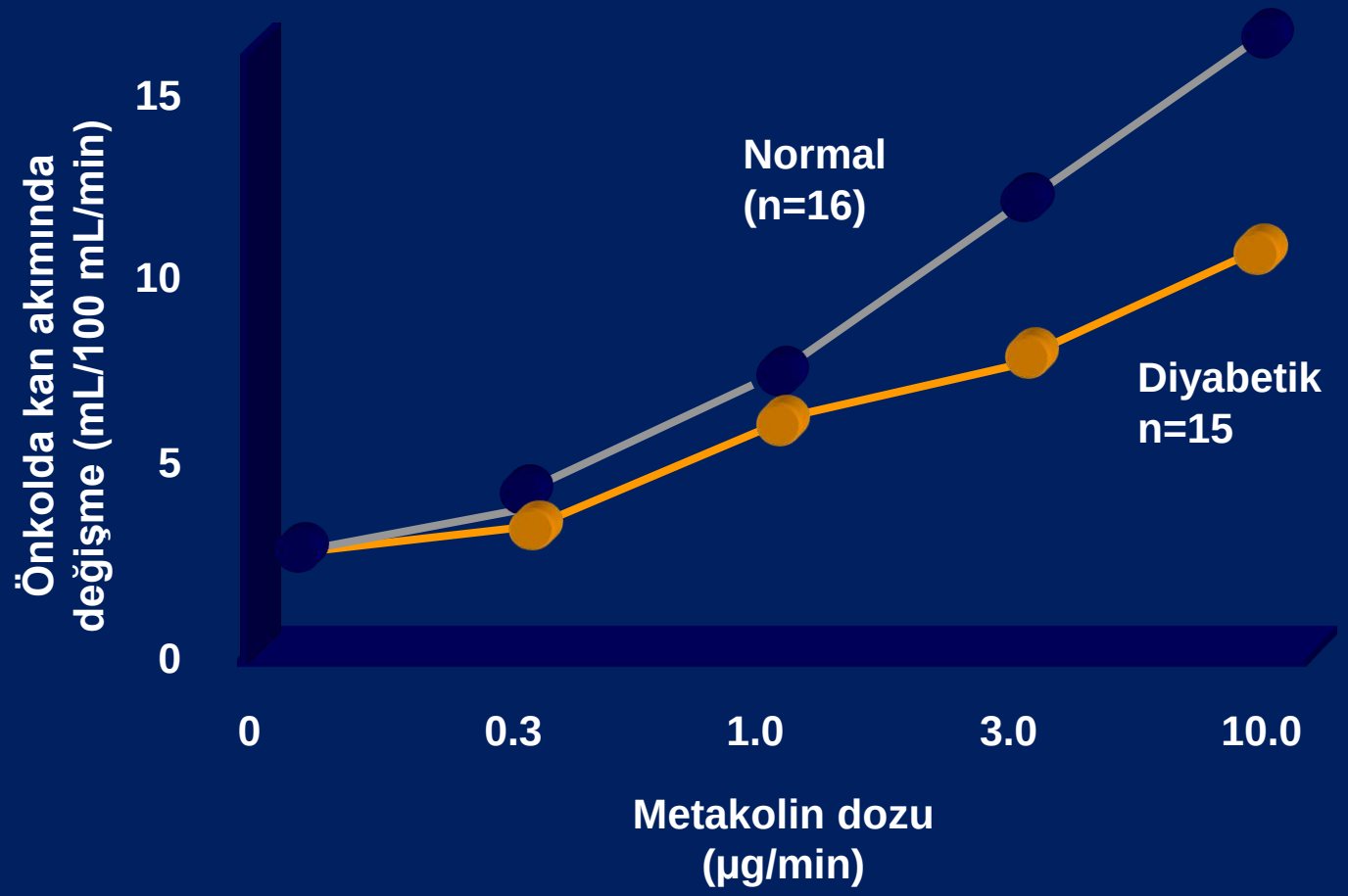




Monnier et al. Diabetes Care 2008


Diabetes
↓ SIRT1
Ac
↑p53
↓H3 deacetylation
↓ methylation
↑p66Shc
ROS
Caspase 3
Apoptosis
Set7/9
p65 NFkB
VCAM-1
MCP-1
↑PKCβII
Thr495(-)
P
eNOS
ONOO-
↓NO
Endothelial dysfunction
Vascular inflammation

Diyabette Endotel Fonksiyonunda Bozulma



Adapted from Johnstone MT. et al. Circulation 1993;888:2510-2516

Scandinavian Journal of Clinical & Laboratory Investigation, 2013; 73: 422–427

informa
healthcare

ORIGINAL ARTICLE

Postload hyperglycemia is associated with increased subclinical inflammation in patients with prediabetes

AYFER COLAK[1], BARIS AKINCI[2], GULDEN DINIZ[3], HAKAN TURKON[4], FARUK ERGONEN[2], HULYA YALCIN[1] & ISIL COKER[1]

Table II. Correlation analyses in all subjects.

	IL-6		IL-8		hsCRP	
	r	*p*	*r*	*p*	*r*	*p*
Age (years)	0.087	NS	0.188	0.006	0.000	NS
BMI	0.237	<0.001	0.114	NS	0.519	<0.001
Fasting glucose	0.200	0.003	0.190	0.006	0.163	0.018
Glucose 2-h	0.274	<0.001	0.200	0.003	0.227	0.001
Fasting insulin	0.084	NS	0.124	NS	0.309	<0.001
HOMA-IR	0.104	NS	0.163	0.017	0.315	<0.001
Triglycerides	0.099	NS	0.265	<0.001	0.220	NS
Cholesterol	0.066	NS	0.145	0.034	−0.020	NS
HDL cholesterol	−0.012	NS	−0.026	NS	−0.002	NS
LDL cholesterol	0.011	NS	0.037	NS	−0.043	NS

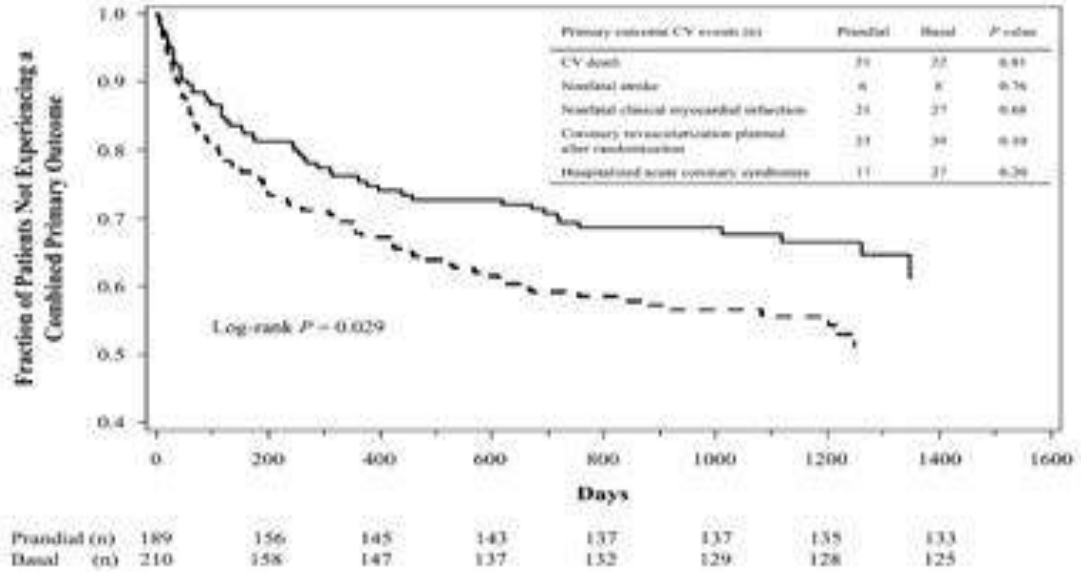
MAGE NİN YÜKSEK OLMASI

DİYABETE BAĞLI KALP RAHATSIZLIKLARININ ANA NEDENİDİR

Clinical Care/Education/Nutrition/Psychosocial Research

BRIEF REPORT

Post Hoc Subgroup Analysis of the HEART2D Trial Demonstrates Lower Cardiovascular Risk in Older Patients Targeting Postprandial Versus Fasting/Premeal Glycemia



DIABETICMedicine

DOI: 10.1111/j.1464-5491.2011.03324.x

Article: Treatment

Meal-induced increases in C-reactive protein, interleukin-6 and tumour necrosis factor α are attenuated by prandial + basal insulin in patients with Type 2 diabetes

P. J. Beisswenger, W. V. Brown*, A. Ceriellot, N. A. Le*, R. B. Goldberg‡, J. P. Cooke§, D. C. Robbins¶[1], S. Sarwat¶[2], H. Yuan¶[3], C. A. Jones¶ and M. H. Tan¶[4] for the IOOI Study Investigators

Section of Endocrinology, Diabetes and Metabolism, Dartmouth Medical School and Dartmouth-Hitchcock Medical Center, Hanover, NH, *Emory Lipid Research Laboratory, Emory University and Atlanta VAMC, Atlanta, GA, USA, †Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS) and Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Barcelona, Spain, ‡School of Medicine, Division of Endocrinology, Metabolism and Diabetes, University of Miami, Miami, FL, §School of Medicine, Stanford University, Palo Alto, CA and ¶Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA

Accepted 18 April 2011

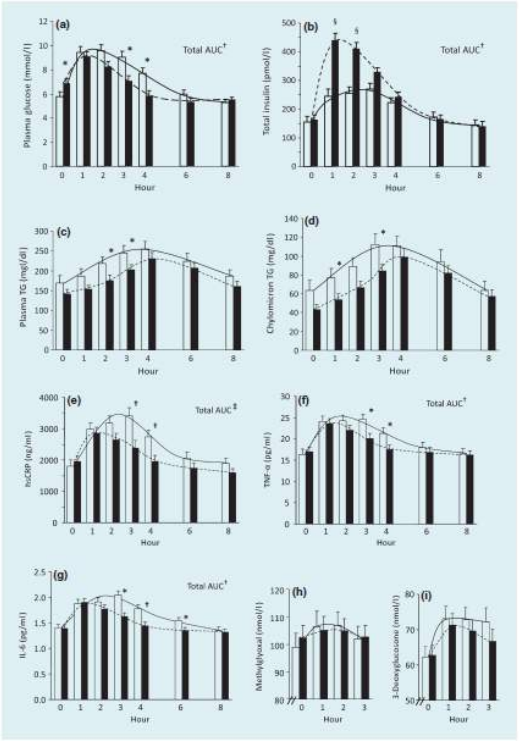


FIGURE 1 Plasma levels of glucose, insulin, TG (plasma/chylomicron), hsCRP, TNF-α, interleukin-6, methylglyoxal and 3-deoxyglucosone after test meal 2. Prior to the test meal, patients were treated for 24 weeks with insulin lispro mix 50 plus metformin (black bar with dashed trend line, $n = 25$) or insulin glargine (white bar with solid trend line, $n = 21$) plus metformin. Results are the mean ± standard error of values measured before (0 h) and after the test meal. Comparisons were between treatments at each time point and between treatments for total AUC. *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$, §$P < 0.0001$. AUC, area under the concentration curve; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TG, triglyceride; TNF-α, tumour necrosis factor alpha.

Table 2 Comparison between the two insulin treatment groups of post-meal incremental area under the curve (AUC) of various biomarkers in test meal 2 at week 24 after randomization*

Biomarker	Prandial + basal† ($n = 25$)	Basal‡ ($n = 21$)	*P*-value
Glucose (mmol/l)·min	323.8 (77.1)	902.8 (98.6)	< 0.001
Insulin (pmol/l)·min§	46 638 (6813.1)	21 418 (5415.5)	< 0.01
TG (mg/dl)·min	23 962 (2661.8)	25 975 (3074.6)	0.46
CTG (mg/dl)·min	15 387 (1845.5)	14 414 (2141.3)	0.99
hsCRP (ng/ml)·min	75 599 (38 756.2)	377 947 (70 693.6)	< 0.001
TNF-α (pg/ml)·min	874.1 (235.8)	2150.1 (435.3)	< 0.01
IL-6 (pg/ml)·min	59.0 (21.3)	138.3 (33.8)	< 0.01
3-DG (nmol/l)·min	1014 (277.2)	1597 (260.9)	0.14
MG (nmol/l)·min	339.6 (310.4)	1004.3 (410.2)	0.23

3-DG, 3-deoxyglucosone; CTG, chylomicron triglycerides; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; MG, methylglyoxal; TG, plasma triglycerides; TNF-α, tumour necrosis factor alpha.

*Data are mean (SEM). The *P*-value calculation included treatment as a fixed effect and baseline value as a covariate.

†Insulin lispro mix 50 plus metformin.

‡Insulin glargine plus metformin.

§Insulin incremental AUC: prandial + basal group, $n = 24$; basal group, $n = 20$.

Torimoto *et al. Cardiovascular Diabetology* 2013, **12**:1
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CARDIO VASCULAR DIABETOLOGY

ORIGINAL INVESTIGATION **Open Access**

Relationship between fluctuations in glucose levels measured by continuous glucose monitoring and vascular endothelial dysfunction in type 2 diabetes mellitus

Keiichi Torimoto, Yosuke Okada, Hiroko Mori and Yoshiya Tanaka*

Table 2 Correlation coefficients between L_RHI and markers of diabetic control and various nonglycemic metabolic variables

	HbA1c	Average[a]	SD[a]	MAGE[a]	MPPGE[a]	Time at <70[a] (n=12)	Time at ≥140[a]	Time at ≥200[a]	LDL-C	HDL-C	TG	SBP	DBP
Average[a] (n=57)	0.14												
SD[a] (n=57)	−0.16	0.36**											
MAGE[a] (n=57)	−0.06	0.30*	0.79**										
MMPGE[a] (n=57)	0.01	0.37**	0.64**	0.58**									
Time at <70[a] with hypoglycemia (n=12)	0.29	−0.69**	−0.38	−0.70*	−0.19								
Time at ≥140[a] (n=57)	0.12	0.84**	0.27*	0.18	0.32*	−0.68							
Time at ≥200[a] (n=57)	0.14	0.95**	0.43**	0.37**	0.39*	−0.70*	0.76**						
LDL-C (n=57)	0.20	0.01	0.25	0.15	0.04	0.03	0.16	0.04					
HDL-C (n=57)	−0.17	0.01	0.31*	0.04	0.19	0.03	0.17	0.05	0.06				
TG (n=57)	0.27*	0.05	−0.21	−0.03	0.06	−0.33	0.04	0.01	0.16	−0.28*			
SBP (n=57)	−0.07	−0.25	−0.09	0.01	−0.03	−0.07	−0.19	−0.22	−0.07	−0.18	0.05		
DBP (n=57)	0.20	−0.20	−0.27*	−0.12	−0.10	−0.07	−0.16	−0.22	0.09	−0.26*	0.17	0.65**	
L_RHI (n=57)	0.12	−0.24	−0.50**	−0.57**	−0.41**	−0.59*	−0.20	−0.29*	0.17	−0.14	0.01	0.11	0.09

[a] Measured by the continuous glucose monitoring system.
Data are results of Pearson correlation analysis for normally distributed variables and Spearman rank correlation for variables with skewed distribution. *P<0.05, **P<0.01.
Abbreviations: *HbA1c* hemoglobin A1c; *SD* standard deviation; MAGE, mean amplitude of glycemic excursions; *MPPGE* mean postprandial glucose excursions; *LDL-C* low-density lipoprotein cholesterol; *HDL-C* high-density lipoprotein cholesterol; *TG* triglyceride; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *L_RHI* the natural logarithmic scaled reactive hyperemia index.

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Journal of Diabetes Mellitus

Comparison of glycemic variability between basal-bolus and premixed insulin therapy*

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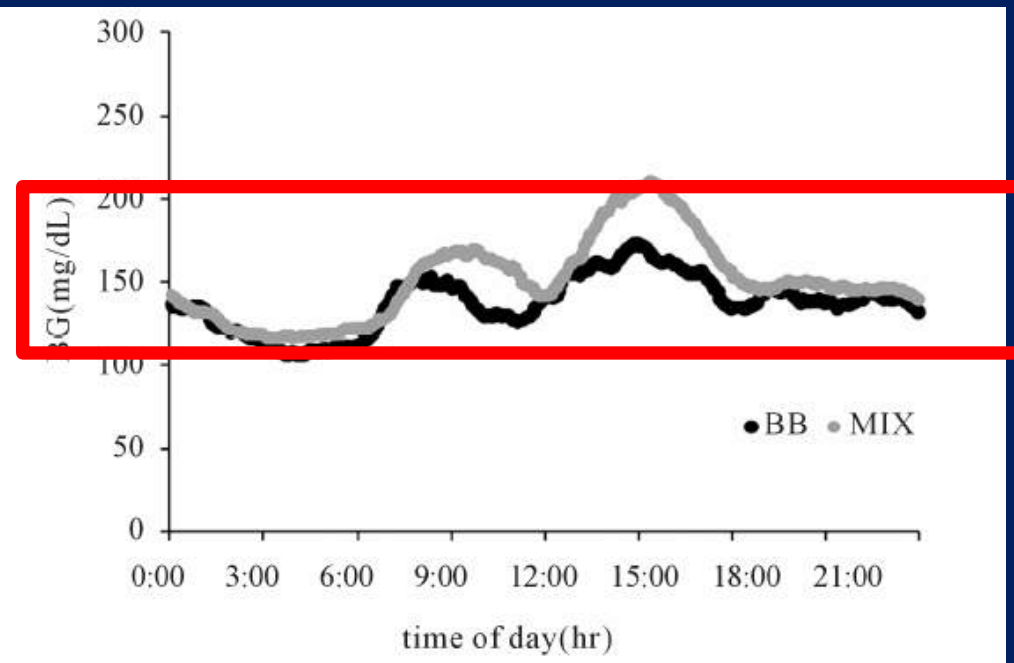
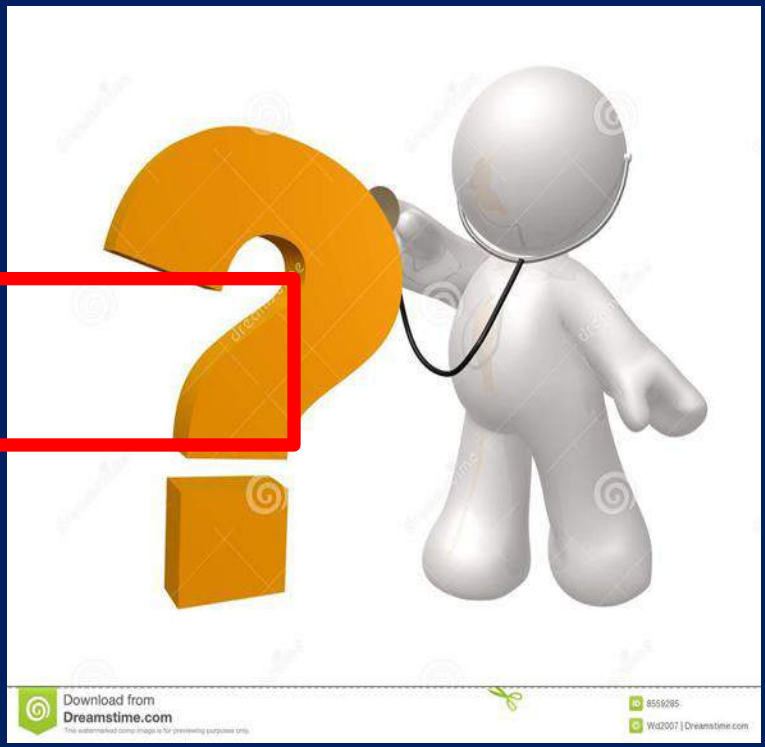


Figure 1. Twenty-four-hour glucose profile in patients treated with basal-bolus insulin (●) or twice-daily injections of premixed insulin analogs (●).



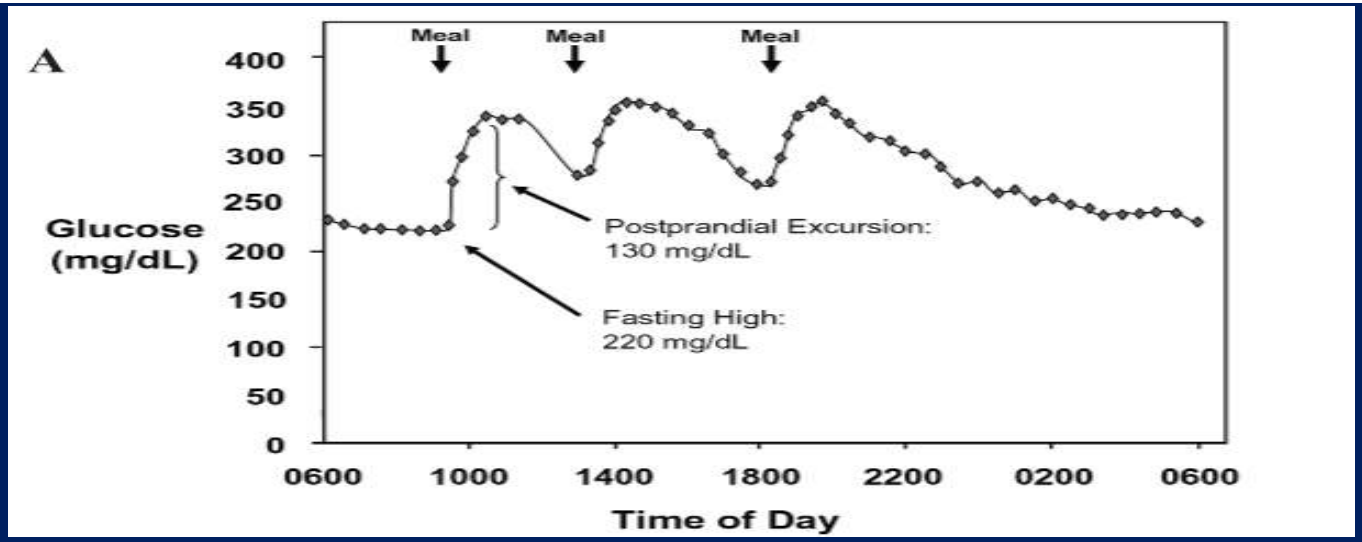
Comparative Effectiveness of Basal-Bolus *Versus* Premix Analog Insulin on Glycemic Variability and Patient-Centered Outcomes during Insulin Intensification in Type 1 and Type 2 Diabetes: A Randomized, Controlled, Crossover Trial

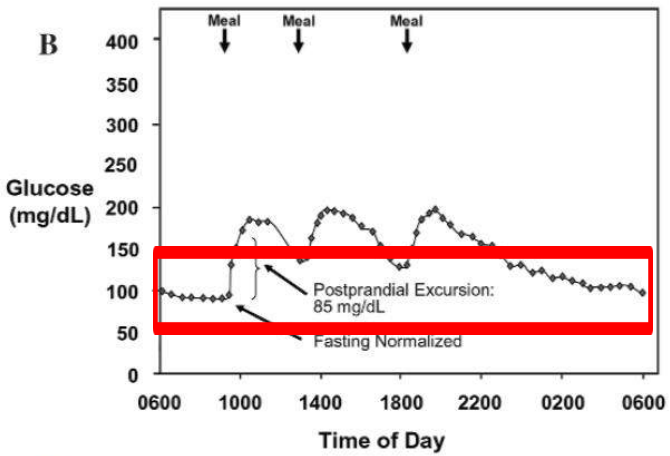
Conclusions: Patient satisfaction was impacted more positively by improved QoL, reduced glucose variability, and better glycemic control with a basal-bolus regimen than negatively by the burden of additional injections, thereby facilitating insulin intensification and the ability to achieve HbA_{1c} below 7.0%. (*J Clin Endocrinol Metab* 97: 3504–3514, 2012)

TABLE 5. CGM results by treatment

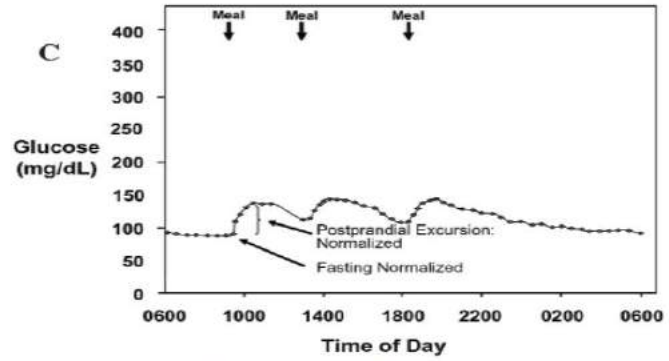
CGM sensor glucose measure	Baseline wk 0/12 covariate	Mean ± SE			Treatment-effect *P* value
		Glargine-glulisine	Premix	Treatment difference (95% CI)	
Daily mean (mg/dl)	164.2	147.8 ± 1.8	160.4 ± 1.9	−13.1 ± 2.7 (−18.4–−7.8)	<0.0001
[illegible]	[illegible]	[illegible]	[illegible]	[illegible] (−8.6–−3.2)	<0.0001
% time >140 mg/dl	57.2	46.1 ± 1.1	53.7 ± 1.1	−7.3 ± 1.6 (−10.4–−4.2)	<0.0001
% time <70 mg/dl	6.4	7.8 ± 0.5	6.7 ± 0.5	1.1 ± 0.7 (−0.2–2.5)	0.094

A Real-World Approach to Insulin Therapy in Primary Care Practice





(B). Use of basal insulin normalizes fasting glucose and reduces postprandial glucose excursions by reducing glucotoxicity



(C). Use of basal and mealtime insulin addresses fasting and postprandial hyperglycemia.

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Clinical Study

Effects of Glucose Load and Nateglinide Intervention on Endothelial Function and Oxidative Stress

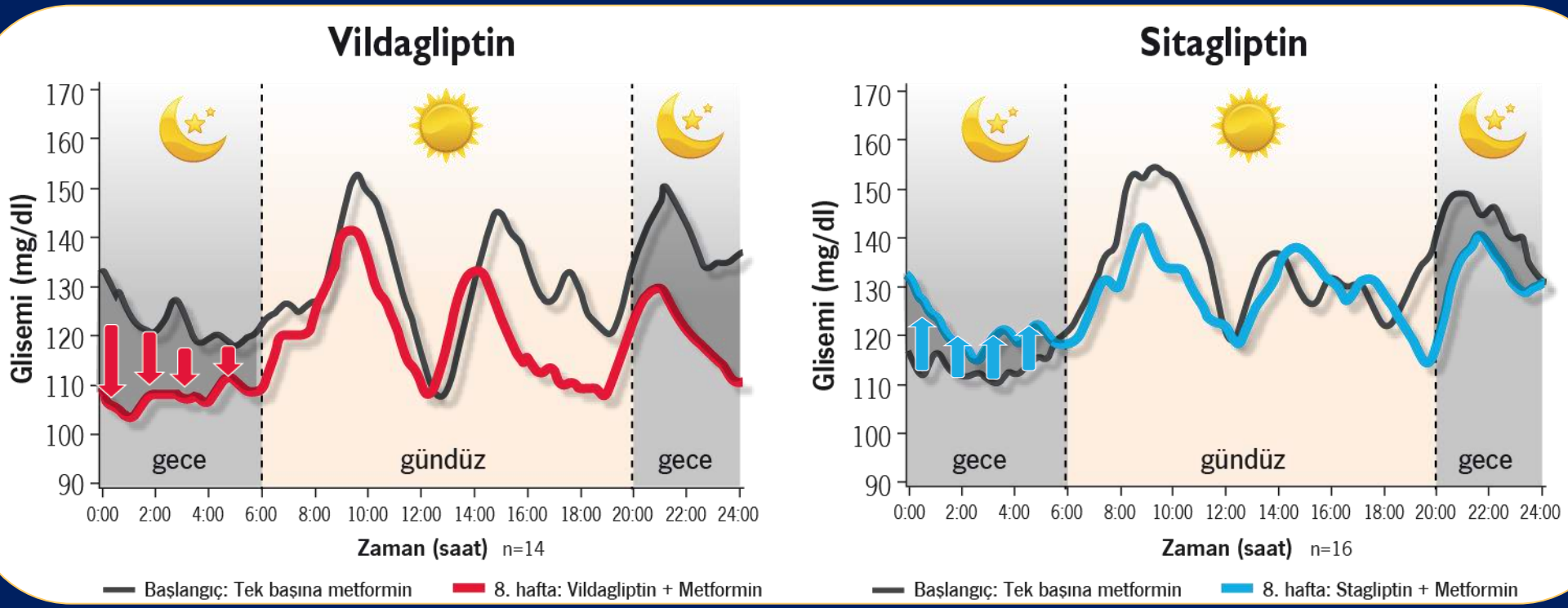
Table 5: Changes in FMEDD, NO, ET-1, MDA, and SOD in newly diagnosed type 2 diabetes after treatment with nateglinide.

Group		Before taking nateglinide	After taking nateglinide	Difference in levels before and after nateglinide treatment	*P* values
Number of patients (M/F)		32 (19/13)	32 (19/13)		
FMEDD	Fasting	12.20 ± 3.21	16.06 ± 4.23	3.86 ± 4.11	<.001
	After glucose load	9.4 ± 3.43	12.81 ± 4.01	3.41 ± 4.50	.0002
NO	Fasting	134.15 ± 58.55	173.64 ± 72.44	39.49 ± 35.22	<.001*
	After glucose load	123.76 ± 53.62	145.18 ± 62.97	20.52 ± 50.96	<0.001*
ET-1	Fasting	2.16 ± 1.81	1.40 ± 1.23	0.75 ± 0.92	<.001*
	After glucose load	2.31 ± 1.88	1.85 ± 1.56	0.46 ± 0.73	<.001*
MDA	Fasting	5.64 ± 1.22	4.66 ± 1.01	0.98 ± 0.77	<.001*
	After glucose load	6.19 ± 1.59	5.39 ± 1.03	0.80 ± 0.95	<.001*
SOD	Fasting	118.53 ± 17.30	146.81 ± 21.02	28.81 ± 15.48	<.001
	After glucose load	99.84 ± 17.09	125.28 ± 16.58	25.44 ± 13.00	.0002

FMEDD: flow-mediated endothelium-dependent dilation; NO: nitric oxide; ET-1: endothelin-1; MDA: malondialdehyde; SOD: superoxide dismutase.
* Using nonparametric analysis method.

OPTIMA Çalışması

Metformine vildagliptin ve sitagliptin eklendikten sonra hipergliseminin seyri



Vildagliptin ile 24 saatlik glisemik kontrol sitagliptinden daha iyidir, bu fark vildagliptin ile gece boyunca daha iyi glisemik kontrol sağlanmasına bağlıdır[1]*

***p<0.05**

Grafikler referanstan uyarlanmıştır. Çalışmada kullanılan dozlar: Vildagliptin 50 mg 2x1 + metformin ≥1500 mg/gün (n=14); Sitagliptin 100 mg 1x1 + metformin ≥1500 mg/gün (n=16). 8 haftalık tedaviden önce ve sonra 72 saatlik subkutanöz olarak sürekli kan şekeri ölçümü uygulanarak günlük glisemi düzeyleri değerlendirilmiştir.

Guerci B et al. Diabetes and Metabolism 2012;38(4):359-66.

Sonuç olarak:

Diyabet, Hiper-Hipoglisemik ataklar ve Mikrovasküler Hastalık ilişkisi, birçok mekanizmanın rol aldığı, karmaşık bir süreçtir.


Kafanız karışmıyorsa, etrafınızda ne olup bittiğini bilmiyorsunuz demektir.
Jack Welch