Vildagliptin; Vasküler olaylar ve glisemik dalgalanma

Prof. Dr. Mustafa Kemal BALCI

Akdeniz Üniversitesi Tıp Fakültesi

Endokrinoloji ve Metabolizma BD

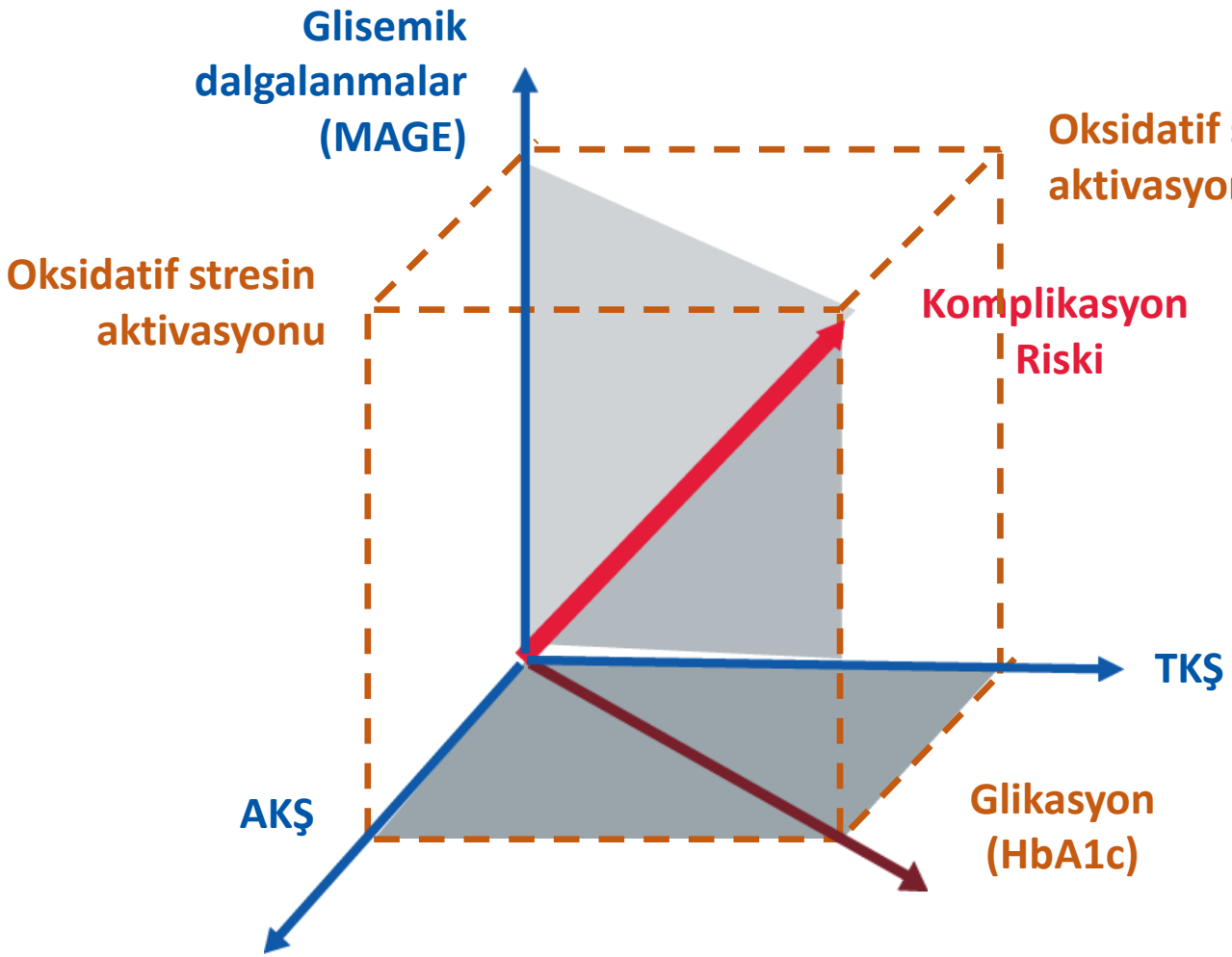
Glisemik Kontrolün Amacı

- Hiperglisemik akut olayları önlemek
- Hiperglisemik kronik olayları önlemek
- Öglisemiyi sağlamak
- Öglisemiyi sağlarken hipoglisemi oluşturmamak
- Glisemik kontrolü sağlarken kronik komplikasyonların gelişimini azaltmak

Diyabette kronik komplikasyonlar

- Makrovasküler olaylar
  - Kardiyak
  - Serebral
  - Periferik
- Mikrovasküler olaylar
  - Nöropati
  - Nefropati
  - Retinopati

Kronik komplikasyonları belirleyen faktörler



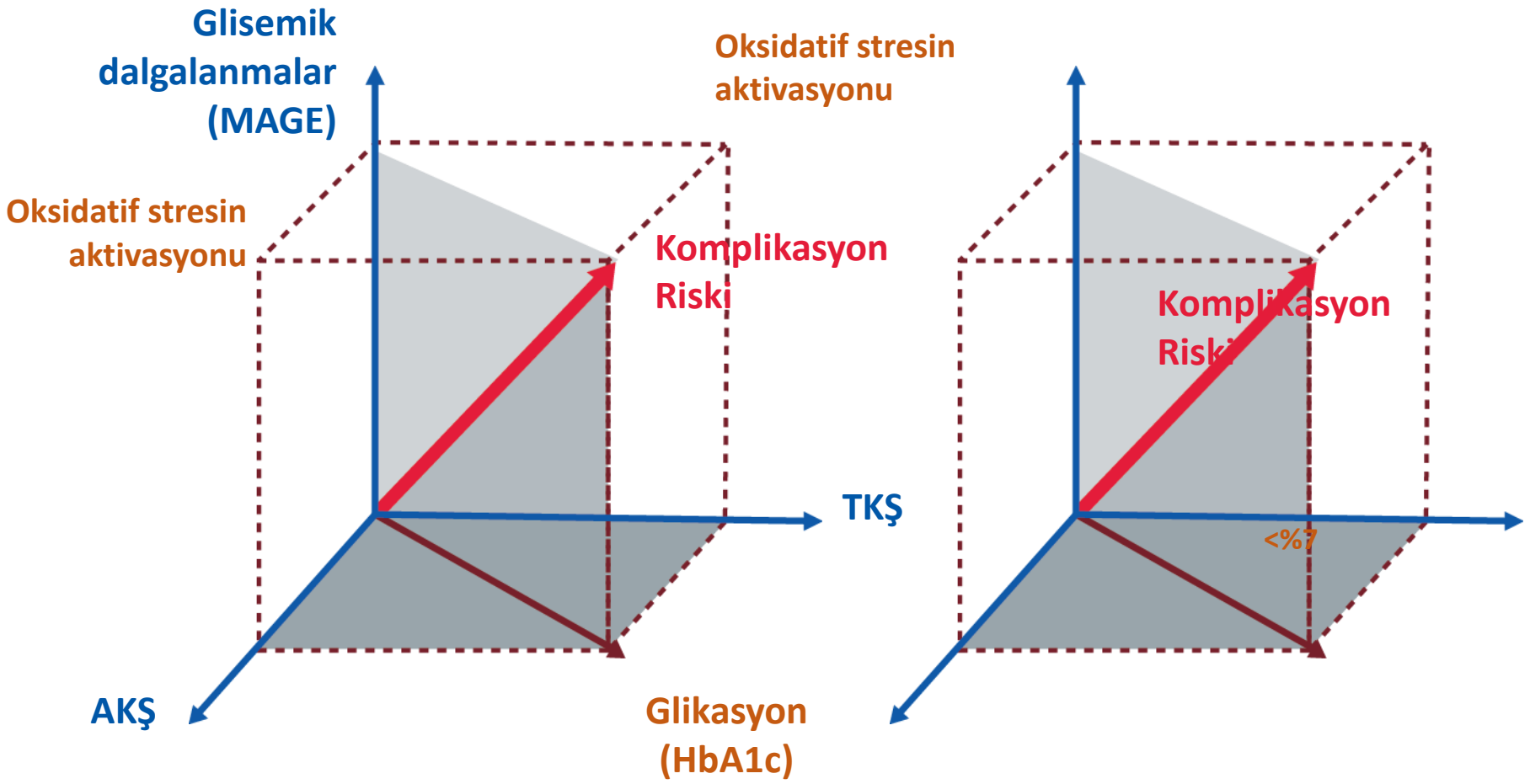
Hiperglisemiye neden olan 3 ana glisemik bozukluk vardır

Hiperglisemi nedeniyle 2 patolojik süreç aktive olur

Sonuç olarak komplikasyon riski artar

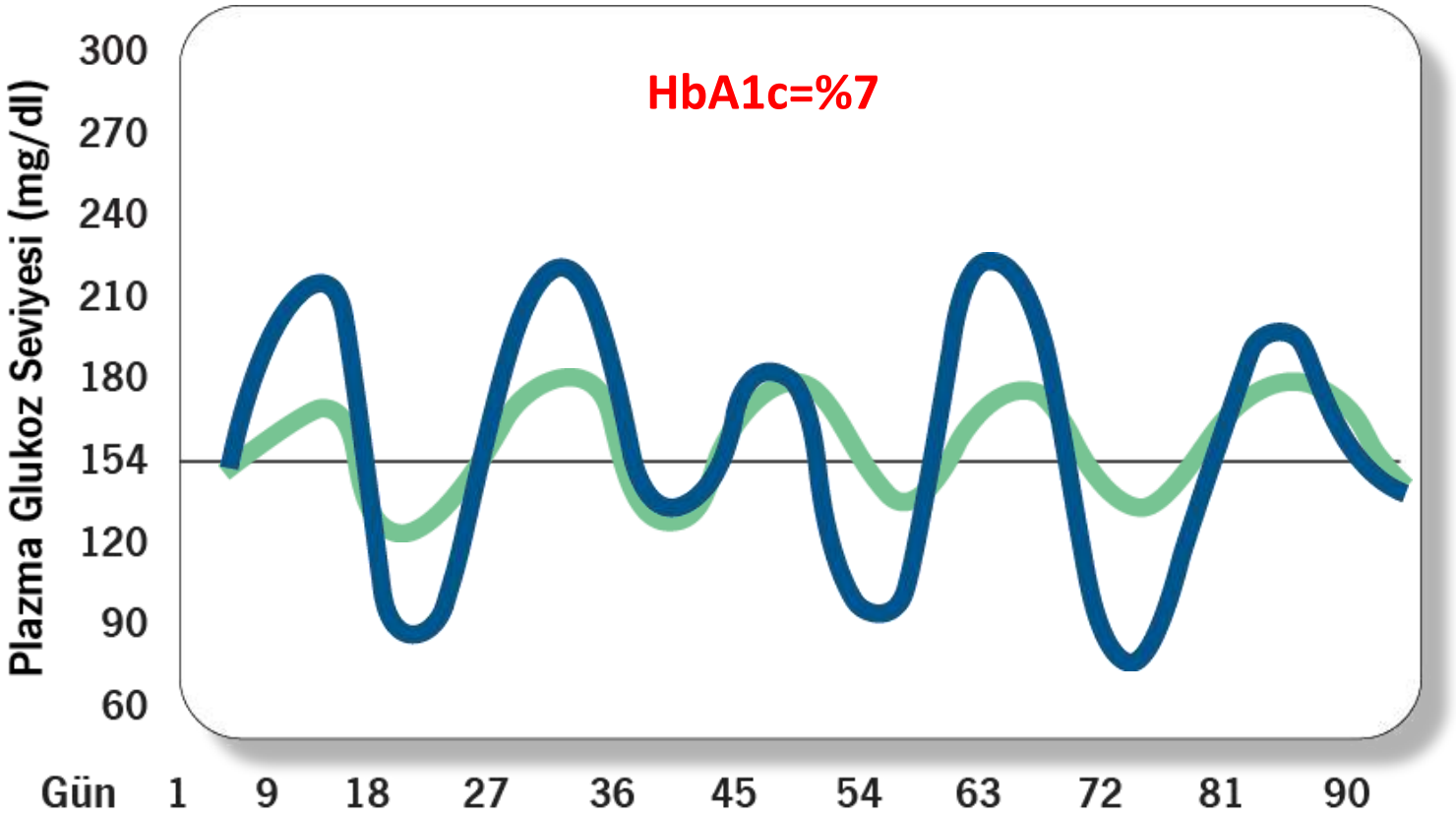
Glisemik dalgalanmalar kan glukoz düzeyinin açlık ve toklukta normal kabul edilen değerlerin üzerinde ve altında seyretmesi olarak tanımlanmaktadır.
MAGE: Glisemik dalgalanmaların ortalama büyüklüğü.
1.Monnier L, Colette C. *Diabetes Care 2008;* 31 (Suppl. 2):S150–S154.

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



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.

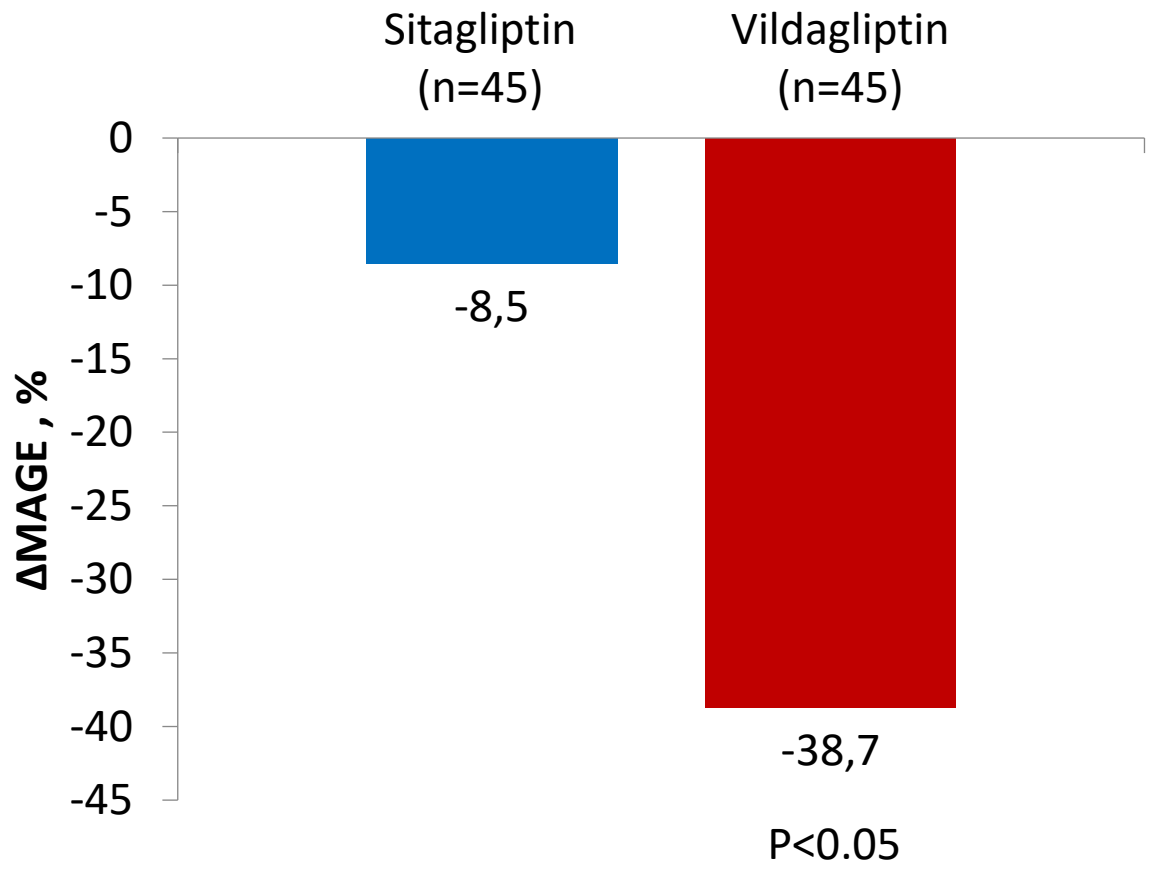
Aynı HbA1c düzeyine sahip 2 hasta farklı glisemik dalgalanma profili gösterebilir



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

Glisemik Dalga ve Vildagliptin

Vildagliptin günlük glisemik dalgalanmaları sitagliptinden daha iyi kontrol eder



3 aylık tedaviden sonra günlük glisemik dalgalanmaların ortalama büyüklüğünde (MAGE) değişim, %

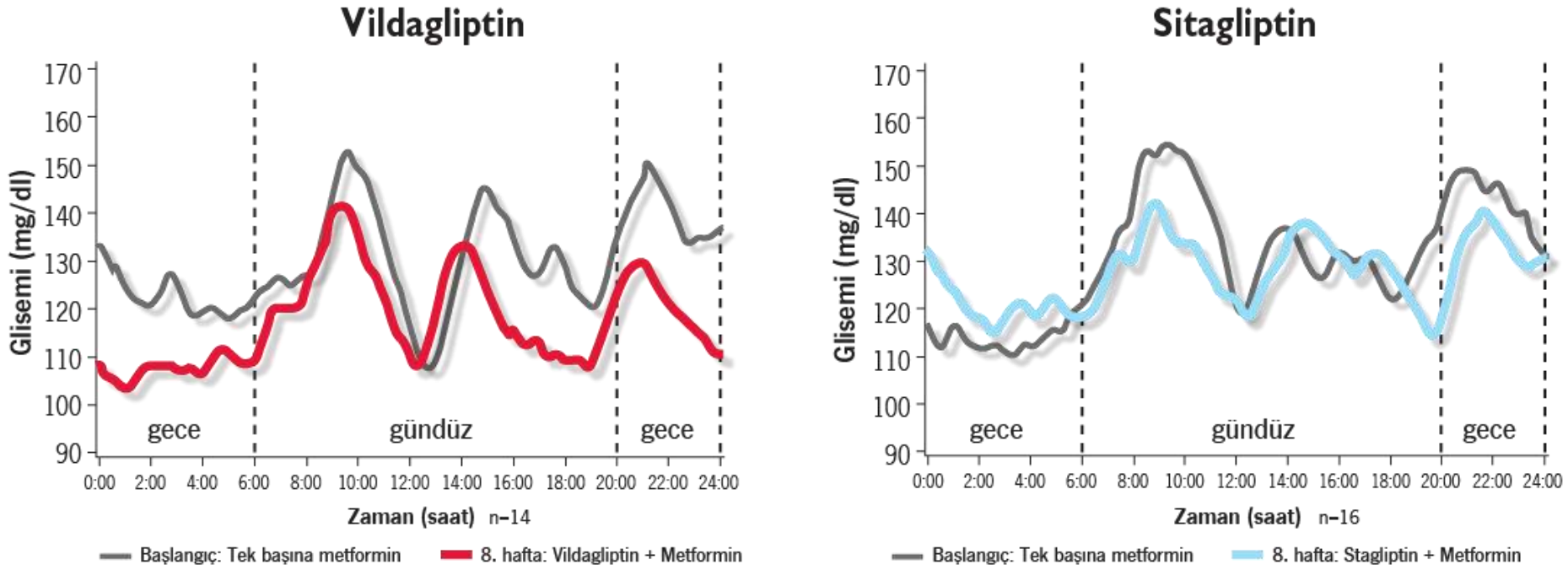
MAGE: (mean amplitude of glycemic excursions)Glisemik dalgalanmaların ortalama büyüklüğü.
başlangıcında ve 3 aylık tedaviden sonra 48 saat süreyle subkutanöz
olarak sürekli kan şekeri ölçümü uygulanarak günlük glisemik dalgalanmalar değerlendirilmiştir.
Çalışma başlangıcı ve sonundaki MAGE değerleri: Sitagliptin 70,8mg/dl / 64,75mg/dl; Vildagliptin 73,9mg/dl / 45,3mg/dl.

MAGE ölçümü için çalışma

1. Rizzo MR et al. Diabetes Care 2012 Oct;35(10):2076-82.

Vildagliptin ile sitagliptine kıyasla daha iyi glisemik kontrol sağlanmıştır (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]*

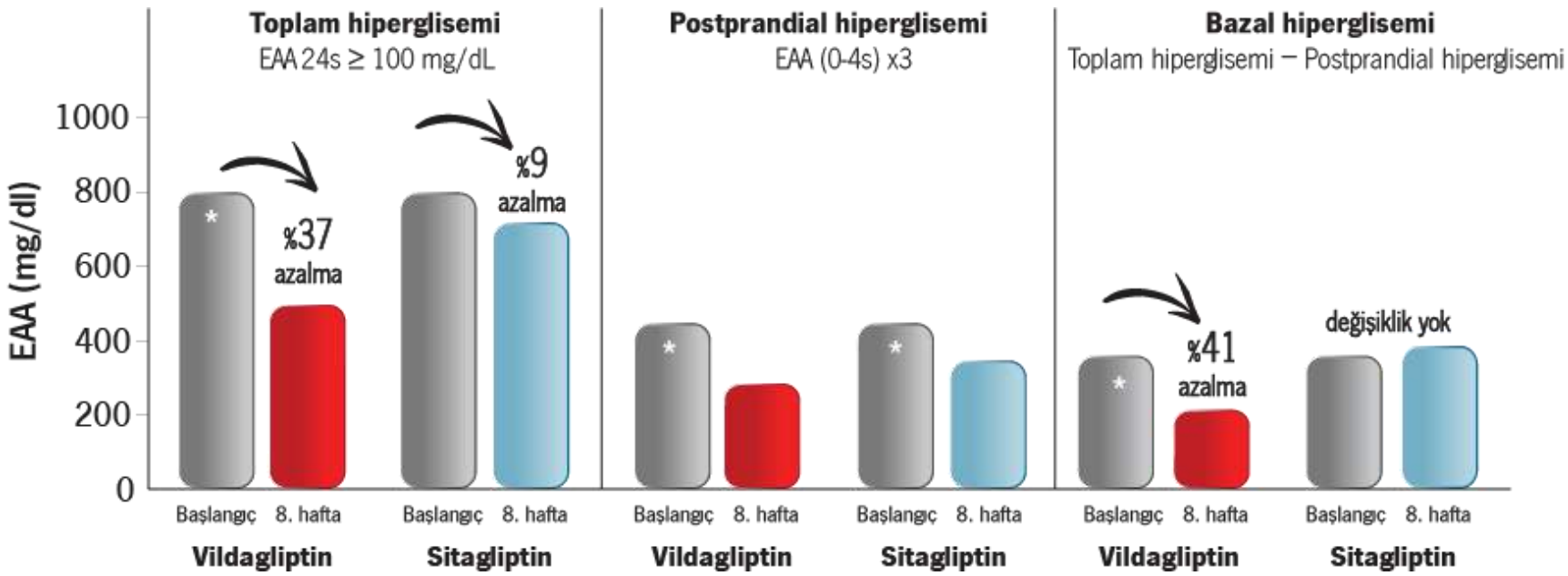
***p<0.05**

Çalışmada kullanılan dozlar: Vildagliptin 50 mg 2x1 +metformin ≥1500 mg/gün(n=14); sitagliptin 100 mg 1x1 + metformin ≥1500 mg/gün (n=16).

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

Vildaglipitin ile 24 saatlik glisemik değişim; Sitagliptine kıyasla anlamlı düşük (Optima çalışması)

8 haftalık tedaviden sonra hiperglisemide başlangıca göre değişim



*p<0.05 başlangıca kıyasla değişim için

EAA: Eğri altında kalan alan. Plazma glukoz konsantrasyonu/zaman eğrisinin altında kalan alanın yüzölçümü.
EAA 24s≥100 mg/dL: 24 saat boyunca kan şekerinin 100 mg/dL'nin üzerinde seyrettiği dönem.
Çalışmada kullanılan dozlar: Vildagliptin50 mg 2x1 +metformin ≥1500 mg/gün(n=14); sitagliptin 100 mg 1x1 + metformin ≥1500 mg/gün (n=16).
1. Guerci B et al. Diabetes and Metabolism 2012;38(4):359-66.

Research Article

Four-Point Preprandial Self-Monitoring of Blood Glucose for the Assessment of Glycemic Control and Variability in Patients with Type 2 Diabetes Treated with Insulin and Vildagliptin

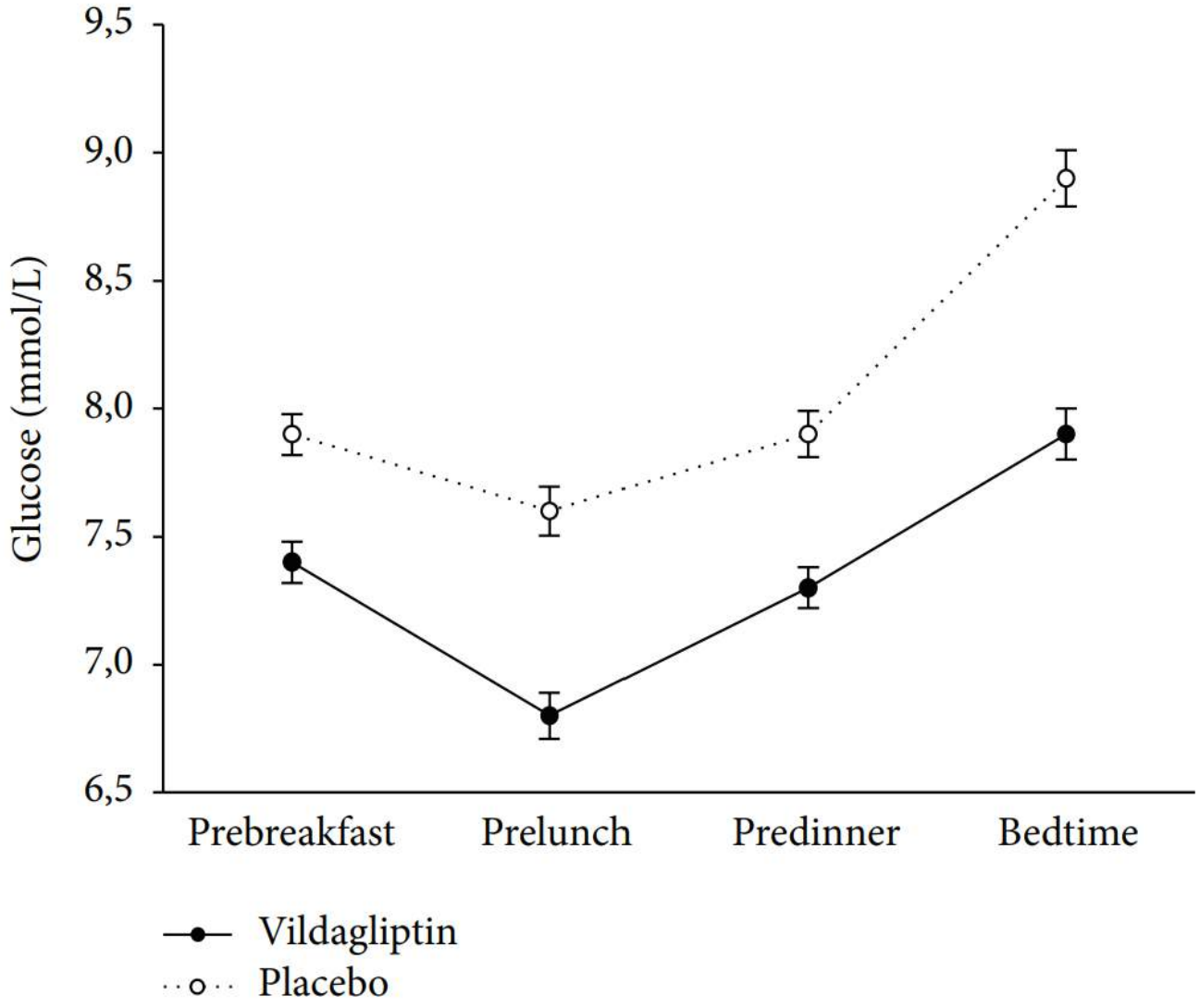
Andrea Tura,[1] Johan Farngren,[2] Anja Schweizer,[3] James E. Foley,[4] Giovanni Pacini,[1] and Bo Ahrén[2]

[1]*CNR Institute of Neuroscience, Corso Stati Uniti 4, 35127 Padova, Italy*
[2]*Department of Clinical Sciences, Lund University, B11 BMC, 22184 Lund, Sweden*
[3]*Novartis Pharma AG, 4002 Basel, Switzerland*
[4]*Novartis Pharmaceuticals Corporation, One Health Plaza, East Hanover, NJ 07936, USA*

Correspondence should be addressed to Andrea Tura; tura@isib.cnr.it

Received 5 May 2015; Revised 2 October 2015; Accepted 5 October 2015

Mean average glucose data before breakfast, before lunch, before dinner, and at bedtime in patients with type 2 diabetes treated with vildagliptin (solid line) or placebo (dotted line) as add-on to insulin in a crossover design (n = 29). Data are mean ± SE.



Indices of glycemic control quality and glycemic variability in patients with type 2 diabetes after placebo and after vildagliptin (data are mean ± SE). For the explanation of the various indices see the Methods section.

	Placebo	Vildagliptin	*P* value
	Indices of glycemic control quality		
Mean (mmol/L)	8.11 ± 0.25	7.36 ± 0.23	<0.0001
Maximum (mmol/L)	16.37 ± 1.80	13.54 ± 0.66	0.007
Minimum (mmol/L)	3.76 ± 0.20	3.66 ± 0.19	0.37
50th percentile (median) (mmol/L)	7.82 ± 0.25	7.13 ± 0.24	0.0001
Percentage below target (3.9 mmol/L) (%)	2.0 ± 0.6	3.1 ± 0.9	0.055
Percentage in target (3.9–11.1 mmol/L) (%)	86.1 ± 2.4	89.8 ± 2.2	0.062
Percentage above target (11.1 mmol/L) (%)	11.9 ± 2.3	7.0 ± 2.0	0.002
GRADE (unitless)	6.61 ± 0.59	5.17 ± 0.52	<0.0001
M-VALUE (unitless)	6.22 ± 1.18	4.97 ± 0.95	0.004
Hypoglycemia index (unitless)	7.67 ± 1.45	5.66 ± 1.07	0.093
Hyperglycemia index (unitless)	1.97 ± 0.20	1.61 ± 0.20	0.002
IGC (unitless)	9.81 ± 1.32	7.32 ± 1.04	0.059
LBGI (unitless)	0.64 ± 0.15	1.03 ± 0.20	0.002
HBGI (unitless)	4.57 ± 0.66	3.12 ± 0.56	<0.0001
ADRR (unitless)	45.0 ± 7.3	35.5 ± 3.8	0.043

Tablo-Devam

	Placebo	Vildagliptin	*P* value
	Indices of glycemic variability		
Standard deviation (mmol/L)	2.27 ± 0.21	2.00 ± 0.17	0.015
Interquartile range (mmol/L)	2.87 ± 0.24	2.68 ± 0.26	0.092
CONGA (mmol/L)	3.12 ± 0.29	2.71 ± 0.22	0.011
J-INDEX (10^{-3} $(mmol/L)^2$)	0.12 ± 0.01	0.09 ± 0.01	<0.0001
MAGE (mmol/L)	4.80 ± 0.48	4.16 ± 0.33	0.010
MAGE (pos.) (mmol/L)	4.82 ± 0.48	4.20 ± 0.32	0.020
MAGE (neg.) (mmol/L)	4.77 ± 0.47	4.13 ± 0.35	0.007

Randomized Study Comparing Vildagliptin vs Glibenclamide on Glucose Variability and Endothelial Function in Patients with Type 2 Diabetes Mellitus and Hypertension

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2020:13

Luciana Neves CosensoMartin Lais Yumi Takaoka Jose Fernando Vilela-Martin Internal Medicine Division, State Medical School at Sao Jose do Rio Preto (FAMERP), Hospital de Base, Sao Jose do Rio Preto, Sao Paulo, Brazil

Proportion of Patients with Mean Blood Glucose Below (MBG)

	After 12 Weeks of Treatment		*P*-value
	MBG <150	**MBG ≥150**	
Baseline MBG <150 mg/dL MBG ≥150 mg/dL	 14 10	 2 18	 0.039

Note: McNemar's test.

Glycemic Variability Evaluated by Median of Standard Deviation (SD) of Mean Blood Glucose Between Baseline and After 12 Weeks, Separated by Drug Groups

	SD	*P*-value
Vildagliptin group		
Baseline	35.2 (13.9–59.7)	0.037
After 12 weeks	30.7 (16.1–64.3)	
Glibenclamide group		
Baseline	37.6 (16.0–54.9)	0.765
After 12 weeks	37.5 (16.5–80.03)	

Note: Wilcoxon test.

Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study C. R. L. Cardoso1 , N. C. Leite1 , C. B. M. Moram2 and G. F. Salles1*

Cardoso et al. Cardiovasc Diabetol (2018) 17:33
https://doi.org/10.1186/s12933-018-0677-0

9 yıllık izlem

Sonuç; 24 .ayda Glisemik değişkenlik; HbA1c lerin ortalaması, AKŞ lerin ortalaması,

- Kardiyovasküler olay gelişiminde etkili
- Retinopatide kötüleşmede etkili
- Renal etkilenme oranında etkili
- Periferal nöropatide kötüleşmede etkili
- Retinopati gelişiminde etki yok,
- Periferal nöropati gelişmesi ve kötüleşmesinde etki yok

Diabetes Ther. 2017 Oct; 8(5): 1111–1122.
Published online 2017 Sep 18. doi: 10.1007/s13300-017-0303-2
PMCID: PMC5630558
PMID: 28921310

Effects of Vildagliptin Add-on Insulin Therapy on Nocturnal Glycemic Variations in Uncontrolled Type 2 Diabetes

Feng-fei Li,[#1] Yun Shen,[#1] Rui Sun,[#1] Dan-feng Zhang,[#1] Xing Jin,[1] Xiao-fang Zhai,[1] Mao-yuan Chen,[1] Xiao-fei Su,[1] Jin-dan Wu,[1] Lei Ye,[2] and Jian-hua Ma[1]

Diabetes Care. 2011 Sep; 34(9): 2072–2077.
Published online 2011 Aug 19. doi: 10.2337/dc10-2421
PMCID: PMC3161271
PMID: 21788633

Vildagliptin Improves Endothelium-Dependent Vasodilatation in Type 2 Diabetes

Pleun C.M. van Poppel, MD,[1] Mihai G. Netea, MD, PHD,[1,2] Paul Smits, MD, PHD,[3] and Cees J. Tack, MD, PHD[1]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Vildagliptin ve vasküler mikro etki

Drug Des Devel Ther. 2014; 8: 239–243.
Published online 2014 Feb 14. doi: 10.2147/DDDT.S52545
PMCID: PMC3931658
PMID: 24627624

Effect of vildagliptin add-on treatment to metformin on plasma asymmetric dimethylarginine in type 2 diabetes mellitus patients

Mustafa Cakirca,[1] Cumali Karatoprak,[1] Mehmet Zorlu,[1] Muharrem Kiskac,[1] Mustafa Kanat,[2] Mehmet Ali Cikrikcioglu,[1] Pinar Soysal,[3] Mehmet Hursitoglu,[4] Ahmet Adil Camli,[1] Reha Erkoc,[1] and Muhammad Abdul-Ghani[5]

Comparison of serum ADMA, CRP, and fibrinogen levels in vildagliptin user and nonuser groups

	Metformin (n=35)	Met-vildagliptin (n=33)	*P*-value
	Mean ± SD	Mean ± SD	
ADMA (μmol/L)	0.90±0.21	0.67±0.22	<0.001
CRP (mg/L)	3.6±5.7	4.1±4.8	0.34
Fibrinogen (mg/dL)	348.5±93.2	373.2±73.7	0.23

Note: Fibrinogen 100–500 mg/dL.

Abbreviations: SD, standard deviation; ADMA, asymmetric dimethylarginine (0.26–0.64 μmol/L); CRP, C-reactive protein (<5 mg/L); Met-vildagliptin, metformin + vildagliptin.

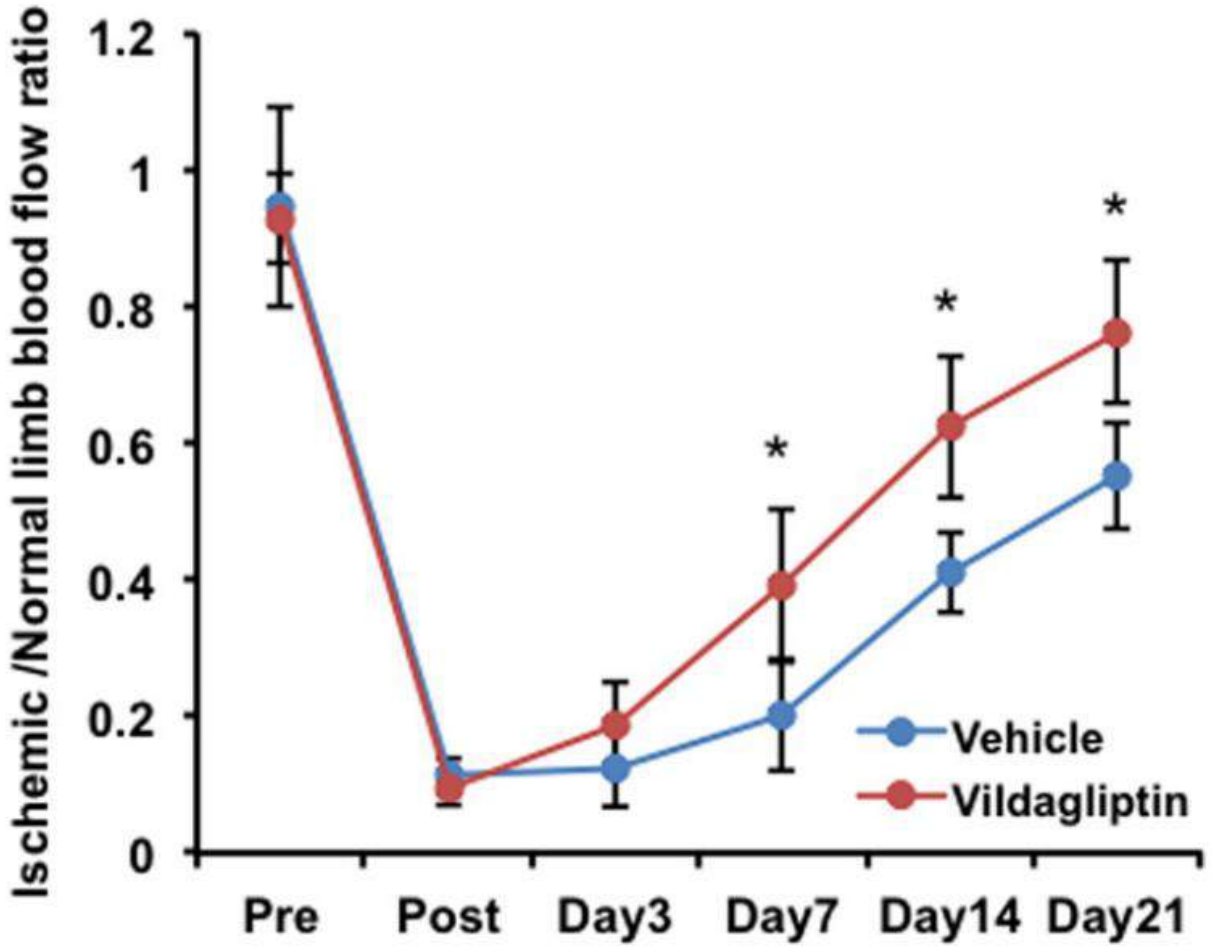
THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 289, NO. 39, pp. 27235–27245, September 26, 2014

Vildagliptin Stimulates Endothelial Cell Network Formation and Ischemia-induced Revascularization via an Endothelial Nitric-oxide Synthase-dependent Mechanism*

Received for publication, February 13, 2014, and in revised form, July 23, 2014 Published, JBC Papers in Press, August 6, 2014, DOI 10.1074/jbc.M114.557835

Masakazu Ishii[‡§], Rei Shibata[‡1], Kazuhisa Kondo[‡], Takahiro Kambara[‡], Yuuki Shimizu[‡], Tohru Tanigawa[¶], Yasuko K. Bando[‡], Masahiro Nishimura[§], Noriyuki Ouchi[‖], and Toyoaki Murohara[‡2]

Vildagliptin promotes revascularization following hindlimb ischemia in mice



International Journal of Nanomedicine 2019:14 7503–7513

International Journal of Nanomedicine

Dovepress

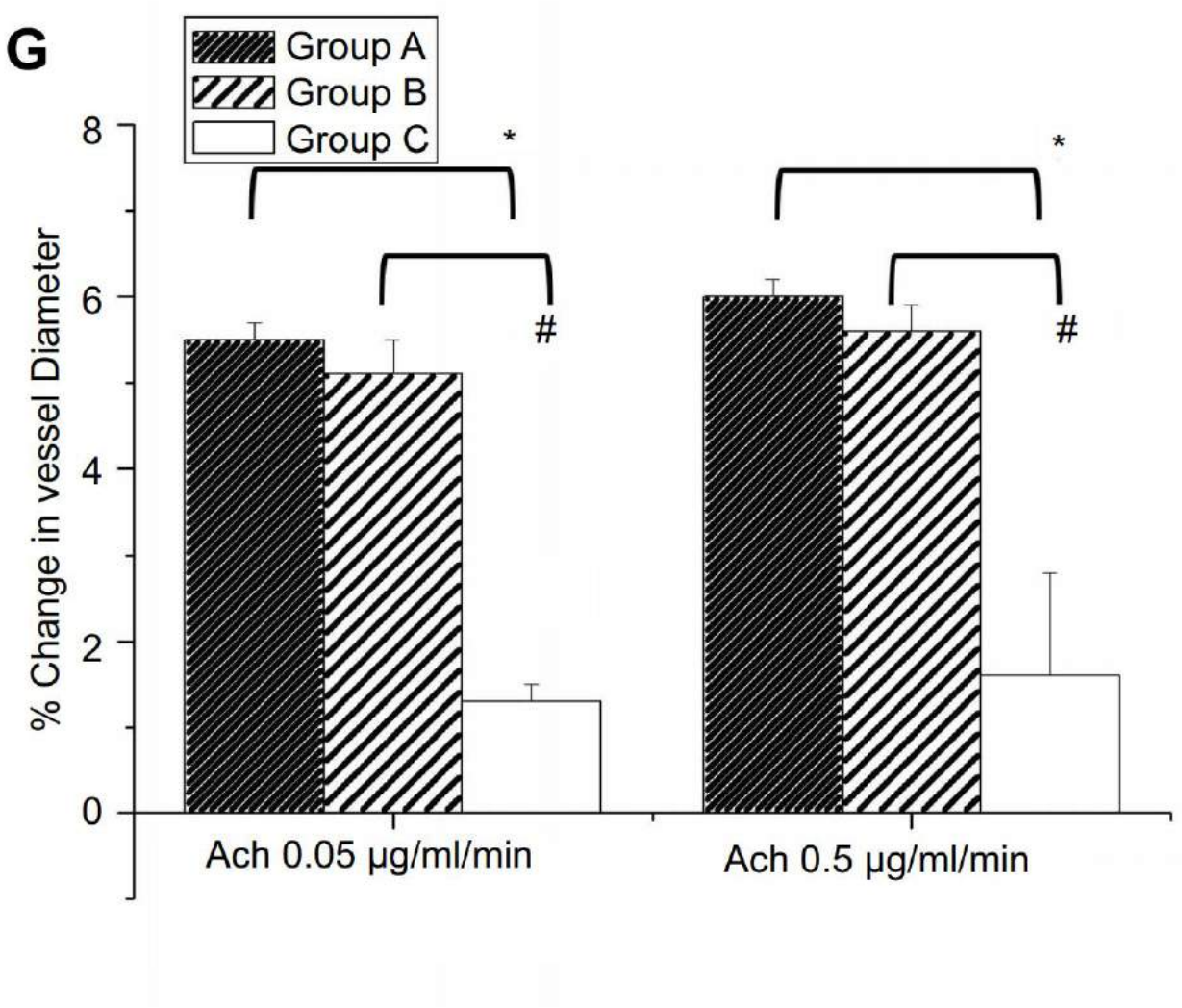
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Nanofibrous vildagliptin-eluting stents enhance re-endothelialization and reduce neointimal formation in diabetes: in vitro and in vivo

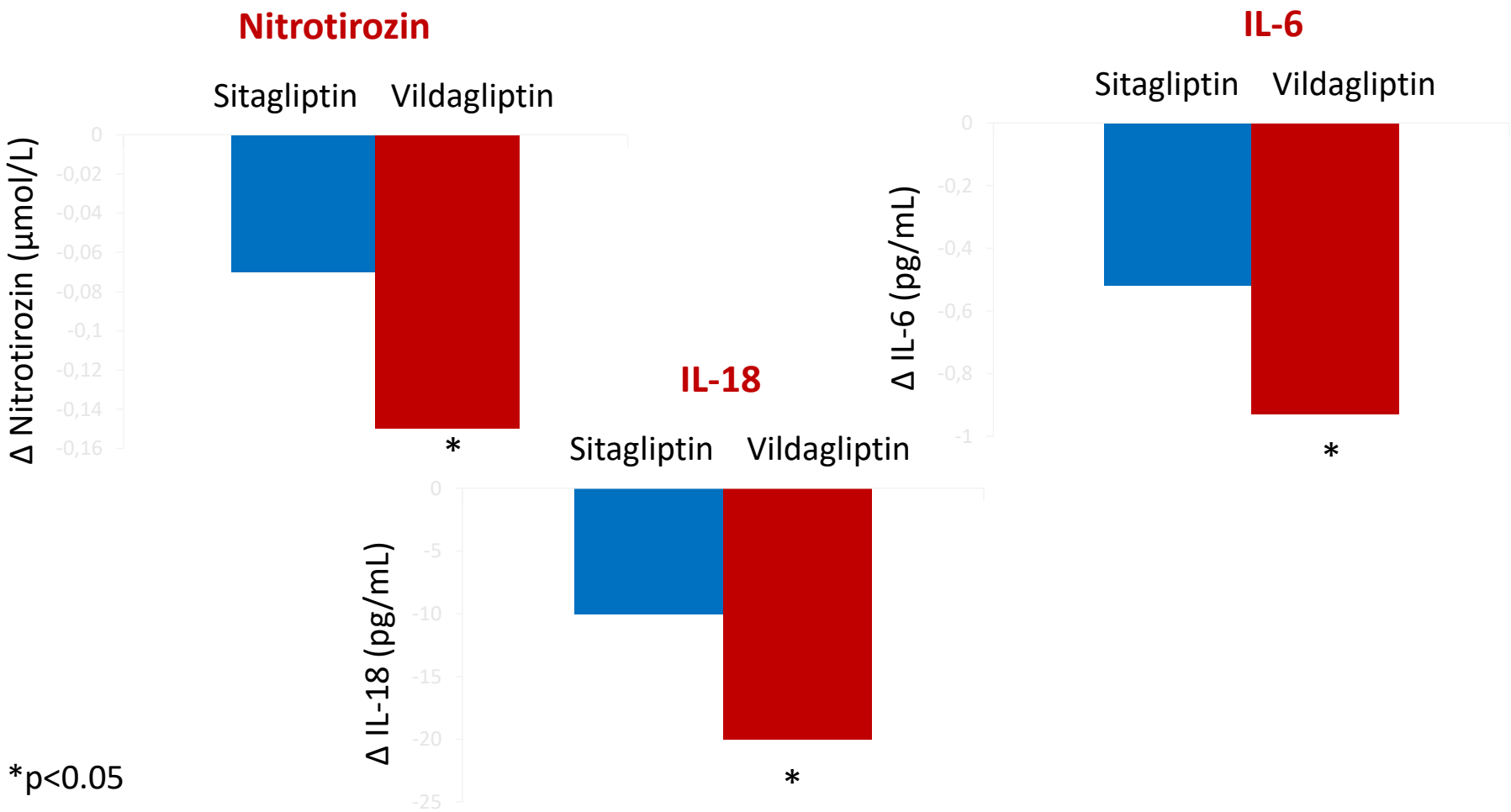
Significantly greater responses in vildagliptin-eluting stent than that in non-drug-eluting stent were observed according to endothelial-dependent vasodilatory reaction to Ach.



* p <0.05
# p<0.05

Vildagliptin oksidatif stres belirteçlerini sitagliptinden daha fazla azaltmıştır

3 aylık tedaviden sonra oksidatif stres belirteçlerinde başlangıca göre değişim



1. Rizzo MR et al. Diabetes Care 2012 Oct;35(10):2076-82.

International Journal of
Molecular Sciences

Review

Vasculoprotective Effects of Vildagliptin. Focus on Atherogenesis

Michał Wiciński [1], Karol Górski [1,*], Eryk Wódkiewicz [1], Maciej Walczak [1], Magdalena Nowaczewska [2] and Bartosz Malinowski [1]

[1] Department of Pharmacology and Therapeutics, Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, M. Curie 9, 85-090 Bydgoszcz, Poland; wicinski4@wp.pl (M.W.); eryk.wodkiewicz09@gmail.com (E.W.); maciej.walczak5@hotmail.com (M.W.); bartosz.malinowski@cm.umk.pl (B.M.)

[2] Department of Otolaryngology, Head and Neck Surgery, and Laryngological Oncology, Faculty of Medicine, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, M. Curie 9, 85-090 Bydgoszcz, Poland; magy_mat@by.onet.pl

* Correspondence: karolgorski-2@gazeta.pl

Received: 17 February 2020; Accepted: 23 March 2020; Published: 25 March 2020

Table 1. Summary of reviewed results.

Authors	Subject of Study	Dose of Vildagliptin	Results
Lee et al. (2016) [13]	LPS stimulated RAW264.7 cells	varied at every stage of the experiment	↓iNOS, ↓ NF-κB, ↓pJNK, ↓TLR-2, ↓TLR-4,
Dei et al. (2017) [14]	rBMVECs	2.5–5 mg/day for 4–12 months	↓ SDF-1α ↓ EPC
Zhang et al. (2018) [15]	HAECs	5 and 10 μM for 24–72 h.	↓ LDH, ↓ ROS, ↓TNF-α, ↓IL-8, ↓ICAM-1, ↓MCP-1, ↓TLR-4, ↓NF-κB
Qi et al. (2019) [16]	HUVECs	2.5 and 5 μM for 24h	↓ LDH, ↓ NAPHD, ↓AMPK, ↓IL-1β, ↓IL-18,
Liu et al. (2019) [17]	HUVECs and diabet mice		
Seo al. (2019) [18]	rabbit aortic rings		
Oeseburg et al. (2010) [19]	HUVECs and diabet fatty rats		
Terasaki et al. (2012 and 2013) [20,21]	Diabetic Apoe (–/–) m		
Khan et al. (2015) [22]	STZ-induced diabeti rats	10 or 20 mg/kg/day for 3 weeks	↓TNF-α, ↑aPTT, ↑NO
Jain et al. (2015) [23]	diabetic rats	varied at every stage of the experiment	↑NO, ↑EDR, ↓ROS, ↓MPO, ↑GSH
Koyama et al. (2016) [24]	rabbits	10 mg/kg/day for 5 weeks	↑eNOS, ↑VGIH
Zhang et al. (2018) [25]	diabetic rats	10 or 20 mg/kg/day for 12 weeks	↓ TCL, ↓ ED, ↓Angptl3, ↓Bhmt,↓ Pon1
Ji et al. (2019) [26]	diabetic mice	35 mg/kg/day for 4 weeks	↓ ERS, ↓ NF-κB,
van Poppel et al. (2011) [27]	DM2 patients	50 mg /day for 4 weeks	↑EDR
Noguchi et al. (2015) [28]	normoglycemic patients	50 mg once	↓ TGL, ↓EDs
Tani et al. (2015) [29]	DM2 patients	50 mg/day for 8 weeks	↓ PAI-1
Evans et al. (2016) [30]	DM2 patients	50 mg once or twice/day for 24 weeks	↓SBP, ↓ DBP, ↓TGL, ↓VLDL,↓LDL, ↑HDL
Duvnjak et al. (2016) [31]	DM2 patients	100 mg/day for 12 weeks	↓TLC,↓LDL, ↓hsCRP, ↓AS, ↓CBP
Park et al. (2017) [32]	DM2 patients	1 mg/twice a day for 12 weeks	↓SDF-1α
Younis et al. (2017) [33]	patients with DM2 and CAD	Metformin + vildagliptin 25 or 50 mg/day	↓ IL-1β, ↓hsCRP
El-Naggar et al. (2019) [34]	DM2 patients with hypertension	50 mg/twice a day + 25 mg/day captopril for 24 weeks	↓BP,↓VEGF

Note: ↓ = reduction, ↑ = increase, p- = phosphorylation, LPS = Lipopolysaccharides, iNOS = inducible nitric oxide synthase, NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells, JNK = c-Jun N-terminal kinase, TLR2 = Toll-like receptor 2, TLR4 = Toll-like receptor 4, rBMVECs = rat brain microvascular endothelial cells, ECs = Human aortic endothelial tumor necrosis factor α, IL-8 = emoattractant protein-1, HUVECs nucleotide phosphate, AMPK = , eNOS = endothelial nitric oxide = adenosine triphosphate, Drp1 = e monophosphate, PKA = protein ase 1, MFCF = macrophages foam erides, CRP = C-reactive protein, ial-dependent relaxation, MPO = tion, Angptl3 = Angiopoietin-like = endoplasmic reticulum stress, DM2 diabetes mellitus type 2, EDS = endothelial dysfunction, PAI-1 = plasminogen activator inhibitor-1, SBP = systolic blood pressure, DBP = diastolic blood pressure, VLDL = very low density lipoprotein, LDL = low density lipoprotein, HDL = high density lipoprotein, hs CRP = high specific C-reactive protein, AS = arterial stiffness, CBP = central blood pressure, SDF-1α = stromal cell-derived factor 1, CAD = coronary artery disease, VEGF = vascular endothelial growth factor.

İnflamasyonun azalması
Lipidler üzerinden aterosklerozu azaltıcı etki
Arteriyel sertlik azalması
Endotel bağımlı vazodilatasyon artışı

Sonuç

- Glisemik değişkenlik diyabette vasküler sistemde olumsuz etki yapmaktadır,
- Vildagliptin glisemik değişkenliği kontrol etmektedir,
- Vasküler sistemde endotel ve düz kas fonksiyonlarını düzeltici etki vasküler sorunların gelişimini önler
- Vildagliptin endotel ve düz kas fonksiyonlarında olumlu etki gösterir.