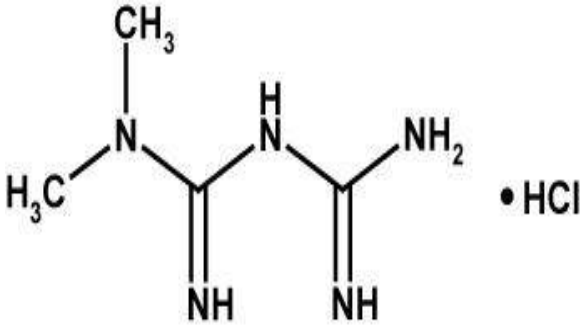
Galega Officinalis, Goat's rue, French Lilac, Italian Fitch, professor -weed

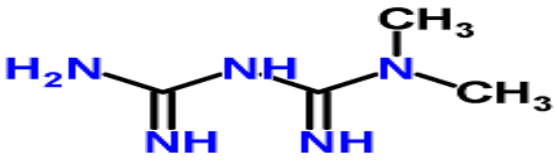
Metformin: Etkinlik, Güvenlik

Prof. Dr. İlhan Yetkin

Gazi Üniversitesi Tıp Fakültesi Endokrinoloji ve Metabolizma Bilim Dalı



Metformin Hydrochloride



Metformin

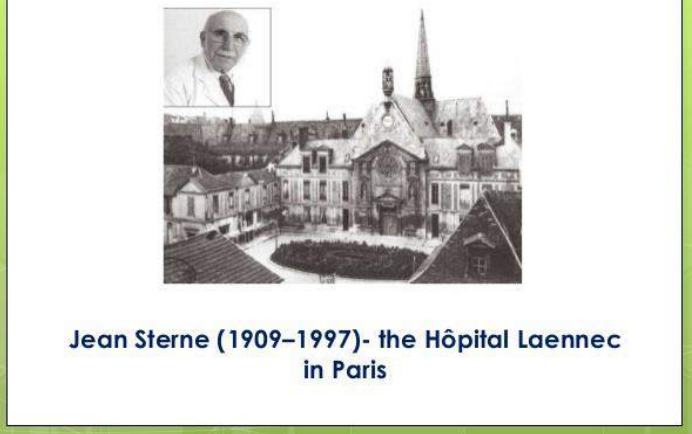
Molecular formula: C4H11N5

Average mass: 129.164 Da

Chemical name: N,N-Dimethylimidodicarbonimidic diamide

Biguanidler: Metformin

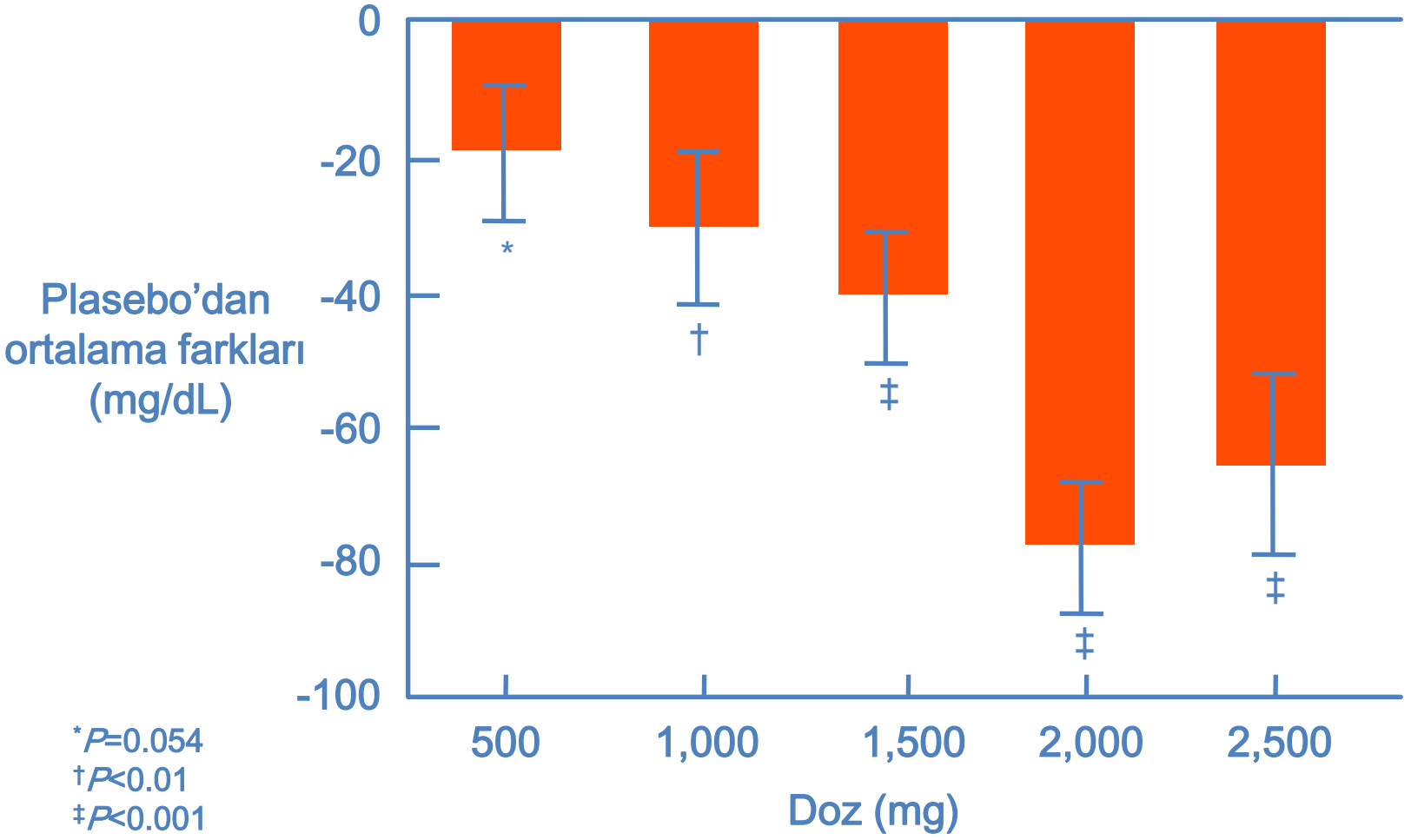
- Biguanidler ilk 1922 yılında Emil Werner ve James Bell tarafından «Galega Biguanialis» «Galega Officinalis» keşfedilmiş
- Bu grupta: **Metformin,** Buformin, Fenformin,
- Metformin FEN ve BUFORMİN'den «daha az lipofilik»tir.
- Metformini «Jean Sterne» geliştirdi.
- 1957 yılında Glukoz yiyen: **«Glucophage»** kullanıma girdi



Metforminin Farmakokinetik Özellikleri

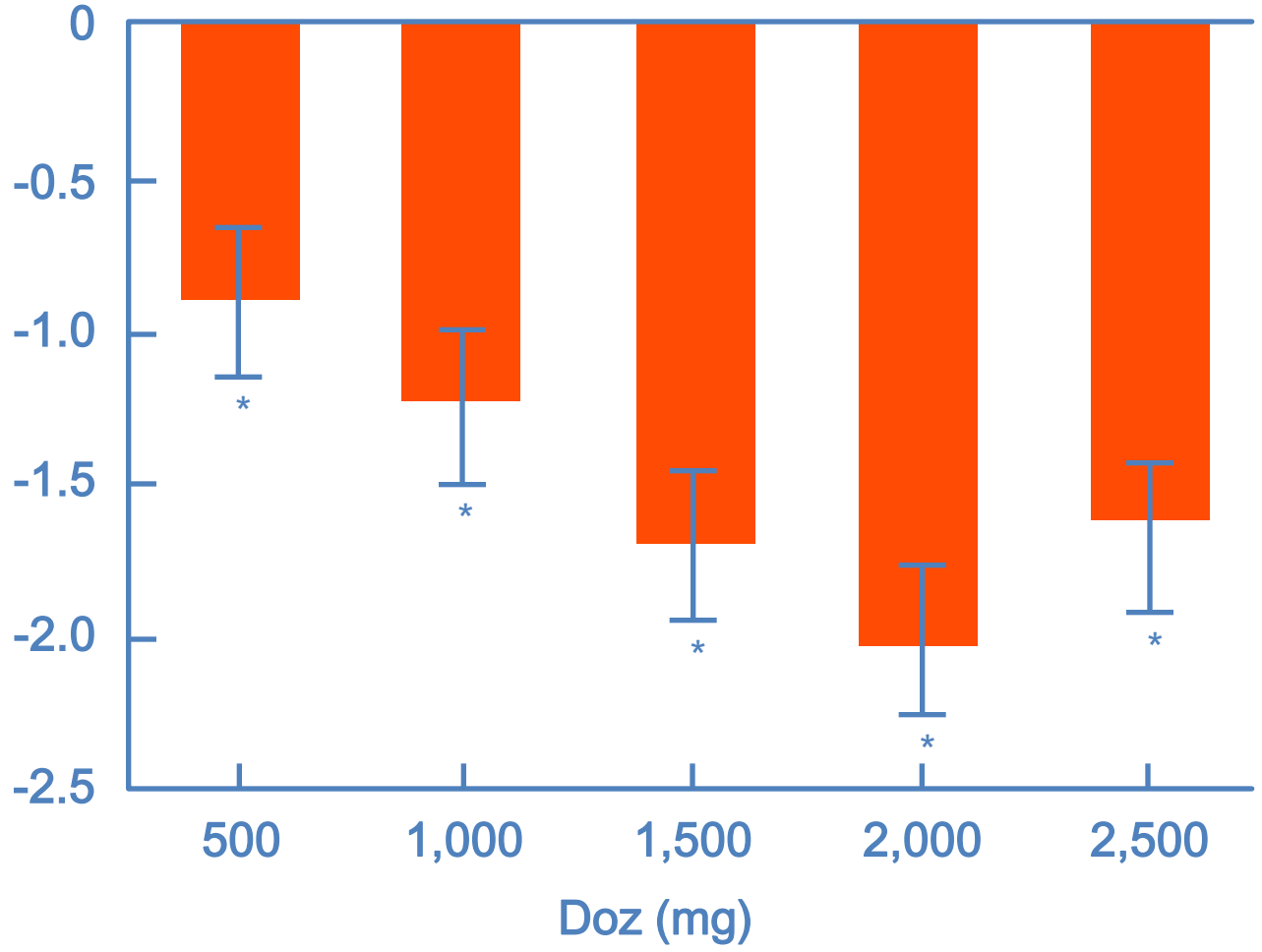
- **Emilim ve Biyo-yararlılık:**
  - **Pik etki:** 2 s
  - **Yarı ömrü:** 2-5 s
  - **Yarılanma süresi:** Plazmada 6 s,
  - **Dolaşımda süresi:** 17 s
- **Doz:** 500 mg/gün başlanır, sonra 10-15 gün aralıklı 500 mg dozlarında artırılır. Gıdalar emilimi az etkiler.
- **Dağılım:** MET plazma proteinlerine çok zayıf bağlanır.
  - Plazma düzeyi 5 mcg/mL düzeyini aşmamalıdır.
- **Metabolizma ve Eliminasyon:**
  - MET idrarla tubuler sekresyonla, değişmeden atılır.
  - KC'in etkisi yok.

Tip 2 DM'de Metformin farklı dozlarının AKŞ üzerine etkileri



Garber AJ et al. *Am J Med.* 1997;103:491-497.

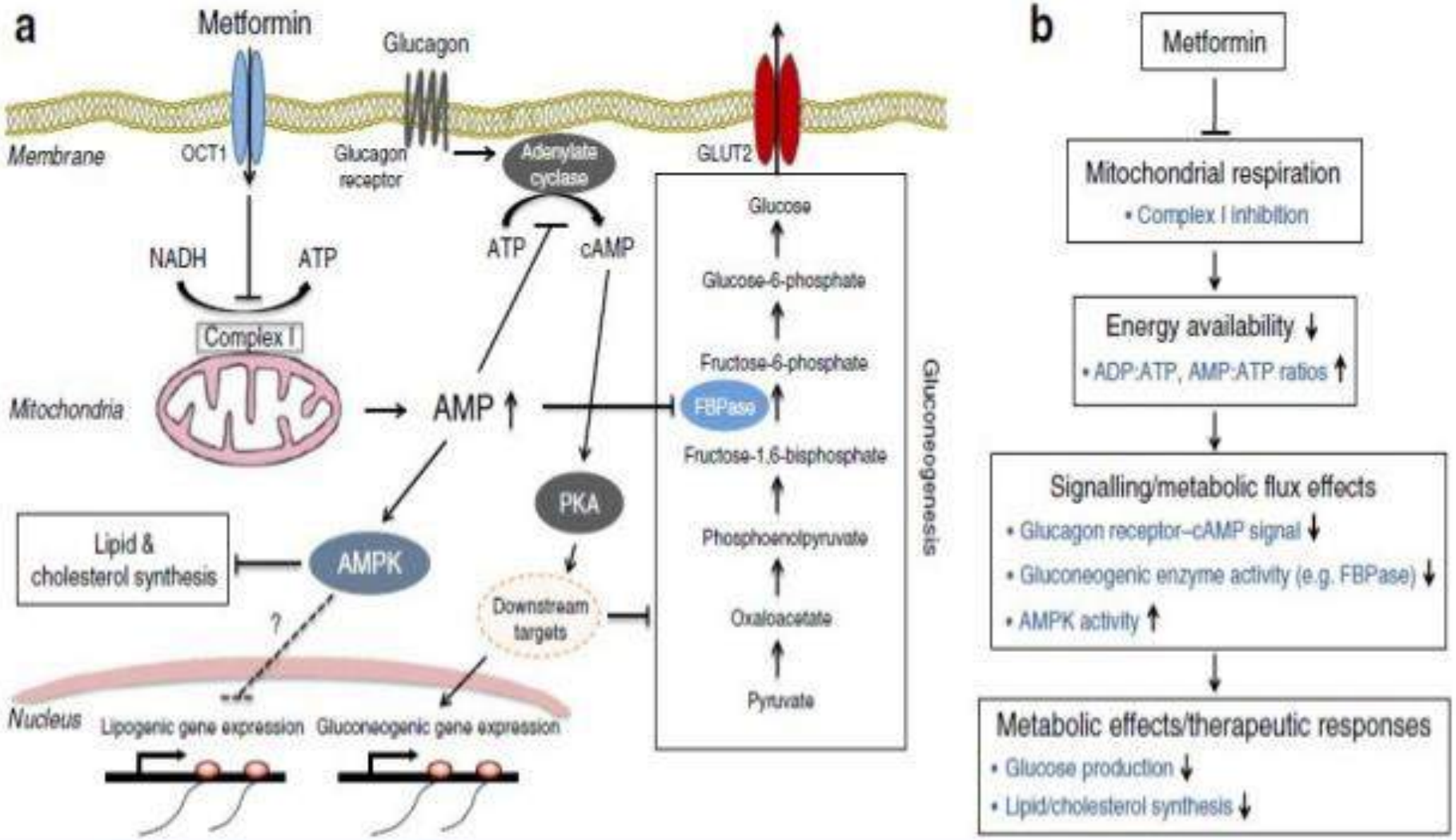
Tip 2 DM'de Metformin dozlarının HbA1c üzerine etkileri



*P<0.001

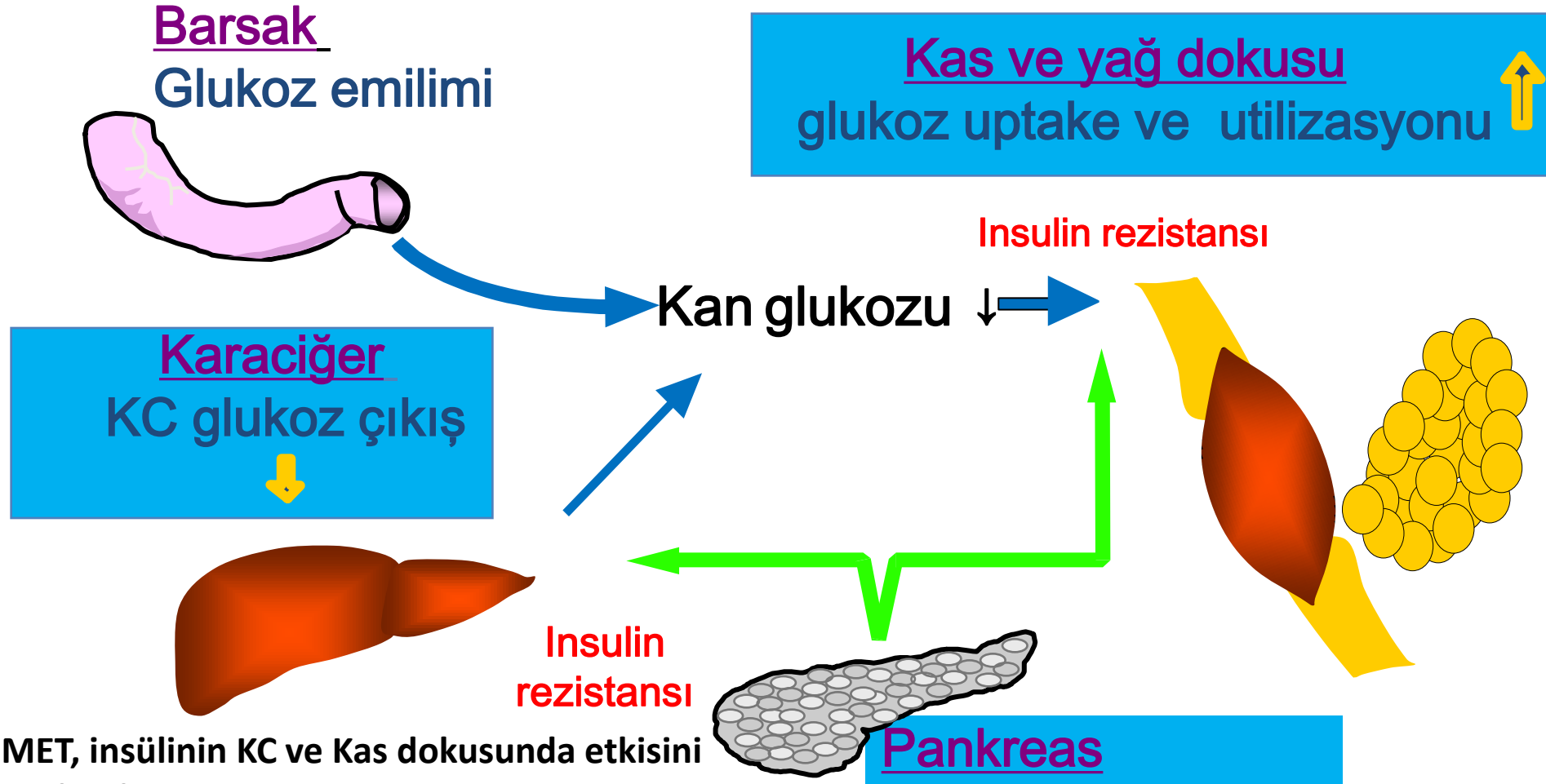
Garber AJ et al. *Am J Med.* 1997;103:491-497.

Metforminin, Moleküler Etki Mekanizmaları



Metformin

Etki mekanizması



MET, insülinin KC ve Kas dokusunda etkisini güçlendirir.

Hostalek U1Therapeutic Use of Metformin in Prediabetes and Diabetes Prevention. Drugs. 2015 Jul;75(10):1071-94.

DeFronzo RA et al. *J Clin Endocrinol Metab.* 1991;73:1294-1301.

Metformin Etkileri

1. KC'de direkt ve indirekt glikoneogenezisi inhibe eder:

   Hepatik glukoz üretimi azalır.

2. Kas dokusunda;

   İnsülin duyarlı glukoz utilizasyonu %20-53 düzeltir

3. İnsülin reseptör:

   Kinaz aktivitesini ve GLUT-4'ü artırır !!!.

4. Postreseptör düzeyde insulin dirençini ↓

5. Barsaktan glukoz emilimini ↓

6. Kilo kaybı daha çok viseral adipoz dokuda.

Tip 2 DM'da Metforminin Olumlu Etkileri

Metformin & Beta Cell Preservation

While insulin resistance lays the foundation for glucose intolerance, the progression to type 2 diabetes does not occur until a degree of beta cell dysfunction has taken place, allowing blood glucose (BG) levels to rise

Class/agent	*↓ BG (Glucose toxicity)*	*↓ FFA (Lipotoxicity)*	*Rests beta cell?*
Sulfonylureas	++	+?	– –
Metformin	++	++	++
Meglitinides	++	+?	–
Acarbose	+	–	+
TZDs	++	++	++
Insulin	++(+)	+	++

Glucose Toxicity and Lipotoxicity are implicated in Beta Cell Dysfunction

CANADIAN JOURNAL OF DIABETES 2003;27(3):277-286

Metforminin Etkileri

Etki	Etki Detayları
Anti-obezite etkileri	• İştah azalması • GLP-1 salınımında artma
Anti-hiperglisemik etkiler	• Kh emiliminde azalma • Hepatik glukoneogenezde inhibisyon • İskelet Kaslarında GLUT-4 aktivitesinde artış ve insülinle uyarılmış glukoz transportunda güçlenme
Anti-lipemik etki	• Adipoz dokuda lipolizin inhibisyonu
Anti-diabetik koruma etkileri	• Gloko ve Lipotoksisiteden beta-hücrelerinin korunması
Hapatoprotektif etkiler	• Hepatik insülin rezistansında azalma ve lipemi düzeyinde düzelme
Kardipoprotektif etkiler	• Toplu etki kilo kaybı ve daha iyi lipid profili sağlar
İskelet kasında insülinle uyarılan glukoz transportunu şiddetlendirir:	GLUT-4 aktivitesini artırır

Başlangıçta Glisemi Üzerine Etkili İlaçın Seçimi

Başlangıç A1C <8.5%

«Metformin başla»

VEYA

Başlangıçtan 2-3 ay sonra yeniden değerlendirilir

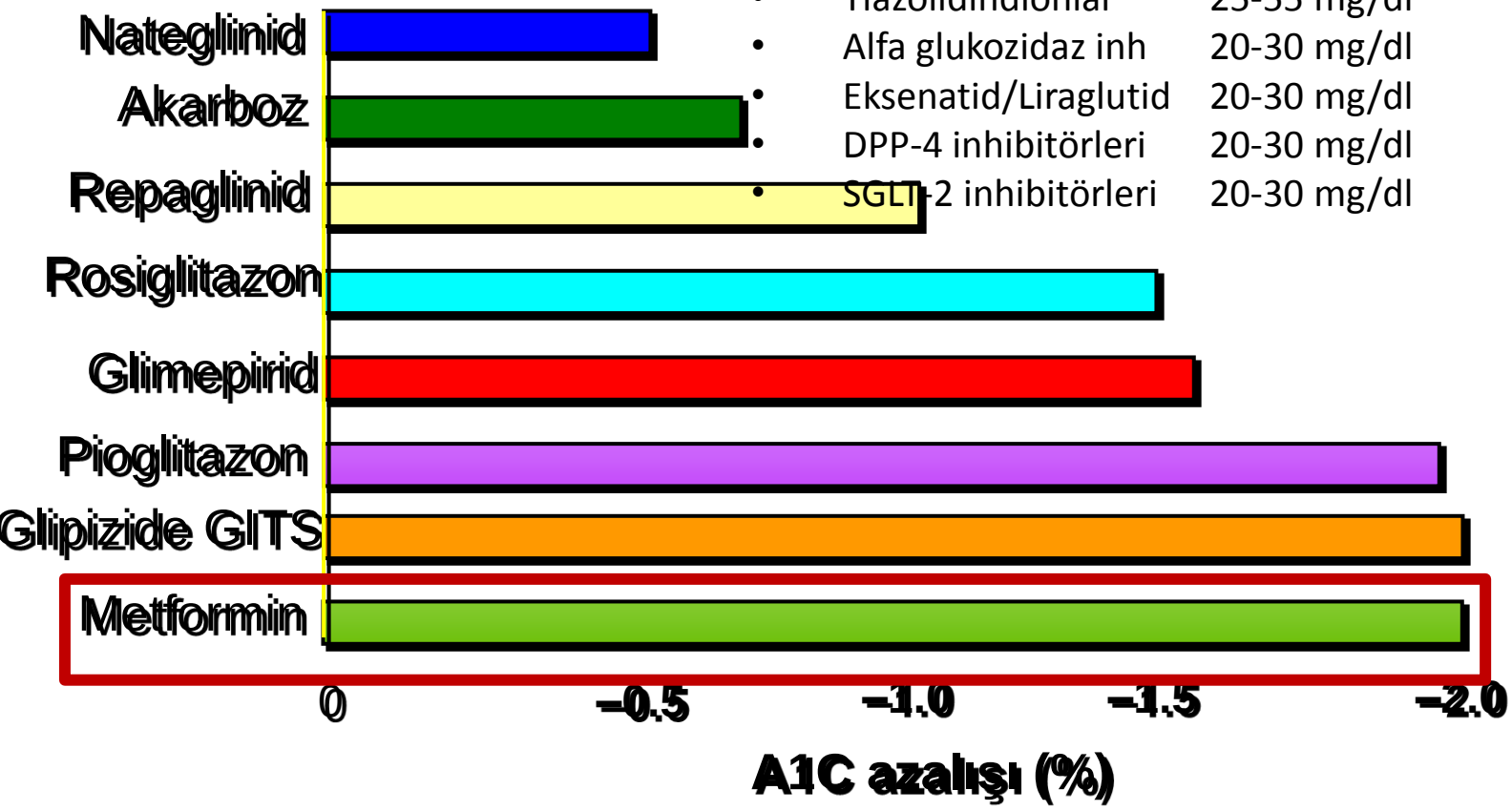
Başlangıç A1C ≥8.5%

«Metformin başla»

Başlanan tedavi ile hedef tedaviye %1.5 A1c düşüş sağlanamazsa MET ilave etmeyi düşün

OAD'lerin Monoterapideki Etkileri

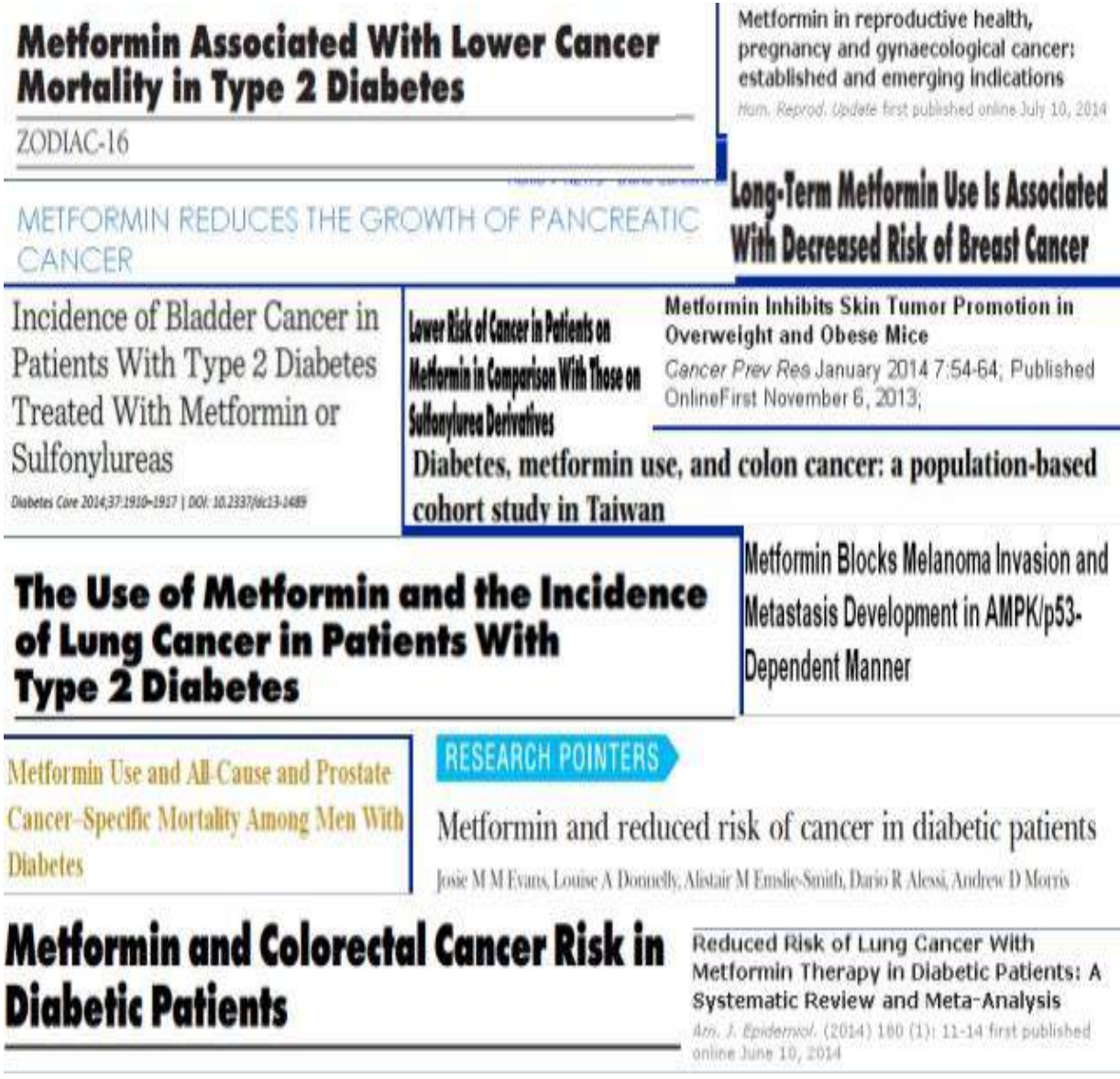
	APG'de azalma	A1Cde azalma
Yaşam tarzı değişimi	40-60 mg/dl	%1.0-2.0
• Metformin	50-70 mg/dl	%1.5-2.0
• İnsülinler	50-80 mg/dl	%1.5-2.5
• Sulfonilüreler	40-60 mg/dl	%1.0-2.0
• Glinidler	30 mg/dl	%1.0-1.5
• Tiazolidindionlar	25-55 mg/dl	%0.5-1.4
• Alfa glukozidaz inh	20-30 mg/dl	%0.5-0.7
• Eksenatid/Liraglutid	20-30 mg/dl	%1.0-1.5
• DPP-4 inhibitörleri	20-30 mg/dl	%0.5-1.0
• SGLT-2 inhibitörleri	20-30 mg/dl	%0.5-1.0



Diabetes Care. 2000;23:202-207; Precose (acarbose) package insert; *Drugs*. 1995;50:263-288; *J Clin Endocrinol Metab*. 2001;86:280-288; *Diabetes Care*. 2000;23:1605-1611; *Diabetes Care*. 1997;20:597-606; *Am J Med*. 1997;102:491-497

Metformin Endikasyonları ve Yeni Tedavi Perspektifleri

- **Diabetes Mellitus:** T2DM tedavisinde ilk seçenek
- **Prediabet:**
- Diyet+Egzersiz+MET tedavi seçenekleri
- **Gestational diabet:** GDM'de etkili, güvenli !!
- **PKOS:** PCOS sıklıkla IR ile birlikte olur.
- **NAFLD/NASH**
- **KANSER**



Pediatrik Grupta Metformin

- **Expert görüşü:**
  - Tip 2 diyabetik pediatrik grupta yararlı olduğu gösterilmiş ve ancak daha iyi kurgulanmış çalışmalara ihtiyaç vardır (ADA ve Pediatric endocrine society).

Tabatabaei-Malazy O. Et al. Drugs for the treatment of pediatric type 2 diabetes mellitus and related co-morbidities. Expert Opin Pharmacother. 2016 Dec;17(18):2449-2460.

MET Kombinasyonlardaki Yeri

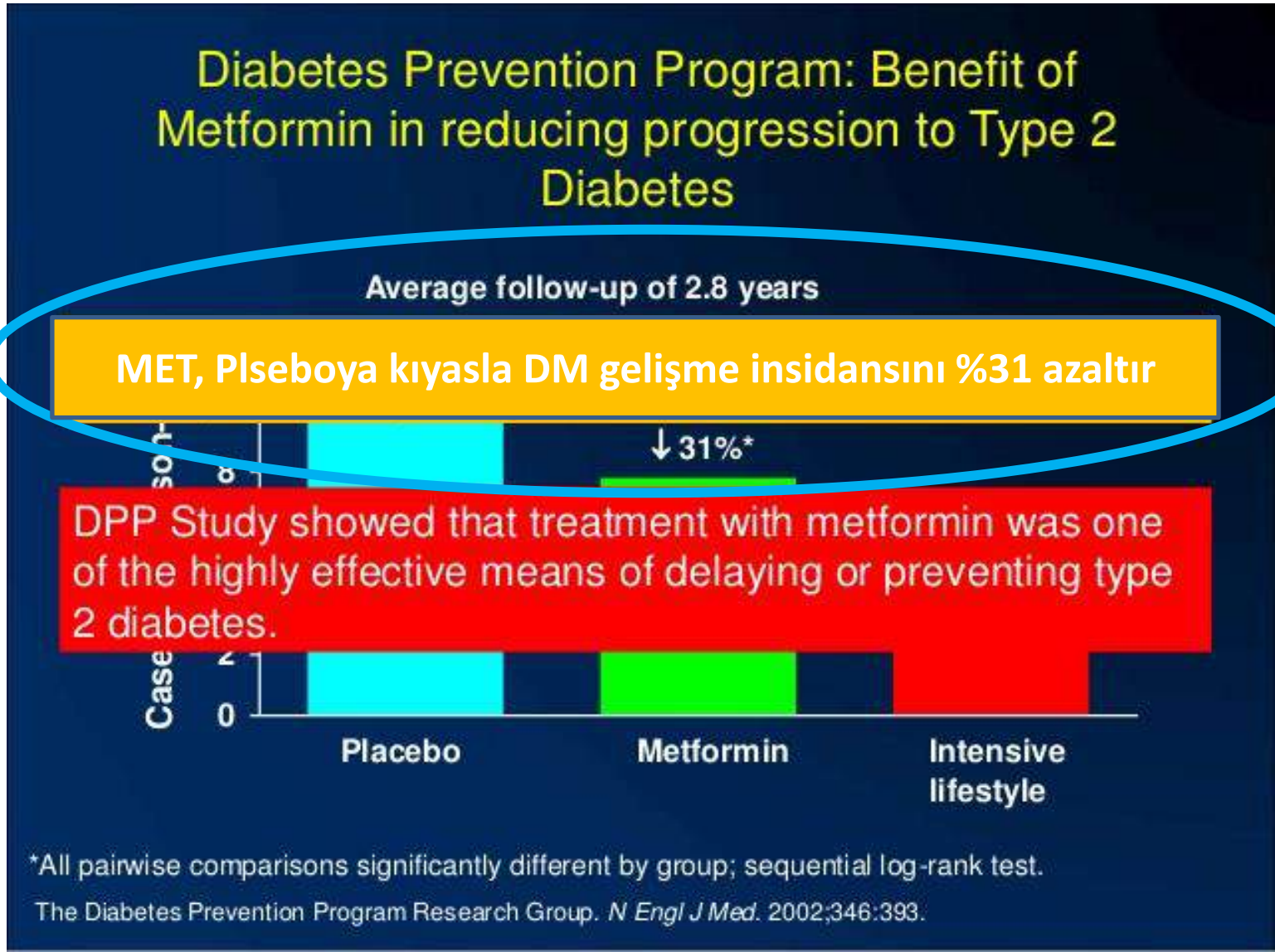
- Glitazonlarla
- İnsülinle
- Sülfonilürelerle
- Glinidlerle
- α-Glukozidaz İnhibitörleri ile
- DPP-4'lerle
- GLP-1 Analoğları ile
- SGLT-2 Reseptör blokerleri ile

Kombine ve sinerjizm

Metformin’in IGT’deki Etkileri

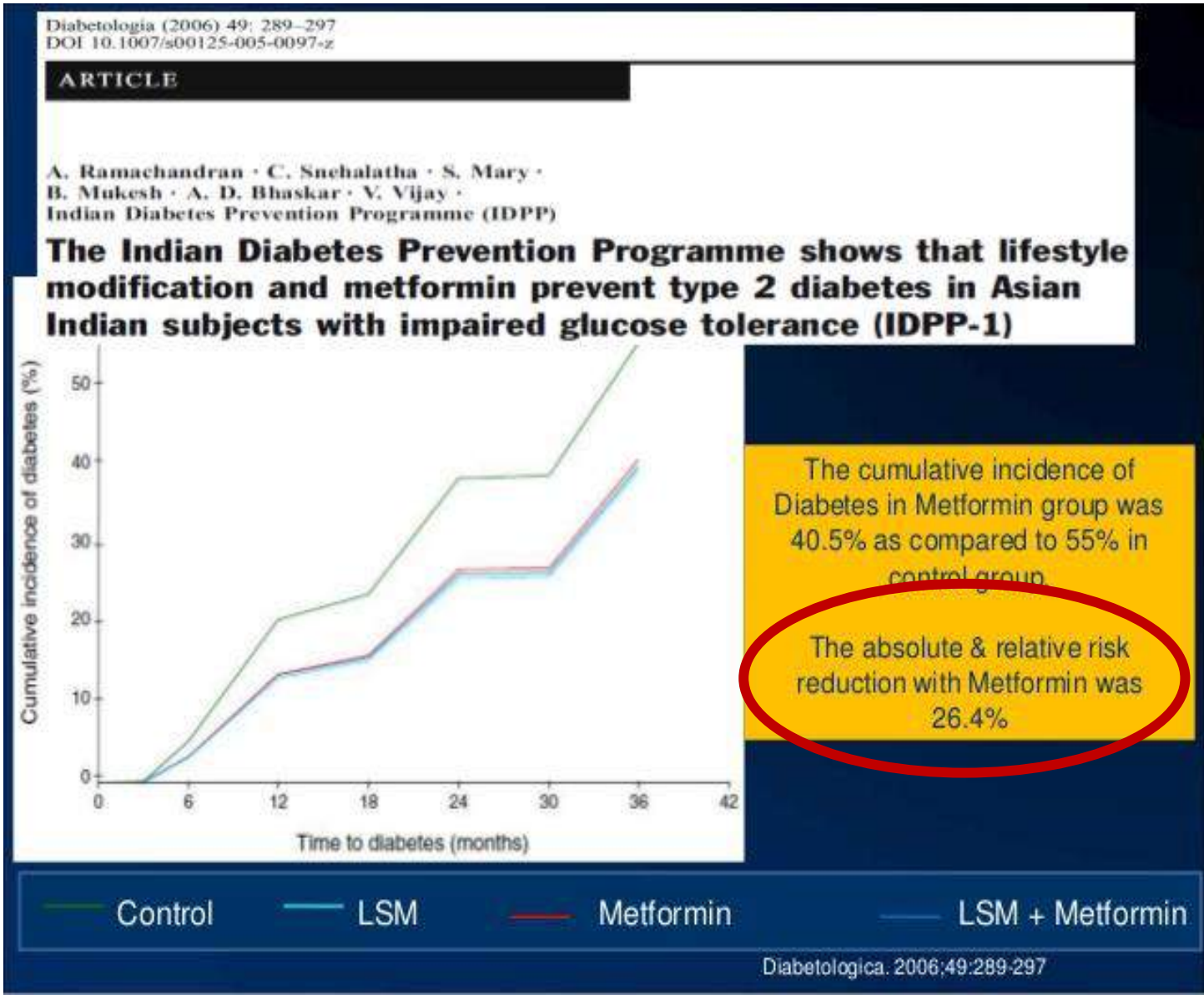
Metformin IGT'de Etkileri

- **MET:** IGT'li olgular da DM başlamasını önler



İndian Diabetes Prevention Programme (IDPP-1) Çalışması

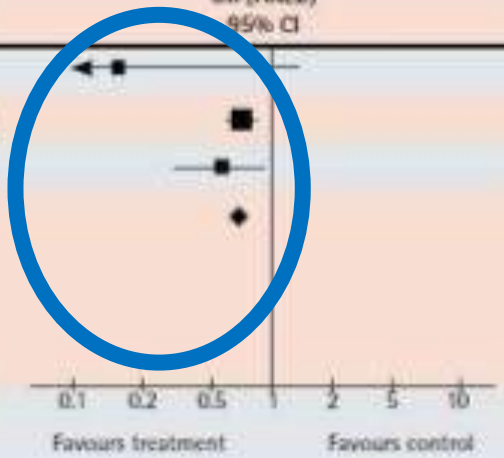
- IGT'li olgularda MET, T2DM gidişini **%26.4** oranında azaltır



Treating prediabetes with metformin

Figure 1. Meta-analysis of studies of effects of metformin on prediabetes using the results of the 3 reviewed studies as the authors reported them

STUDY OR SUBCATEGORY	TREATMENT n/N	CONTROL n/N	OR (FIXED) 95% CI	WEIGHT %	OR (FIXED) (95% CI)
Li et al[22]	1/33	6/37		1.88	0.16 (0.02-1.42)
Knowler et al (ITT)[24]	233/1073	313/1082		83.56	0.68 (0.56-0.83)
Ramachandran et al[23]	52/128	73/133		14.56	0.56 (0.34-0.92)
Total (95% CI)	1234	1252		100	0.65 (0.55-0.78)
Total events: 286 (treatment), 392 (control)					
Test for heterogeneity: $\chi^2_3 = 2.12$, $P = .35$, $I^2 = 5.8\%$					
Test for overall effect: $Z = 4.60$, $P < .00001$					



CI—confidence interval, ITT—intention to treat, OR—odds ratio.

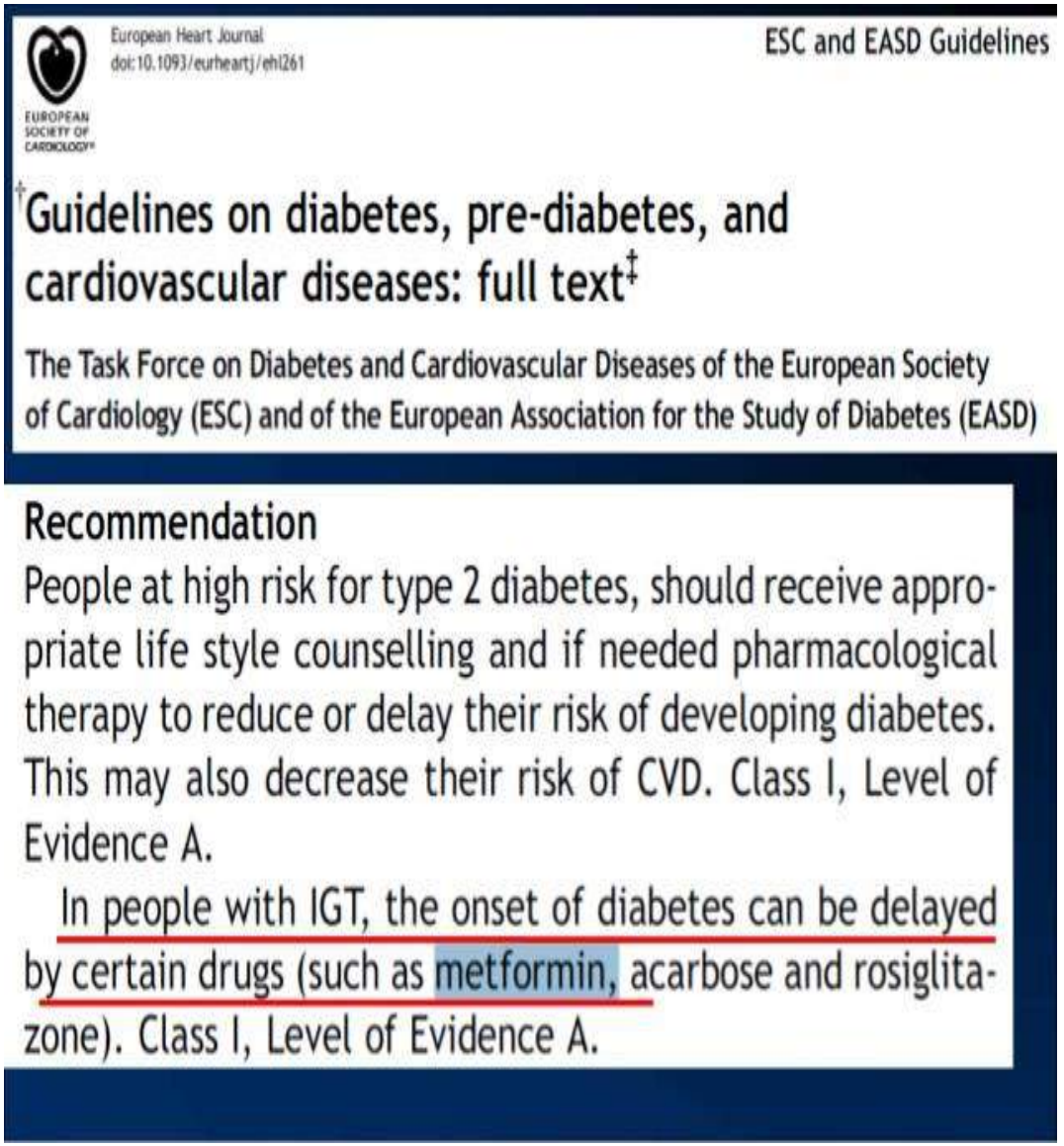
- 3 RCTs varied in ethnicity of the population studied, in the rates of conversion to diabetes from prediabetes, and in the dose of metformin used.
- M
  - ing 3 times daily).

MET, Prediyabetten diyabete geçişi azaltır
DOZ: 2X850 veya,
3X250

Can Fam Physician 2009;55:363-9

Metformin Sonuç:
T2DM'in Önlenmesindeki Önemi

- IGT'li olgularda T2DM gelişmesinin önlenmesinde yararlı ilaçlar (Metformin, Acarbose, Rosiglitazone) **Class I, kanıt düzey A.** (ESC and EASD Guidelines)



European Heart Journal
doi:10.1093/eurheartj/ehl261

ESC and EASD Guidelines

EUROPEAN SOCIETY OF CARDIOLOGY

†Guidelines on diabetes, pre-diabetes, and cardiovascular diseases: full text‡

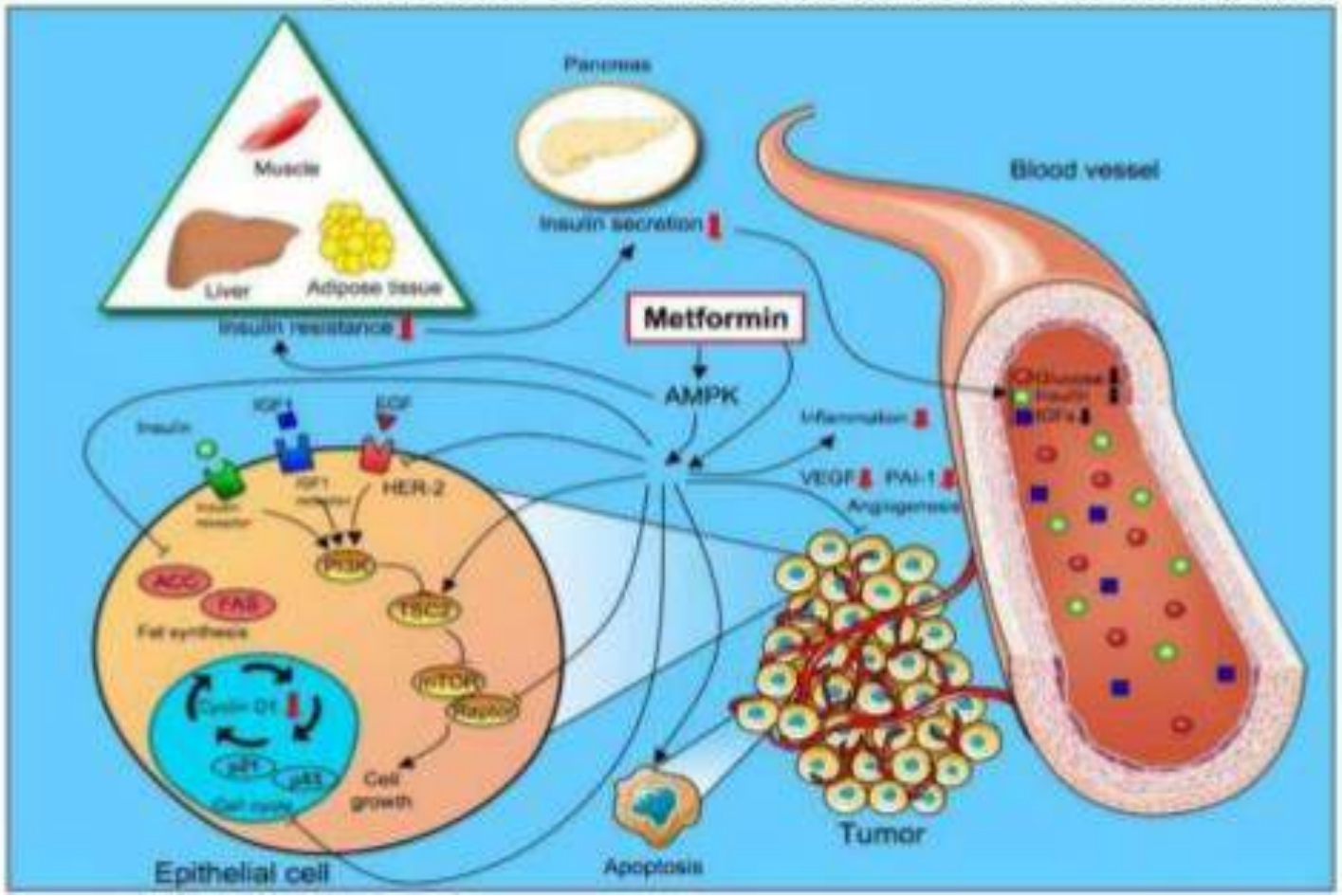
The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD)

Recommendation

People at high risk for type 2 diabetes, should receive appropriate life style counselling and if needed pharmacological therapy to reduce or delay their risk of developing diabetes. This may also decrease their risk of CVD. Class I, Level of Evidence A.

In people with IGT, the onset of diabetes can be delayed by certain drugs (such as metformin, acarbose and rosiglitazone). Class I, Level of Evidence A.

MET: Antikanser Etkileri



Albini A. Cancer Prevention and Interception: A New Era for Chemopreventive Approaches. Clin Cancer Res. 2016 Sep 1;22(17):4322-7.

Metformin ve Beyin

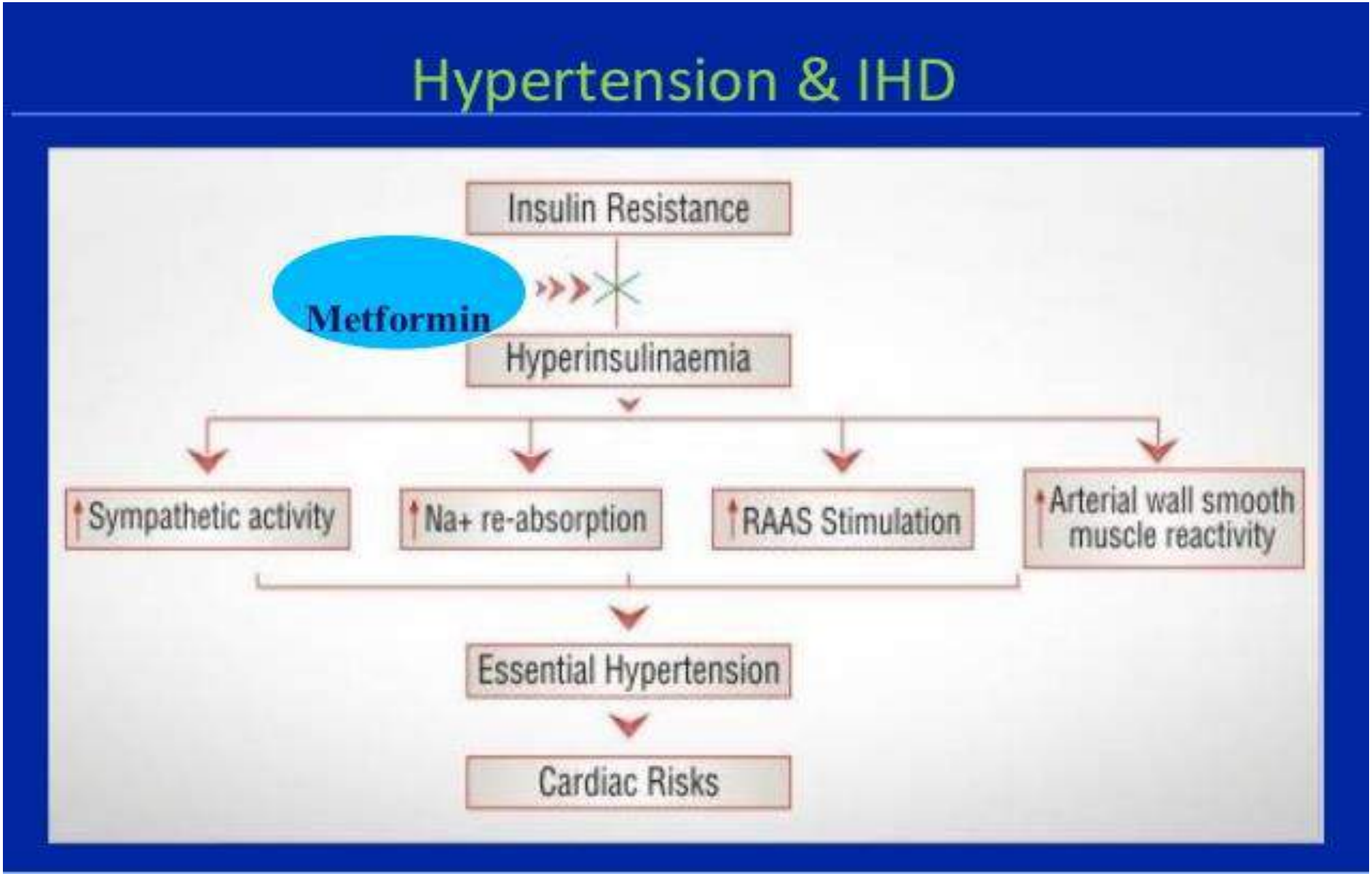
MET Beyin ve Kardiovasküler-Serebrovasküler Morbidite

- Bellek için önemli olan hipokampal bölge hücrelerinde artış
- Beyin hücrelerinin büyümesini ve mekansal bellekte düzelmeye neden olur
- Yeni beyin hücre gelişimini artırır
- Alzheimer'lı hastalarda MET ile hastalık semptomları geriler (kan şekeri ayarından bağımsız)
- Sinyal hücrelerinden yeni beyin hücresi oluşmasına neden olur
- **UKPDS çalışması: İnme riski: % 41 azalmış**

UKPDS 34, Lancet 1998; 352:854-865

MET Kardiovasküler Etkiler

MET Kardioprodüktif Etkiler



Metformin:
UKPDS Çalışması

Metformin

UKPDS - Substudy

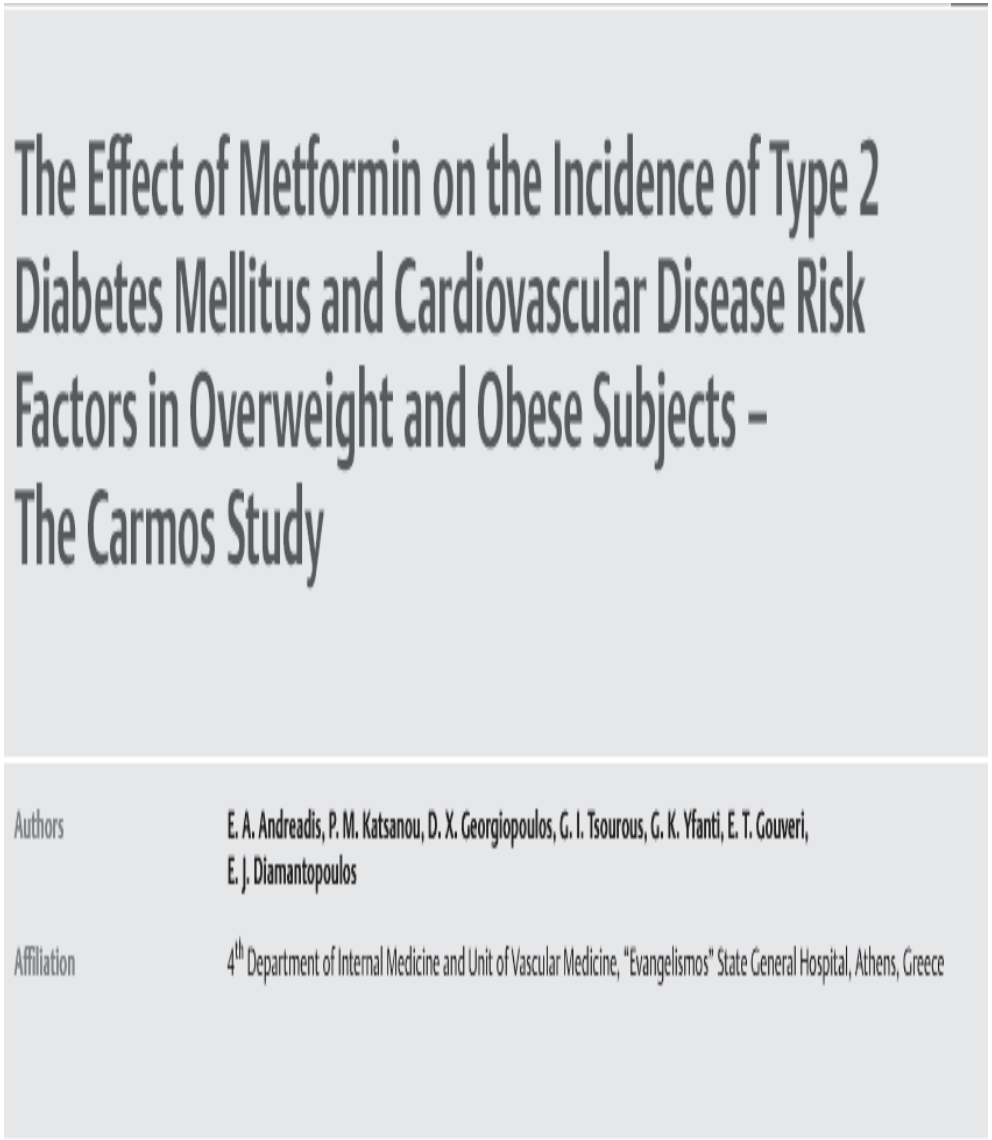
Aggregate Endpoint	ARR	RRR	p
Any diabetes related endpoint	13.5 %	32%	0.0023
Microvascular disease	2.5%	29%	0.19
Myocardial infarction	7.0%	**39%**	**0.010**
All-cause mortality	7.1%	**36%**	**0.011**

342 overweight patients
Median followup of 10.7 years (6-20)
Mean HbA1c only 0.6% lower

UKPDS 34. Lancet 1998;352:837-853

Carmos Çalışması

- 366 fazla kilolu-obez hasta
- 95 hastaya MET
- 12 aylık takip
- **Diyabet gelişme sıklığı:**
  - **MET alan grupta %1.1**
  - **MET almayan grupta %8.1**
- Sonuç: Metabolik Sendrom riskini azaltmakta



The Effect of Metformin on the Incidence of Type 2 Diabetes Mellitus and Cardiovascular Disease Risk Factors in Overweight and Obese Subjects – The Carmos Study

Authors: E. A. Andreadis, P. M. Katsanou, D. X. Georgiopoulos, G. I. Tsourous, G. K. Yfanti, E. T. Gouveri, E. J. Diamantopoulos

Affiliation: 4th Department of Internal Medicine and Unit of Vascular Medicine, "Evangelismos" State General Hospital, Athens, Greece

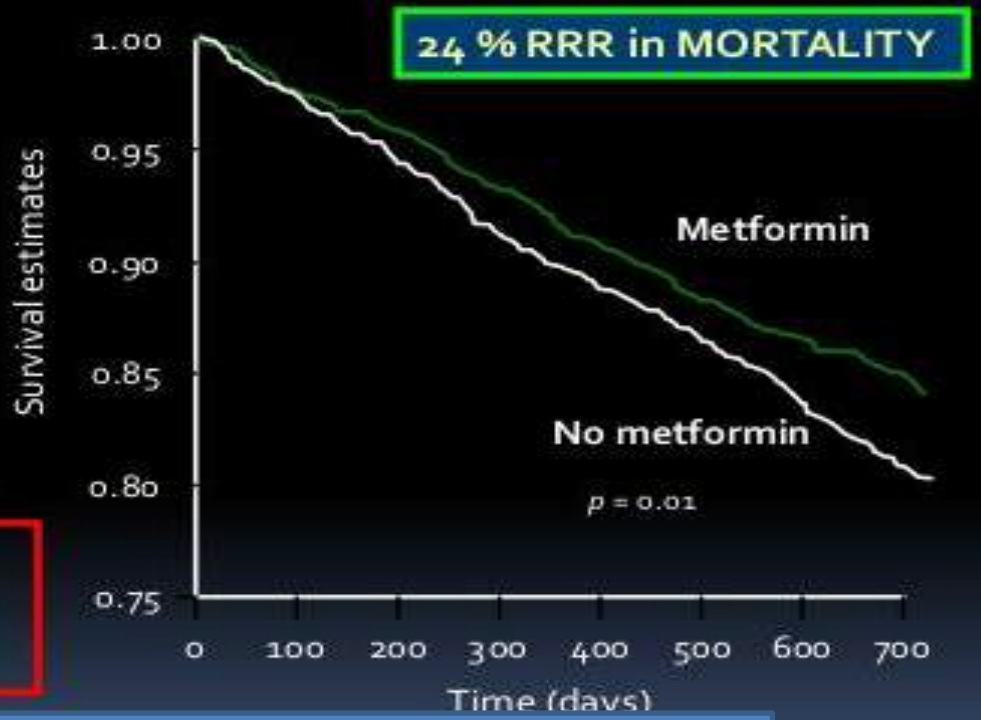
Kalp Yetmezlikli Hastalarda MET Kullanımı

Metformin Use in Heart Failure Patients

Veterans Affairs

- 6,185 with CHF & DM
- Oral antihyperglycemic:
  - With metformin (n=1,561)
  - Without metformin
- Statistically adjusted for co-variables

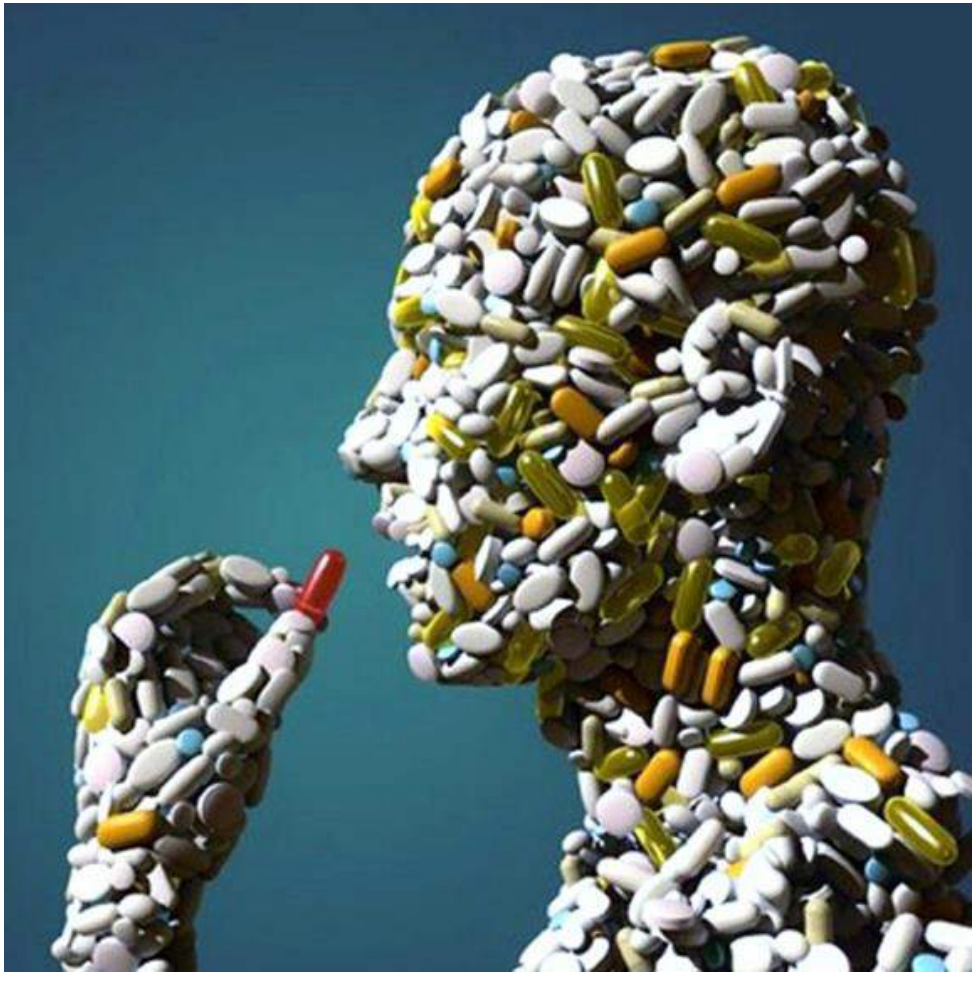
Death:	0.76 (0.63-0.92) $p < 0.01$
CHF hospitalization:	0.93 (0.74-1.18) $p = 0.56$
Total hospitalization:	0.94 (0.83-1.07) $p = 0.35$



Mortalite de %24 azalma saptanmış

Aguilar D, et al. Circ Heart Fail 2011;4:53-8.

MET Yan Etkileri



Metformin Etkin mi?

Metformin Yan Etki ve Kontrendikasyonları

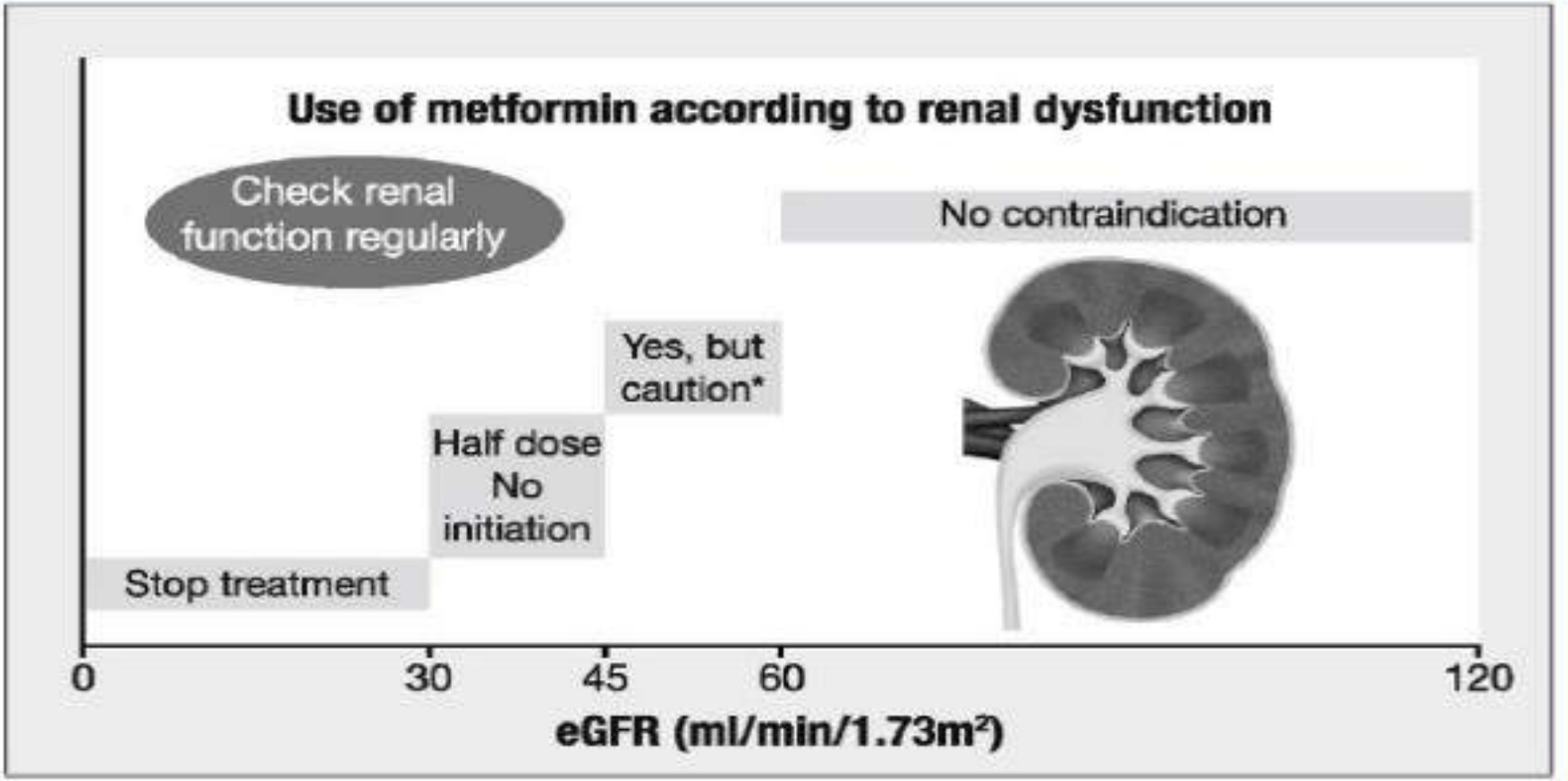


Fig. 2. Proposed recommendations for the use of metformin according to renal function as estimated by glomerular filtration rate (eGFR). * Increase monitoring of renal function (every 3–6 months), avoid any nephrotoxic drugs and stop metformin if dehydration arises.

MET Yan Etkileri

Yan Etkiler	MET HCl Monoterapi (n=141)	Plasebo (n=145)
	Hastaların %	
Diare	53.2	11.7
Bulantı/Kusma	25.5	8.3
Flatulens	12.1	5.5
Asteni	9.2	5.5
Hazımsızlık	7.1	4.1
Abdominal Discomfort	6.4	4.8
Baş ağrısı	5.7	4.8

MET: kullanımında doz artışından sonra en sık GİS yan etkileridir. GİS huzursuzluğu doz azaltımıyla azalır. Uzun kullanımda homosistein düzeyi artar ve B12 emilimi bozulur.

Laktik Asidozis

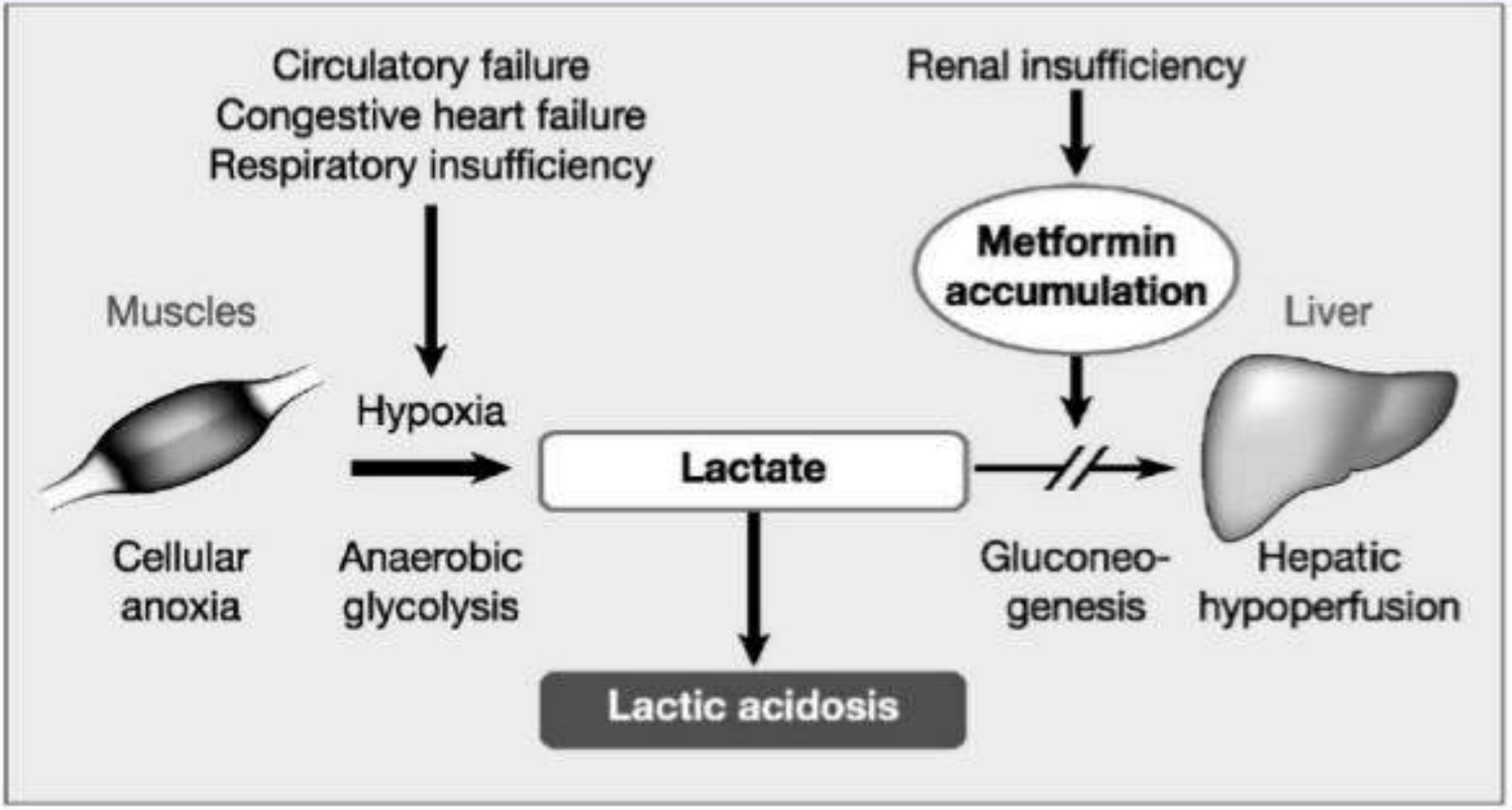
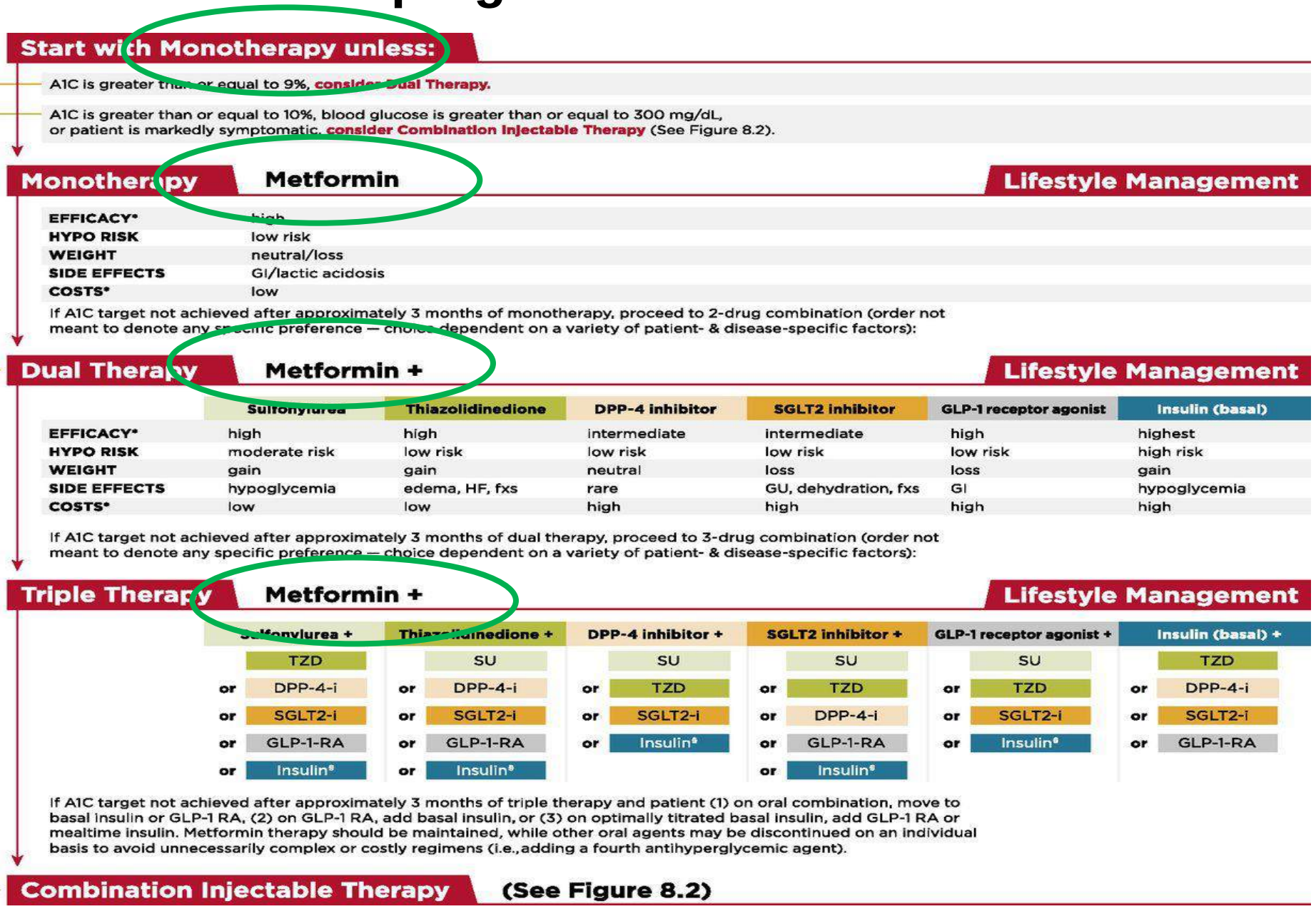


Fig. 1. Lactic acidosis and the special circumstances that might increase the risk associated with metformin therapy.

Uluslar arası ve Ulusal Klavuzlar ne diyor?

ADA Guideline-2017

T2DM'de Antihiperglisemik tedavi: Genel Öneriler



American Diabetes Association Dia Care 2017;40:S64-S74

AACE/ACE COMPREHENSIVE TYPE 2 DIABETES MANAGEMENT ALGORITHM

2017

TASK FORCE

Alan J. Garber, MD, PhD, FACE, *Chair*

M
J
L
Z
M
S
R

U

AACE/ACE Guideline-2017

 DOI 10.4158/EP161682.CS

PREDIABETES ALGORITHM

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

TREAT ASCVD RISK FACTORS

WEIGHT LOSS THERAPIES

TREAT HYPERGLYCEMIA
FPG > 100 | 2-hour PG > 140

ASCVD RISK FACTOR MODIFICATIONS ALGORITHM

- DYSLIPIDEMIA ROUTE
- HYPERTENSION ROUTE

NORMAL GLYCEMIA

Progression

OVERT DIABETES

PROCEED TO HYPERGLYCEMIA ALGORITHM

1 PRE-DM CRITERION

Intensify Weight Loss Therapies

MULTIPLE PRE-DM CRITERIA

Low-risk Medications
- Metformin
- Acarbose

Consider with Caution
- TZD
- GLP-1 RA

If glycemia not normalized

LEGEND

Orlistat, lorcaserin, phentermine/topiramate ER, naltrexone/bupropion, liraglutide 3 mg, or bariatric surgery as indicated for obesity treatment

 DOI 10.4158/EP161682.CS

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

 DOI 10.4158/EP161682.CS

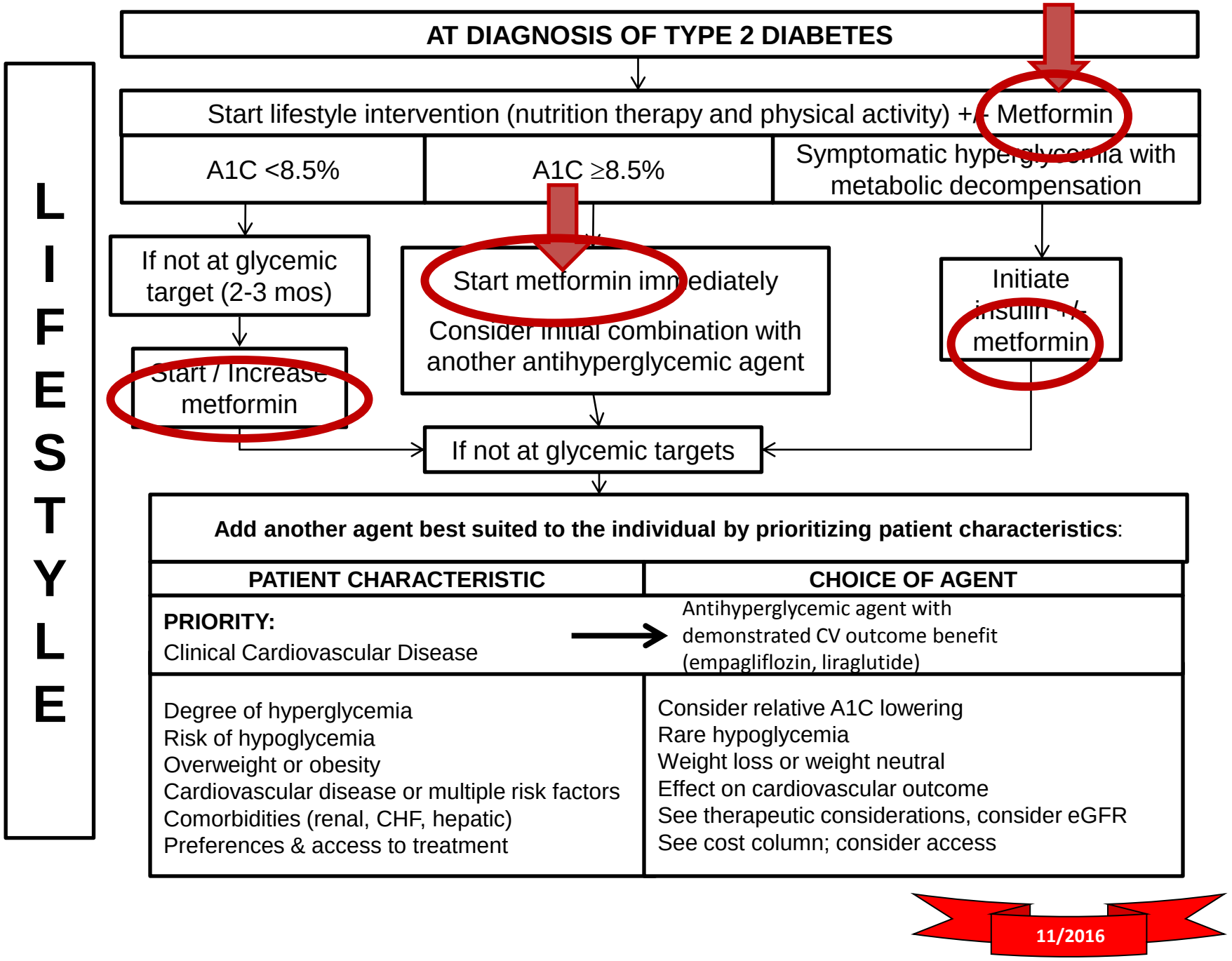
American College of Physicians

Disease/Condition	Type 2 diabetes
Target Audience	Internists, family physicians, other clinicians
Target Patient Population	Adults with type 2 diabetes
Interventions Evaluated	Oral pharmacologic treatments: metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors
Outcomes Evaluated	Clinical outcomes: all-cause mortality, cardiovascular and cerebrovascular morbidity and mortality, retinopathy, nephropathy, neuropathy Intermediate outcomes: HbA_{1c}; weight; systolic blood pressure; harms: hypoglycemia, gastrointestinal side effects, genital mycotic infections
Benefits	Clinical Outcomes Metformin monotherapy was associated with a lower risk for cardiovascular mortality than sulfonylurea monotherapy. HbA_{1c} Most drugs reduced HbA_{1c} to similar levels. DPP-4 inhibitors reduced HbA_{1c} levels less than metformin or sulfonylureas. All combination therapies with metformin were superior to metformin monotherapy. Weight Metformin was better than thiazolidinediones, sulfonylureas, or DPP-4 inhibitors for weight. Combinations of metformin and SGLT-2 inhibitor agonists reduced weight more than metformin monotherapy. Thiazolidinediones and sulfonylureas, either alone or in combination therapy, were associated with worse weight outcomes. Systolic Blood Pressure SGLT-2 inhibitors, as monotherapy or combined with metformin, reduced systolic blood pressure compared with metformin monotherapy.
Harms	Metformin: increased risk for gastrointestinal side effects Sulfonylureas: increased risk for hypoglycemia compared with other drugs Thiazolidinediones: increased risk for heart failure SGLT-2 inhibitors: increased genital mycotic infections
Recommendations	*Recommendation 1: ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)* *Recommendation 2: ACP recommends that clinicians consider adding a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.*
Clinical Considerations	Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss. Management of type 2 diabetes often involves pharmacologic and nonpharmacologic therapies and includes patient education, evaluation, patient self-management for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors. Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss or lifestyle modification fails. Metformin monotherapy effectively decreases glycemic levels when used in monotherapy and combination therapy with a second agent. Metformin also reduces body weight. Although combination therapy reduces HbA_{1c} levels more effectively than monotherapy, it is associated with more adverse events. The DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease. Metformin is considered safe for patients with mild chronic kidney disease and some patients with moderate kidney impairment (but is contraindicated in those with an estimated glomerular filtration rate <30 mL/min/1.73 m^2).

Canadian Diabetes Association
Clinical Practice Guidelines

Pharmacologic Management of Type 2 Diabetes

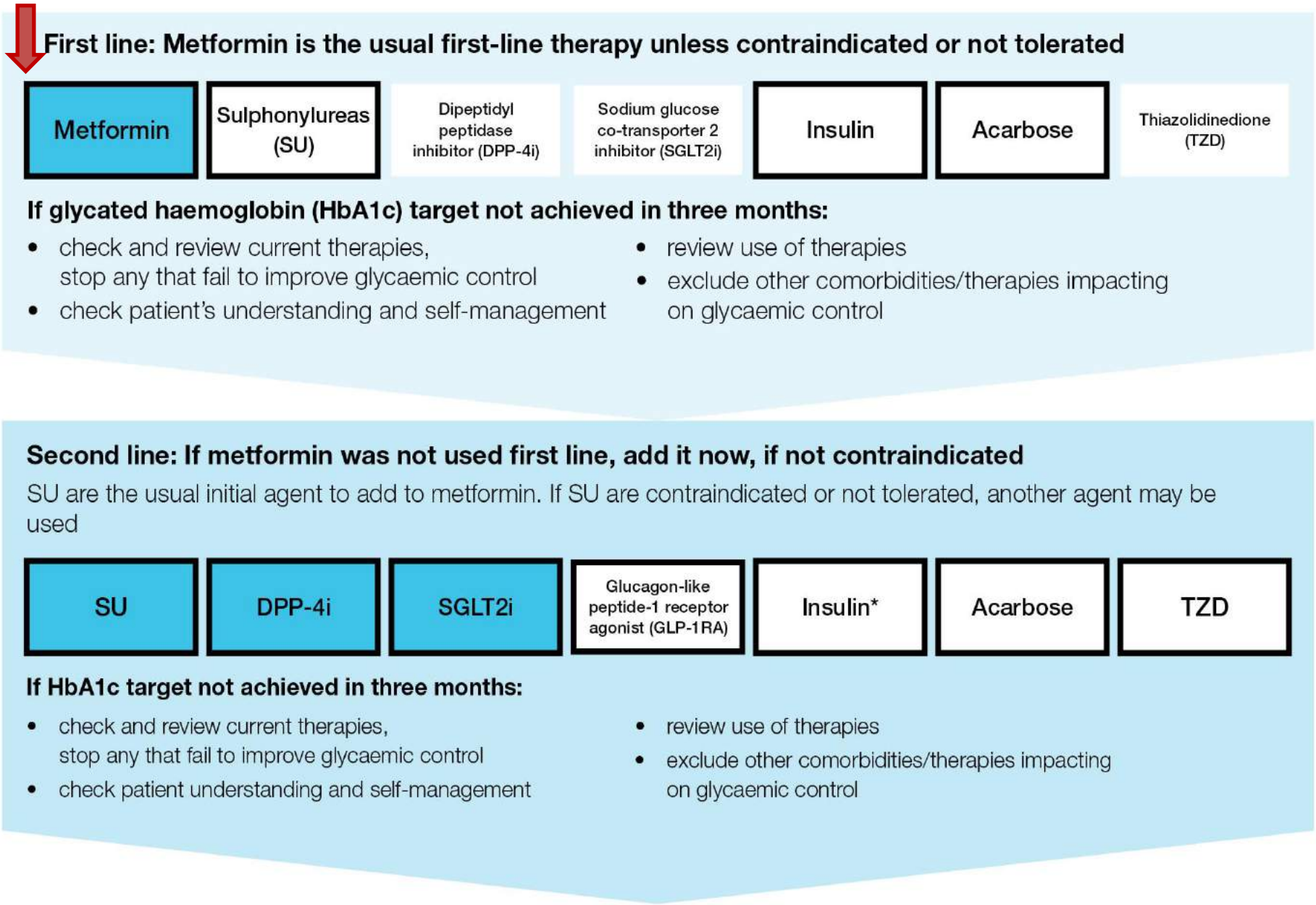
2016


AT DIAGNOSIS OF TYPE 2 DIABETES
Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin
A1C <8.5%
A1C ≥8.5%
Symptomatic hyperglycemia with metabolic decompensation
If not at glycemic target (2-3 mos)
Start / Increase metformin
Start metformin immediately
Consider initial combination with another antihyperglycemic agent
Initiate insulin +/- metformin
If not at glycemic targets
LIFESTYLE
Add another agent best suited to the individual by prioritizing patient characteristics:
PATIENT CHARACTERISTIC
CHOICE OF AGENT
PRIORITY:
Clinical Cardiovascular Disease
Antihyperglycemic agent with demonstrated CV outcome benefit (empagliflozin, liraglutide)
Degree of hyperglycemia
Risk of hypoglycemia
Overweight or obesity
Cardiovascular disease or multiple risk factors
Comorbidities (renal, CHF, hepatic)
Preferences & access to treatment
Consider relative A1C lowering
Rare hypoglycemia
Weight loss or weight neutral
Effect on cardiovascular outcome
See therapeutic considerations, consider eGFR
See cost column; consider access
11/2016

Australian Guideline-2017

The Australian blood glucose treatment algorithm for type 2 diabetes (Figure 4) is an evidence-based algorithm developed by the Australian Diabetes Society (ADS) in consultation with all key stakeholders including the RACGP

Figure 4. Australian diabetes algorithm and clinical medication table



Almanya-Hollanda-Macaristan Yaklaşımı

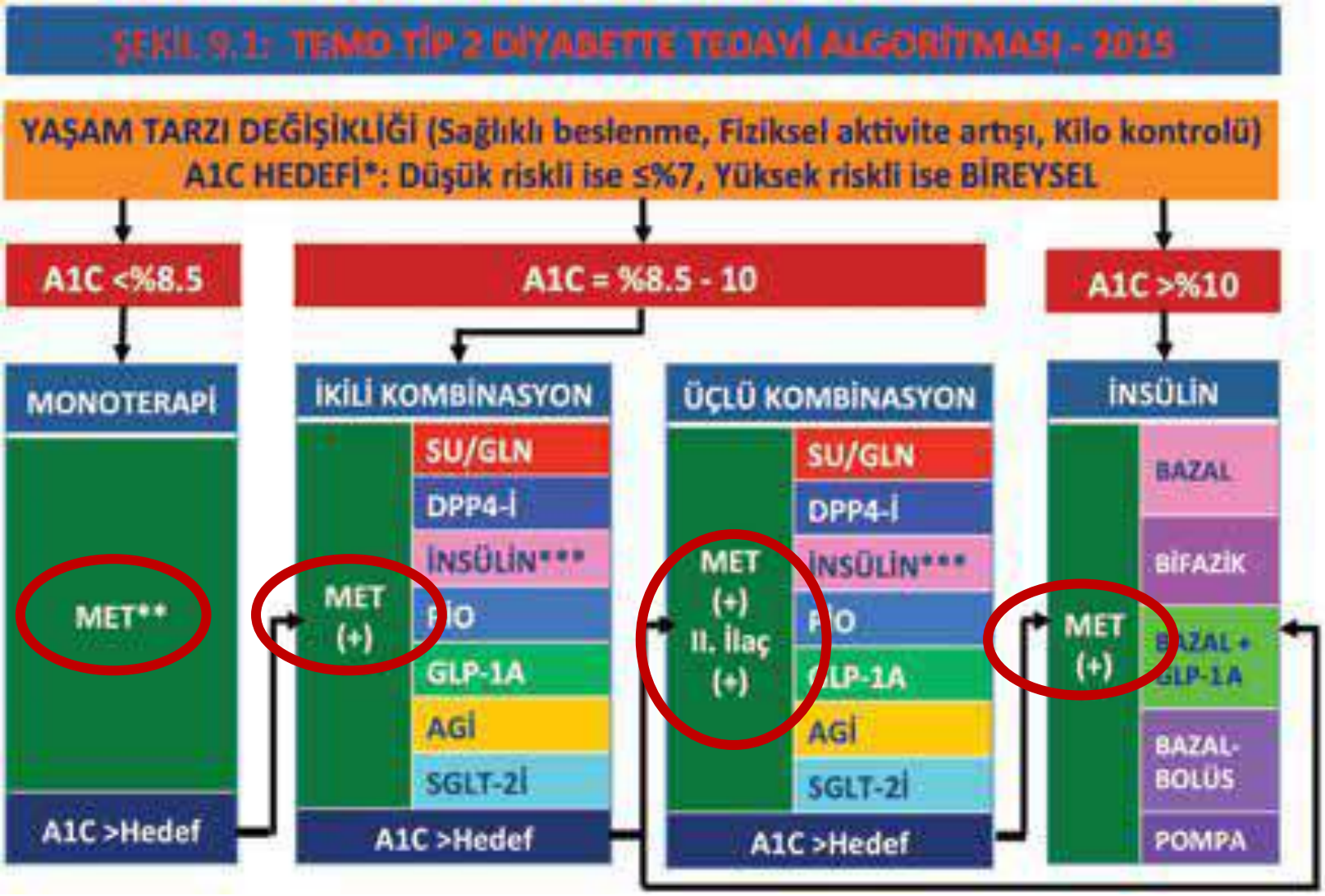
- Modern T2DM tedavisinde ilk basamak ilaç MET'dir **(Almanya)**
- İlk tercih MET olması önerilmektedir. 70 yaş ve 80 yaş üzeri bireylerde de MET yararlı olmaktadır **(Hollanda)**
- Metformin T2DM tedavisinde temel ilaçtır **(Macaristan)**

Boels AM1. et al. Personalised treatment targets in type 2 diabetes patients: The Dutch approach. Prim Care Diabetes. 2017 Feb;11(1):71-77.

Winkler G. [Metformin - new data for an "old", but efficient, safe and reliable antidiabetic drug]. Orv Hetil. 2016 Jun 5;157(23):882-91. (Macaristan)

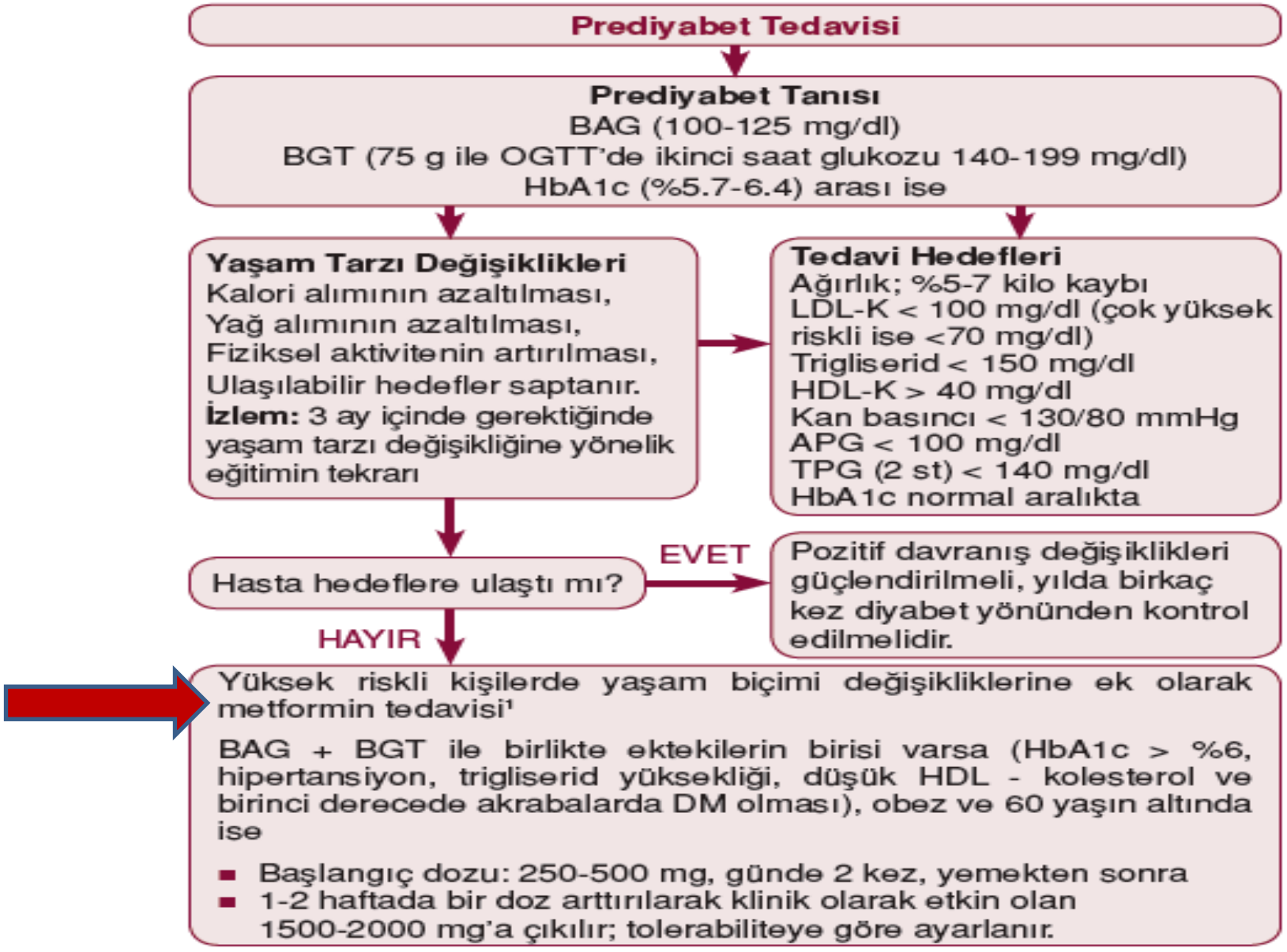
TEMD Klavuzu

TÜRKİYE ENDOKRİNOLOJİ ve METABOLİZMA DERNEĞİ


ŞEKİL 9.1: TEMD TİP 2 DİYABETTE TEDAVİ ALGORİTMASI - 2015
YAŞAM TARZI DEĞİŞİKLİĞİ (Sağlıklı beslenme, Fiziksel aktivite artışı, Kilo kontrolü)
A1C HEDEFİ*: Düşük riskli ise ≤%7, Yüksek riskli ise BİREYSEL
A1C <%8.5
A1C = %8.5 - 10
A1C >%10
MONOTERAPİ
MET**
A1C >Hedef
İKİLİ KOMBİNASYON
MET (+)
SU/GLN
DPP4-İ
İNSÜLİN***
PİO
GLP-1A
AGİ
SGLT-2İ
A1C >Hedef
ÜÇLÜ KOMBİNASYON
MET (+) II. İlaç (+)
SU/GLN
DPP4-İ
İNSÜLİN***
PİO
GLP-1A
AGİ
SGLT-2İ
A1C >Hedef
İNSÜLİN
MET (+)
BAZAL
BİFAZİK
BAZAL + GLP-1A
BAZAL-BOLÜS
POMPA

Türkiye Diyabet Vakfı
Diyabet Tedavi Rehberi

TDV Diyabet Tanı ve Tedavi Rehberi 2016



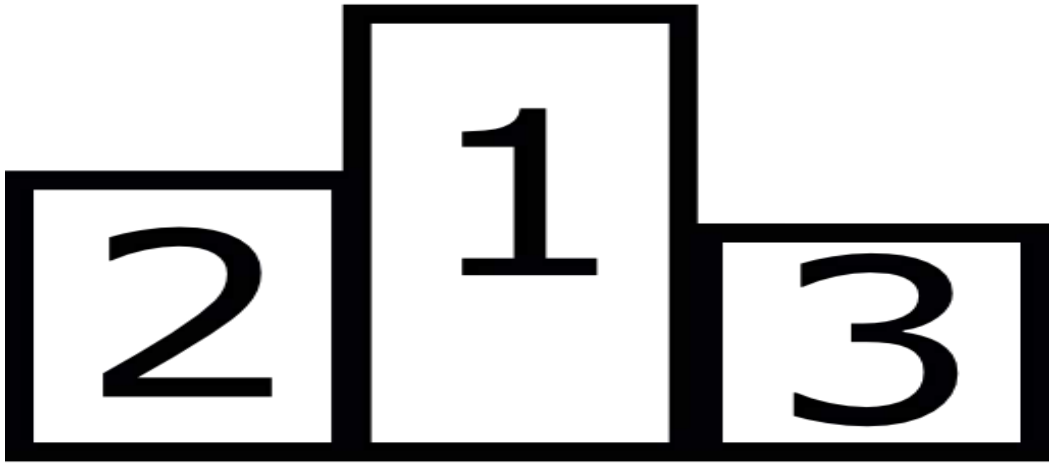
(1) ADA ve Kanada Diyabet Birliği önerisidir.

DAHA ÖNCE TANI ALMIŞ TEDAVİ ALTINDAKİ TİP 2 DİYABETTE TEDAVİ YAKLAŞIMI

HbA1c		TEDAVİ PLANI	TEDAVİ SEÇENEKLERİ			
<7.5	↓ ↑	MONOTERAPİ	Yaşam Şekli Değişikliği	Metformin		
7.5 - 9	↓ ↑	İKİLİ KOMBİNASYON	Metformin Sülfonilüre	Metformin Pioglitazon	Metformin DPP4 İnhibitör	
	↓ ↑	ÜÇLÜ KOMBİNASYON	Metformin Sülfonilüre İnkretin Bazlı Tedaviler	Metformin Sülfonilüre Pioglitazon	Metformin İnkretin Bazlı Tedaviler Pioglitazon	Kombi Tedavisi-1
>9	↓ ↑	BAZAL İNSÜLİN KOMBİNASYONLARI	Metformin Bazal İnsülin	Metformin Bazal İnsülin Glinid	Metformin Bazal İnsülin İnkretin Bazlı Tedaviler	Kombi Tedavisi-2
>9	↓ ↑	ÇOKLU DOZ İNSÜLİN KOMBİNASYONLARI	Metformin Hazır Karışım İnsülinler (25 / 30 / 50)	Metformin Çoklu doz insülin Tedavisi	Metformin Çoklu Doz İnsülin Tedavisi İnkretin Bazlı Tedaviler	

- Yaşam şekli değişikliği tüm basamaklarda önerilmelidir.
- Akarboz tüm basamaklarda kombinasyon olarak kullanılabilir.
- En fazla 3 aylık tedaviye rağmen HbA1c %7.5'in üstünde ise bir sonraki basamağa geçmelidir.
- Etkin bir oral antidiyabetik tedavisine rağmen HbA1c %9'un üzerinde ise doğrudan insülin tedavisine geçilmelidir.
- Tip 2 diyabette glisemi regülasyonu sağlandıktan sonra dinamik izlem sürdürülmeli, gerekirse tekrar bir önceki basamağa dönülerek ilaçlar ve dozları azaltılmalıdır.
- Kombinasyon Tedavisi-1: Seçilmiş vakalarda kişiye özel ek farklı kombinasyonlar yapılabilir.
- Kombinasyon Tedavisi-2: Seçilmiş vakalarda kişiye özel pioglitazon yada farklı oral antidiyabetik kombinasyonu yapılabilir.

Metformin Neden İlk Seçenek



T2DM: Metformin Kanıtları

- **MET:** HbA1c, Kilo, T. Kol., LDL-K, TGs, İnsülin, Diastolik Kan Basıncı azalır, İnsülin artar, MI azalır. (The Cochrane Library 2009, Issue 1)

Çalışma	Temel Bulgular
Randomize çalışmalar	
UKPDS 34	Makrovasküler komp. Riski azalır
Kooy et al	Makrovasküler olaylar azalır
Gözlemsel çalışmalar	
PRESTO	Her hangi bir klinik son azalır: MI, Ölüm
Johnson et al	Ölüm riski %40 azalır, Mortalite, hastaneye yatış ve kardiovasküler ölüm azalır
Eurich et al	Ölüm riski %30 azalır, Ölüm veya Hospitalizasyon riski %17 azalır
Evans et al	**Kardiovasküler mortalite riski 3.7 kat azalır**
REACH Kayıtları	Aterosklerozlu hastalarda mortalite riskini %24 azaltır

Cliffort J, Ian Campell, Metformin: The Gold Standart

Metformini Birinci Yapan Nedenler

Metformin Etkileri	Olumlu Etki	Olumsuz Etki
1-Glisemiyi düşürme	50-70 mg/dl	Ø
2-HbA1c azaltma	%1-2 azalma	Ø
Yan etki:	Bulantı, Kusma, İshal, Huzursuzluk	Ø
Kardiak olumlu etki	√	Ø
Hipertansiyon	√	Ø
Endotel etkisi	√	Ø
Ateroskleroz etkisi	√	Ø
Kullanım	√ (KOLAY)	Ø
Kombinasyonlara uyum	√	Ø
Fiyatı	√	Ø
Kilo artışı	√	Ø
Hipoglisemi	√	Ø
İştahta azalma	√	Ø
Tüm nedenlere bağlı mortalite:	√ 2 yıllık takiplerde %24 oranında azaltır	Ø
IGT'de Etki	√ T2DM'ye gidişi %26.4 azaltır	Ø

Metformin