51 ULUSAL DİYABET KONGRESİ

22- 26 Nisan 2015 - Rixos Sungate Hotel - Beldibi/ Antalya

Üçlü oral antidiyabetik kombinasyonları

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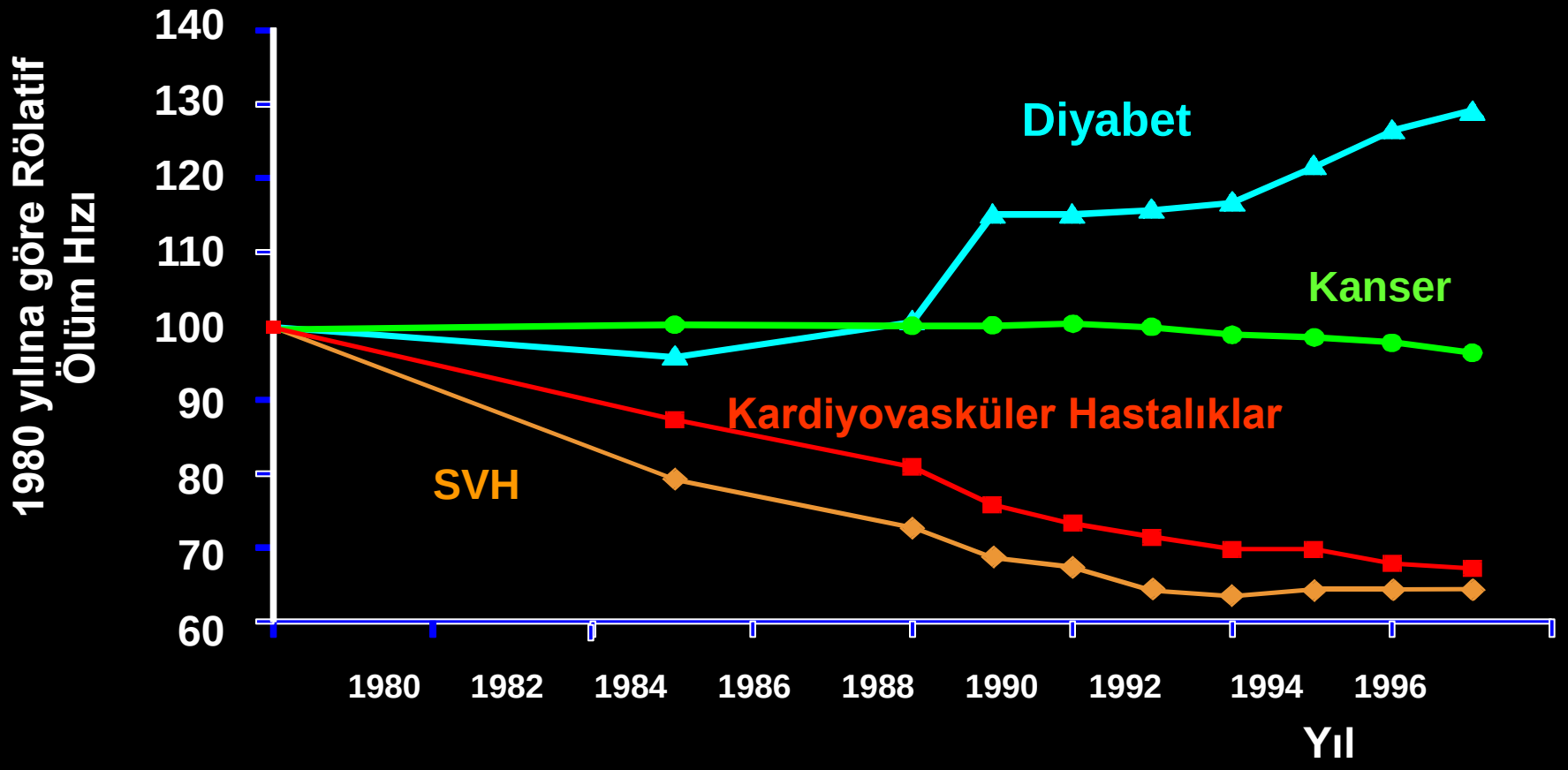
Endokrinoloji ve Metabolizma Hastalıkları Bilim Dalı

FARKLI HASTALIKLARA BAĞLI ÖLÜM HIZLARI



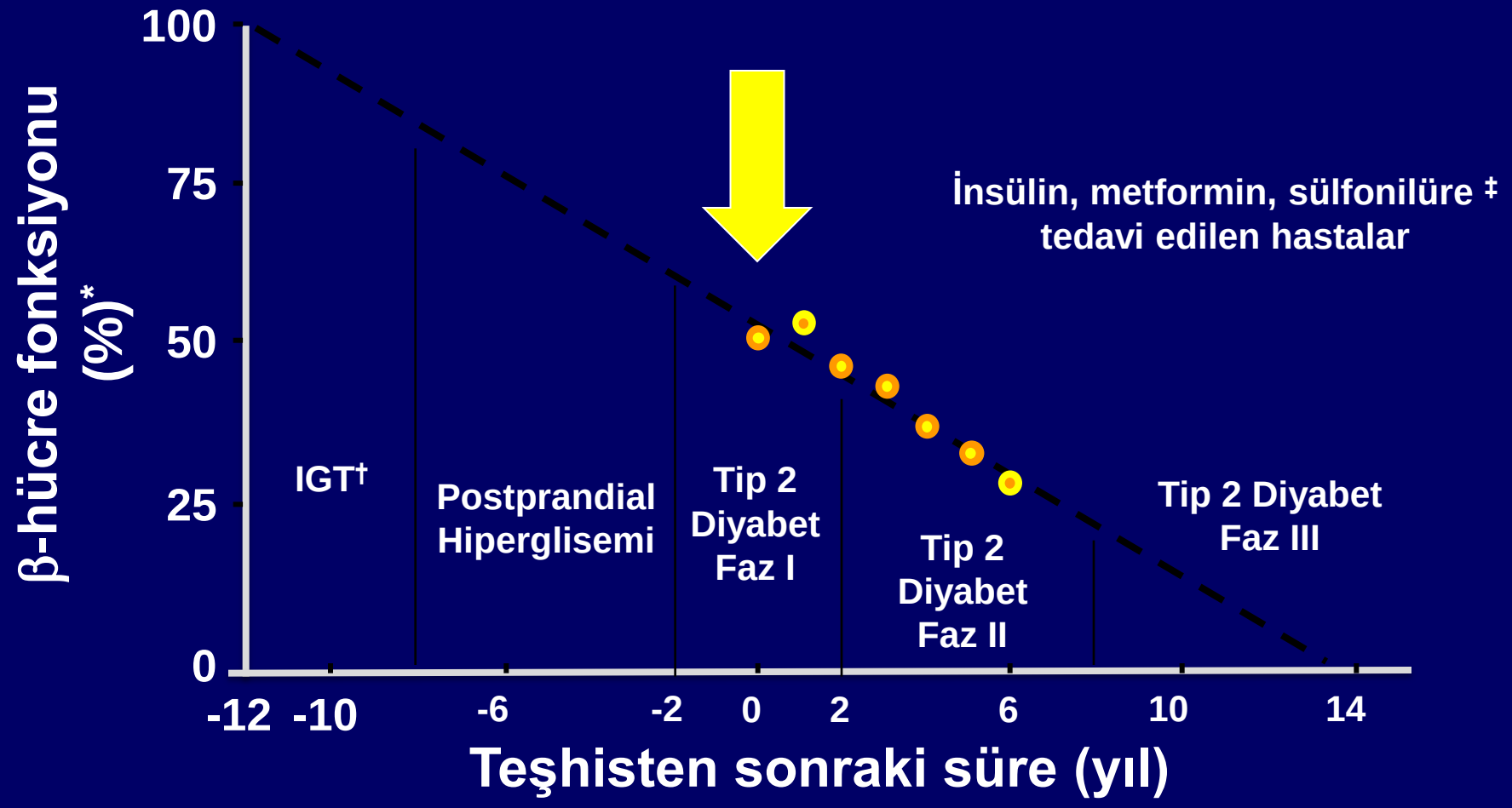
National Centre for Health Statistics, 1998

McKinlay J 2000.356(9231)757-61

Antidiyabetikler
İnsülin dışı oral ve enjektabl tedaviler

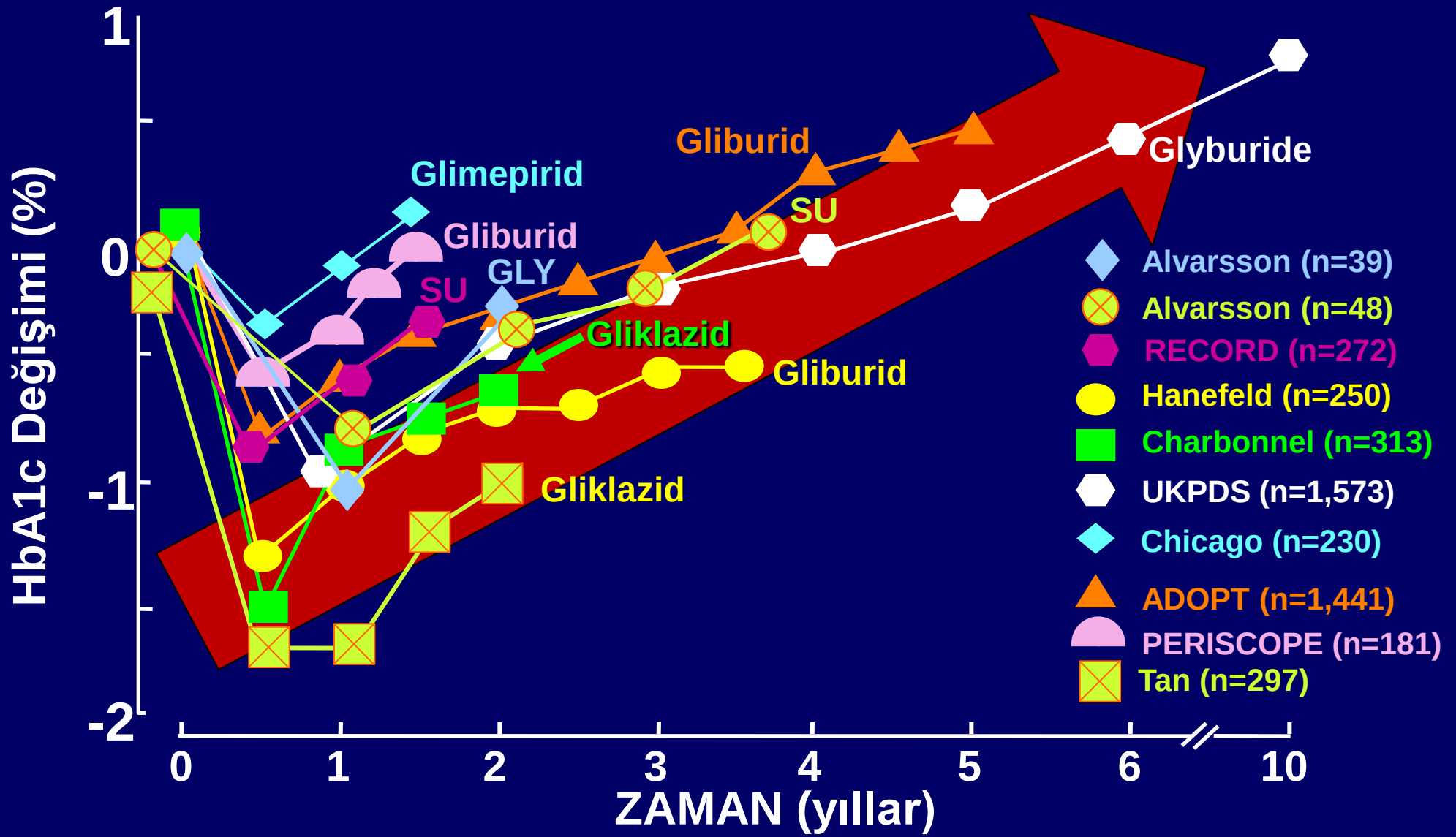
- İnsülin duyarlaştırıcılar
  - Biguanidler; metformin
  - Tiazolidinedionlar; pioglitazon
- İnsülin salgılatıcılar
  - Sulfonilüreler
  - Glinidler
- Glukoz emilimini inhibe edenler
  - α- glukozidaz inhibitörü; akarboz
- İnkretin temelli ilaçlar
  - DPP-4 inhibitörleri
  - GLP-1 analogları
- SGLT2 inhibitörleri

UKPDS: β-hücre fonksiyon azalması değiştirilebiliyor mu?



•Dashed line shows extrapolation forward and backward from years 0 to 6 from diagnosis based on Homeostasis Model Assessment (HOMA) data from UKPDS.
•Lebovitz HE. *Diabetes Rev.* 1999;7:139-153.

GLİSEMİK KONTROL SÜRDÜREBİLİRLİK



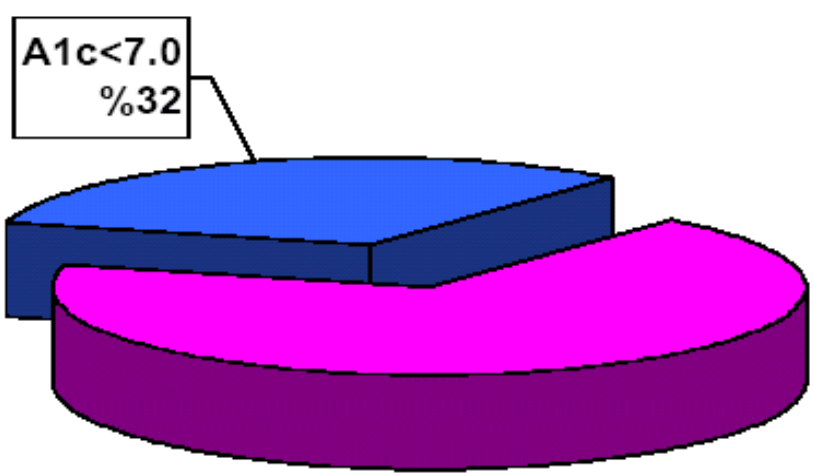
Tip 2 diyabette insülin tedavisi gerekliliği

Tanıdan ~ 5 yıl sonra hastaların ~ %50'sinde

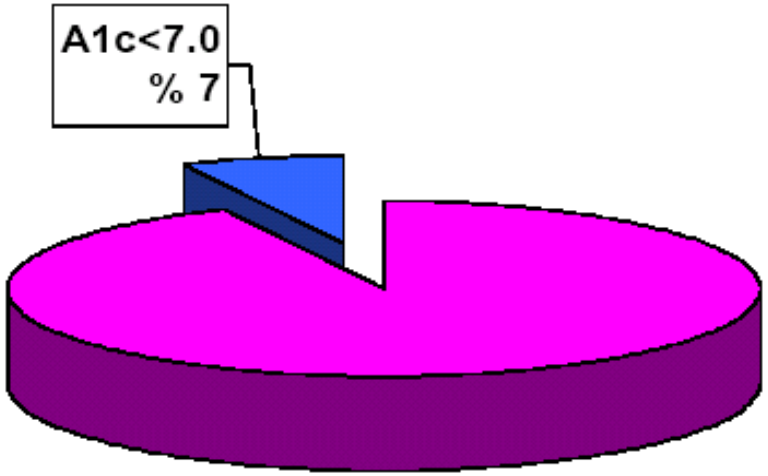
A1C hedefine ulaşmak için
İnsülin kullanımı gerekecektir

Sülfonüre alan hastaların 4-5 yıl sonra
~ 70 %' inde sekonder yetersizlik

Diyabetli Hastaların Tedavisinde Ne Kadar Hedefteyiz?



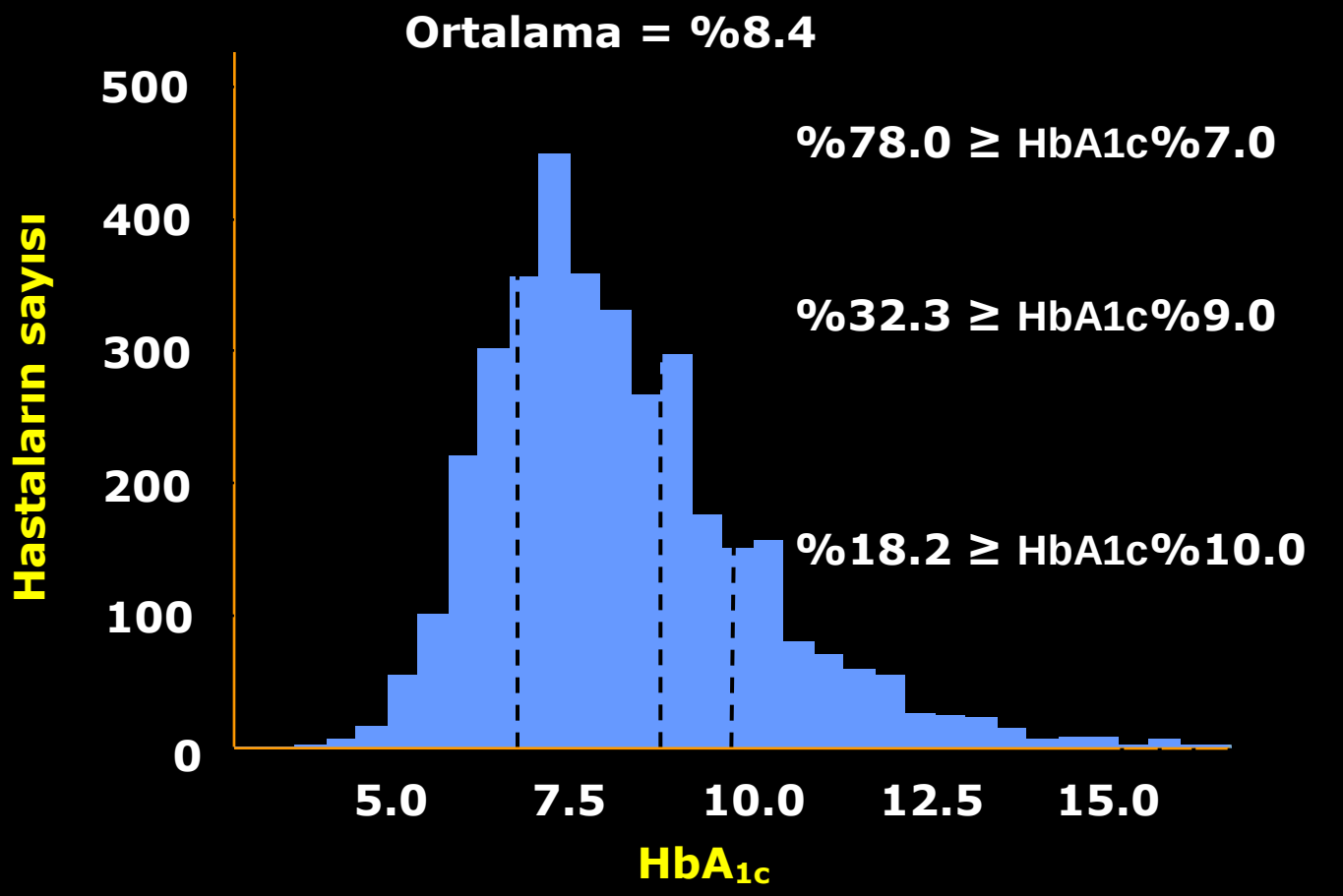
Tip 1 DM Hastaları



Tip 2 DM Hastaları

Ükinç K, Ersöz HÖ, Erem C et al TJEM 2004

İnsülin kullanımına rağmen kan şekeri kontrolü: YETERSİZ



n = 3,658
insülin kullanan hastalar

Gough ADA 2006

- İlaç nedir ?
- Doğru etki ve zararsız
- Patogenezi net bilmiyoruz, yatırımlar ve çalışmalar yanlış bakış açısına göre yapıldı
- Kumar - Rastlantı
- 10-15 YIL
- Negatif sonuçlar yayınlanmıyor. Çalışmaların çoğu saklanmış oluyor

TEDAVİ AMACI

Diyabetin Yönetiminde Hedefler

Daha Fazla Hasta Becerisi ↓ En İyi Metabolik Kontrol ↓ Geç Doku Hasarından Sakınma	Daha Fazla Kendine Bakım ↓ En Az Hipoglisemi Atağı ↓ Akut Problemlerden Sakınma	Daha Az Belirgin Kaşı Koyma “İnkar” ↓ Kendine Güvenli Yaşam Tarzı

DAHA FAZLA YAŞAM KALİTESİ

Onay öncesi KV güvenirlilik görülmeli mi ?

- Upjohn şirketi 1961 Tolbutamid çalışması, firma ile FDA dek bazı akademisyenler arasında ilişki saptandı. Gecikmeli olarak 1970 yılında ölüm nedeniyle durdurudu. Tüm ilaç firmaları sonlanım çalşmalarını bıraktı FDA kan şekeri düşüşü gösteren neredeyse her ilacı onayladı
- Muraglitazar 2005 yılında KV olayları arttırma eğilimde olduğu halde KV markerlara iyi gelmesi sebebi ile FDA'den 8 e karşı bir onay alırken metformin 7e karşı 2 ile onay alabildi. Aynı yılın sonunda aynı neredeyse aynı veriler ile Nissen ve arkadaşları > 2kat ölüm saptadı. FDA firmadan ek KV uzun dönem çalışması istedi. Çalışmanın tamamlanması ile gecikmeli olarak ilaç toplatıldı.
- Roziglitazon
-

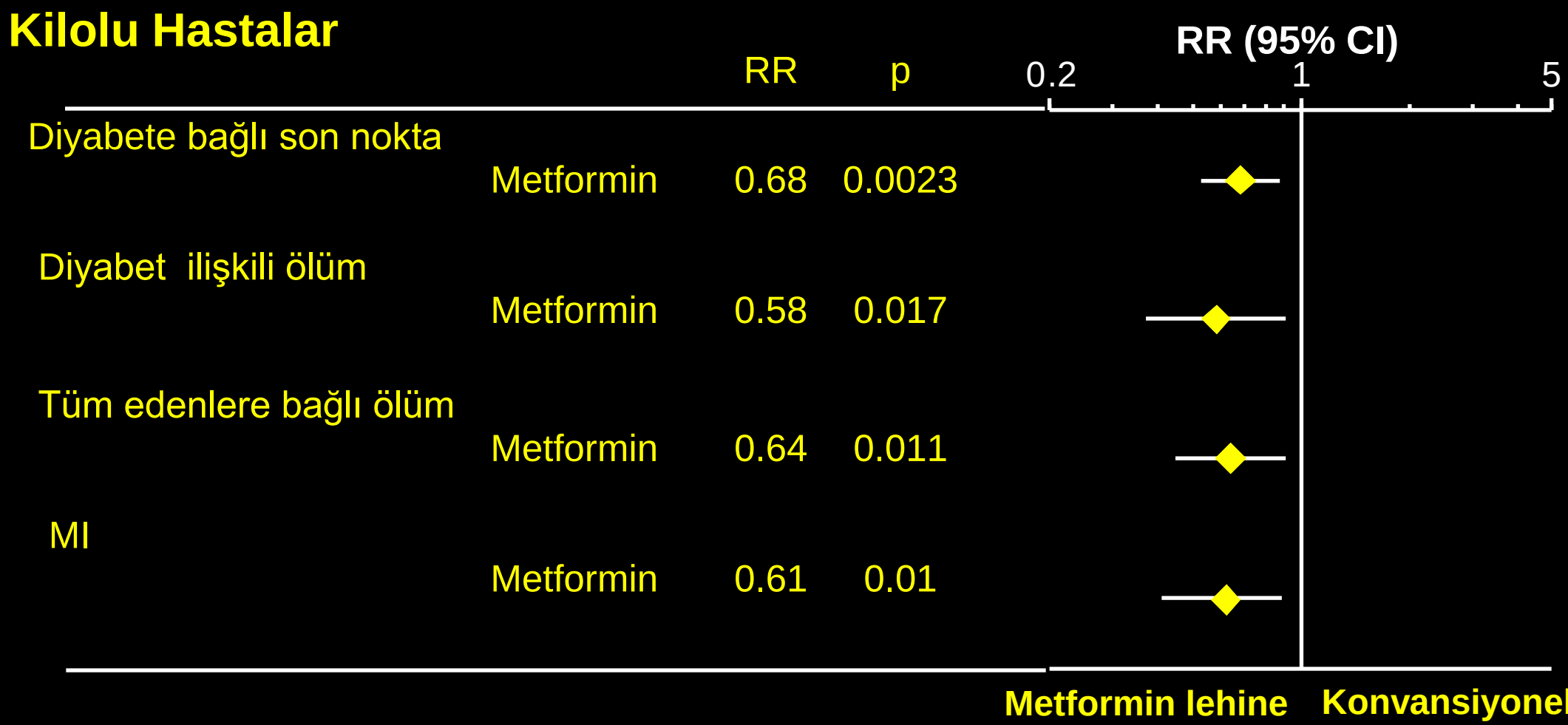
Fransız leylağı- keçisedefi

Antidiyabetik ilaçlar
KV güvenirlilik karşılaştırması –Kanıt Düzeyi

	Kanıt düzeyi
Tüm nedenlere Bağlı Ölüm	Düşük, çok düşük
Kardiyovasküler nedenlere Bağlı Ölüm	Düşük, çok düşük
Ölümcül olmayan MI, Felç	Düşük, çok düşük
Periferik Damar Hastalığı	Düşük, çok düşük
Mikrovasküler Hastalık	Düşük, çok düşük

Bolen Ann IM, 2011

Metformin Karşılaştırması



İnkretin Bazlı ilaçların KV Sonlanım
Meta-analizler

Drug Name/Class	Number of Studies Analyzed	N	CV Events
Exenatide BID[1]	12	3945 (2316 exenatide BID; 1629 comparator)	Risk ratio 0.70 (95% CI 0.38−1.31)
Liraglutide[2]	15	6638 (4257 liraglutide; 2381 comparator)	Incidence ratio 0.73 (95% CI 0.38−1.41)
Linagliptin[3]	8	5239 (3319 linagliptin; 1920 comparator)	Hazard ratio 0.34 (95% CI 0.16−0.70)
Saxagliptin[4]	8	4607 (3356 saxagliptin; 1251 comparator)	Relative risk 0.43 (95% CI 0.23−0.80)
Sitagliptin[5]	25	14,611 (7726 sitagliptin; 6885 comparator)	Incidence ratio 0.83 (95% CI 0.53−1.30)
GLP-1 receptor agonists[6]	37*	15,398 (8619 GLP-1 RA; 6779 comparator)	Odds ratio 0.78 (95% CI 0.54−1.13)
DPP-4 inhibitors[7]	70†	41,959	Odds ratio 0.71 (95% CI 0.59−0.86)

*25 trials reported ≥1 CV event and were included in the main analysis.
†63 trials reported ≥1 CV event and were included in the main analysis.

1. Ratner R, et al. *Cardiovasc Diabetol*. 2011;10:22. 2. Marso SP, et al. *Diab Vasc Dis Res*. 2011;8:237-240. 3. Johansen OE, et al. *Cardiovasc Diabetol*. 2012;11:3. 4. Frederich R, et al. *Postgrad Med*. 2010;122:16-27. 5. Engel SS, et al. *Cardiovasc Diabetol*. 2013;12:3. 6. Monami M, et al. *Diabetes Obes Metab*. 2014;16:38-47. 7. Monami M, et al. *Diabetes Obes Metab*. 2013;15:112-120.

KV sonlanım Çalışmaları

Trial Name	Comparators	Population	Estimated Primary Completion Date
SAVOR-TIMI 53[1]	Saxagliptin vs placebo	T2DM with history of CVD or CV risk	Completed
EXAMINE[2]	Alogliptin vs placebo	T2DM with recent ACS	Completed
TECOS[3]	Sitagliptin vs placebo	T2DM with pre-existing CVD	Dec 2014
ELIXA[4]	Lixisenatide vs placebo	T2DM with ACS	Jan 2015
LEADER[5]	Liraglutide vs placebo	T2DM with CV risk	Oct 2015
EXSCEL[6]	Exenatide ER vs placebo	T2DM	Dec 2017
CARMELINA[7]	Linagliptin vs placebo	T2DM with CV risk	Jan 2018
CAROLINA[8]	Linagliptin vs glimepiride	T2DM with CV risk	Sep 2018

GLP1 reseptör Agonisti

- Pankreas Güvenliği : EMA ve FDA kesin sonuca henüz ulaşamadı; şimdiki datanın desteklemediğini belirtiyorlar
- Bulantı, kusma, ishal: hidrasyon çok önemli

Egan AG NEJM 2014,370

- İlk oral diyabet ilacının kliniğe girişinden 50 yıldan fazla zaman geçti
- Diyabet ilaçlarının makrovasküler hastalığı sonlanım noktası olarak gören İyi dizayn edilmiş, yeterli, istatistiki güçte karşılaştırmalı etkinlik çalışması yok
- Bunun sebebi daha önceki sağlık politikasının tedavi hedefi olarak glukosentrik olması (etkinlik A1c)
- Çoğunda yüksek kardiyovasküler risk elimine edildi
- Güvenlik sorunu olunca hastalar yeni güvenlik datası olmayan ürünlere yöneldirler (Rozi…DPP4 inh)

- Metanaliz ve posthoc çalışmalarına randomize çalışma olmadığından değer gereğinden fazla veriliyor.
- ACCORD'da ölüme yol açan etkeni bulmakta bu yüzden zorlanıyoruz

- DENGE …..İlaç gelişimi ve güvenlik

UKPDS (HbA1c düşürmek)

Hemoglobin A1C 7.9% versus 7.0%

- Any end point ↓ 12% *P*=0.03
- Microvascular disease ↓ 24% *P*=0.01
- Macrovascular disease ↓ 16% *P*=0.052

Blood Pressure 154/87 versus 144/82

- Any end point ↓ 24% *P*=0.005
- Microvascular disease ↓ 37% *P*=0.009
- Macrovascular disease ↓ 44% *P*=0.013

	AKŞ'de azalma	A1C'de azalma	KİLO
Yaşam tarzı değişikliği	40-60 mg/dl	%1.0-2.0	- (2-4 kg)
Metformin (1995)	50 mg/dl	%1.5	-(0-2 kg)
İnsülin (1921)	50-80 mg/dl	%1.5-2.5	+(2-4 kg)
Sulfonilüreler (1946)	40-60 mg/dl	%1.0-2.0	+(1-2 kg)
Glinidler (1997)	30 mg/dl	%1.0-1.5	+
Tiazolidinedionlar (1997)	25-55 mg/dl	%0.5-1.4	+(2-4 kg)
Alfa-glukozidaz inhibitörleri (1995)	20-30 mg/dl	%0.5-0.7	Nötral
GLP-1 analogları (2005)	20-30 mg/dl	%0.5-1.2	-(1-3 kg)
DPP-4 inhibitörleri (2006)	20-25 mg/dl	%0.5-0.8	Nötral

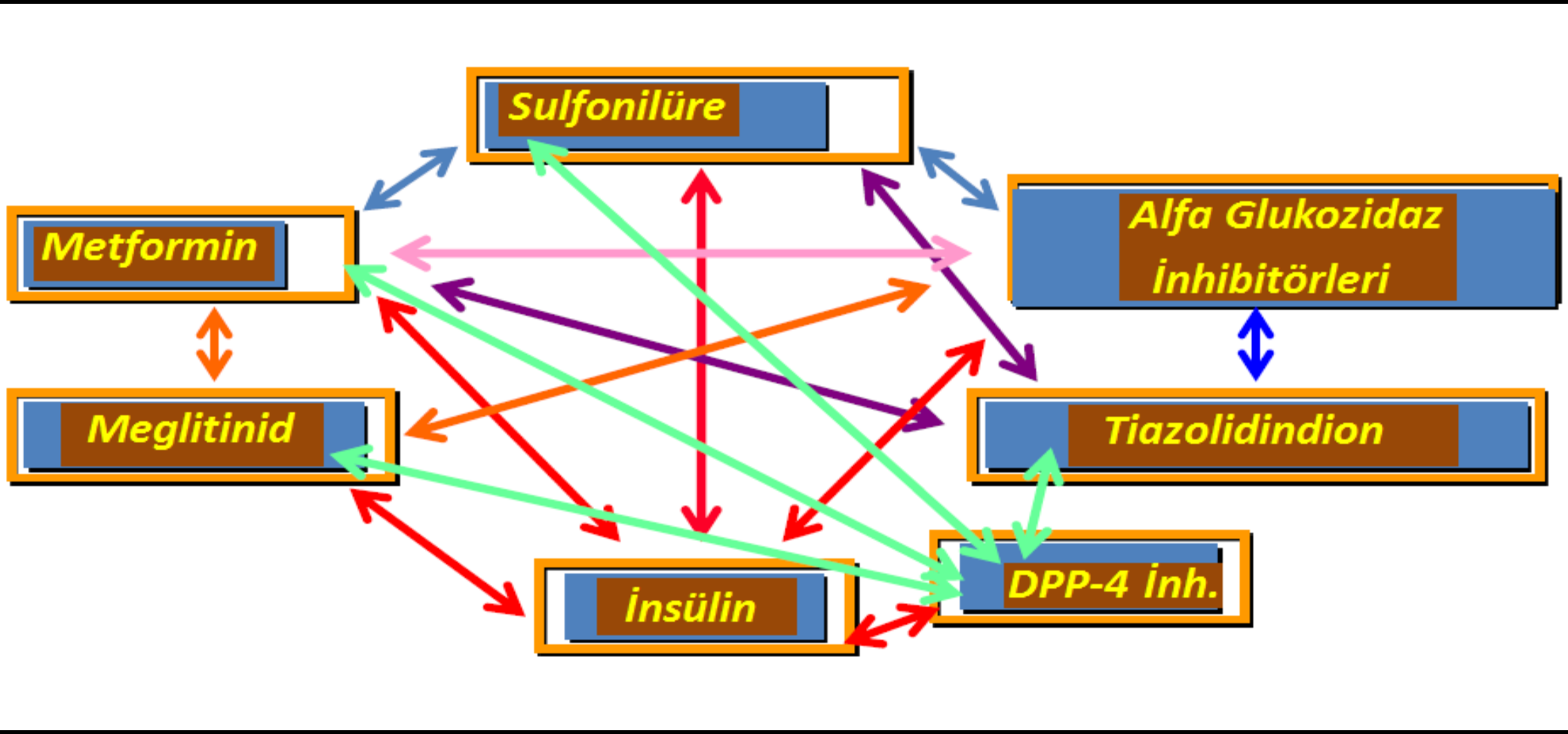
Antidiyabetik ilaçlar ve kan şekerine etkileri

İlaç	Kan şekerine etki
Alfa-glukozidaz inhibitörleri	Tokluk
Safra asit sekastranı	Tokluk
Metformin	Açlık
DPP-4 inhibitörleri	Tokluk
Dopamin agonistleri	Tokluk
Glinidler	Tokluk
GLP-1 agonistleri	Kısa etkili TKŞ; Uzun etkili AKŞ+TKŞ
SU	AKŞ+TKŞ
Tzd	AKŞ+TKŞ
Bazal insülin	Açlık
Bolus insülin	Tokluk

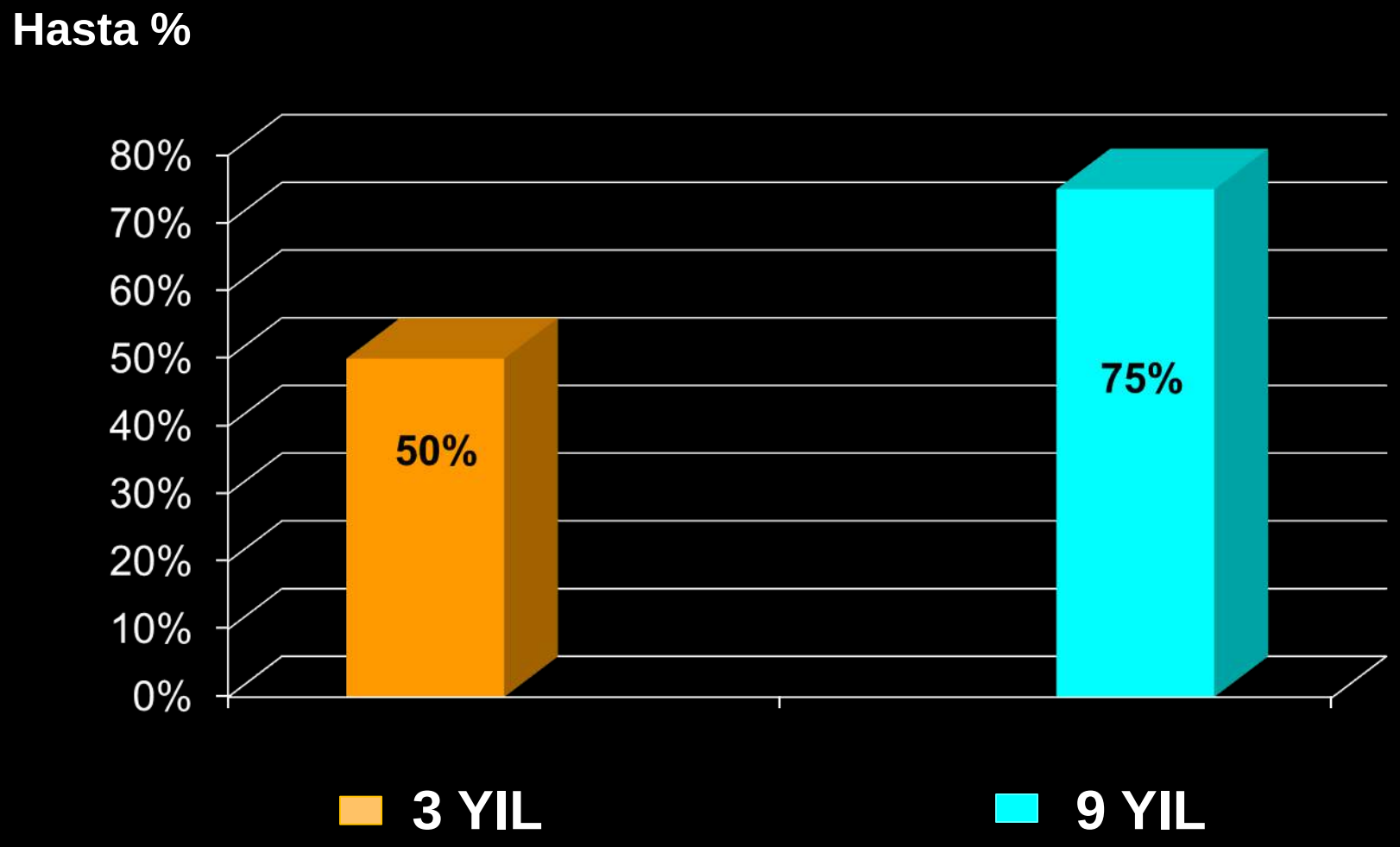
EN İYİ ZAMAN

Kombine edilmiş ajanlar : ilk ana öğün (sabah) öncesi verilebilir

Kombinasyon Tedavisi



Kombinasyon Tedavi İhtiyacı (UKPDS)




REPEAT VISITS
Diagnostic Tests
Take between meals
Hospital Appointment
To be taken three times daily with food

MŞ26

KOMBİNASYON TEDAVİSİ
SİNERJİSTİK / ADİTİF Mİ?

- **1+1≠ 2**

- **İlk ilaç olarak (-1.5%)- (-2%)**
- **İkinci ilaç eklenmesi (-1%)- (-1.5%)**
- **Üçüncü ilaç eklenmesi (-0.5%)- (-1%)**

KOMBİNASYON ADİTİF Mİ ?

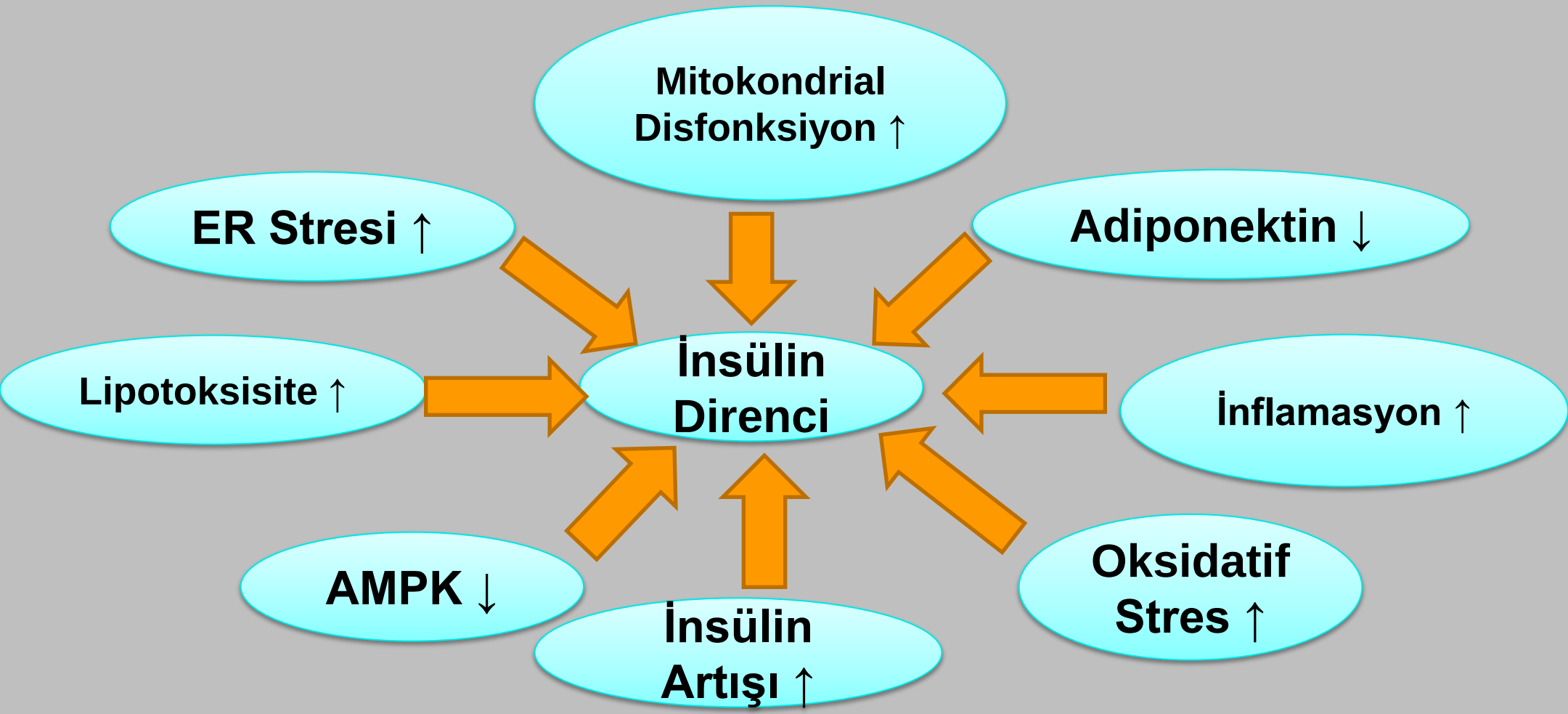
Study	Group	Change in HbA_{1c}, %	
Glimepiride add-on to metformin monotherapy[a]	Metformin	0.07	0.34
	Glimepiride	0.27	
	Metformin + Glimepiride	-0.74	
Vildagliptin and pioglitazone in drug naïve patients[b]	Pioglitazone 30 mg	-1.4	-2.5
	Vildagliptin 100 mg	-1.1	
	Vildagliptin 100 mg + Pio 30 mg	-1.9	
	Vildagliptin 100 mg + Pio 15 mg	-1.7	
Saxagliptin and metformin in drug naïve patients[c]	Metformin	-2.0	-3.7
	Saxagliptin 10 mg	-1.7	
	Saxagliptin 10 mg + Metformin	-2.5	
	Saxagliptin 5mg + Metformin	-2.5	
Alogliptin and pioglitazone in drug naïve patients[d]	Pioglitazone 30 mg	-1.2	-2.2
	Alogliptin 5 mg	-1.0	
	Alogliptin 25 mg + Pioglitazone 30 mg	-1.7	
Dapagliflozin and saxagliptin add-on to metformin monotherapy[e]	Saxagliptin + Metformin	-0.88	-2.08
	Dapagliflozin + Metformin	-1.20	
	SAXA + DAPA + Metformin	-1.47	

a. Charpentier G, et al. *Diabet Med*. 2001;18:828-834[5]; b. Rosenstock J, et al. *Diabetes Obes Metab*. 2007;9:175-185[6]; c. Jadzinsky M, et al. *Diabetes Obes Metab*. 2009;11:611-622[7]; d. Rosenstock J, et al. *Diabetes Care*. 2010;33:2406-2408[8]; e. Rosenstock J, et al. ADA 2014. Abstract 127-LB.[1]

YENİ TANI KOMBİNASYON TEDAVİSİ: DEFRONZO

Diabetes 58:773-795, 2009

İnsulin direncinin olası mekanizmaları

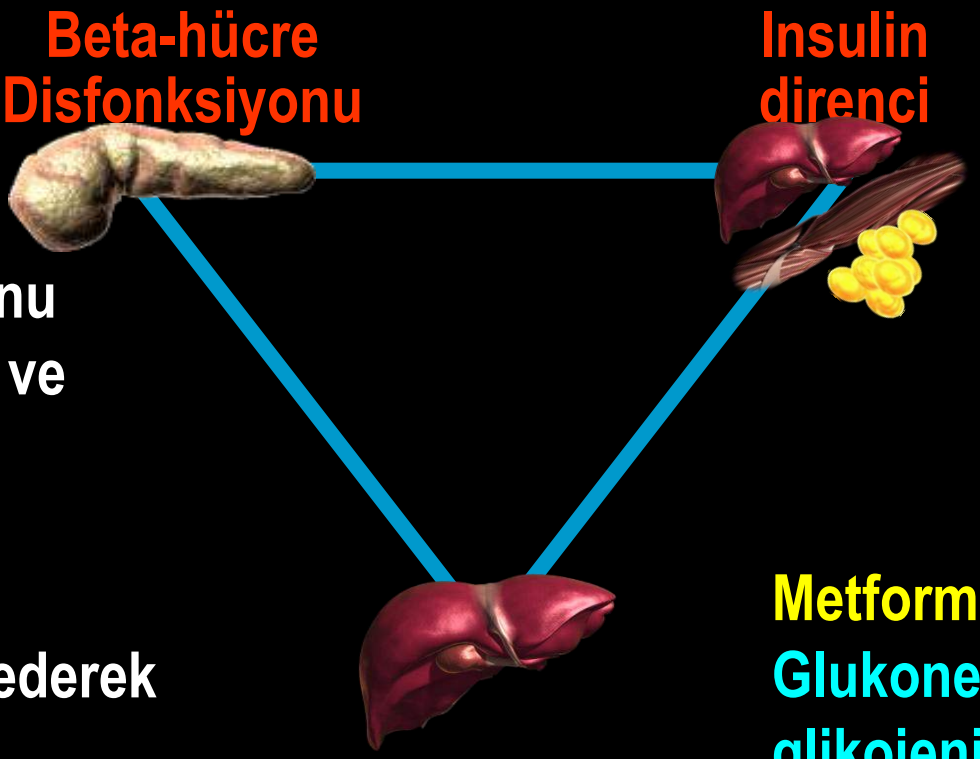


OAD
Tamamlayıcı Etkiler

Etki	Metformin	SU	Glinidler	TZD	AGİ	GLP-1 RA	DPP-4 inhibitörleri
↑ Insulin sekresyonu							
↑ Insulin sensitivite ve etkisi							
↓ Hepatik glukoz üretimi							
↓ Mide boşalma/glukoz emilimi							
↑ Tokluk							
Ağırlık	↓	↑	↑	↑	0	↓↓	0

Rodbard H, *Endocr Pract*. 2009;15:540-559; Drucker D, *Diabetes Care*. 2010;33:428-433.

Sitagliptin ve Metformin T2DM metabolik defektleri hedefler



Sitagliptin
Beta hücre fonkisyonunu düzeltir; insülin sentez ve sekresyonunu arttırır

Metformin
insülin sensitivitesini arttırır (KC> Kas, Yağ)

Sitagliptin
Glukagonu süprese ederek HGÇ azaltır

Metformin
Glukoneogenez ve glikojenilizi azaltarak HGÇ azaltır

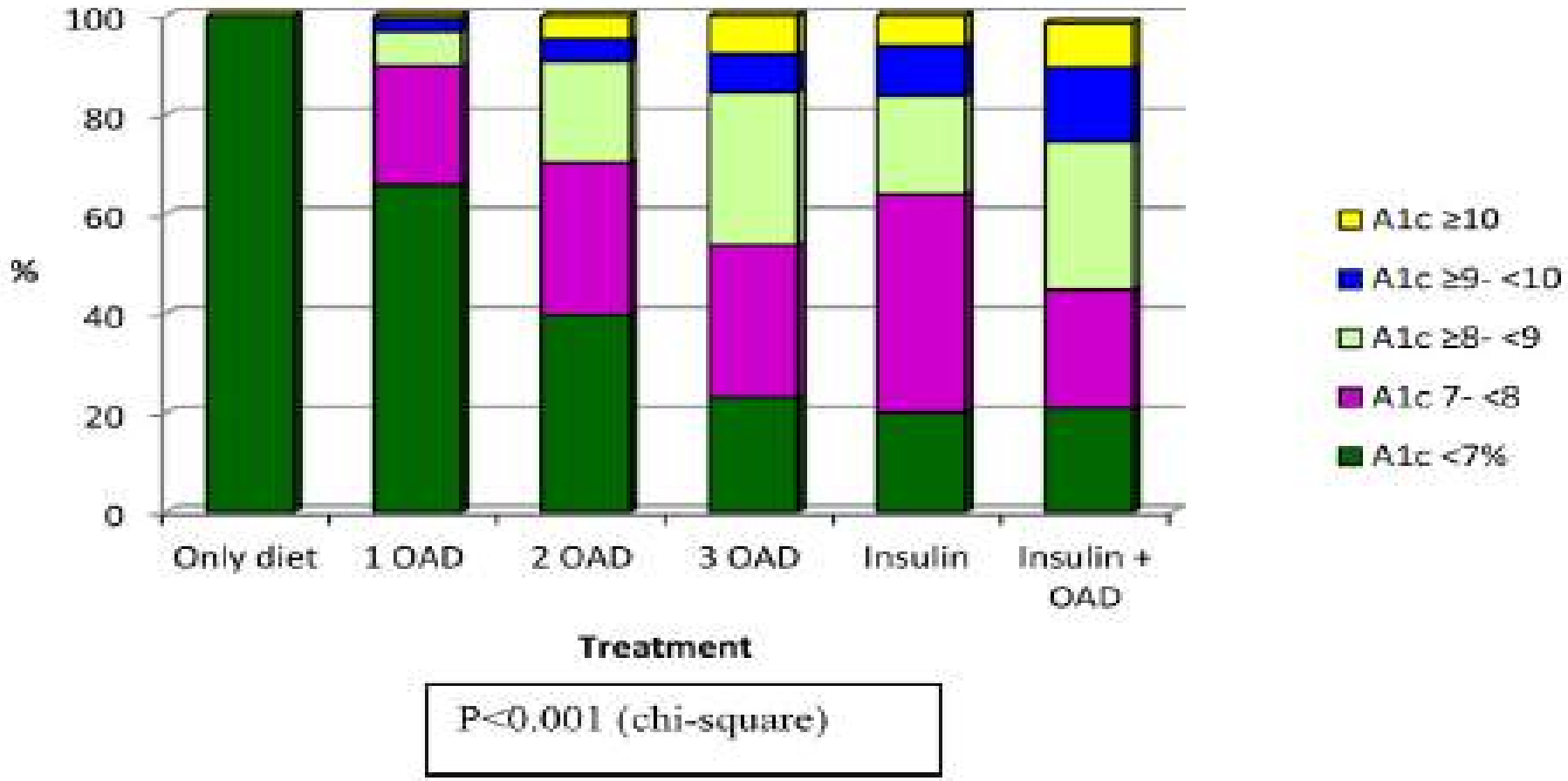


Fig. 1 – A1c values according to the type of treatment. OAD: oral antidiabetics.

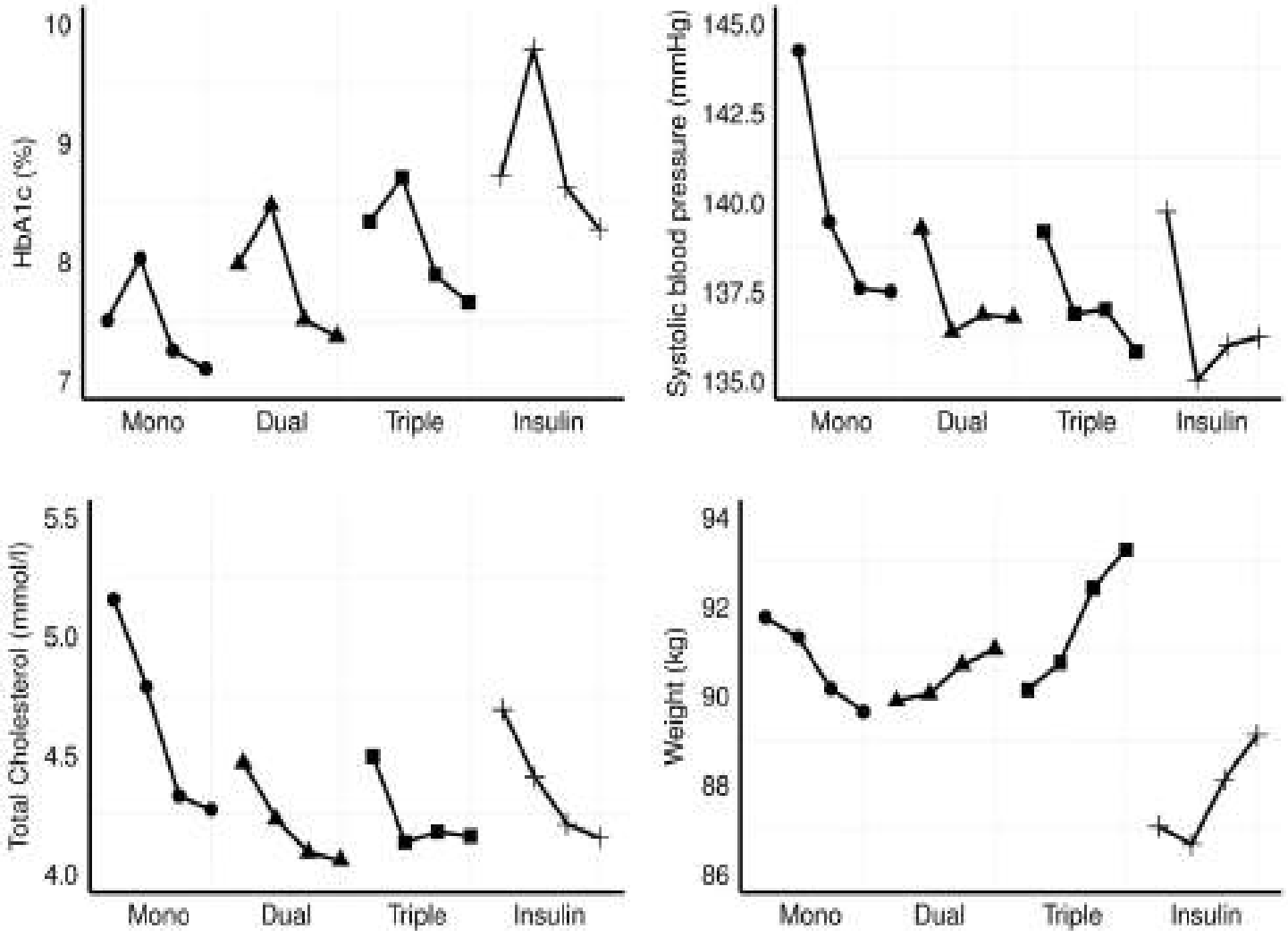
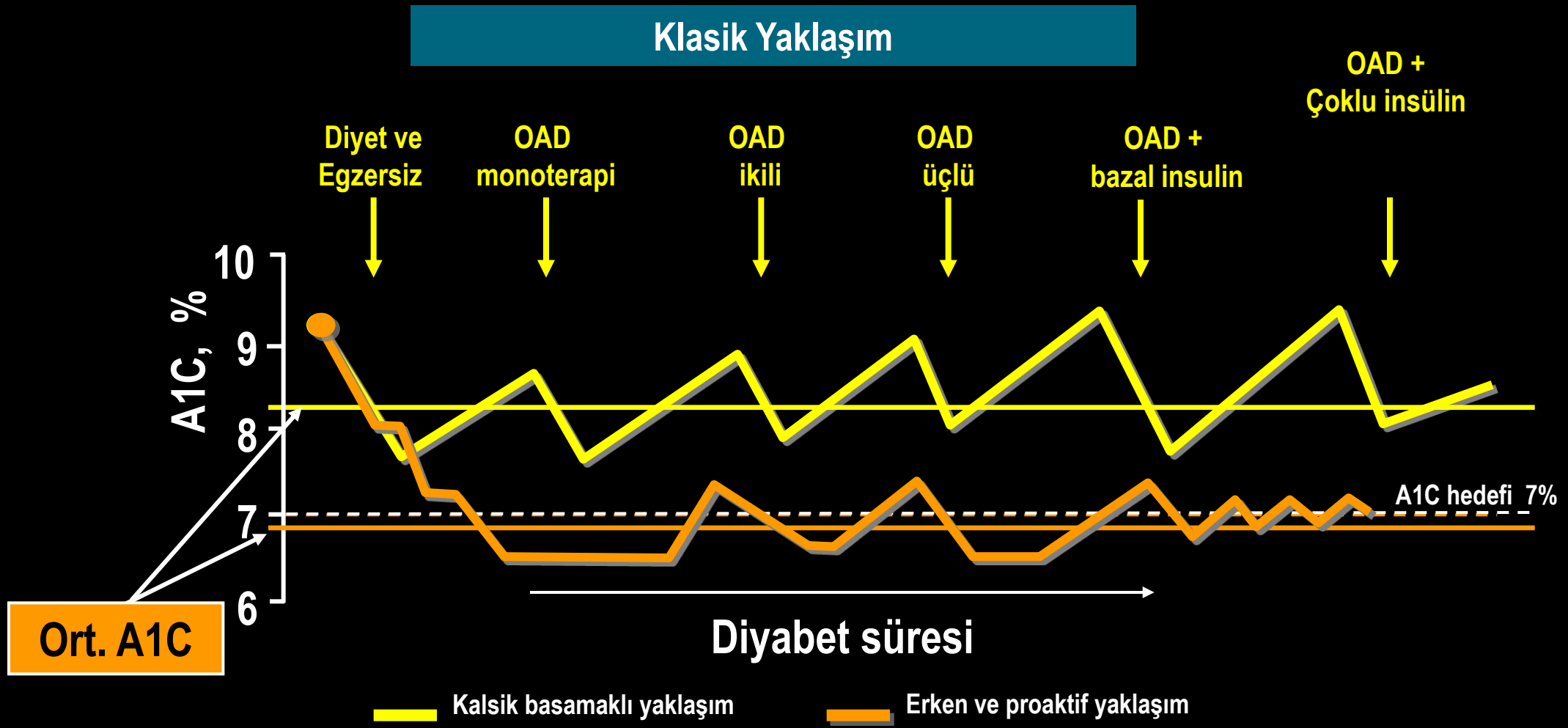


Fig. 1 Risk factor profiles before (1st and 2nd *points*) and after (3rd and 4th *points*) therapy escalation for each patient cohort

Erken ve uygun yaklaşım hedefe ulaşmayı kolaylaştırır



Del Prato S et al. *Int J Clin Pract.* 2005;59(11):1345–1355.

Yeni Tanı T2DM hastalarında başlangıçta üçlü tedavi-basamaklı klasik ekleme

- Metformin + Pioglitazon + Exanatid
- Metformin + Sülfonüre + Bazal insülin
- Daha iyi kontrol
- Hipoglisemi daha az
- Kilo azalması 1.2 kg

Defronzo ekibi

original article

Diabetes, Obesity and Metabolism 17: 268–275, 2015.

Initial combination therapy with metformin, pioglitazone and exenatide is more effective than sequential add-on therapy in subjects with new-onset diabetes. Results from the Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT): a randomized trial

M. A. Abdul-Ghani[1], C. Puckett[1], C. Triplitt[1], D. Maggs[2], J. Adams[1], E. Cersosimo[1] & R. A. DeFronzo[1]

[1]*Diabetes Division, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA*
[2]*GI Dynamics, Lexington, MA, USA*

Aim: To test our hypothesis that initiating therapy with a combination of agents known to improve insulin secretion and insulin sensitivity in subjects with new-onset diabetes would produce greater, more durable reduction in glycated haemoglobin (HbA1c) levels, while avoiding hypoglycaemia and weight gain, compared with sequential addition of agents that lower plasma glucose but do not correct established pathophysiologic

Methods: Drug-naïve, recently diagnosed subjects with type 2 diabetes mellitus (T2DM) were randomized in an open-fashion design study to metformin/pioglitazone/exenatide (triple therapy; n = 108) or an escalating dose of metformin followed by sequential additi and glargine insulin (conventional therapy; n = 115) to maintain HbA1c levels at <6.5% for 2 years.

Results: Participants receiving triple therapy experienced a significantly greater reduction in HbA1c level than those receiving convent vs. 6.50%; p < 0.001). Despite lower HbA1c values, participants receiving triple therapy experienced a 7.5-fold lower rate of hypogl with participants receiving conventional therapy. Participants receiving triple therapy experienced a mean weight loss of 1.2 kg vers gain of 4.1 kg (p < 0.001) in those receiving conventional therapy.

Conclusion: The results of this exploratory study show that combination therapy with metformin/pioglitazone/exenatide in pa diagnosed T2DM is more effective and results in fewer hypoglycaemic events than sequential add-on therapy with metformin, sulf basal insulin.

Keywords: combination therapy, conventional therapy, durability, glycaemic control

Date submitted 30 September 2014; date of first decision 16 October 2014; date of final acceptance 20 November 2014

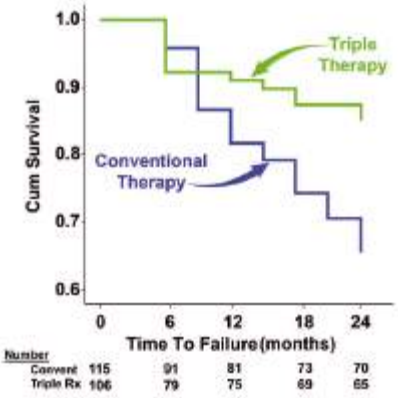
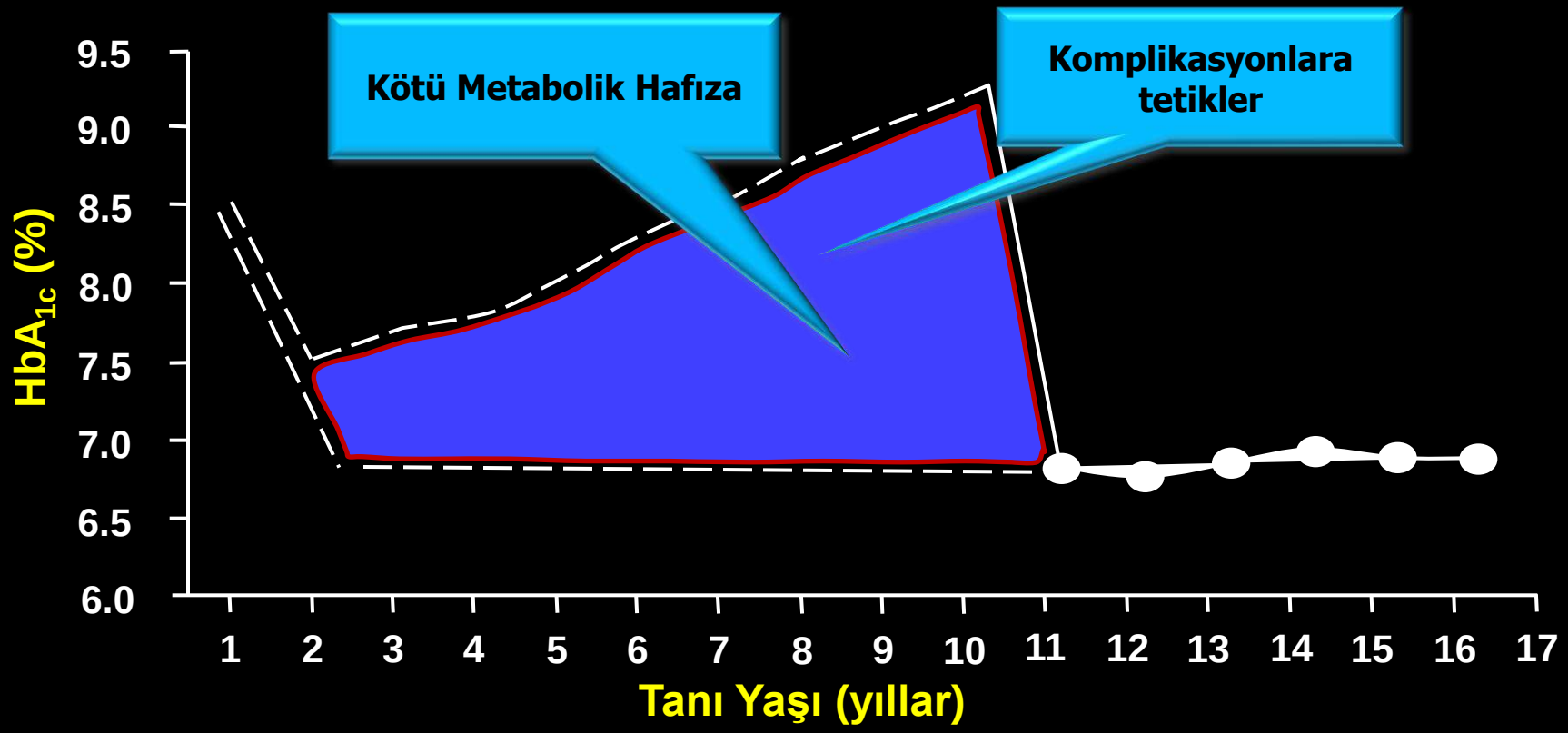


Figure 3. Kaplan–Meier plot of time to treatment failure, defined as glycated haemoglobin (HbA1c) > 6.5%, in the conventional (convent) therapy and triple (Rx) therapy groups (p < 0.001). Cum, cumulative.

Kötü Metabolik Hafıza

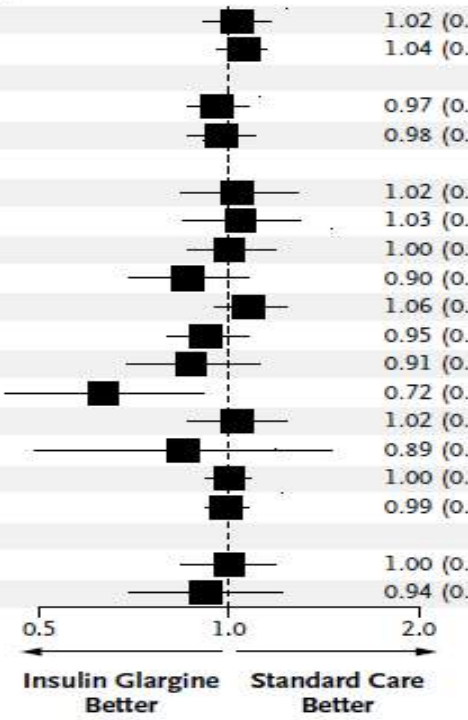


Del Prato S *Int J Clin Pract* 2010;64:295–304.

Erken insulin tedavisi – Tip 2 Diyabet

Prediyabet veya diyabet ile birlikte kardiovasküler risk faktörleri olan hastalarda başlangıçta Glarjin tedavisi (N=12,537)

Outcome	Insulin Glargine (N=6264)		Standard Care (N=6273)		Hazard Ratio (95% CI)	P Value
	no. (%)	*no./100 patient-yr*	*no. (%)*	*no./100 patient-yr*		
First coprimary outcome	1041 (16.6)	2.94	1013 (16.1)	2.85	1.02 (0.94–1.11)	0.63
Second coprimary outcome	1792 (28.6)	5.52	1727 (27.5)	5.28	1.04 (0.97–1.11)	0.27
Microvascular outcomes	1323 (21.1)	3.87	1363 (21.7)	3.99	0.97 (0.90–1.05)	0.43
Total mortality	951 (15.2)	2.57	965 (15.4)	2.60	0.98 (0.90–1.08)	0.70
Total myocardial infarctions	336 (5.4)	0.93	326 (5.2)	0.90	1.02 (0.88–1.19)	0.75
Total strokes	331 (5.3)	0.91	319 (5.1)	0.88	1.03 (0.89–1.21)	0.69
Death from cardiovascular causes	580 (9.3)	1.57	576 (9.2)	1.55	1.00 (0.89–1.13)	0.98
Hospitalization for congestive heart failure	310 (4.9)	0.85	343 (5.5)	0.95	0.90 (0.77–1.05)	0.16
Revascularization	908 (14.5)	2.69	860 (13.7)	2.52	1.06 (0.96–1.16)	0.24
Angina	709 (11.3)	2.07	743 (11.8)	2.17	0.95 (0.85–1.05)	0.29
Unstable	238 (3.8)	0.66	261 (4.2)	0.72	0.91 (0.76–1.08)	0.28
New	100 (1.6)	0.27	138 (2.2)	0.38	0.72 (0.56–0.93)	0.01
Worsening	455 (7.3)	1.29	446 (7.1)	1.26	1.02 (0.89–1.16)	0.80
Limb or digit amputation	47 (0.8)	0.13	53 (0.8)	0.14	0.89 (0.60–1.31)	0.55
Cardiovascular hospitalization	2081 (33.2)	6.98	2071 (33.0)	6.91	1.00 (0.94–1.07)	0.90
Noncardiovascular hospitalization	2339 (37.3)	7.90	2349 (37.4)	7.93	0.99 (0.94–1.05)	0.85
Any cancer	476 (7.6)	1.32	477 (7.6)	1.32	1.00 (0.88–1.13)	0.97
Death from cancer	189 (3.0)	0.51	201 (3.2)	0.54	0.94 (0.77–1.15)	0.52



ORIGIN Trial Investigators. *N Engl J Med*. 2012;367:319-328.

Original Investigation

Association Between Intensification of Metformin Treatment With Insulin vs Sulfonylureas and Cardiovascular Events and All-Cause Mortality Among Patients With Diabetes

Christianne L. Roumie, MD, MPH; Robert A. Greevy, PhD; Carlos G. Grijalva, MD, MPH; Adriana M. Hung, MD, MPH; Xulei Liu, MD, MS; Harvey J. Murff, MD, MPH; Tom A. Elasy, MD, MPH; Marie R. Griffin, MD, MPH

OBJECTIVE To compare time to acute myocardial infarction (AMI), stroke, or death in a cohort of metformin initiators who added insulin or a sulfonylurea.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort constructed with national Veterans Health Administration, Medicare, and National Death Index databases. The study population comprised veterans initially treated with metformin from 2001 through 2008 who subsequently added either insulin or sulfonylurea. Propensity score matching on characteristics was performed, matching each participant who added insulin to 5 who added a sulfonylurea. Patients were followed through September 2011 for primary analyses or September 2009 for cause-of-death analyses.

MAIN OUTCOMES AND MEASURES Risk of a composite outcome of AMI, stroke hospitalization, or all-cause death was compared between therapies with marginal structural Cox proportional hazard models adjusting for baseline and time-varying demographics, medications, cholesterol level, hemoglobin A_{1c} level, creatinine level, blood pressure, body mass index, and comorbidities.

RESULTS Among 178 341 metformin monotherapy patients, 2948 added insulin and 39 990 added a sulfonylurea. Propensity score matching yielded 2436 metformin + insulin and 12 180 metformin + sulfonylurea patients. At intensification, patients had received metformin for a median of 14 months (IQR, 5-30), and hemoglobin A_{1c} level was 8.1% (IQR, 7.2%-9.9%). Median follow-up after intensification was 14 months (IQR, 6-29 months). There were 172 vs 634 events for the primary outcome among patients who added insulin vs sulfonylureas, respectively (42.7 vs 32.8 events per 1000 person-years; adjusted hazard ratio [aHR], 1.30; 95% CI, 1.07-1.58; $P = .009$). Acute myocardial infarction and stroke rates were statistically similar, 41 vs 229 events (10.2 and 11.9 events per 1000 person-years; aHR, 0.88; 95% CI, 0.59-1.30; $P = .52$), whereas all-cause death rates were 137 vs 444 events, respectively (33.7 and 22.7 events per 1000 person-years; aHR, 1.44; 95% CI, 1.15-1.79; $P = .001$). There were 54 vs 258 secondary outcomes: AMI, stroke hospitalizations, or cardiovascular deaths (22.8 vs 22.5 events per 1000 person-years; aHR, 0.98; 95% CI, 0.71-1.34; $P = .87$).

CONCLUSIONS AND RELEVANCE Among patients with diabetes who were receiving metformin, the addition of insulin vs a sulfonylurea was associated with an increased risk of a composite of nonfatal cardiovascular outcomes and all-cause mortality. These findings require further investigation to understand risks associated with insulin use in these patients.

BİREYSEL TEDAVİ

- Yaş

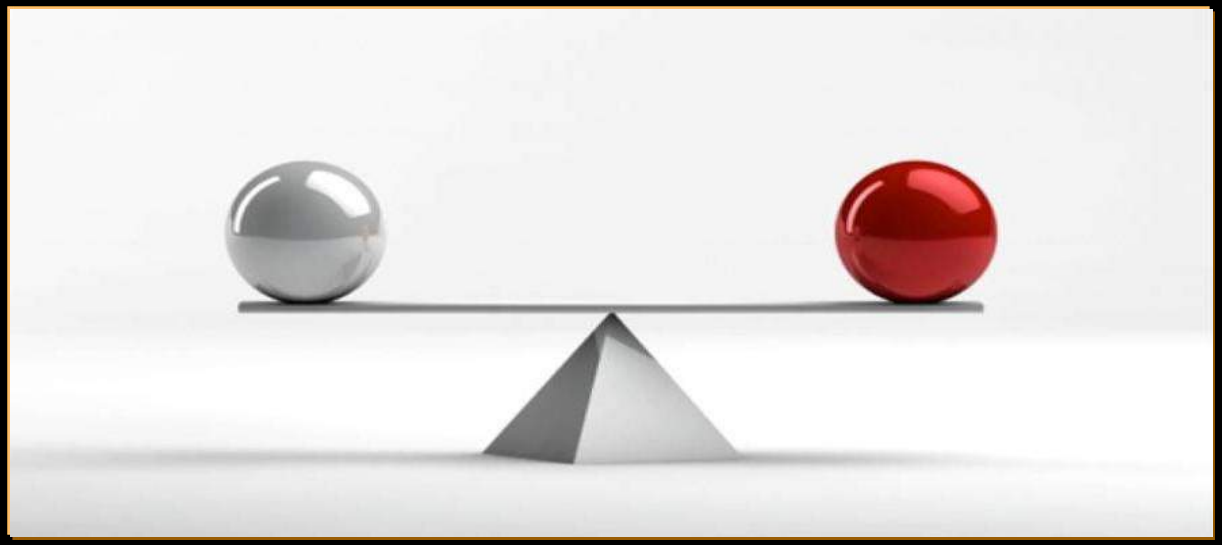
AACE HbA1c < 6.5
ADA HbA1c < 7

- Vücut Ağırlığı
- Komplikasyonlar / Hipoglisemi riski
- Süre / Yaşam beklentisi
- Fiyat / Eğitim

AACE
İlk HbA1c < 7.5 ikili
İlk HbA1c < 7.5 üçlü

Inzucchi Diatetes Care 2015

Risk-Yarar Dengesi (Hipoglisemi ve kilo artışı)



Hiperglisemi tedavisine yaklaşım

Diabetes Care 2015

Hasta Eğitimi

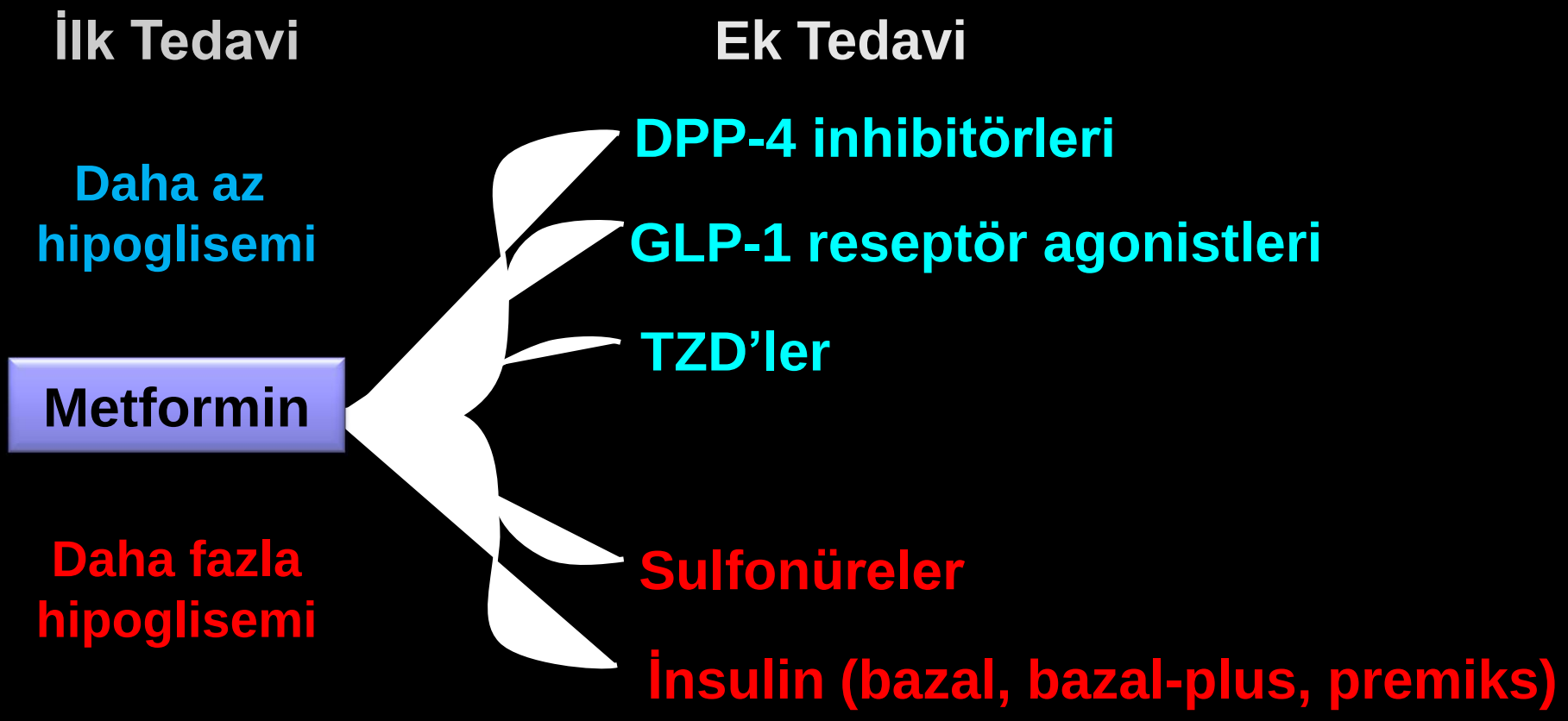
- **‘En çok bilen diyabet hastası en uzun yaşar’**
  Elliott Joslin MD

- **Hasta için neyin önemli olduğunu anlamak**
- **Çekincelerini tartışmak**
- **Hasta ile birlikte tedavi kararını vermek,**

KOMORBİDİTELER

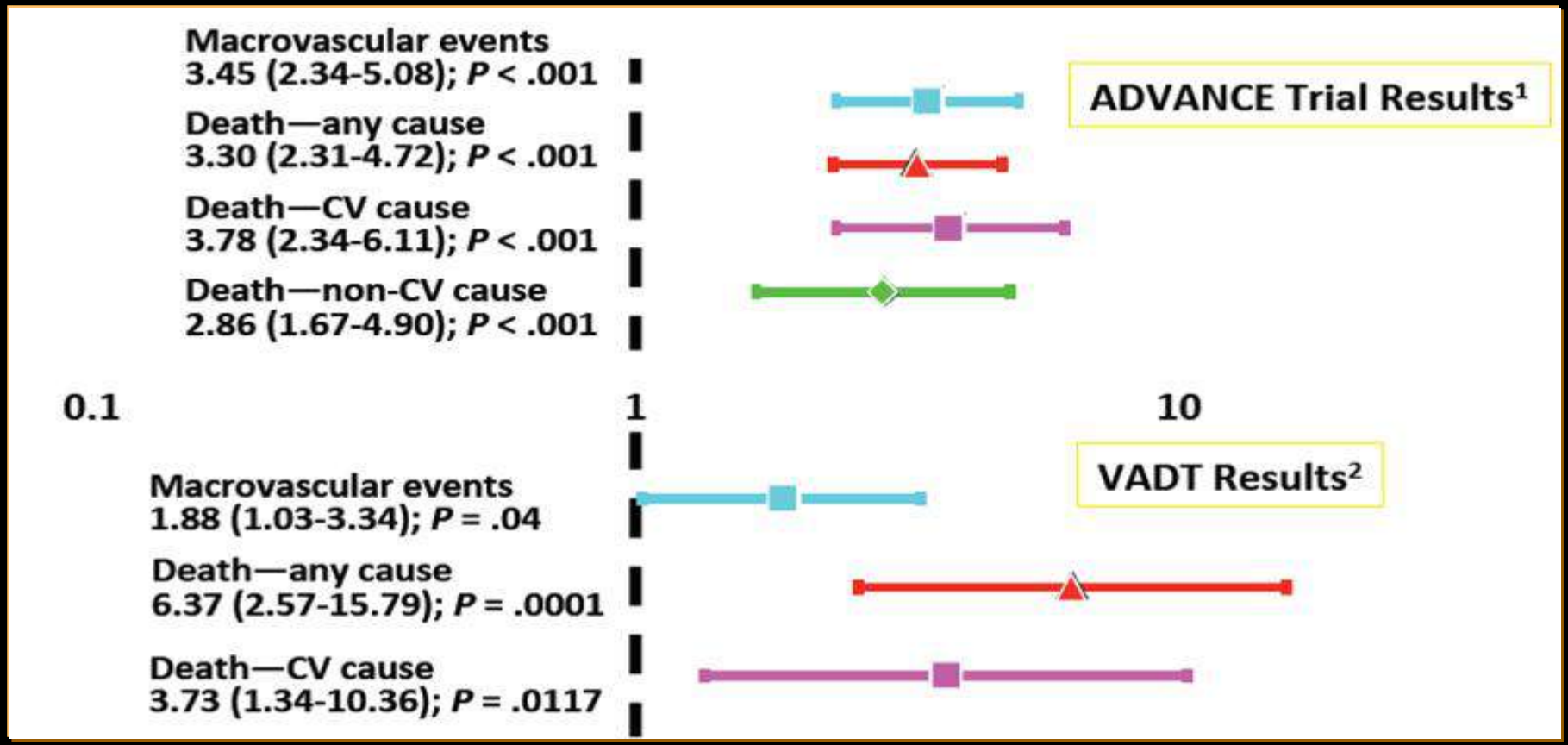
- **KAH…….Metformin KVH açısından yararlı (UKPDS),Hipoglisemiden kaçın, SU ? ve TZD ? kaçın; inkretin bazlılarda sonuçlar henüz çıkmadı**
- **Kalp Yetmezliği……Çoğu durumda metformin verilmeli, tzd verme, inkretin bazlı tedavide DPP4 dikkat et..**
- **Renal Hastalık……hipoglisemi riski artar; metformin ile laktik asidoz riski; SU riskli; inkretin bazlılarda doz ayarı; GFR <30 olanlarda hiçbirini verme**
- **Karaciğer Hastalığı……Karaciğer yağlanmasında Metformin, DPP4 ve pio uygun kişilere verilebilir; yetmezlikte insülin**
- **Hipoglisemi……. Mortaliteyi arttırır; ilaç seçimide çok önemli**

Metfromine eklenen ajana göre Hipoglisemi Riski



Moghissi E,. *Endocr Pract*. 2013;Feb 20:1-33

Ciddi Hipoglisemi - Mortalite ve KVO riski



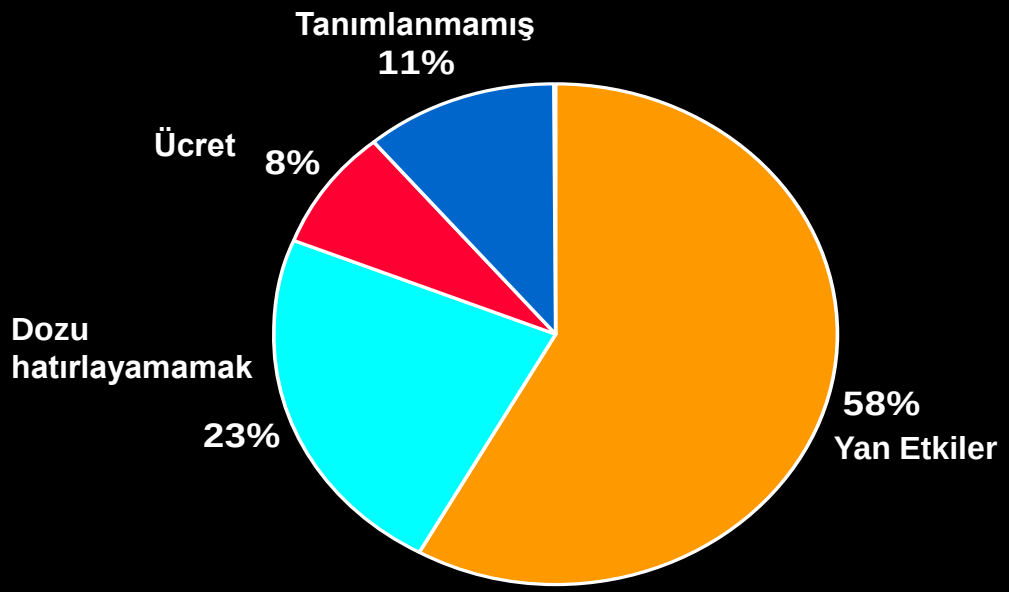
Antidiyabetik Ajanlar ve Kilo

sınıf	İlaçlar	Kilo Etkisi
Amilin analoğu	Pramlintid	↓
Biguanid	Metformin	↓
GLP-1 reseptör agonistleri	Exenatide, exenatide XR,	↓
SGLT-2 inhibitörü	Canagliflozin	↓
α-Glucozidaz inhibitörleri	Akarboz, miglitol	↔
Safra Asit Sekastranı	Colesevelam	↔
DPP-4 inhibitörleri	Alogliptin, linagliptin, saxagliptin, sitagliptin	↔
Dopamin-2 agonistleri	Bromokriptin	↔
Glinidler	Nateglinid, repaglinid	↑
Sulfonüreler	Glimepirid, glipizid, gliklazid, glyburid	↑
İnsulin	Aspart, detemir, glargine, glulisine, lispro, NPH, regular	↑↑
Tzd (	Pioglitazone, rosiglitazone	↑↑

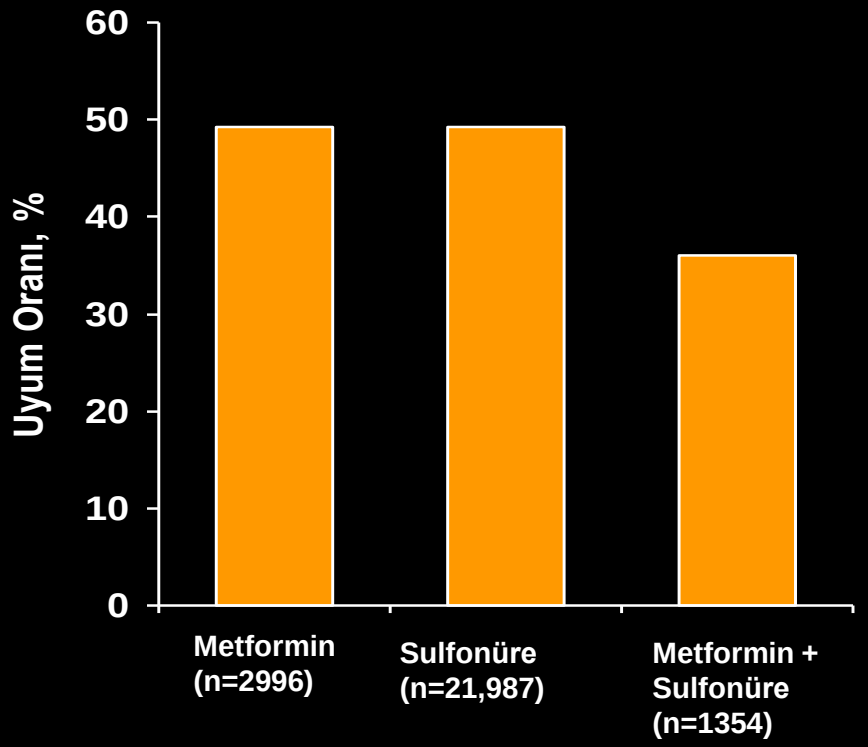
Inzucchi SE,. *Diabetes Care.* 2012;35:1364-1379. Garber AJ, et al. *Endocr Pract.* 2013;19:327-336.

Ek Yan Etkiler ve Komplians azalması
Kombinasyon tedavisine karşı iki potansiyel engel

Uyum ile ilgili en sık sorunlar



Multi-ilaç Tedavisi Uyumu Azaltıyor



Grant RW *Diabetes Care*. 2003;26:1408–1412.

Dailey G *Clin Ther*. 2001;23:1311–1320.

Metformin ilaç eklenmesi

	Avantaj	Dezavantaj
SU	Deneyim fazla; ucuz; Oral	Hipoglisemi, kilo alımı, KV güvenilirlik?
DPP4 inh.	Kilo nötral; Oral	KKY ?, Pankreatit?, pahalı
TZD	Sürdürülebilirlik; Oral; değişken fiyat	Ödem; KKY, kilo alımı, kırık, mesane kanseri ?
GLP-1 agonisti	Kilo ve kan basıncı azalması	GI YE, pankreatit ?, injeksiyon, pahalı
SGLT-2 inhibitörleri	Kilo kaybı, düşük SKB, oral, hipoglisemi riski düşük	Genital mikotik infeksiyon, hipotansiyon, yüksek fiyat, KV güvenlik ?? LDL artışı ??

	Metformin	SU	TZD	Akarboz	İnsülin	DPP-4 inhibitörleri	GLP-1 R Agonistleri
Etkinlik	++	++	++	+	+++	++,+	++
Hastalık progresyonuna etki	-	-	?	-	-	?	?
Kardiyovasküler ertkiler	+	Rosi.(-) R. ve P. Volüm ↑	+	-	+	-	+
Tolerans	orta	orta	orta	kötü	orta	Çok iyi	Orta
Ağırlık artışı	-	+	+	-	+	-	Kilo kaybı
Tek başına hipoglisemi	-	+	-	-	+	-	-

Milan k. Patel, Br j Clin Pharmacol 2010; 70 Parks M et al N Engl Med.2010; 362:774-7

Sınırlılık	İlaç
Hipoglisemi	SU, glinidler, insulin
Kilo alımı	SU, Glinidlar, glitazonlar, insulin
Ödem	Glitazonlar, insulin
GI yan etkileri	Metformin, alfa-glukozidaz inhibitörleri
Laktik asidoz	Metformin
Yaşlı, böbrek yetm. ve kalp yetmezliği güvenlik	Glitazonlar, metformin, sulfonüreler
Kötü cevap oranı	Tüm ilaçlar
Süreklilik	Glitazon dışında tüm ilaçlar

Oral Antidiyabetiklerin Maliyeti

Oral Antidiyabetikler	Kutu Fiyatı	Tane Fiyatı	Günlük Maliyet
Matofin 500 mg 100 XR Tb	9.32 TL	0.093 TL	0.280 TL
Glucophage 850 mg 100 Tb	14.72 TL	0.147 TL	0.442 TL
Glukofen 1000 mg 100 Tb	12.74 TL	0.127 TL	0.382 TL
Metfull 500 mg 100 Efervesan Tb	8.12 TL	0.081 TL	0.244 TL
Amaryl 3 mg 30 Tb	5.22 TL	0.174 TL	0.348 TL
Glucotrol XL 5 mg 20 Tb	8.72 TL	0.436 TL	0.436 TL
Diamicron MR 60 mg 30 Tb	9.69 TL	0.323 TL	0.646 TL
Novonorm 1 mg 90 Tb	17.49 TL	0.194 TL	0.583 TL
Starlix 120 mg 84 Tb	39.23 TL	0.467 TL	1.401 TL
Glucobay 50 mg 30 Tb	5.35 TL	0.107 TL	0.321 TL
Actos 30 mg 28 Tb	39.47 TL	1.071 TL	1.071 TL
Dropia-Met 15/850 mg 30 Tb	24.27 TL	0.809 TL	1.618 TL
Galvus 50 mg 56 Tb	102.22 TL	1.825 TL	5.476 TL
Galvus Met 50/1000 mg 60 Tb	93.74 TL	1.562 TL	3.125 TL
Januvia 100 mg 28 Tb	87.07 TL	3.110 TL	3.110 TL
Janumet 50/1000 mg 56 Tb	87.07 TL	1.555 TL	3.110 TL
Onglyza 5 mg 28 Tb	91.38 TL	3.264 TL	6.527 TL

		Gün	SGK (TL)	ECZANE (TL)
Sitagliptin	1x100mg	30	**69**	**102**
Vildagliptin	2x50mg	30	**84.60**	**109,50**
Exenatide	2x10mcg	30	**173.10**	**224,70**
Metformin	3x850mg	30	8,40	13,50
Metformin	2x1000mg	30	7,20	9,00
Gliclazide MR	1x60mg	30	12,73	16,31
Gliclazide MR	1x120mg	30	25,46	32,62
Repaglinid	4x0.5mg	30	15,60	25,20
Repaglinid	4x2mg	30	15,60	25,20

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Effect of Antihyperglycemic Agents Added to Metformin and a Sulfonylurea on Glycemic Control and Weight Gain in Type 2 Diabetes: A Network Meta-analysis

Ann Intern Med. 2011;154(10):672-679. doi:10.7326/0003-4819-154-10-201105170-00007

Figure Legend:

Network meta-analysis of antihyperglycemic agents.Green dots account for the estimated probability (the higher the probability, the larger the dot). DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1. Left. The estimated probability that each treatment is ranked first, second, or third as the most effective for changing hemoglobin A_{1c} levels. Right. The estimated probability that each treatment is ranked first, second, or third as the most effective for avoiding an increase in weight.

Table 3. Network Meta-analysis Comparing All Noninsulin Antihyperglycemic Agents and Insulins: Mean Changes in HbA_{1c} Level and Weight

Treatment	Change in HbA_{1c} Level (95% CrI), %					
	Placebo	GLP-1 Agonists	Insulin	Thiazolidinediones	DPP-4 Inhibitors	Acarbose
Placebo	–	–	–	–	–	–
GLP-1 agonists	−1.01 (−1.38 to −0.66)	–	–	–	–	–
Insulin	−1.08 (−1.41 to −0.77)	−0.07 (−0.41 to 0.25)	–	–	–	–
Thiazolidinediones	−0.95 (−1.27 to −0.65)	0.05 (−0.35 to 0.5)	0.12 (−0.16 to 0.41)	–	–	–
DPP-4 inhibitors	−0.94 (−1.58 to −0.36)	0.07 (−0.6 to 0.67)	0.14 (−0.51 to 0.77)	0.01 (−0.67 to 0.69)	–	–
Acarbose	−0.70 (−1.33 to −0.08)	0.31 (−0.4 to 1.03)	0.38 (−0.28 to 1.06)	0.25 (−0.39 to 0.93)	0.24 (−0.56 to 1.13)	–
	Change in Weight (95% CrI), *kg*					
	Placebo	GLP-1 Agonists	Insulin	Thiazolidinediones	DPP-4 Inhibitors	Acarbose
Placebo	–	–	–	–	–	–
GLP-1 agonists	−1.63 (−2.71 to −0.60)	–	–	–	–	–
Insulin	2.84 (1.76 to 3.90)	4.47 (3.71 to 5.26)	–	–	–	–
Thiazolidinediones	4.25 (2.76 to 5.66)	5.89 (4.54 to 7.2)	1.42 (0.29 to 2.55)	–	–	–
DPP-4 inhibitors	NA	NA	NA	NA	–	–
Acarbose	−0.96 (−2.77 to 0.73)	0.67 (−1.37 to 2.63)	−3.79 (−5.91 to −1.88)	−5.21 (−7.53 to −2.98)	NA	–

CrI = credible interval; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1; HbA_{1c} = hemoglobin A_{1c}; NA = not available.

Üçlü tedavi rejimleri

Bazal HbA1c % 6,5-% 7,5				
Metformin	+	GLP-1 R agonisti	+	TZD
		DPP-4 inhibitörü		Glinid veya SÜ

TZD: tiazolidindion
SÜ: sülfonilüre

Endocr pract, 2009, 15:540-59

Üçlü tedavi rejimleri

Bazal HBA1c % 7,6-% 9,0				
Metformin	+	GLP-1 R agonisti veya DPP-4 inhibitörü	+	TZD
		GLP-1 R agonisti veya DPP-4 inhibitörü	+	SÜ
		TZD		

Endocr Pract, 2009; 15:540-549

Üçlü tedavi rejimleri

Bazal HbA1c > %9		**asemptomatik ise:**		
Metformin	+	GLP-1 R agonisti veya DPP-4 inhibitörü	+	SÜ
		TZD		
		GLP-1 R agonisti veya DPP-4 inhibitörü		TZD

TZD: tiazolidindion
SÜ: sülfonilüre

Endocr pract, 2009, 15:540-59

- TZD ciddi insülin direnci olan ve yüksek kardiovasküler riski olan bireylerde (MI ve felç sonrası ?) fayda oranı zarar oranını geçeceğini düşündüğümüz hastalara

- YAŞLI dehidratasyona yatkın bireylerde SGLT2 verme
- Genital mantar öyküsü olan bayanlara vermeyelim
- Mesane kanser riski olan bireylere TZD ve SGLT2 verilmemeli

Tip 2 Diyabet Tedavisi: 3. Ajan

ikili Tedavi yetersiz kalınca

Dual oral

Metformin + Sulfonüre / DPP4

HbA1c > 7-7.5 %

Üçlü oral tedavi

İnjeksiyona alternatif

Injeksiyonlar

Metformin + SUs/DPP4
+ SGLT2-inhibitör

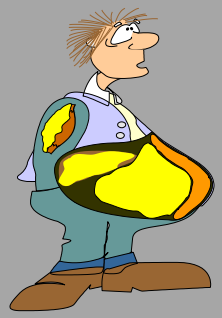
İnsulin

GLP1-agonistleri

Genel Öneri

Pio eklemek yerine

Obez ve hipertansif hastalarda hipoglisemi riski fazla olanlarda



Clifford Bailey, PhD

Monoterapi-Kombine Terapi Kıyaslaması

- Ancak ortalama HbA1c düzeyi düşürme etkisine bakıldığı zaman ikili ilaç kombinasyonlarının, monoterapilere göre %1 daha fazla düşüş sağladığı görülüyor

- Çeşitli diğer kombinasyon tedavileri de HbA1c düşürme açısından benzer etkiye sahip

Mevcut İlaçlar Arasında Seçim

- Yararları
- Etki/sınıf modalitesi
- Yan etkileri
- Maliyet

gözününe alınarak belirlenir

Diyabette Akılcı İlaç Kullanımında Dikkat Edilecek Noktalar

Tedavi Hedefleri

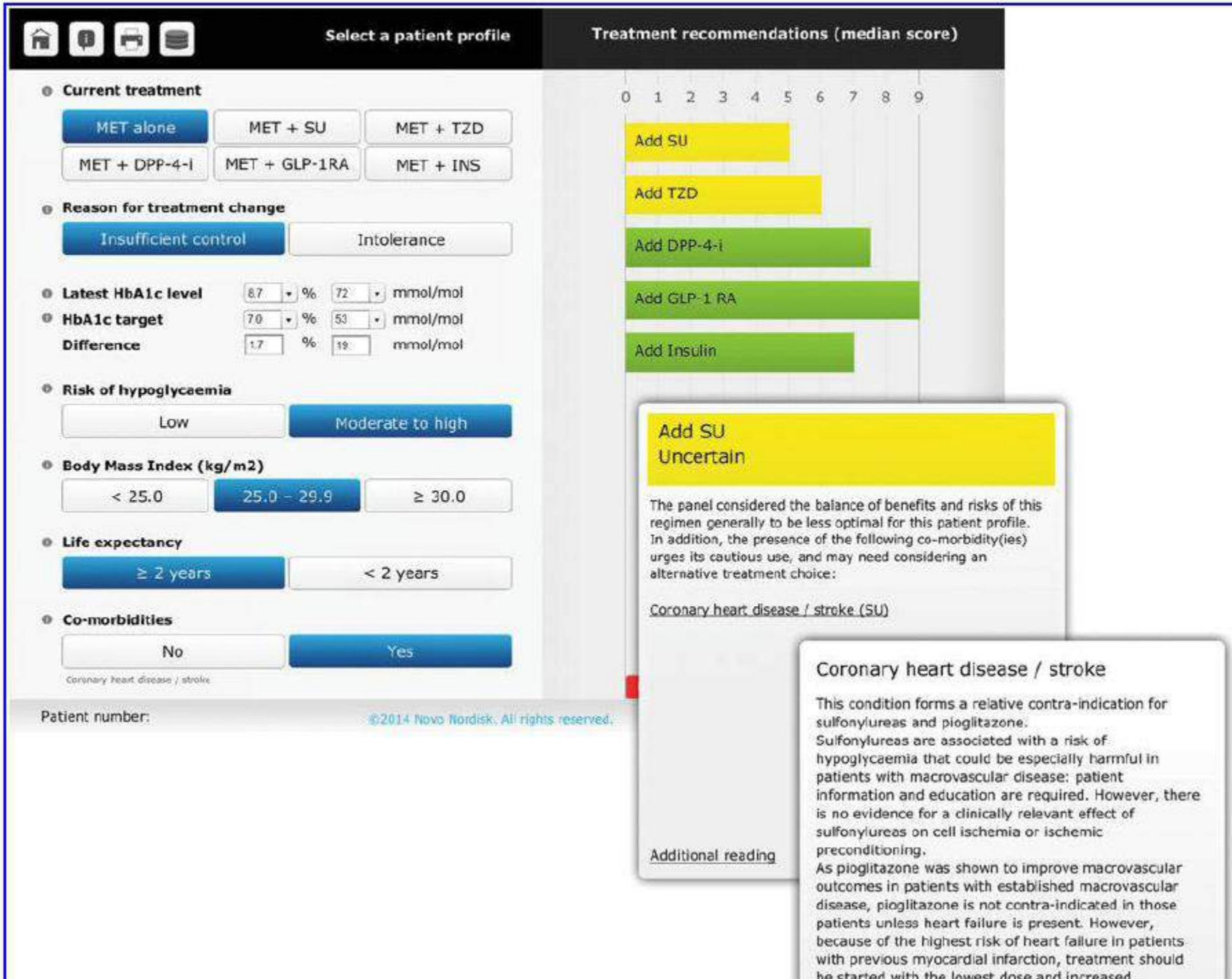
- Glisemik kontrolü veya Hemoglobin A1c (HbA1c)
- Vücut ağırlığı
- LDL kolesterol
- HDL kolesterol
- Trigliserid
- Kan Basıncı

İstenmeyen olaylar ve yan etkiler

- Hipoglisemi (Hafif ve orta derecede)
- Gastrointestinal (Gİ) yan etkiler
- Konjestif kalp yetmezliği
- Karaciğer hasarı
- Kalça ve kalça harici kırıklar
- Uzun vadeli klinik sonuçlar

Tüm nedenlere bağlı ölüm

- Kardiyovasküler ölüm
- Ölümcül olmayan miyokard infarktüsü ve inme
- Mikrovasküler sonuçları (retinopati, nefropati, nöropati)


Select a patient profile
Treatment recommendations (median score)
Current treatment
MET alone
MET + SU
MET + TZD
MET + DPP-4-i
MET + GLP-1RA
MET + INS
Reason for treatment change
Insufficient control
Intolerance
Latest HbA1c level
8.7 % 72 mmol/mol
HbA1c target
7.0 % 53 mmol/mol
Difference
1.7 % 19 mmol/mol
Risk of hypoglycaemia
Low
Moderate to high
Body Mass Index (kg/m2)
< 25.0
25.0 - 29.9
≥ 30.0
Life expectancy
≥ 2 years
< 2 years
Co-morbidities
No
Yes
Coronary heart disease / stroke
Patient number:
©2014 Novo Nordisk. All rights reserved.
0 1 2 3 4 5 6 7 8 9
Add SU
Add TZD
Add DPP-4-i
Add GLP-1 RA
Add Insulin
Add SU
Uncertain
The panel considered the balance of benefits and risks of this regimen generally to be less optimal for this patient profile. In addition, the presence of the following co-morbidity(ies) urges its cautious use, and may need considering an alternative treatment choice:
Coronary heart disease / stroke (SU)
Additional reading
Coronary heart disease / stroke
This condition forms a relative contra-indication for sulfonylureas and pioglitazone.
Sulfonylureas are associated with a risk of hypoglycaemia that could be especially harmful in patients with macrovascular disease: patient information and education are required. However, there is no evidence for a clinically relevant effect of sulfonylureas on cell ischemia or ischemic preconditioning.
As pioglitazone was shown to improve macrovascular outcomes in patients with established macrovascular disease, pioglitazone is not contra-indicated in those patients unless heart failure is present. However, because of the highest risk of heart failure in patients with previous myocardial infarction, treatment should

- İkili-Üçlü tedavi karşılaştırılması
- Üçlü- OAD+bazal insüln karşılaştırılması
- Üçlü-premiks insülin karşılaştırması

Guideline-Based Antihyperglycemic Use

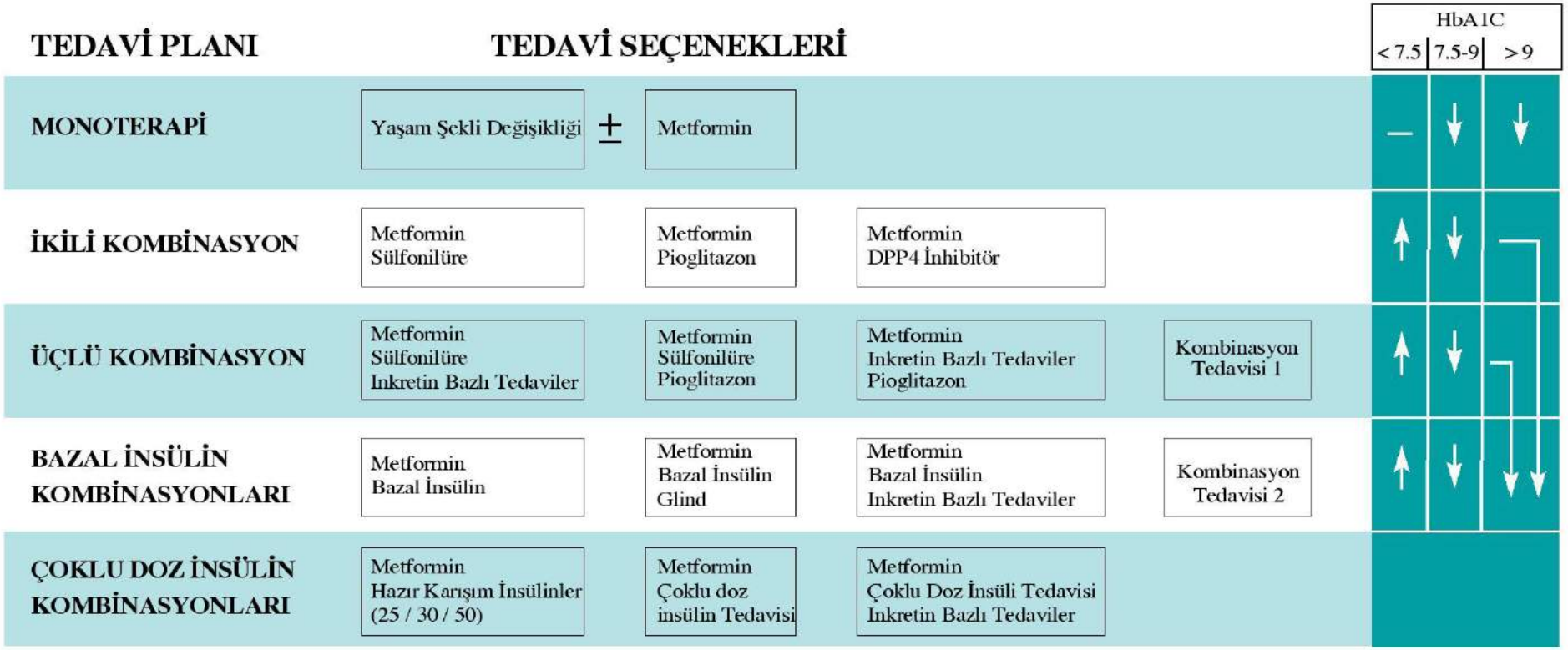
Initial drug monotherapy*	Metformin					
2-drug combinations†	Metformin + SU	Metformin + TZD	Metformin + DPP-4-i	Metformin + SGLT2-i	Metformin + GLP-1-RA	Metformin + Insulin (basal)
3-drug combinations‡	**Metformin + SU + (select 1) TZD DPP-4-i SGLT2-i GLP-1-RA Insulin**	**Metformin + TZD + (select 1) SU DPP-4-i SGLT2-i GLP-1-RA Insulin**	**Metformin + DPP-4-i + (select 1) SU TZD SGLT2-i Insulin**	**Metformin + SGLT2-i + (select 1) SU TZD DPP-4-i Insulin**	**Metformin + GLP-1-RA + (select 1) SU TZD Insulin**	**Metformin + Insulin (basal) + (select 1) TZD DPP-4-i SGLT2-i GLP-1-RA**
Combination injectable therapy	**Basal insulin + mealtime insulin or GLP-1-RA**					

Healthy eating, weight control, increased physical activity

*If needed to reach individualized HbA_{1c}, target after ~3 months, proceed to 2-drug combination.
†If needed to reach individualized HbA_{1c}, target after ~3 months, proceed to 3-drug combination.
‡If need to reach HbA_{1c} target after ~3 months:
-if patient on oral combination, proceed to injectables
-if patient on GLP-1 RA, add-on basal insulin
-if patient on basal insulin, add-on GLP-1 RA or mealtime insulin

Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149.[2]

DAHA ÖNCE TANI ALMIŞ TEDAVİ ALTINDAKİ TİP 2 DİYABETTE TEDAVİ YAKLAŞIMI



- 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.

YENİ TANI ALAN TİP2 DİYABETTE TEDAVİ YAKLAŞIMI

HBA1C (%)	BETA HÜCRE REZERVİ	TEDAVİ PLANI
<8	Yeterli	YSD + Metformin
8 - 10	Yeterli	İkili Kombinasyon
>10	Yeterli	İkili / Üçlü Kombinasyon
>10	Sınırda Yetersiz	Bazal insülin + OAD/GLP1 analog
>10	Yetersiz	İnsülin Çoklu Doz

*Beta Hücre Rezervi Yeterli (C Peptid: >2ng/ml), SınırdaYetersiz (C peptid: 0.5 - 2ng/ml) Yetersiz: (C Peptid: <0.5 ng/ml)

* Beta Hücre Rezervi Yetersiz (C Peptid <0.5ng/ml) tüm hastalar HbA1C den bağımsız olarak insülinle tedavi edilmelidir.

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

ENTRY A1c < 7.5%

MONOTHERAPY*
- Metformin
- GLP-1 RA
- DPP4-i
- AG-i
- SGLT-2 **
- TZD
- SU/GLN

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

ENTRY A1c ≥ 7.5%

DUAL THERAPY*

MET or other first-line agent +
- GLP-1 RA
- DPP4-i
- TZD
- ** SGLT-2
- Basal insulin
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

If not at goal in 3 months proceed to triple therapy

TRIPLE THERAPY*

MET or other first-line agent + 2ND LINE AGENT
- GLP-1 RA
- TZD
- ** SGLT-2
- Basal insulin
- DPP4-i
- Colesevelam
- Bromocriptine QR
- AG-i
- SU/GLN

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

ENTRY A1c > 9.0%

NO SYMPTOMS	SYMPTOMS
DUAL THERAPY OR TRIPLE THERAPY	INSULIN ± OTHER AGENTS

ADD OR INTENSIFY INSULIN

* Order of medications listed are a suggested hierarchy of usage

** Based upon phase 3 clinical trials data

LEGEND

✓ = Few adverse events or possible benefits ⚠ = Use with caution

PROGRESSION OF DISEASE

Profiles of Antidiabetic Medications

	MET	DPP-4i	GLP-1 RA	TZD	AGI	COLSVL	BCR-QR	SU / GLN	INSULIN	SGLT-2	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe / Mild	Moderate to Severe	Neutral	Neutral
WEIGHT	Slight Loss	Neutral	Loss	Gain	Neutral	Neutral	Neutral	Gain	Gain	Loss	Loss
RENAL/ GU	Contra-indicated Stage 3B,4,5	Dose Adjustment May be Necessary (Except Linagliptin)	Exenatide Contra-indicated CrCl < 30	May Worsen Fluid Retention	Neutral	Neutral	Neutral	More Hypo Risk	More Hypo Risk & Fluid Retention	Infections	Neutral
GI Sx	Moderate	Neutral	Moderate	Neutral	Moderate	Mild	Moderate	Neutral	Neutral	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit			Neutral			Safe	?			
BONE	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral	? Bone Loss	Neutral

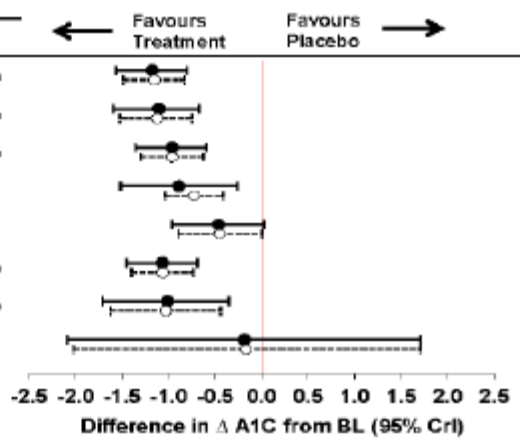
Few adverse events or possible benefits — Use with caution — Likelihood of adverse effects

Figure 5. Forest plot of all antidiabetic drugs added as third-line pharmacotherapy.

CADTH 2010 (●) and Updated Network Meta-Analyses (○) for A1C (%) (A), Weight (kg) (B)

A

Treatment added-on to metformin and a sulfonylurea	NMA Estimate (95% CrI)	
	CADTH 2010	CADTH 2012
Basal Insulin	−1.17 (−1.57, −0.81)	−1.15 (−1.49, −0.83)
Biphasic Insulin	−1.10 (−1.59, −0.67)	−1.12 (−1.52, −0.75)
Thiazolidinediones	−0.96 (−1.35, −0.59)	−0.96 (−1.30, −0.62)
DPP-4 Inhibitors	−0.89 (−1.51, −0.26)	−0.72 (−1.03, -0.42)
AG Inhibitors	−0.46 (−0.96, 0.03)	−0.45 (−0.90, 0.01)
GLP-1 Analogues	−1.06 (−1.45, −0.69)	−1.06 (−1.40, −0.73)
Bolus Insulin	−1.01 (−1.71, −0.35)	−1.02 (−1.62, −0.44)
Meglitinides	−0.18 (−2.08, 1.71)	−0.17 (−2.02, 1.71)



B

Treatment added-on to metformin and a sulfonylurea	NMA Estimate (95% CrI)	
	CADTH 2010	CADTH 2012
Basal Insulin	1.9 (0.5, 3.1)	1.9 (0.7, 3.0)
Biphasic Insulin	3.4 (1.7, 5.0)	3.3 (1.9, 4.7)
Thiazolidinediones	3.0 (1.7, 4.4)	3.1 (1.9, 4.3)
DPP-4 Inhibitors	1.1 (−1.4, 3.6)	0.7 (−0.8, 2.2)
AG Inhibitors	−0.4 (−2.2, 1.4)	−0.5 (−2.1, 1.2)
GLP-1 Analogues	−1.6 (−3.0, −0.2)	−1.6 (−2.8, −0.4)
Bolus Insulin	5.0 (2.5, 7.4)	5.0 (2.8, 7.2)
Meglitinides	2.7 (−0.9, 6.3)	2.6 (−0.7, 6.0)

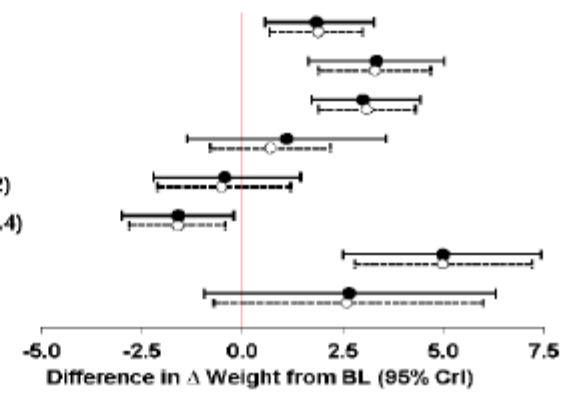


Table 9. Cumulative lifetime incidence of diabetes-related complications, by third-line treatment option.

	Regimen			
	MET+SULF (Reference)	MET+SULF +GLP-1	MET+SULF +DPP-4	MET+SULF +Insulin
Event Type	**Incidence (%)**			
Ischemic heart disease	7.2	7.0	6.8	6.8
Myocardial infarction	27.9	26.3	26.7	26.3
Congestive heart failure	12.4	10.6	11.5	11.6
Stroke	13.4	12.0	12.5	12.1
Amputation	3.9	2.5	3.1	2.5
Blindness	6.4	5.6	5.9	5.4
Renal failure	1.9	1.9	1.9	2.0
Diabetes-related death	24.6	23.0	23.8	23.6

MET: Metformin; SULF: Sulfonylurea; GLP-1: Glugacon-like peptide-1 agonist; DPP-4: Dipeptidyl peptidase-4 inhibitor

Type 2 diabetes mellitus treatments –Triple therapy combination table (see page 22 for key)

Grouped by class> / Grouped by class v	Met + Gliclazide	Met + Pioglitazone	Met + linagliptin	Met + sitagliptin	Met + canagliflozin	Met + dapagliflozin	Met + Exenatide	Met + Exenatide MR	Met + liraglutide	Met + lixisenatide	Met + insulin	Gliclazide + sitagliptin	Gliclazide+ linagliptin	Gliclazide + pioglitazone	Gliclazide+ exenatide	Gliclazide+ exenatide MR	Gliclazide+ lixisenatide	Gliclazide + liraglutide	Gliclazide + insulin
Metformin												Y	Y	Y	Y	Y	Y	Y	Y
Metformin MR												Y	Y	Y	Y	Y	Y	Y	Y
Glicazide		Y	Y	Y	Y	NICE*	Y	Y	Y	Y	Y								
Gliclazide MR		L	L	L	L	L	L	L	L	L	L								
Linagliptin	Y	NICE*			L	L	L	L	L	L	NICE*			L	L	L	L	L	L
Sitagliptin	Y	NICE*			L	L	L	L	L	L	NICE*			L	L	L	L	L	L
Pioglitazone	Y		NICE*	NICE*	Y	L	Y	Y	L	L	L	L	L		L	L	L	L	L
Exenatide	Y	Y	L	L	L	L					Y	L	L	L					L
Exenatide MR	Y	Y	L	L	L	L					L	L	L	L					L
Lixisenatide	Y	Y	L	L	NICE	NICE					Y	L	L	L					L
Liraglutide	Y	Y	L	L	NICE	NICE					Y	L	L	L					L
Canagliflozin	Y	Y	L	L			L	L	NICE	NICE	Y	L	L	L	L	L	NICE	NICE	NICE
Dapagliflozin	NICE*	L	L	L			L	L	NICE	NICE	Y	L	L	L	L	L	NICE	NICE	NICE
Acarbose	Y	L	L	L	NICE	NICE	L	L	L	L	L	L	L	L	L	L	L	L	L
Insulin	Y	L	NICE*	NICE*	Y	Y	Y	L	Y	Y		L	L	L	L	L	L	L	

Choice of therapy in patients with type 2 diabetes inadequately controlled with metformin and a sulphonylurea: a systematic review and mixed-treatment comparison meta-analysis

Brendan McIntosh, Chris Cameron, Sumeet R. Singh, Changhua Yu, Lisa Dolovich, Robyn Houlden

ABSTRACT

Background: Metformin and a sulphonylurea are often used in combination for the treatment of type 2 diabetes mellitus. We conducted a systematic review and meta-analysis to evaluate the comparative safety and efficacy of all available classes of antihyperglycemic therapies in patients with type 2 diabetes inadequately controlled with metformin and sulphonylurea combination therapy.

Methods: MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, EMBASE, BIOSIS Previews, PubMed and the Cochrane Central Register of Controlled Trials were searched for randomized controlled trials published in English from 1980 to November 2009. Additional citations were obtained from the grey literature and conference proceedings and through stakeholder feedback. Two reviewers independently selected the studies, extracted the data and assessed risk of bias. Key outcomes of interest were hemoglobin A_{1c}, body weight, hypoglycemia, patients' satisfaction with treatment, quality of life, long-term diabetes-related complications, withdrawals due to adverse events, serious adverse events and mortality. Mixed-treatment comparison meta-analyses were conducted to calculate mean differences between drug classes for changes in hemoglobin A_{1c} and body weight. When appropriate, pairwise meta-analyses were used to estimate differences for other outcomes.

Results: We identified 33 randomized controlled trials meeting the inclusion criteria. The methodologic quality of the studies was generally poor. Insulins (basal, biphasic, bolus), dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogues and thiazolidinediones (TZDs) all produced statistically significant reductions in hemoglobin A1c in combination with metformin and a sulphonylurea (−0.89% to −1.17%), whereas meglitinides and alpha-glucosidase inhibitors did not. Biphasic insulin, bolus insulin, and TZDs were associated with weight gain (1.85–5.00 kg), whereas DPP-4 inhibitors and alpha-glucosidase inhibitors were weight-neutral, and GLP-1 analogues were associated with modest weight loss. Treatment regimens containing insulin were associated with increased hypoglycemia relative to comparators, but severe hypoglycemia was rare across all treatments.

Interpretation: Third-line agents for the treatment of type 2 diabetes are similar in terms of glycemic control but differ in their propensity to cause weight gain and hypoglycemia. Longer-term studies with larger sample sizes are required to determine if any of the drug classes are superior with regard to reducing diabetes-related complications.

PHARMACOLOGICAL MANAGEMENT OF GLYCAEMIC CONTROL IN PEOPLE WITH TYPE 2 DIABETES

REVIEW AND SET GLYCAEMIC TARGET: HbA1c <7% (53 mmol/mol) OR INDIVIDUALISED AS AGREED

1st LINE OPTIONS in addition to lifestyle measures; START ONE OF

Metformin (MF)

Sulphonylurea* (SU)
- If intolerant of metformin or
- If weight loss/osmotic symptoms

Review and if not reaching target move to 2nd line

2nd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD ONE OF

Sulphonylurea* (SU)

Thiazolidinedione*
- If hypos a concern (eg driving, occupational hazards, at risk of falls) and
- If no congestive heart failure

DPP-IV inhibitor*
- If hypos a concern (eg driving, occupational hazards, at risk of falls)
- If weight gain a concern

Review and if not reaching target move to 3rd line

3rd LINE OPTIONS in addition to lifestyle measures, adherence to medication and dose optimisation; ADD OR SUBSTITUTE WITH ONE OF

ORAL (continue MF/SU if tolerated)

Thiazolidinedione* If no congestive heart failure

DPP-IV inhibitor* If weight gain a concern

INJECTABLE (if willing to self inject; continue MF/SU if tolerated)

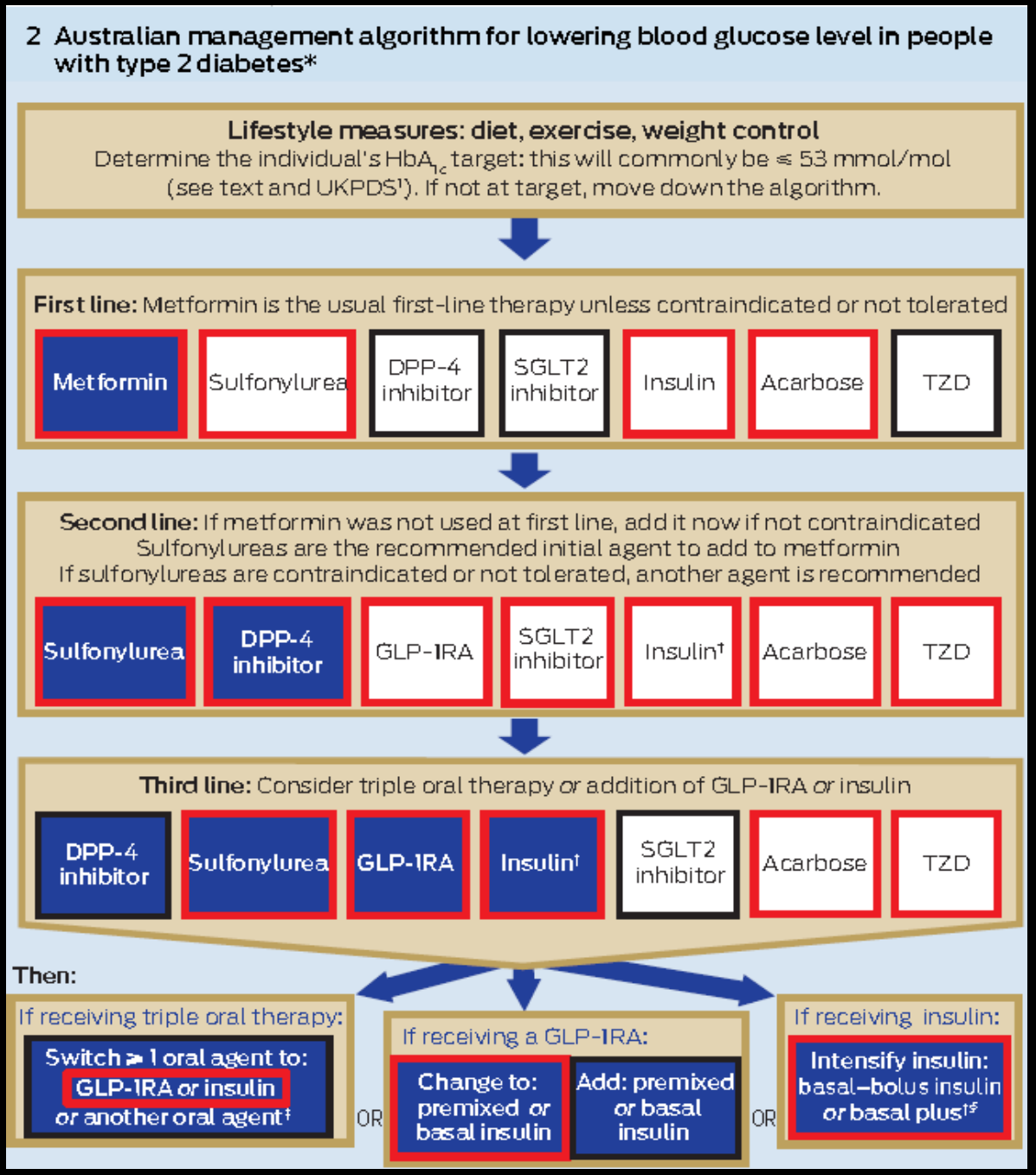
Insulin* (inject before bed)
- If osmotic symptoms/rising HbA1c; NPH insulin initially
- If hypos a concern, use basal analogue insulin as an alternative
- Add prandial insulin with time if required

GLP-1 agonists*
- If BMI >30 kg/m^2
- If a desire to lose weight
- Usually <10 years from diagnosis

Prescribers should refer to the British National Formulary (www.bnf.org) and the Scottish Medicines Consortium (www.scottishmedicines.org.uk) for updated guidance on licensed indications, full contraindications and monitoring requirements.

	Usual approach
	Alternative approach. Special considerations
*	Continue medication if EITHER individualised target achieved OR HbA1c falls >0.5% (5.5 mmol/mol) in 3-6 months

2 Australian management algorithm for lowering blood glucose level in people with type 2 diabetes*



- **“İnsülin diyabet için kür sağlamaz, sadece tedavi sağlar„ Frederick G Banting - 1925 Nobel konuşması**
- **Henüz hiçbir ilaç kür sağlamamıştır.**