Prediyabeti tedavi edelim mi?

Doç. Dr. Seda Sancak

SBÜ Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi

Endokrinoloji ve Metabolizma Hastalıkları

İç HastalıkLarı Kliniği

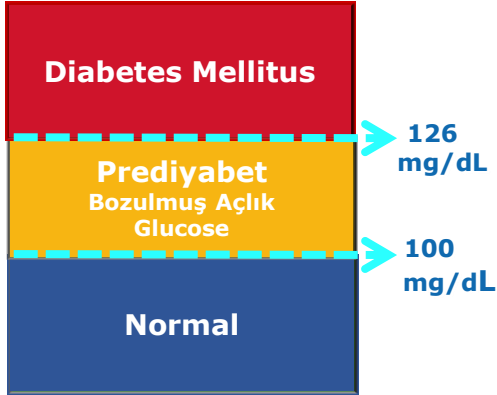**9.İstanbul Dahiliye Klinikleri Buluşması/1-3 Kasım /İstanbul**

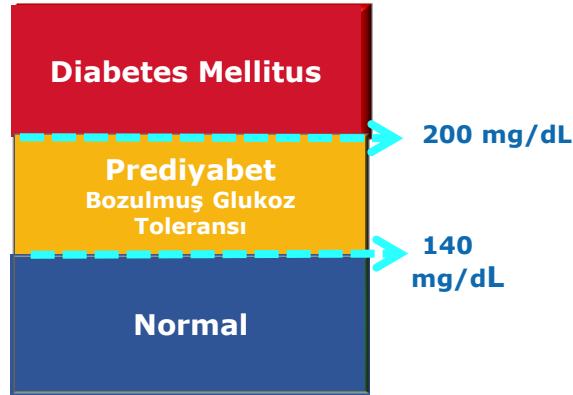## Prediyabet tanımlaması ilk defa ne zaman kullanılmıştır?

- 1979 : Sınırda diyabet, şimik, latent diyabet
- 1985 : WHO tarafından resmen tanımlandı.
- 1997 : IFG (BAG) eklendi
- 1999 : WHO, ADA tanı kriterlerini kabul etti.
- 2003 : BAG 100 mg/dl

2010 : A1c ≥% 5.7-6.4

(% 6 - 6.4 Yüksek riskli)

Prediyabet; plazma glukoz düzeylerinin normalin üzerinde olduğu ancak diyabet sınırlarına ulaşmadığı durumlardır.
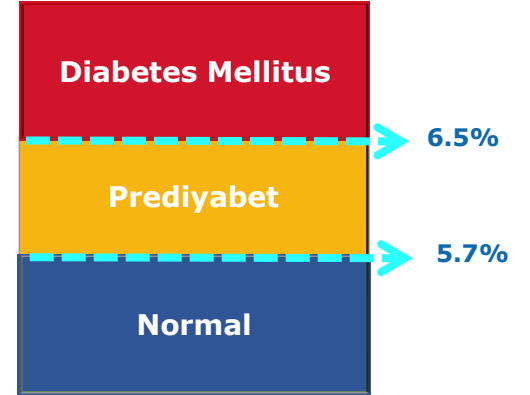
Açlık Plazma Glukozu

Diabetes Mellitus
→ 126 mg/dL
Prediyabet Bozulmuş Açlık Glucose
→ 100 mg/dL
Normal

OGTT de 2.saat plazma glukozu

Diabetes Mellitus
→ 200 mg/dL
Prediyabet Bozulmuş Glukoz Toleransı
→ 140 mg/dL
Normal

Hemoglobin A1C

Diabetes Mellitus
→ 6.5%
Prediyabet
→ 5.7%
Normal

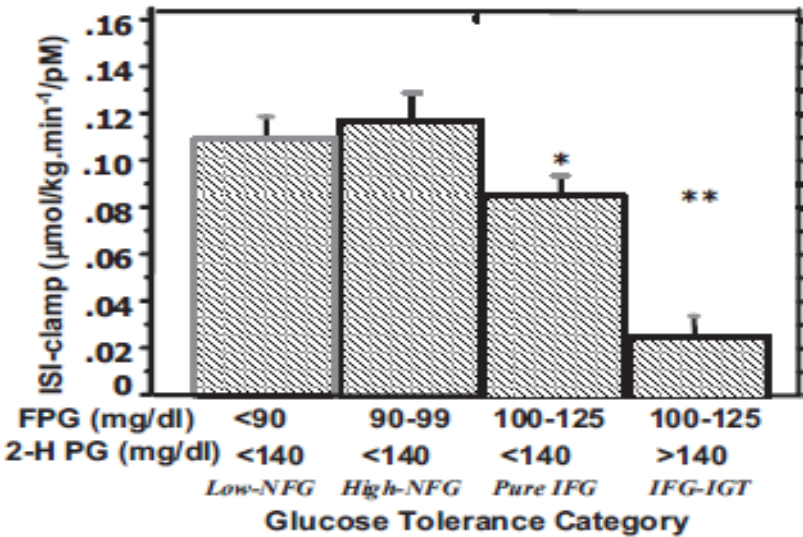# PREDİYABETİN PATOFİZYOLOJİK DEFEKTLERİ

Glucoregulatory Physiology in Subjects with Low-Normal, High-Normal, or Impaired Fasting Glucose
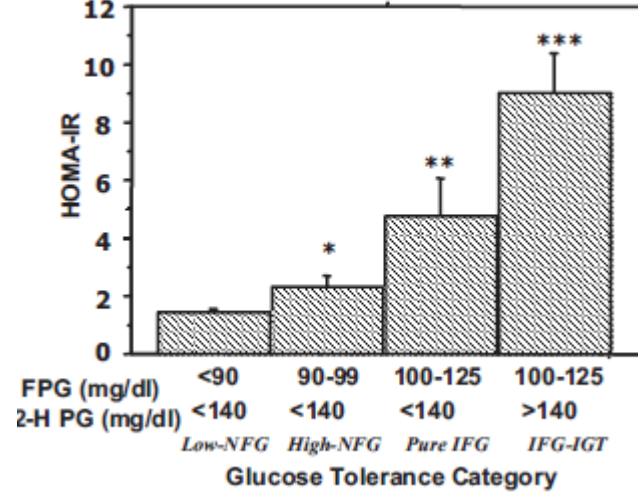
Samuel Dagogo-Jack, Hasan Askari, and Gunjan Tykodi

İnsülin sensitivitesi

İnsülin direnci
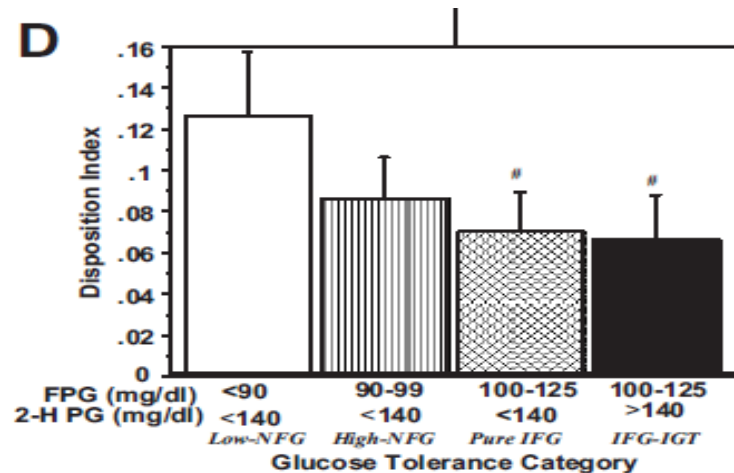
Disposition index

ß-hücre kitlesi ve açlık plazma glukozu

Ritzel *et al. Diabetes* Care 2006;29:717
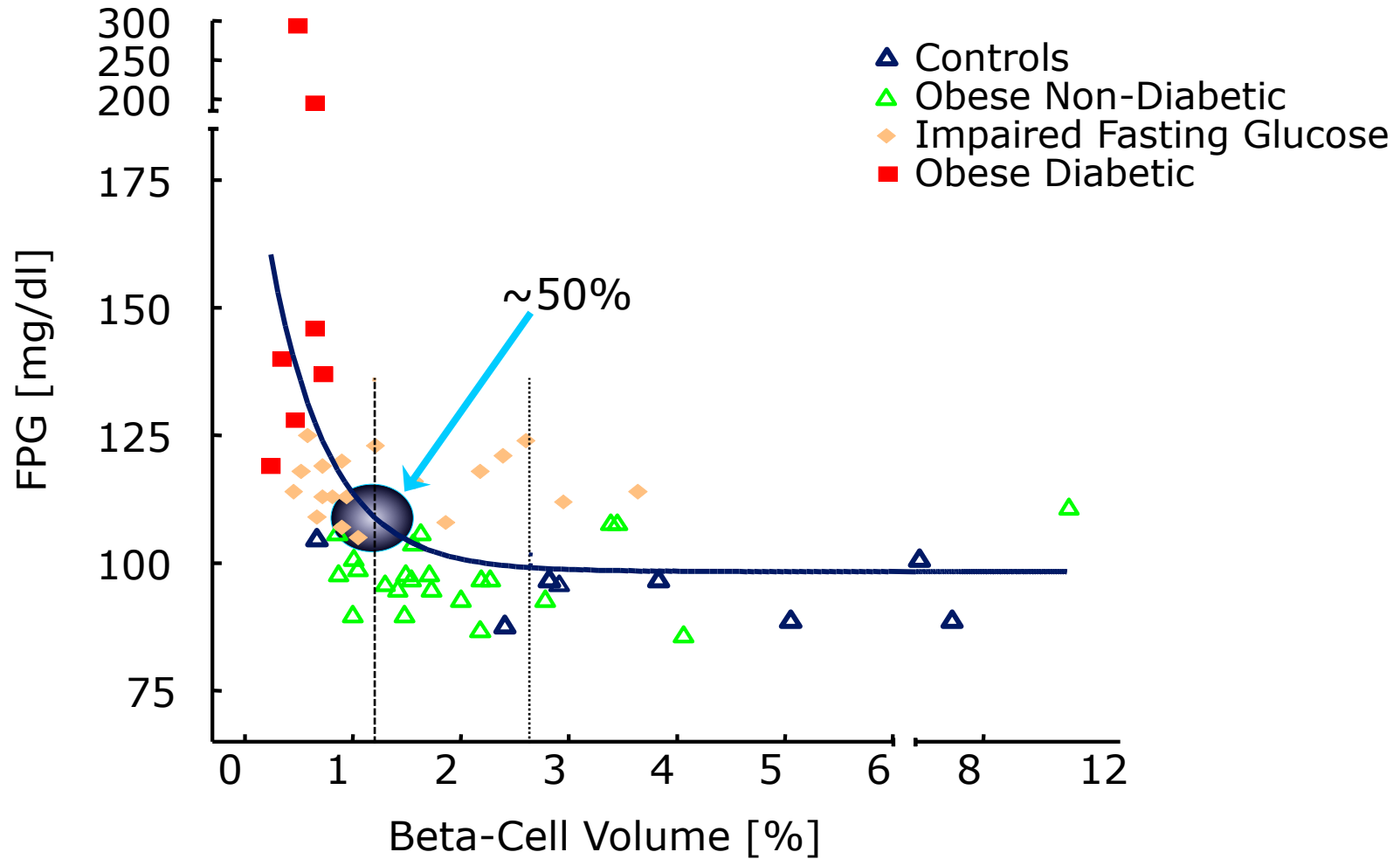
ß-hücre fonksiyonu azaldıkça glisemi artar
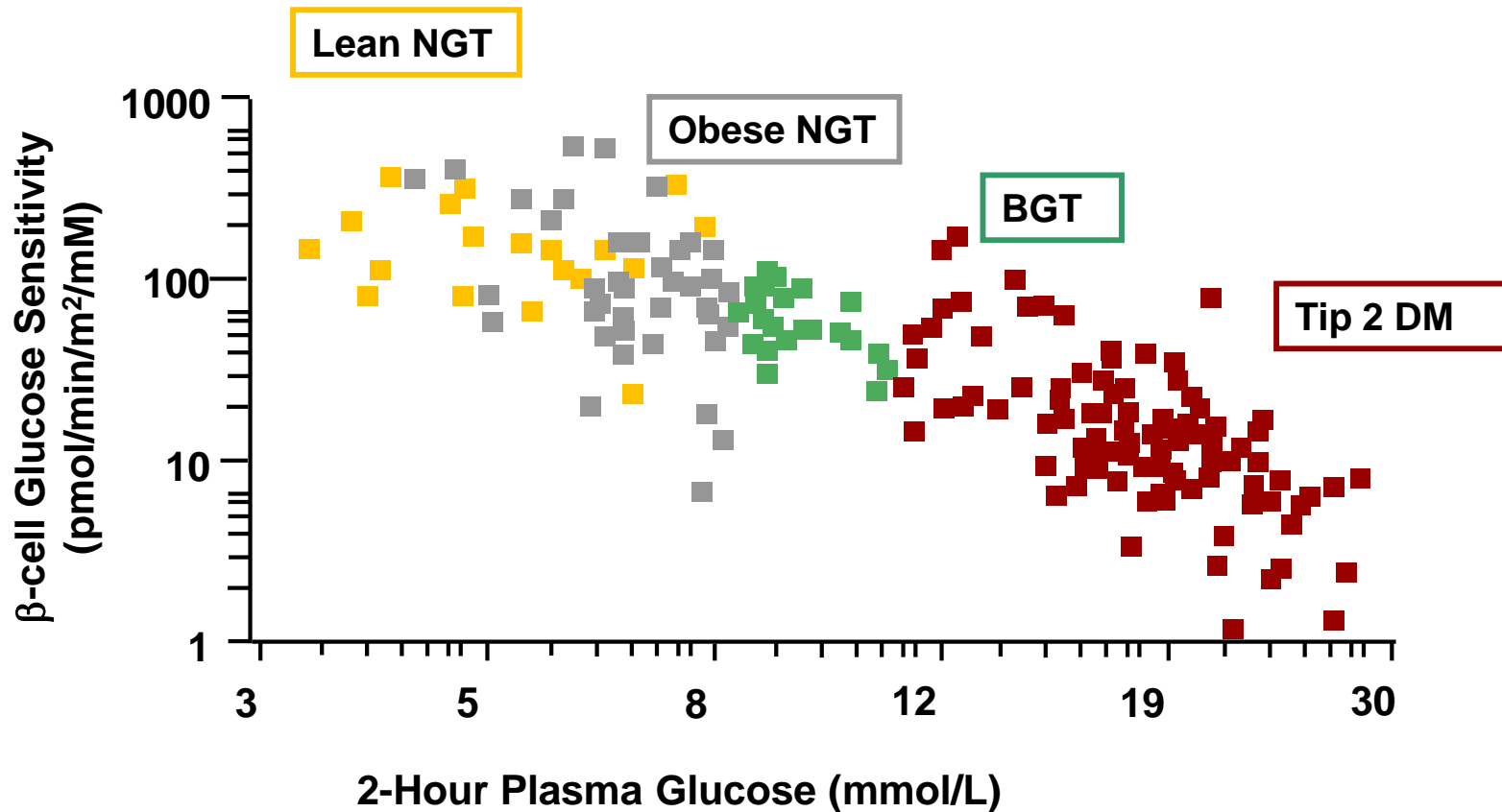
Ferrannini et al. *J Clin Endocrinol Metab* 2005

Azalmış GLP-1 düzeyleri
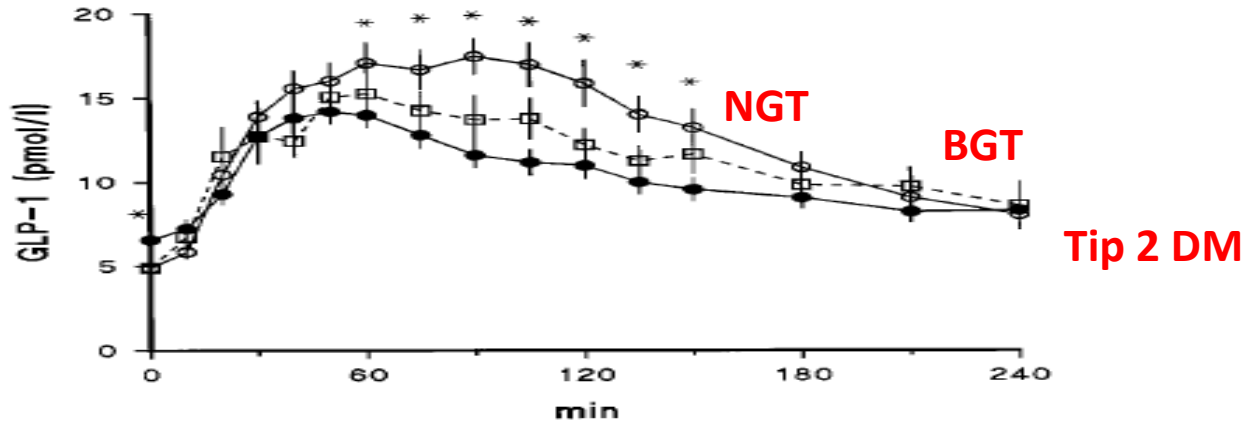
FIG. 3. Plasma GLP-1 concentrations in T2DM patients (●), NGT subjects (○), and IGT subjects (□) during a 240-min meal test. The meal was started at time zero and finished in the 10- to 15-min period. *, $P < 0.05$ between the T2DM and NGT group.

Bozulmuş glukagon supresyonu

Figure 1. Mean (±SE) Arterial Plasma Glucose, Insulin, and Glucagon Concentrations before and after Glucose Ingestion in 16 Normal Subjects (○) and 15 Subjects with Impaired Glucose Tolerance (●).

Tip 2 DM ve prediyabette patofizyolojik defektler
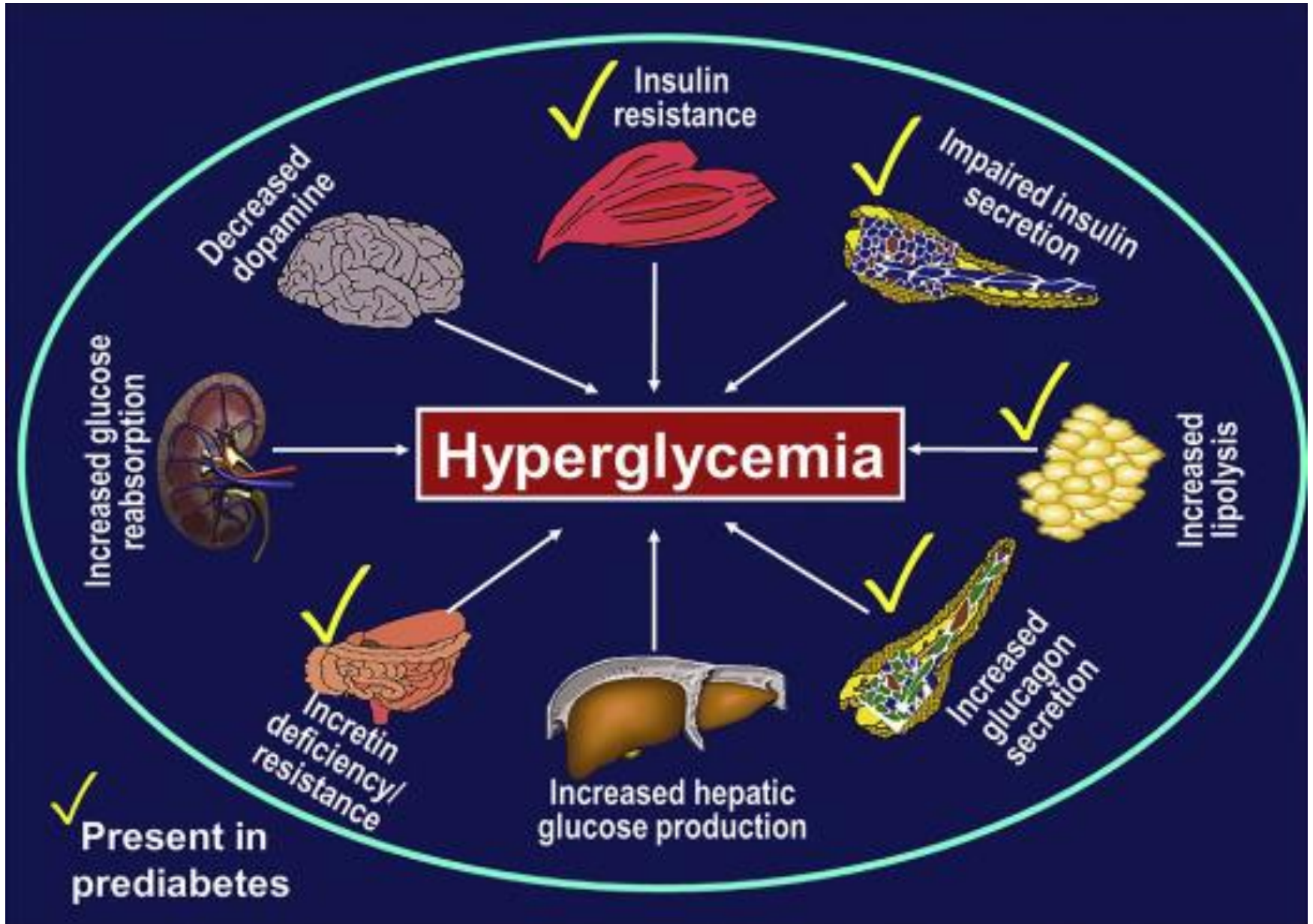
Prediyabet – Epidemi

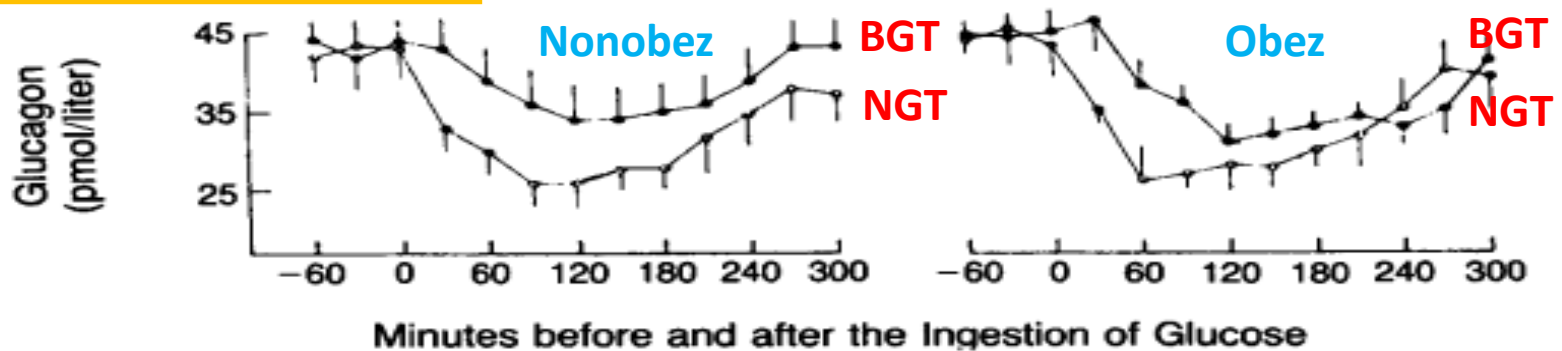Bozulmuş glukoz toleransı olan bireylerin 2010 ve 2030'da ki olası prevalansı

2010 da dünya genelinde 400 milyon prediyabet
2014'de 470 milyon
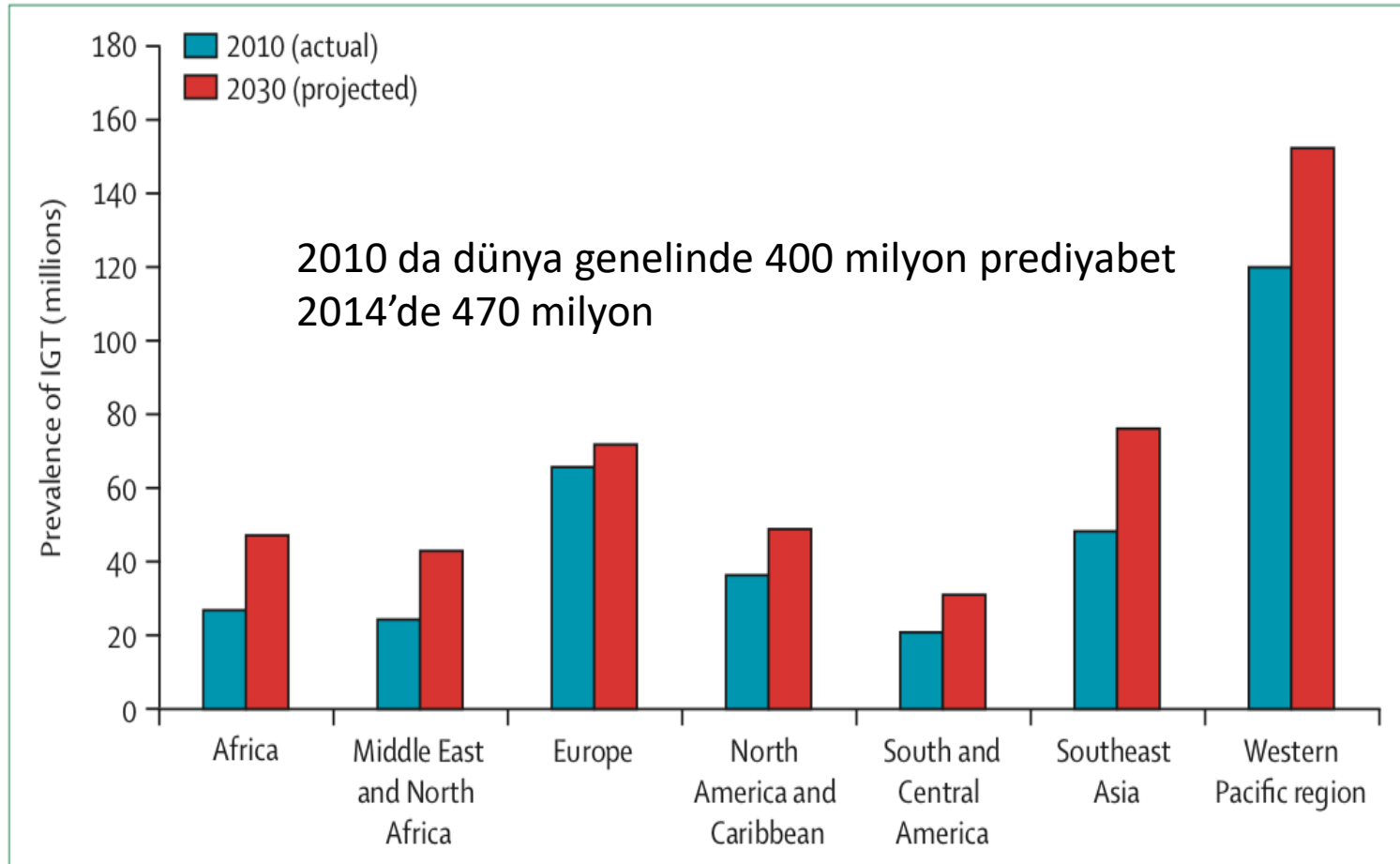
Diyabet Prevalansı, Prediyabet Türkiye - 1998-2000

≥20 yaş n=24788,

DM %7.2

PreDM %6.7

3.2 milyon

Satman İ, et al. Population-based study of diabetes and risk characteristics in Turkey: results of the turkish diabetes epidemiology study (TURDEP)Diabetes Care. 2002 Sep;25(9):1551-6.

Diyabet Prevalansı, Prediyabet– Türkiye 2010

≥20 yaş n=26499

DM %13.7

PreDiyabet %30,4

Satman İ, et al. Twelve –year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults.Europeean Journal of EpidemiologyDOI : 10.1007/s10654-013-9771-5.3.İ Satman ve TURDEP Çalışma Grubu, 2011

Önleyici müdahale olmadan, prediyabetik hastalarda 10 yıllık T2DM riski ne kadardır?

A) ~%10

B) ~%25

C) ~%40

D) ~%50

Bozulmuş Glukoz Toleransının(BGT) Doğal Hikayesi

%25   IGT

BGT - 10 yıl sonra

%25   NORMAL

Tip 2 DM

%50

N Engl J Med. 2002;346:393-403
Lancet Diabetes Endocrinol. 2016 Jan;4(1):44-51
Nat Rev Endocrinol. 2016 Mar;12(3):127-8
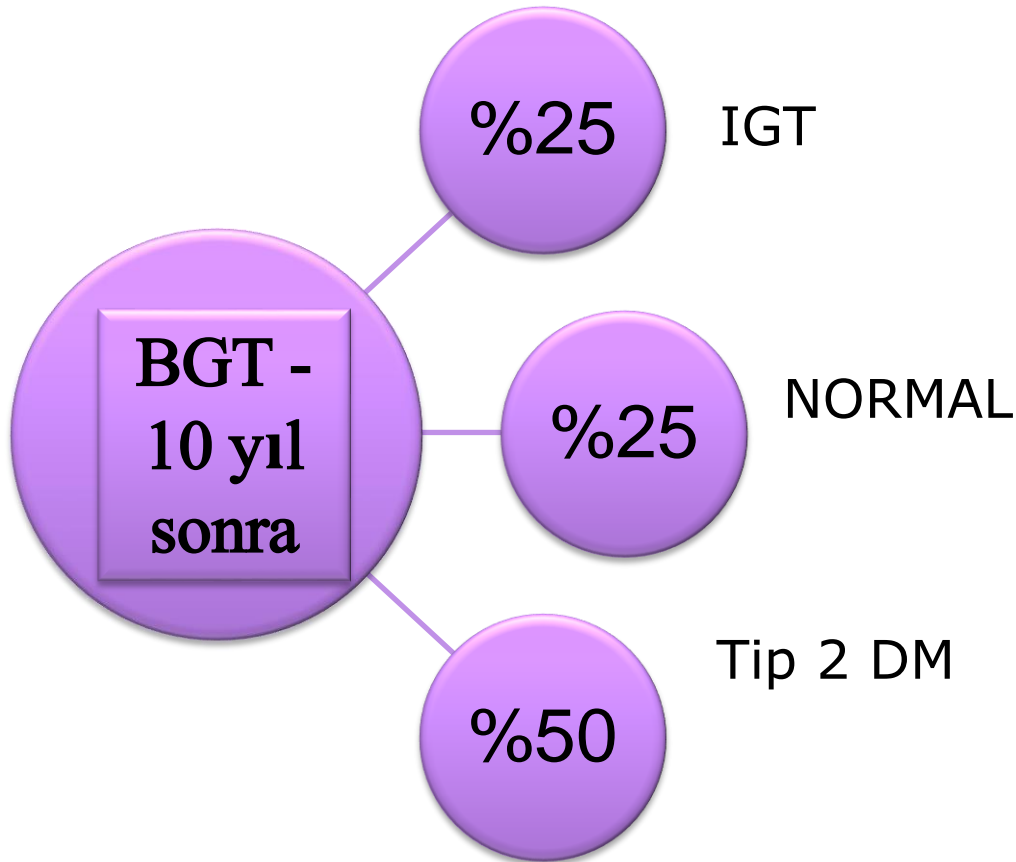
Prediyabet Diyabeti predikte eder mi?

11 yıllık takip sonucu BGT/BAG'nun DM'a progresyonu
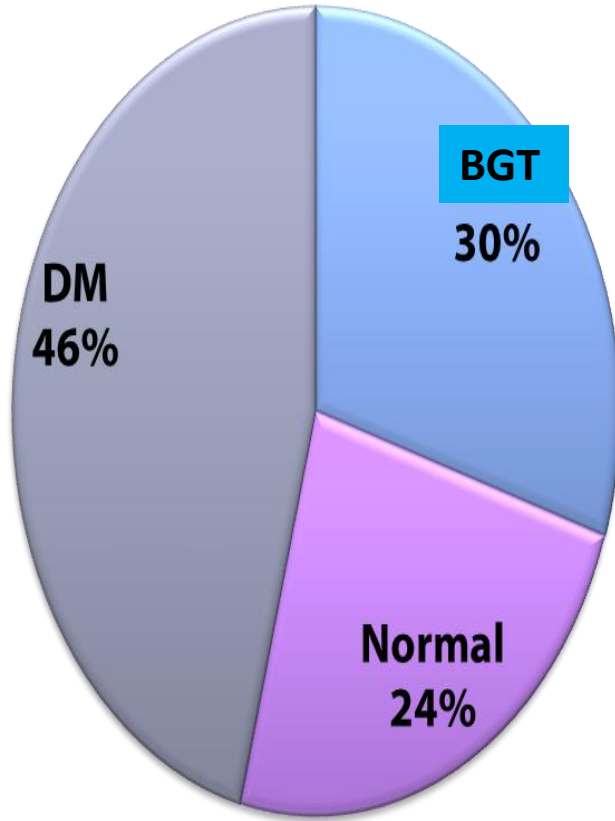
BGT olan kişiler

BAG olan kişiler

Lifetime risk of developing impaired glucose metabolism and eventual progression from prediabetes to type 2 diabetes: a prospective cohort study

Symen Ligthart*, Thijs T W van Herpt*, Maarten J G Leening, Maryam Kavousi, Albert Hofman, Bruno H C Stricker, Mandy van Hoek, Eric J G Sijbrands, Oscar H Franco, Abbas Dehghan

n=10050 Rotterdam Study, 1997-2012
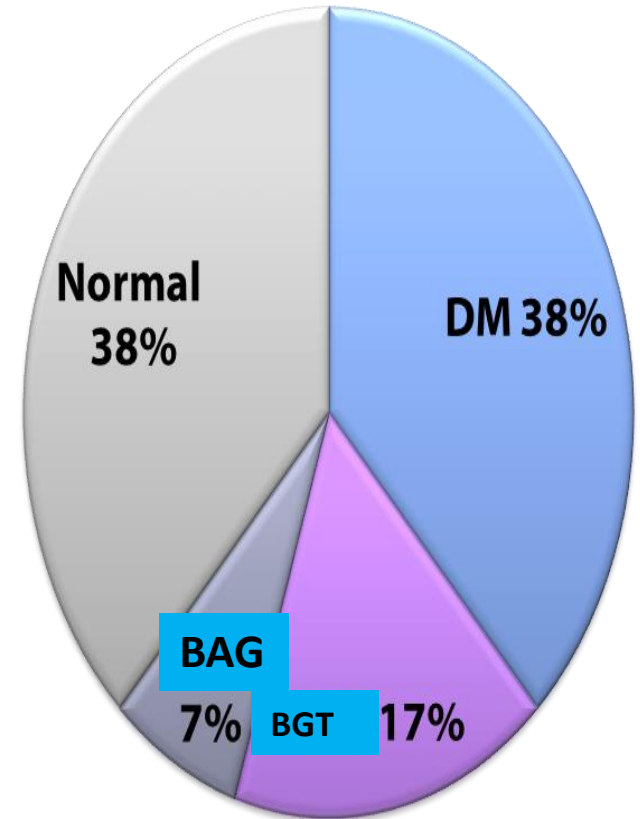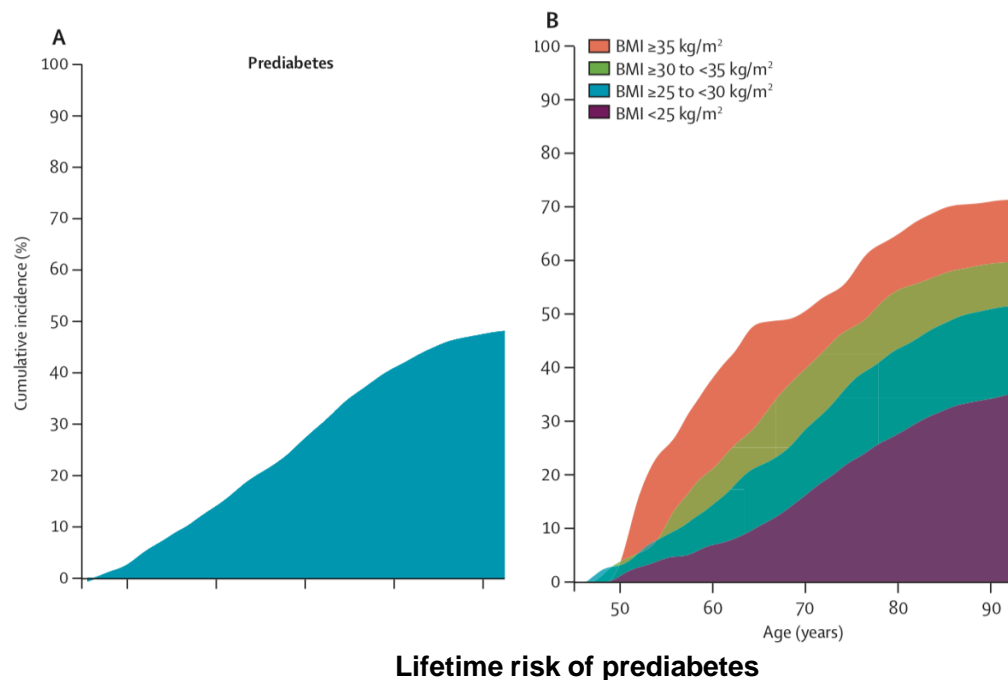
Zaman içinde , BAG,BGT veya her ikisi birlikte olan bireyler önleyici tedavi almazlarsa Tip 2 DM oluyorlar

	n	Prediabetes to diabetes (95% CI)
Unstratified	1382	74·0% (67·6–80·5)
BMI (kg/m²)		
<25	269	35·9% (18·4–53·4)
≥25 to <30	680	76·3% (68·9–83·7)
≥30 to <35	311	87·7% (79·4–96·0)
≥35	112	80·9% (65·9–95·9)
Waist circumference*		
Small	202	49·8% (28·6–70·9)
Medium	369	70·0% (56·4–83·7)
Large	752	78·8% (70·4–87·1)

Lifetime risk of prediabetes

Waist circumference categories represent the WHO classification scheme (for men: small <94 cm, medium 94–102 cm, and large ≥102 cm; for women: <80 cm, 80–88 cm, and ≥88 cm).

Prediyabet makro ve mikro komplikasyonlara yol açar
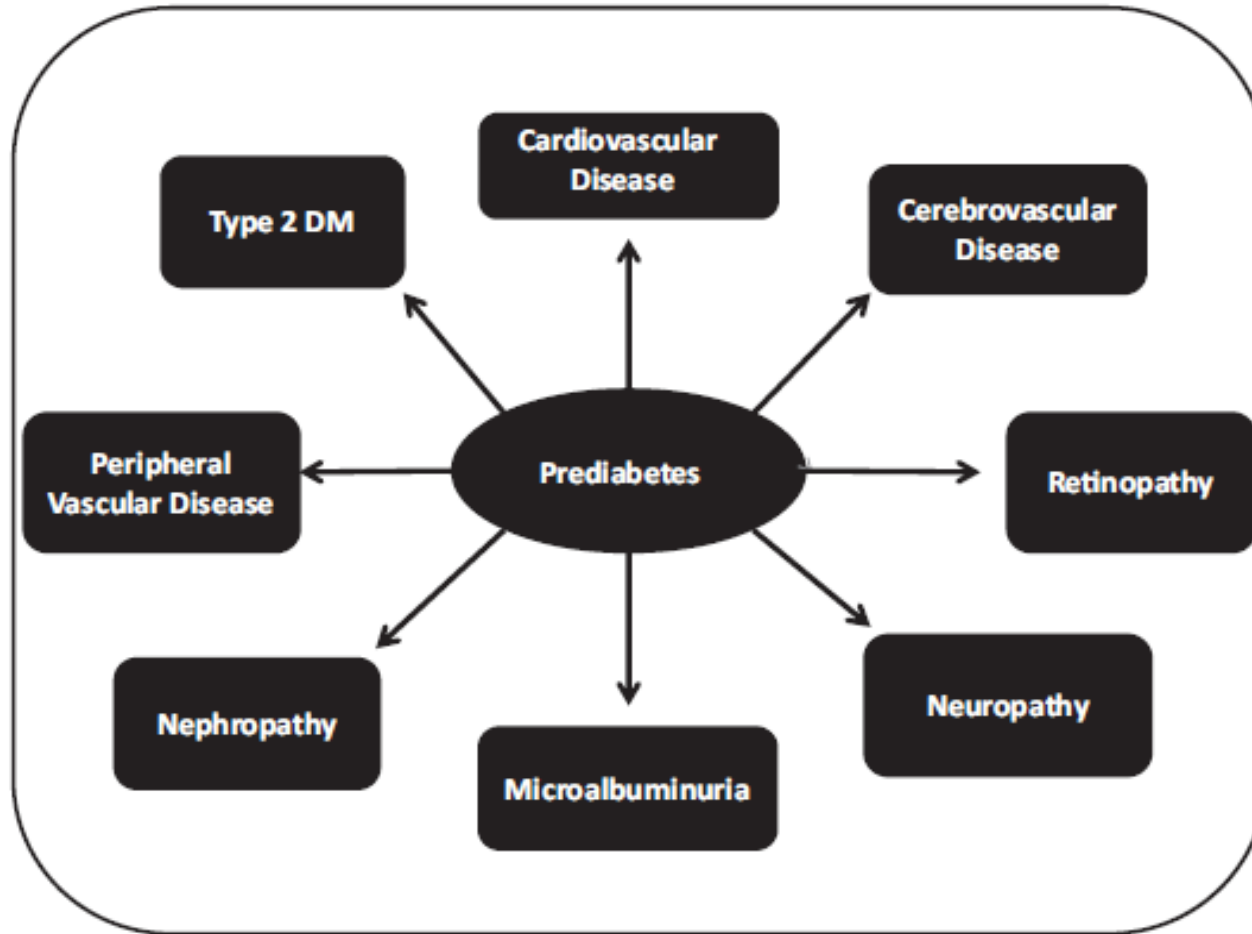
Nondiyabetik Bireylerde Koroner Olay Risk Belirteci: Yüksek-Normal HbA1c

HbA1c: % 5.0-5.4

HbA1c %	Göreceli Risk Artışı
5.5 – 5.9	% 23
6.0- 6.4	% 78
≥ 6.5	% 95

Ne zaman tedavi?

Prediyabeti önleyici tedaviler konusundaki deliller?

Ve tedavi prediyabetin doğal seyrini değiştiriyor mu?

Kimler prediyabet ve diyabet için taranmalı?

45 yaşından itibaren
Obez/kilolu (BKİ ≥25 kg/m²), özellikle santral obez –bel çevresi kadında ≥80 cm, erkekte ≥94 cm– kişiler
Yaştan bağımsız olarak BKİ ≥25 kg/m² olan ve aşağıdaki risk gruplarından birine mensup kişiler
1. dereceden bir veya 2. Dereceden iki veya daha fazla yakınında diyabet bulunan kişiler
İri bebek doğuran (>4000 gr) veya daha önce GDM tanısı almış kadınlar
Hipertansif bireyler (KB >140/90 mmHg)
Dislipidemisi olan bireyler (HDL-kolesterol <35 mg/dL veya trigliserid >150 mg/dL)
Polikistik over sendromu olan kadınlar
İnsülin direnci ile ilgili klinik hastalığı veya bulguları [akantozis nigrikans veya skin tags (et beni)] bulunan kişiler
Koroner, periferik veya serebrovasküler hastalığı bulunanlar
Düşük doğum tartılı doğan kişiler (2500 gram ve altı)
Sedanter yaşam süren veya fizik aktivitesi düşük olan kişiler
Şizofreni hastaları ve atipik antipsikotik ilaç kullanan kişiler
Majör depresyon tanısı almış kişiler
Solid organ transplantasyonu yapılmış hastalar
Nonalkolik steatohepatit
Ürik asit yüksekliği
Uyku apne sendromu
Diyabet gelişim riski taşıyan ilaç (kortikosteroidler, beta blokerler, antipsikotikler, tiyazid diüretikler, immunsupresifler) kullanan kişiler

Aşağıdaki hayat tarzı önerilerinden hangisi **prediyabetli** bireyler için doğrudur?

A) Sadece yüksek riskli prediyabetli bireyler hayat tarzı değişikliği yapmalıdır

B) Kan basıncı ve lipid düzeylerinin kontrolü diyabetiklere göre daha az ciddi ele alınmalıdır

C) Prediyabetli kişiler vücut ağırlığının %7'sini kaybetmeli ve bu durum uzun süreli olmalıdır

D) Düşük dirençli fiziksel aktivite günlük 15 dk olmalı ve haftada 4-5 gün olmalı

# Tip 2 DM Önlem Çalışmaları: Hayat tarzı değişikliği

Study	Country	N	Baseline BMI (kg/m²)	Intervention period (years)	Relative Risk Reduct. (%)	Number Needed To Treat
Diabetes Prevention Program	USA	3234	34.0	2.8	58	21
Diabetes Prevention Study	**Finland**	**523**	**31**	**4**	**39**	**22**
Da Qing	China	577	25.8	6	51	30

T2D, type 2 diabetes.

DPP Research Group. *N Engl J Med*. 2002;346:393-403. Eriksson J, et al. *Diabetologia*. 1999;42:793-801. Li G, et al. *Lancet*. 2008;371:1783-1789. Lindstrom J, et al. *Lancet*. 2006;368:1673-1679.

Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study

Guangwei Li, Ping Zhang, Jinping Wang, Yali An, Qiuhong Gong, Edward W Gregg, Wenying Yang, Bo Zhang, Ying Shuai, Jing Hong, Michael M Engelgau, Hui Li, Gojka Roglic, Yinghua Hu, Peter H Bennett
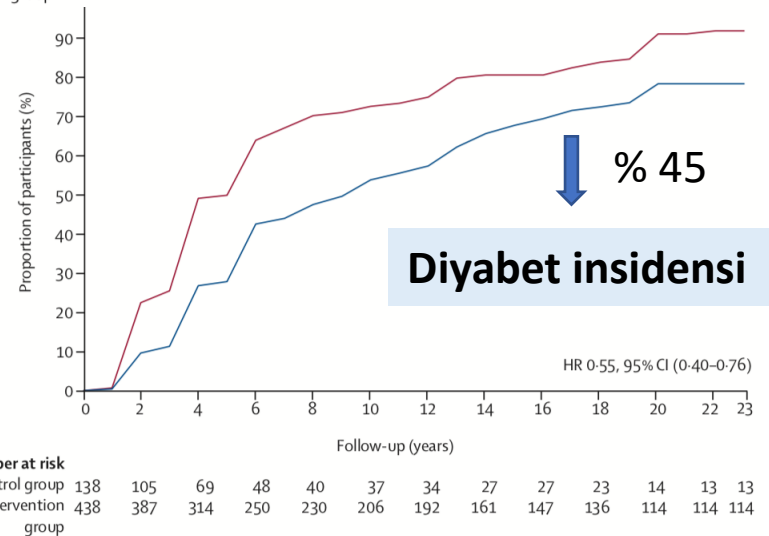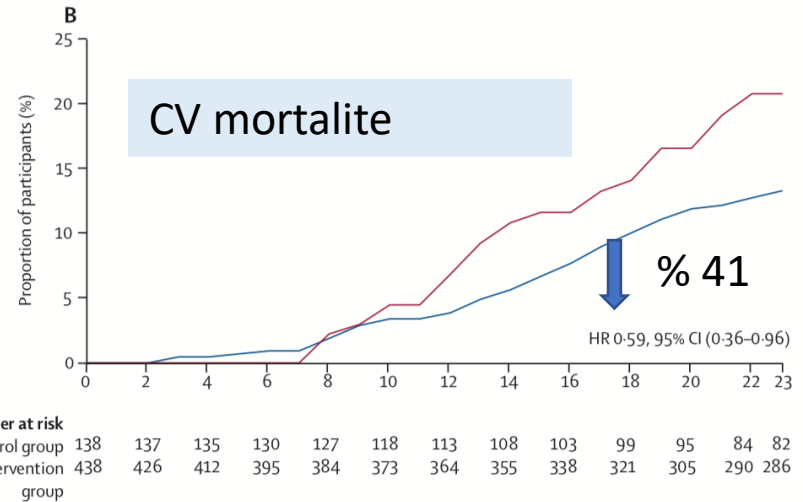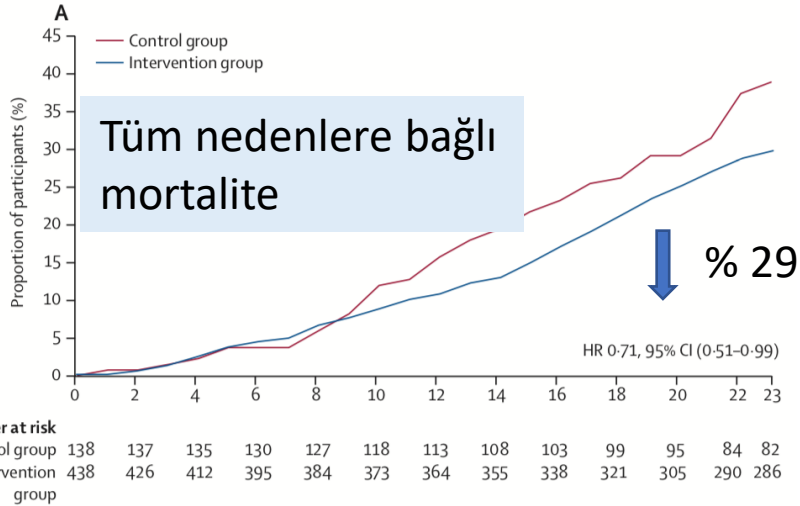
IGT, impaired glucose tolerance.

Li G, et al. *Lancet Diabetes Endocrinol*. 2014;2:474-478.
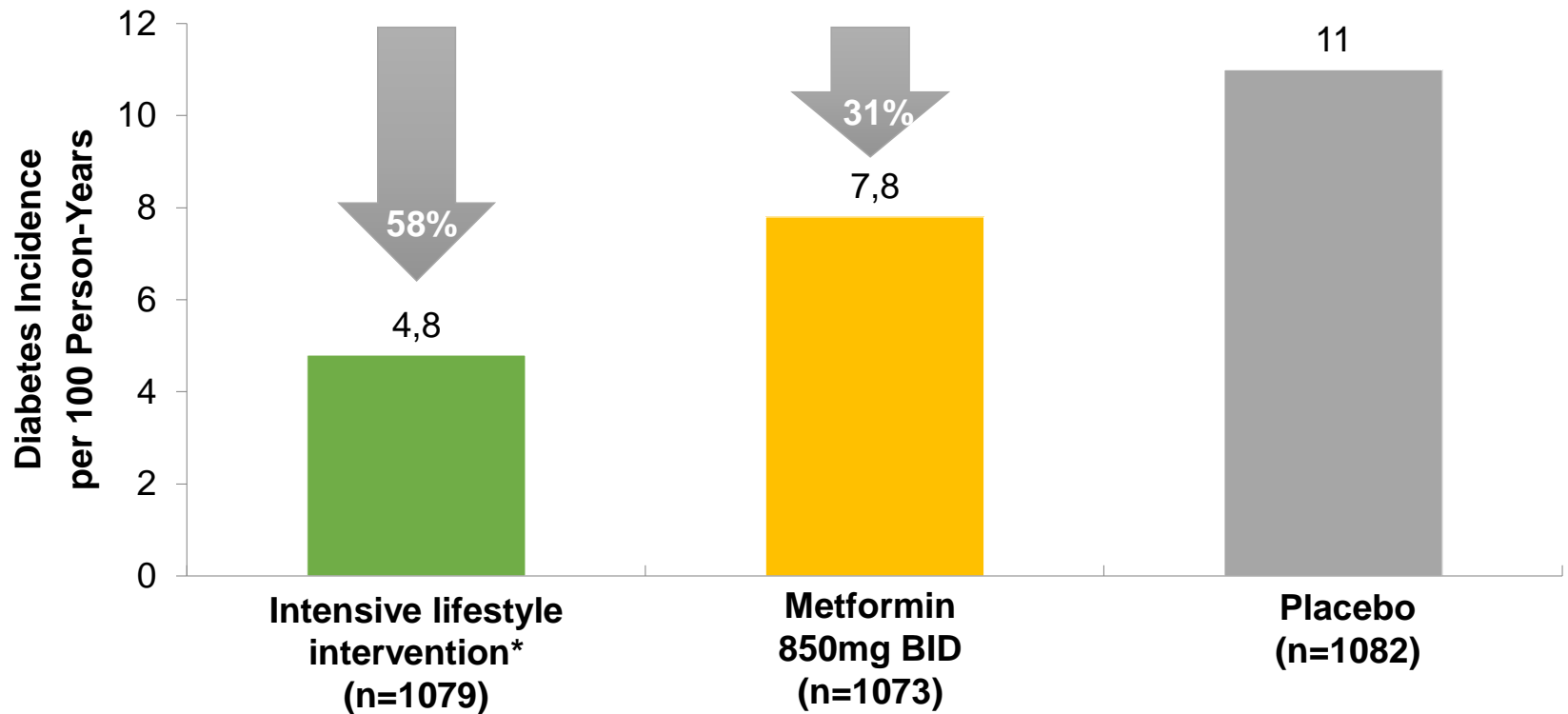
Prediyabet önleme çalışmaları

Table 2
Pertinent prediabetes intervention studies

Study	Intervention	Number of Subjects	Study Population	Risk Reduction	Years
Da Qing[117]	Diet and exercise	577	Chinese IGT adults, mean age 46, BMI 26	31%–46% after 6 y	1986–1992
Finnish DPS[115]	Diet and exercise	522	IGT adults, mean age 55, BMI 31	58% after 3.2 y	1993–1998
STOP-NIDDM[118]	Acarbose	1428	IGT adults, mean age 55, BMI 31	25% after 3.3 y	1995–1998
DPP[116]	Diet and exercise	3234	IGT adults, mean age 54 y, BMI 34	Metformin 31%, lifestyle 58% after 2 y	1996–1999
XENDOS[120]	Orlistat and diet and exercise	3305	Swedish, BMI >30, mean age 43, 21% with IGT	Entire group 37%, IGT 45% after 4 y	1997–2002
DREAM[121]	Rosiglitazone	5269	IGT and/or IFG subjects mean age 54.7 y, BMI 30.9	62% after approximately 3 y	2001–2003
IDDP-1[124]	Lifestyle modifications and metformin or lifestyle modifications	531	Indian, IGT mean age 46 y, BMI 25.8	Diet and exercise 28.5%, metformin 26.4%, diet and exercise and metformin 28.2% after 30 mo	2001–2004
ACT-NOW[127]	Pioglitazone	602	IGT, mean age 53, BMI 33	72% with pioglitazone over 2.4 y	2004–2006
CANOE[122]	Combination rosiglitazone and metformin vs placebo	207	IGT, mean age 50, BMI 31.3	26% in the combination group after 3.9 y	2004–2006
IDDP-2[125]	Lifestyle modifications or pioglitazone and lifestyle modifications	407	Indian IGT, mean age 45.3, BMI 25.9	28% though pioglitazone not additive to lifestyle modification	2006–2009
NAVIGATOR[123]	Nataglinide and lifestyle modifications or Valsartan and lifestyle modifications	9306	IGT, mean age 63.7, BMI 30.5	Nataglinide none, Valsartan 14%	2005–2010

Abbreviations: BMI, body mass index; IGT, impaired glucose tolerance.

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

Diabetes Prevention Program
(N=3234)

Diabetes Incidence per 100 Person-Years

- Intensive lifestyle intervention* (n=1079): 4,8 — 58%
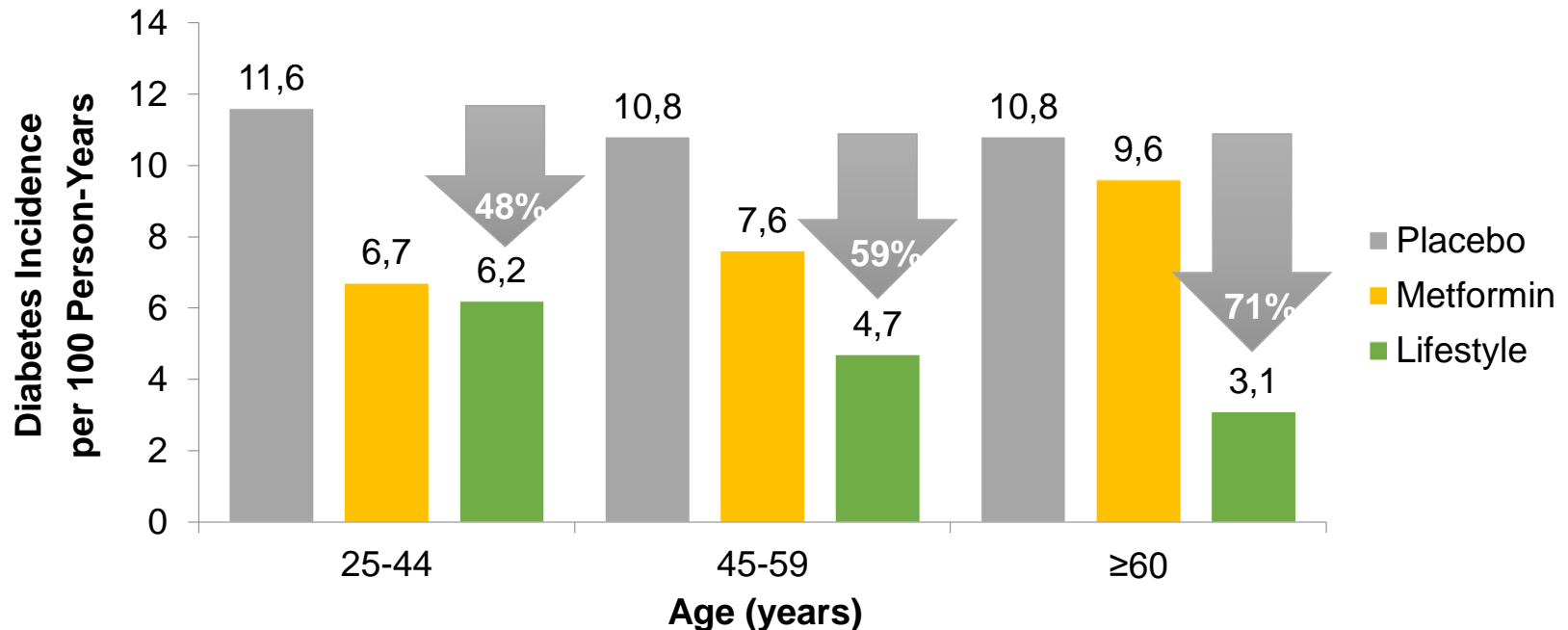- Metformin 850mg BID (n=1073): 7,8 — 31%
- Placebo (n=1082): 11

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

IGT, impaired glucose tolerance; T2D, type 2 diabetes.

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN
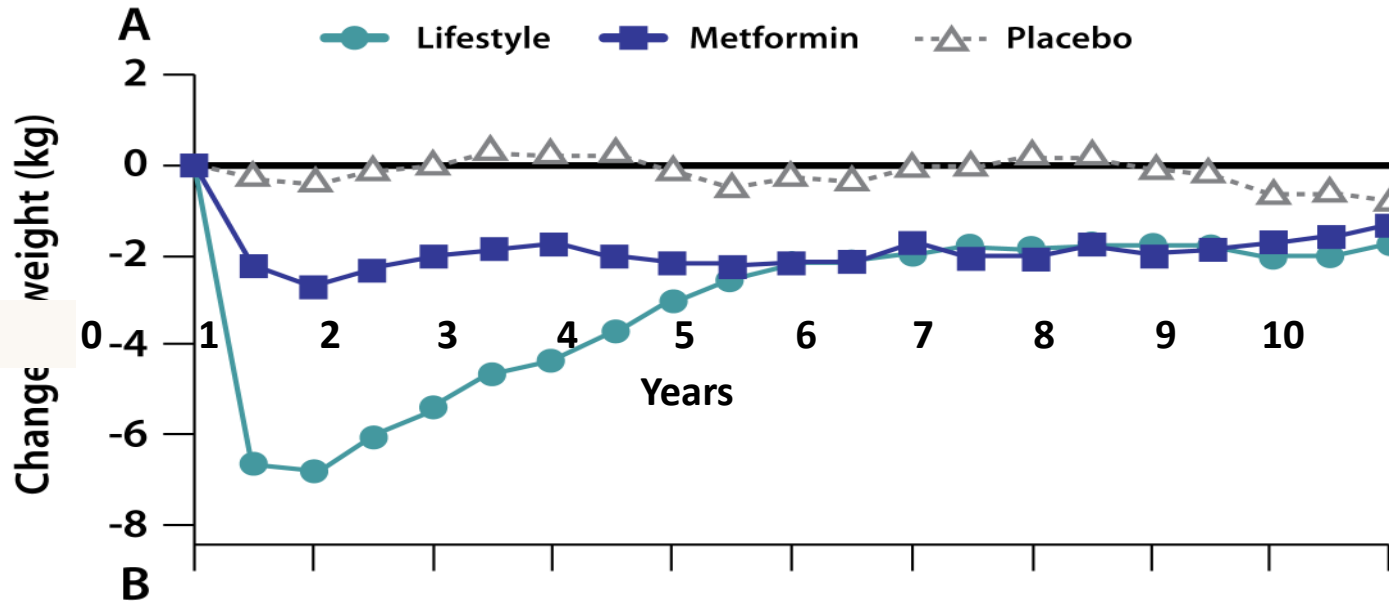
Diabetes Prevention Program
(N=3234)

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

DPP Research Group. *N Engl J Med.* 2002;346:393-403.

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

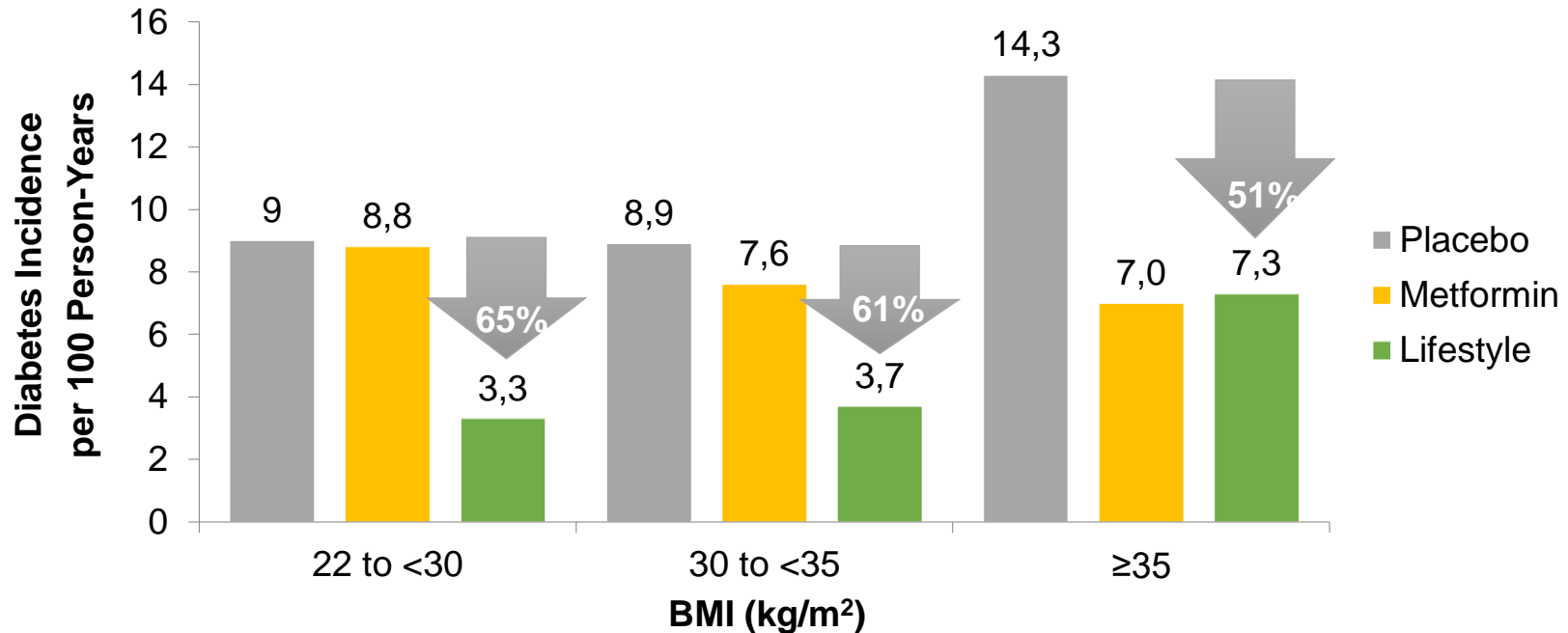## DPP Outcomes Study
(N=2766)

Yıllar içinde kilo kaybının devamlılığı

REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN

Diabetes Prevention Program
(N=3234)

> Kilo arttıkça yaşam tarzı değişikliği diyabeti önleme açısından etkisini kaybediyor
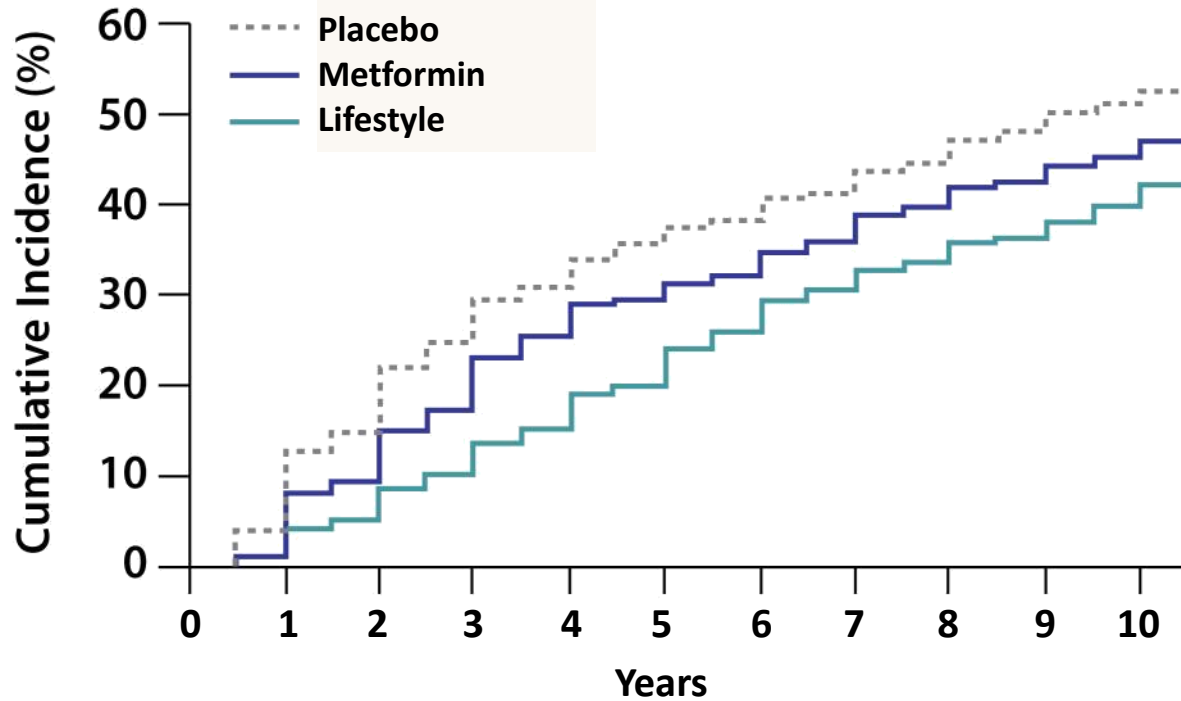
*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

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REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN
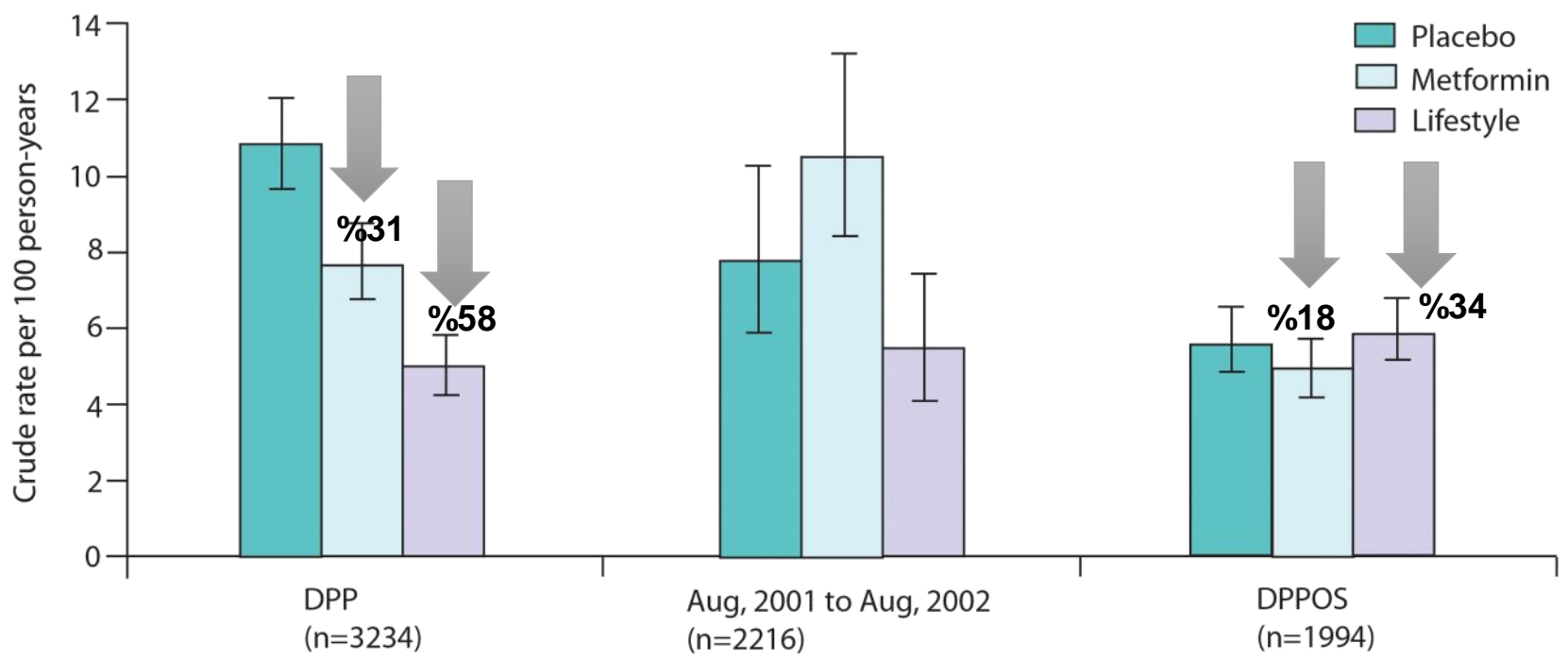
DPP Outcomes Study
(N=2766)

Tip 2 DM'un 10 yıllık insidensi

10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study

10-Yıllık Tip 2 DM insidansı

XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study

A randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients
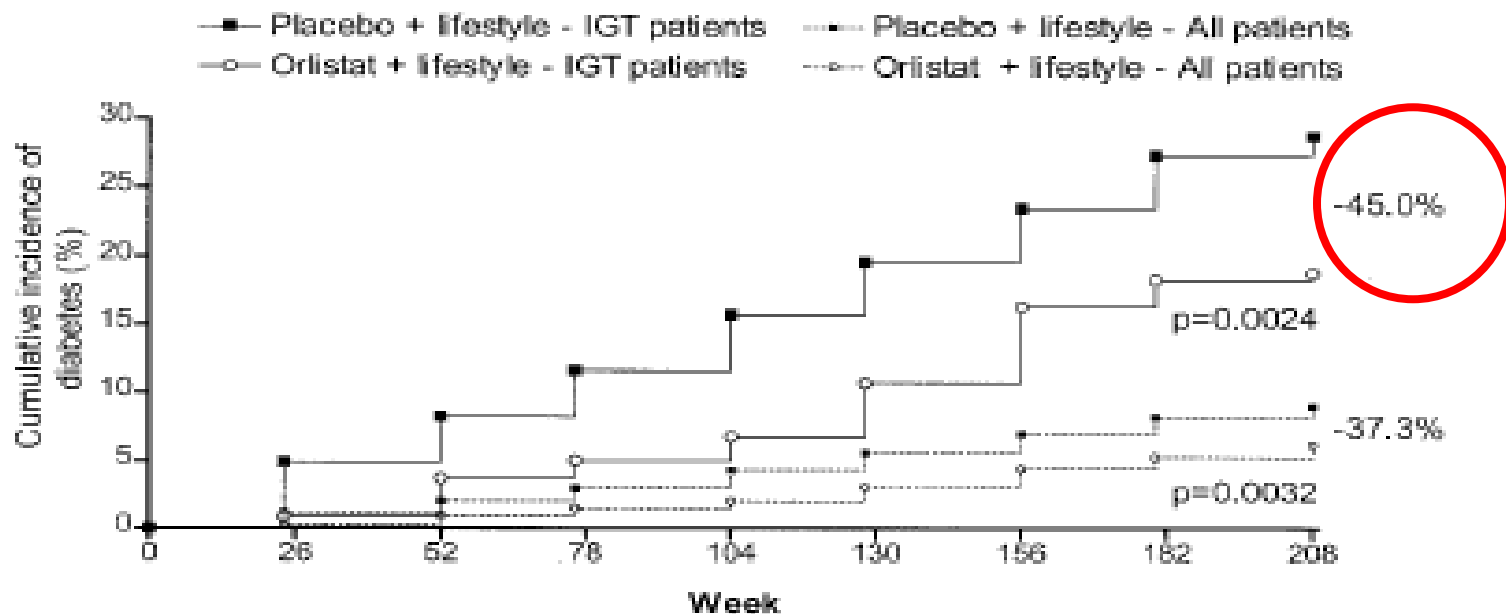
Diabetes Care 2004

Figure 1—Cumulative incidence of diabetes by study group in all obese patients (IGT or NGT at baseline) and only in obese patients with IGT at baseline. The decrease in the risk of developing diabetes with orlistat plus lifestyle compared with placebo plus lifestyle is indicated. P values shown are for the log-rank test.

Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Subjects With and Without Pre-Diabetes

IGT +IGF Normalleşme
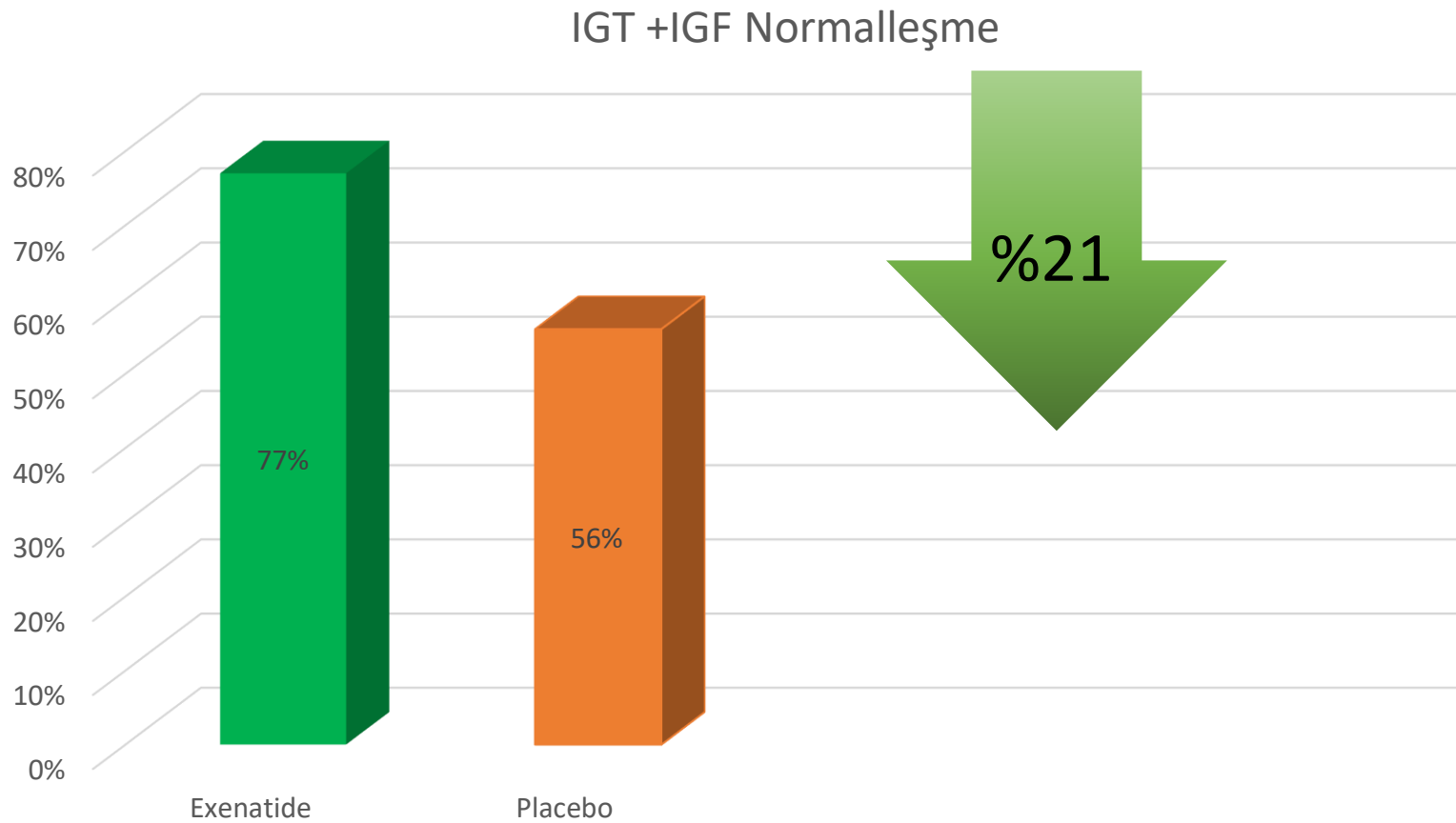
A Randomized, Controlled Trial of 3.0 mg of Liraglutide in Weight Management
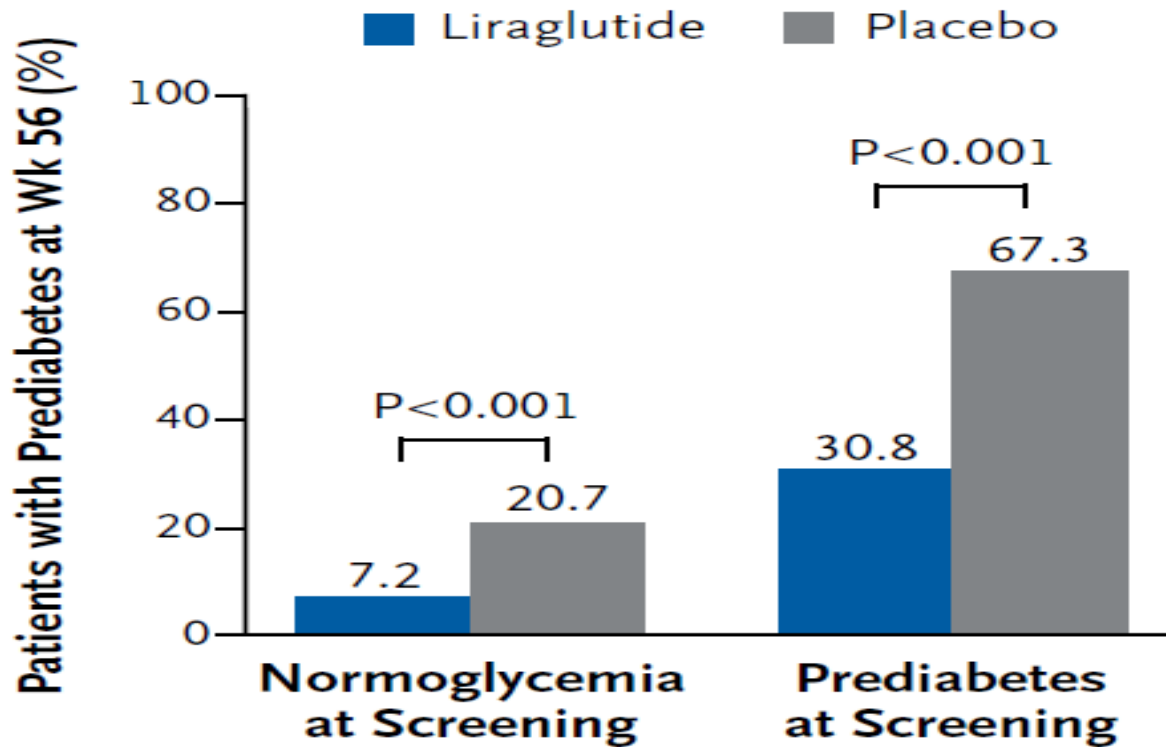
Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial.

N: 1429 BGT
3.3 yıl
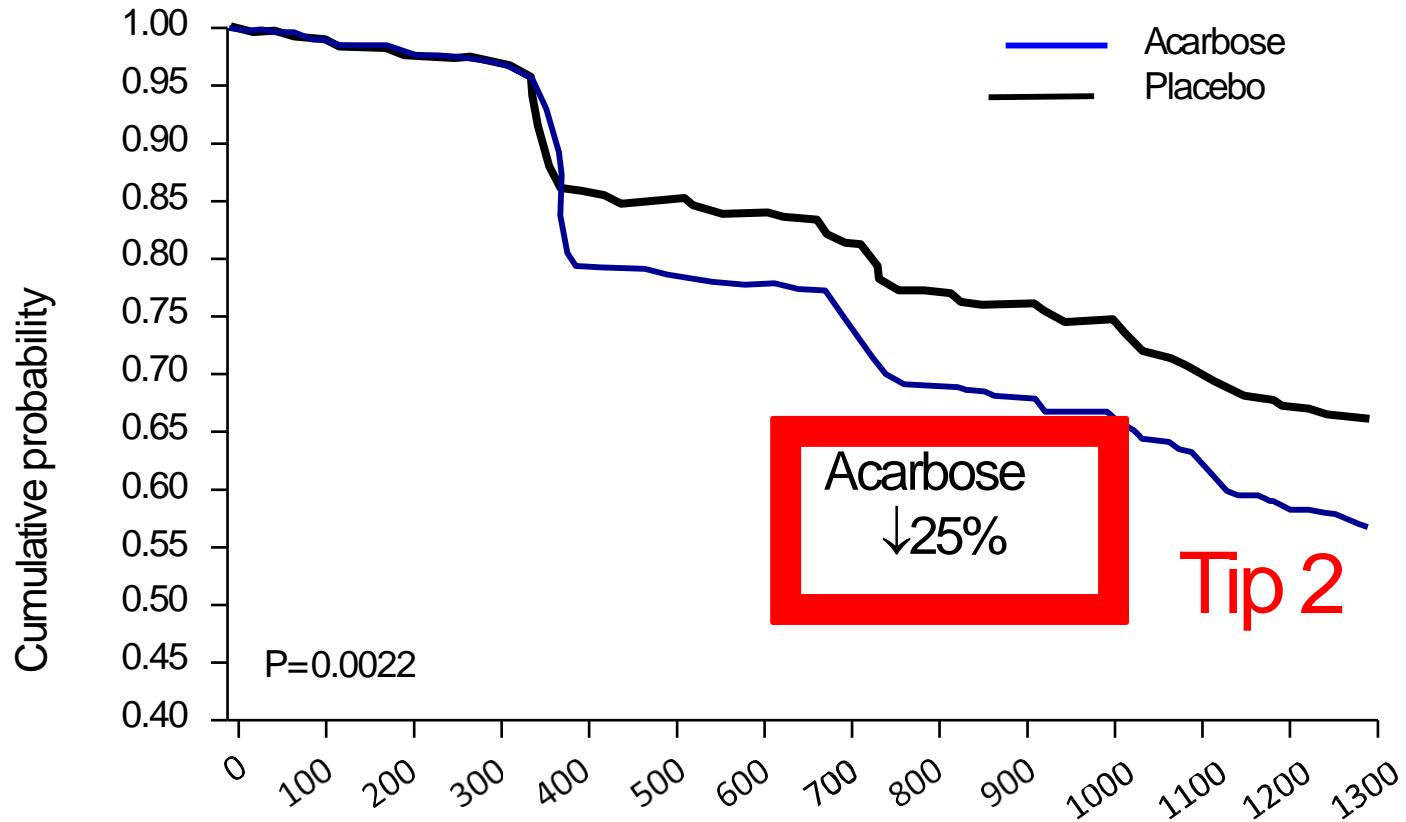
Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance

- 600 BGT'li
- + 1-2 Metabolik sendrom komponenti
- Pioglitazon 30-45 mg/gün
- İzlem süresi: medyan 2.4 yıl.

Figure 2. Kaplan–Meier Plot of Hazard Ratios for Time to Development of Diabetes.

Belirgin kilo artışı ve ödem!!

Prediyabet önleme çalışmaları

Table 2
Pertinent prediabetes intervention studies

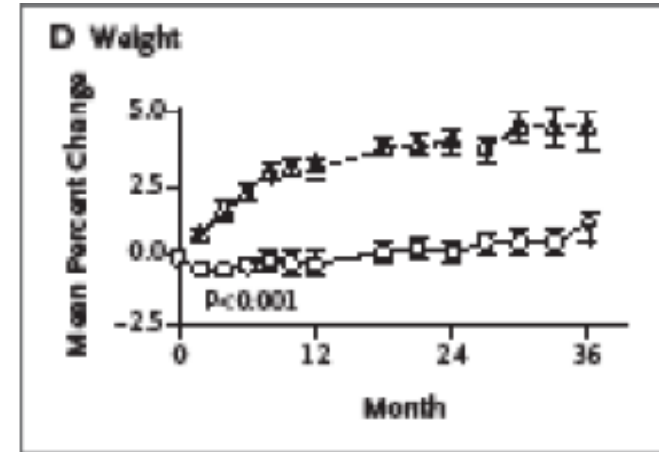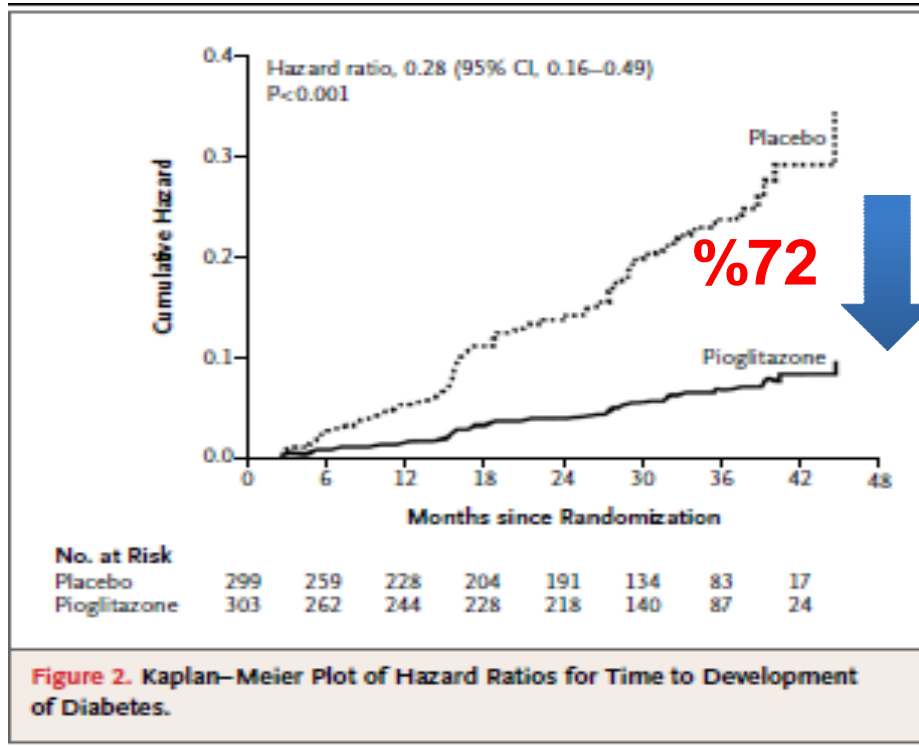| Study	Intervention	Number of Subjects	Study Population	Risk Reduction	Years
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Finnish DPS[115]	Diet and exercise	522	IGT adults, mean age 55, BMI 31	58% after 3.2 y	1993–1998
STOP-NIDDM[118]	Acarbose	1428	IGT adults, mean age 55, BMI 31	25% after 3.3 y	1995–1998
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ACT-NOW[127]	Pioglitazone	602	IGT, mean age 53, BMI 33	72% with pioglitazone over 2.4 y	2004–2006
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NAVIGATOR[123]	Nataglinide and lifestyle modifications or Valsartan and lifestyle modifications	9306	IGT, mean age 63.7, BMI 30.5	Nataglinide none, Valsartan 14%	2005–2010

Abbreviations: BMI, body mass index; IGT, impaired glucose tolerance.

Effect of Nateglinide on the Incidence of Diabetes and Cardiovascular Events

The NAVIGATOR Study Group*

NEJM,2010

A

Hazard ratio, 1.07 (95% CI, 1.00–1.15)
P=0.05

Nateglinide

Placebo

Incidence of Diabetes (%)

Years since Randomization
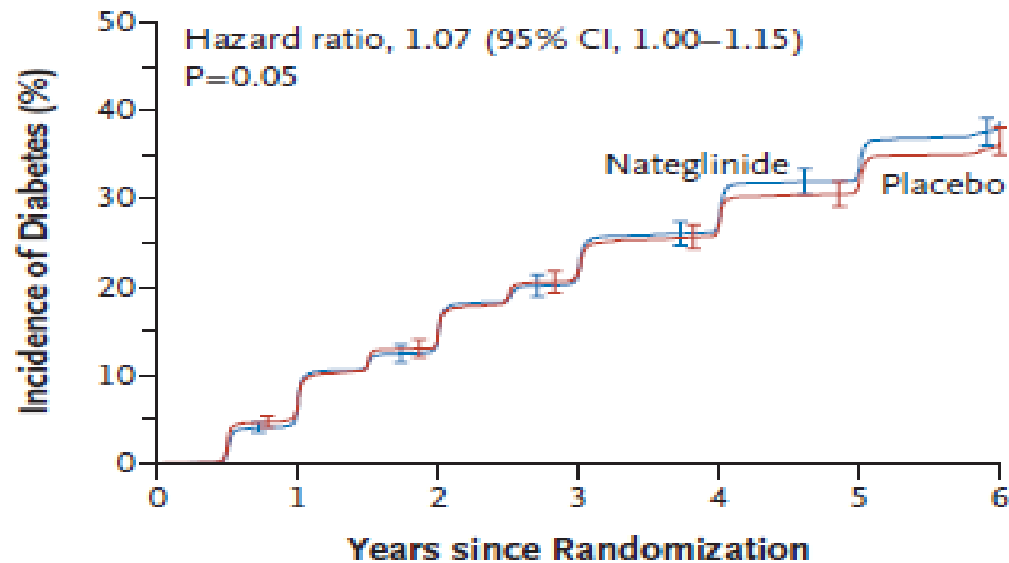
No. at Risk

Nateglinide	4645	3766	3302	2767	2396	2086	1408
Placebo	4661	3761	3281	2807	2481	2192	1528

Pioglitazone does not enhance the effectiveness of lifestyle modification in preventing conversion of impaired glucose tolerance to diabetes in Asian Indians: results of the Indian Diabetes Prevention Programme-2 (IDPP-2)

A. Ramachandran · C. Snehalatha · S. Mary ·
S. Selvam · C. K. S. Kumar · A. C. Seeli ·
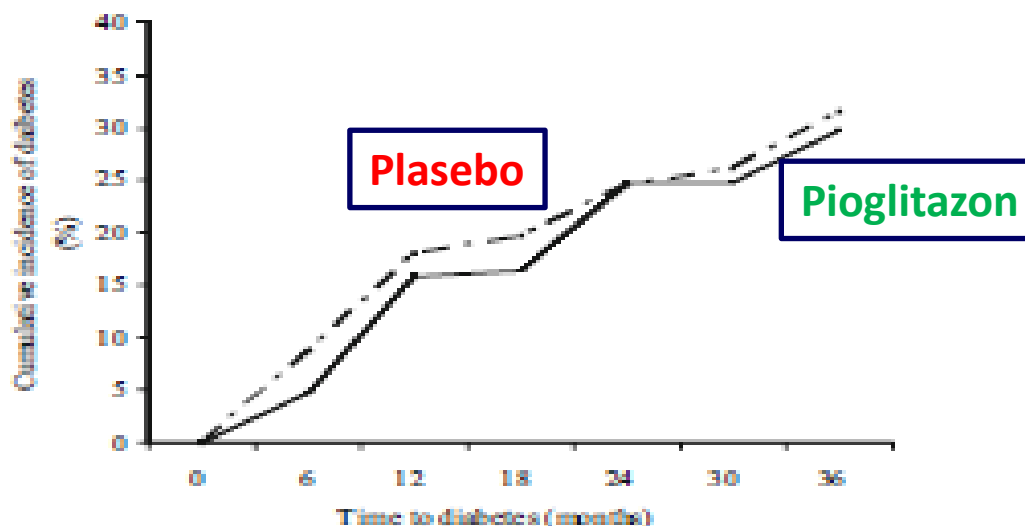A. S. Shetty

Fig. 2 Cumulative incidence of diabetes in the study groups estimated using the Kaplan–Meier survival test. The incidences were not significantly different: unadjusted HR 1.084 (95% CI 0.753–1.560), $p=0.665$; adjusted HR 0.984 (95% CI 0.672–1.443), $p=0.936$. The solid line represents the pioglitazone group and the broken line represents the placebo group

METFORMİN

- Yaşam tarzı değişikliği yetersiz yada uygulamaya rağmen glisemik parametrelerde gerileme olmayan yada ilerleyen hastalar

- VKİ > 35 kg/m2 ve < 60 yaş

- BAG ve BGT kombine durum

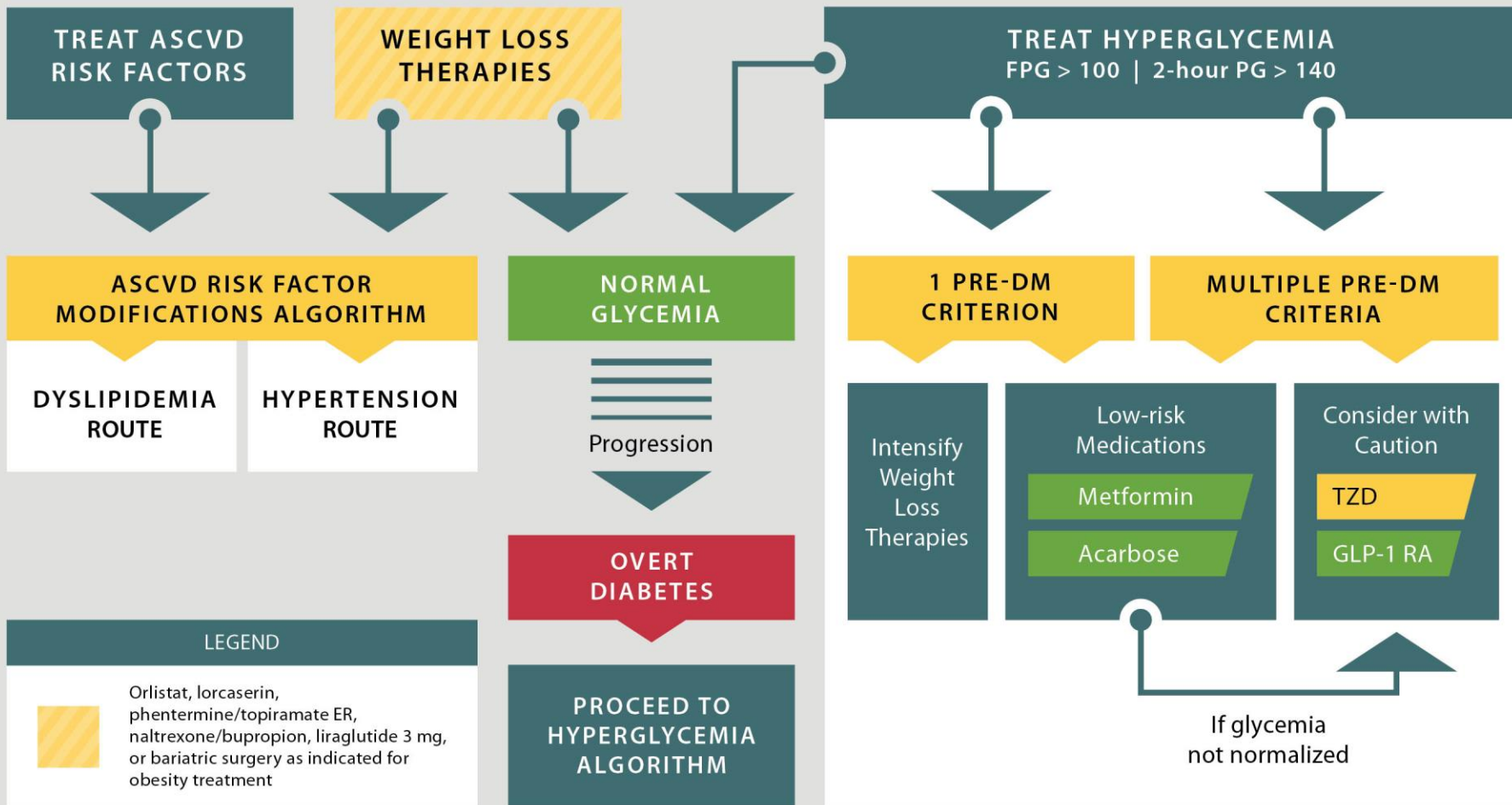- GDM öyküsü olan prediyabetik kadınlar

SONUÇ

- İnsülin direnci ve prediyabet sadece diyabete gidiş sürecinde kilometre taşları değildir. Tedavi edilmesi gereken durumlardır.

- Yaşam tarzı değişikliği tedavi tüm olgulara önerilmelidir.

- Farmakolojik tedavi seçilmiş olgularda kanıta dayalı bilgiler doğrultusunda uygulandığında etkin olabilir.

PREDIABETES ALGORITHM

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

MULTIPLE PRE-DM CRITERIA

Intensify Weight Loss Therapies

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

Teşekkürler