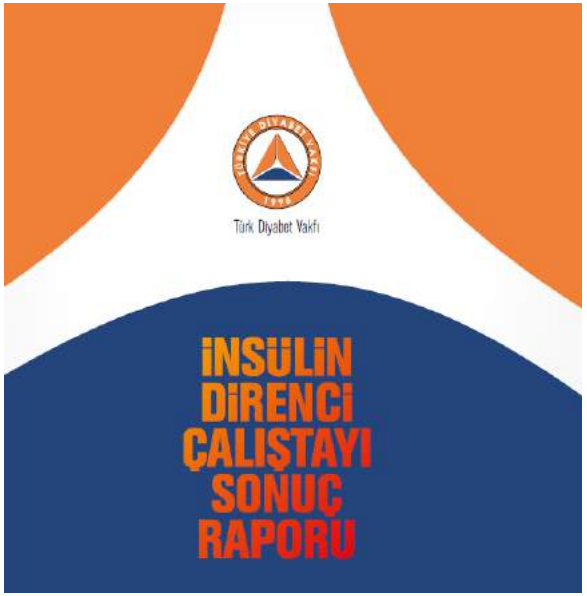
53. ULUSAL DİYABET KONGRESİ
TÜRKİYE DİYABET VAKFI
TÜRK DİYABET CEMİYETİ

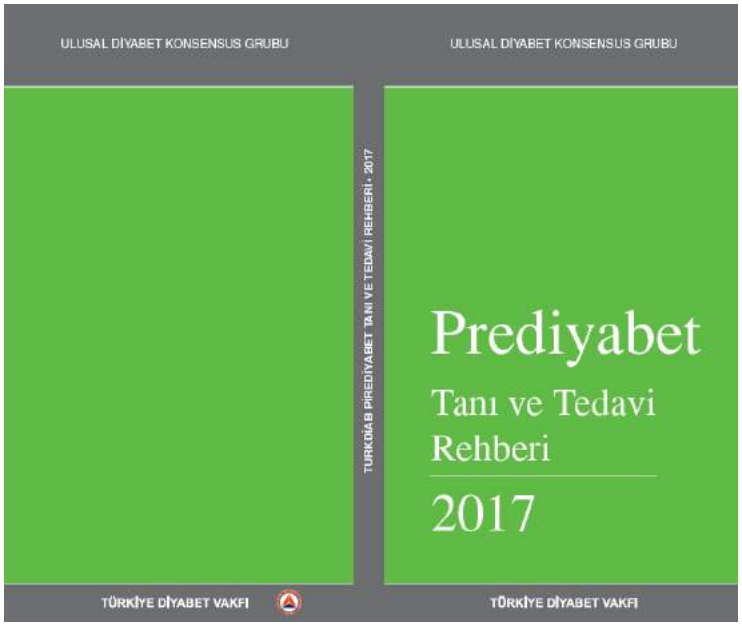
İnsülin Direnci ve Prediyabetin Yönetimi

Okan Bakıner

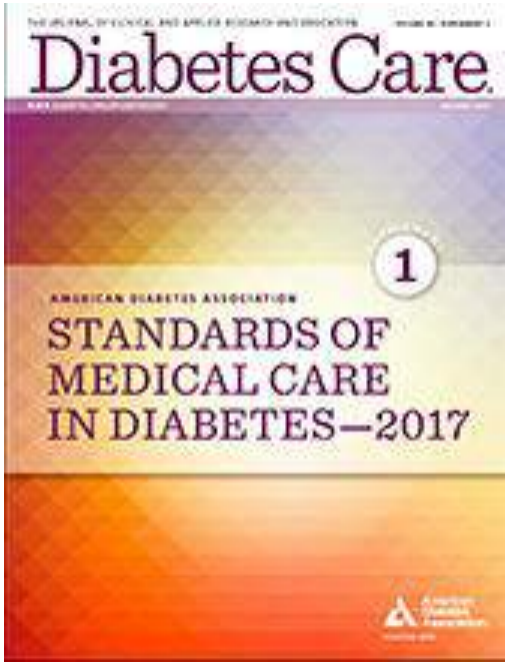
20 Nisan 2017, Perşembe

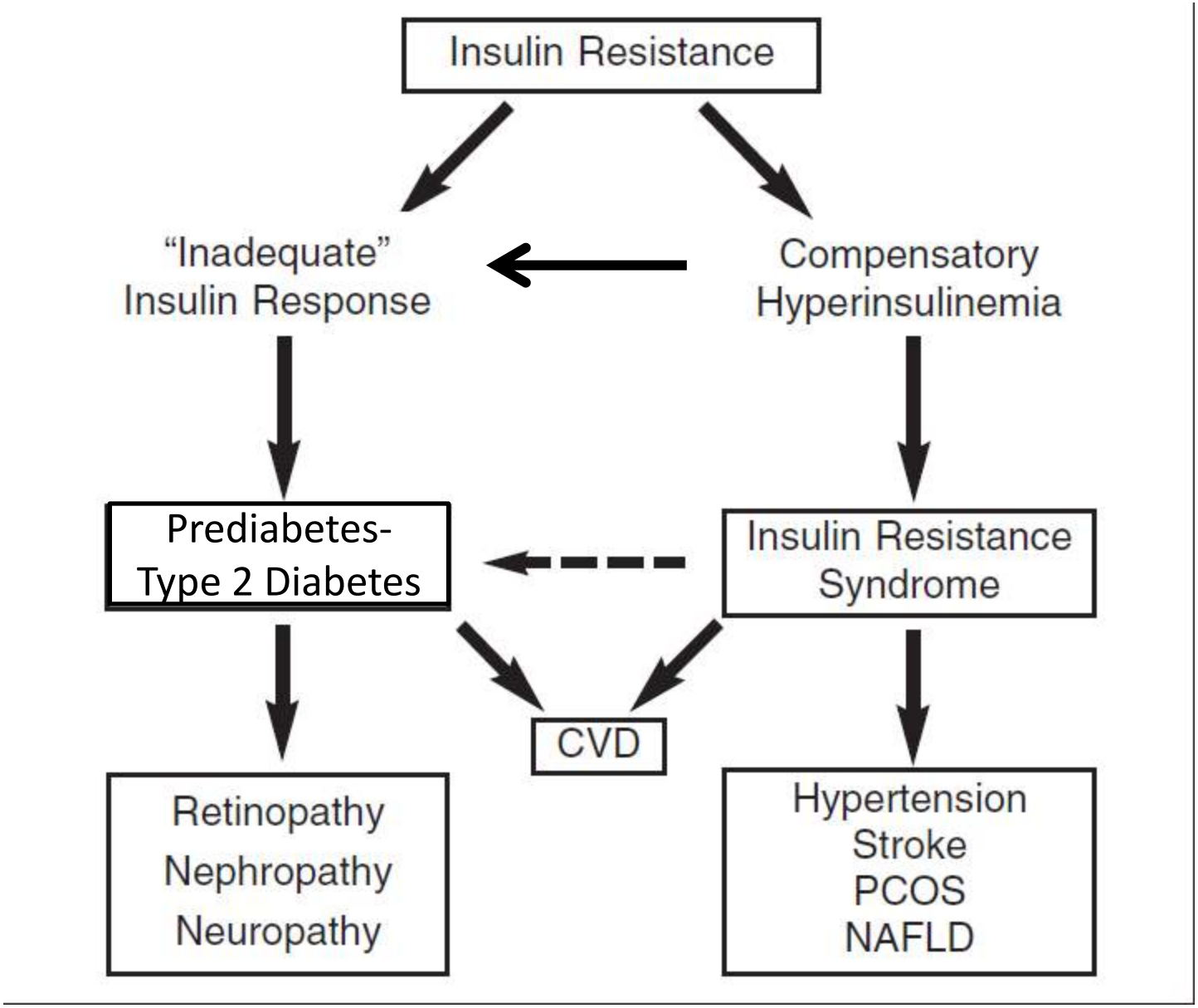
BAŞKENT ÜNİVERSİTESİ


Türk Diyabet Vakfı
İNSÜLİN DİRENCİ ÇALIŞTAYI SONUÇ RAPORU


ULUSAL DİYABET KONSENSUS GRUBU
ULUSAL DİYABET KONSENSUS GRUBU
TÜRKDİAB PREDİYABET TANI VE TEDAVİ REHBERİ - 2017
Prediyabet
Tanı ve Tedavi Rehberi
2017
TÜRKİYE DİYABET VAKFI
TÜRKİYE DİYABET VAKFI


Türkiye Endokrinoloji ve Metabolizma Derneği
DİABETES MELLİTUS VE KOMPLİKASYONLARININ TANI, TEDAVİ VE İZLEM KILAVUZU
Diabetes Mellitus Çalışma ve Eğitim Grubu


Diabetes Care
1
AMERICAN DIABETES ASSOCIATION
STANDARDS OF MEDICAL CARE IN DIABETES—2017



ACE Position Statement on the Insulin Resistance Syndrome, Endocr Pract. 2003;9(No. 3) 241

İnsülin direnci ve prediyabet yönetimi ana hedefleri

- 1. Diyabete progresyonu durdurmak
- 2. Kardiyova ak
- 3. Mikrovas nları ve diğer komorbid d

Nonfarmakolojik tedavi

Farmakolojik tedavi

Metabolik Cerrahi

Da Qing Study

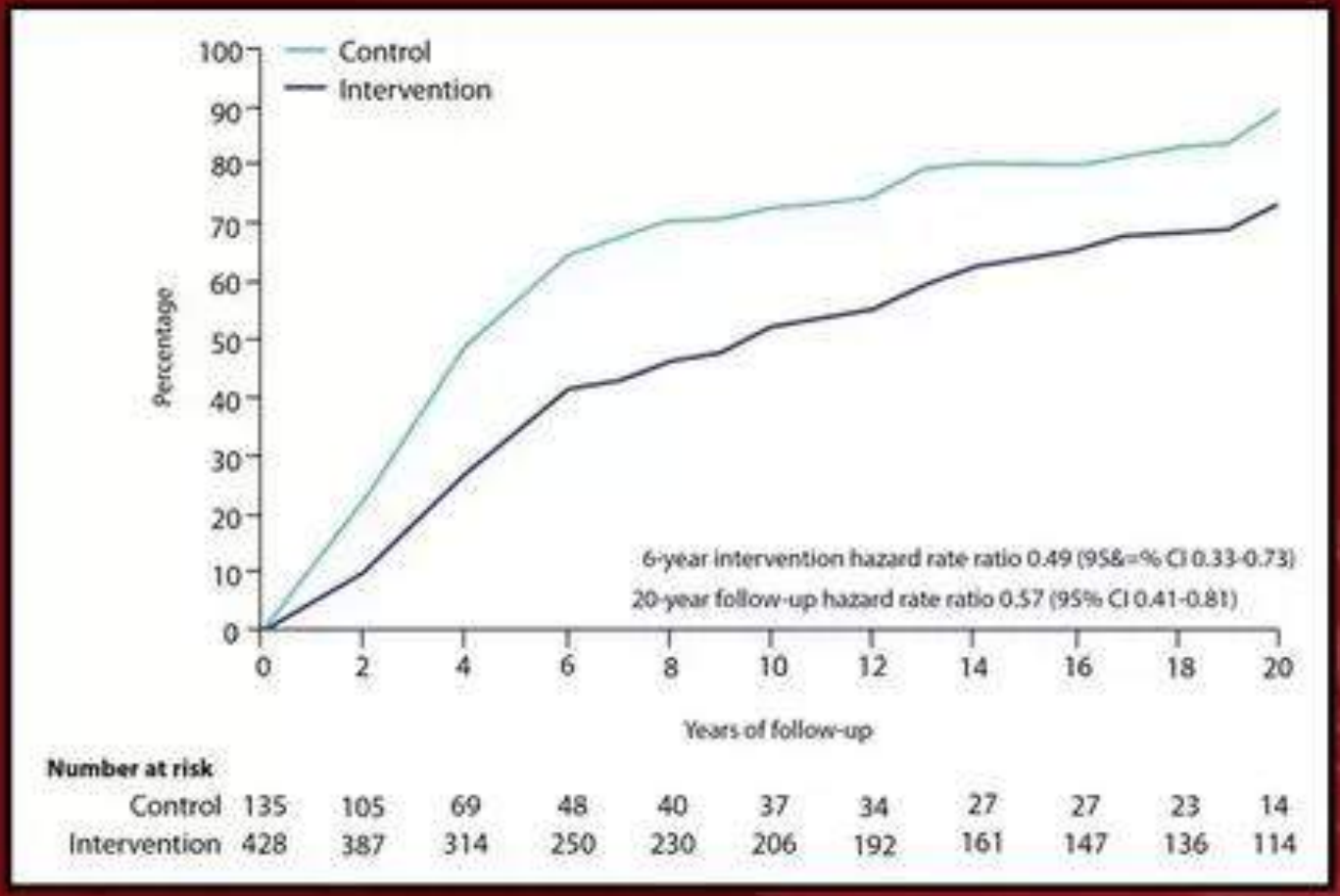
N= 577, süre= 6 yıl

6-year Cumulative Incidence of Type 2 Diabetes in Patients with Impaired Glucose Tolerance

	Incidence (%)	Reduction in Relative Risk (%)
Control	67.7	–
Diet	43.8	31
Exercise	41.1	46
Diet + Exercise	46.0	42

Pan XR, et al. Diabetes Care. 1997;20:537-544.

Cumulative T2DM Incidence During Follow-up in the Chinese Da Qing Diabetes Prevention Study

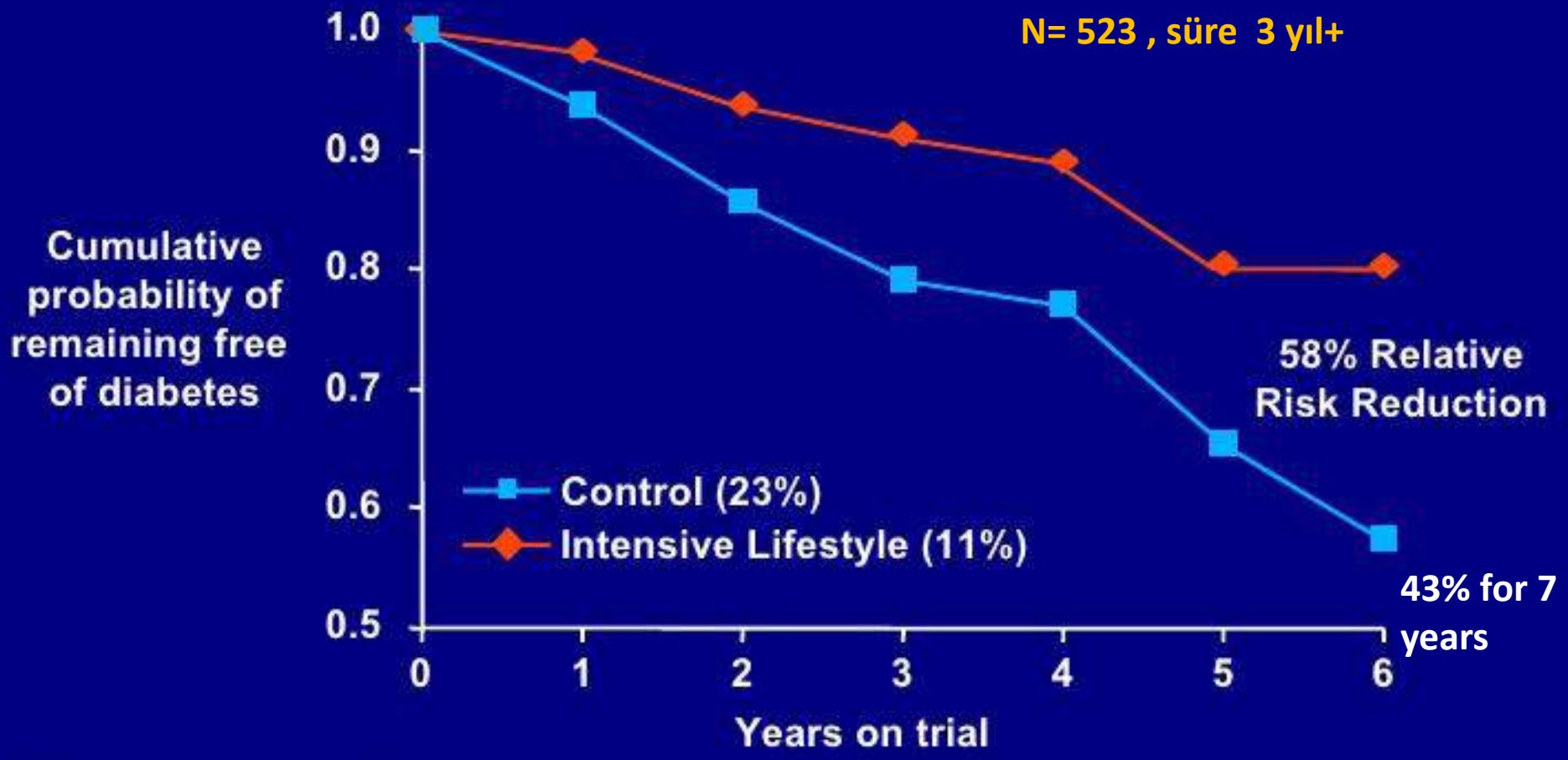


43% risk reduction

CI, confidence interval; DPP, Diabetes Prevention Program; T2DM, type 2 diabetes mellitus.

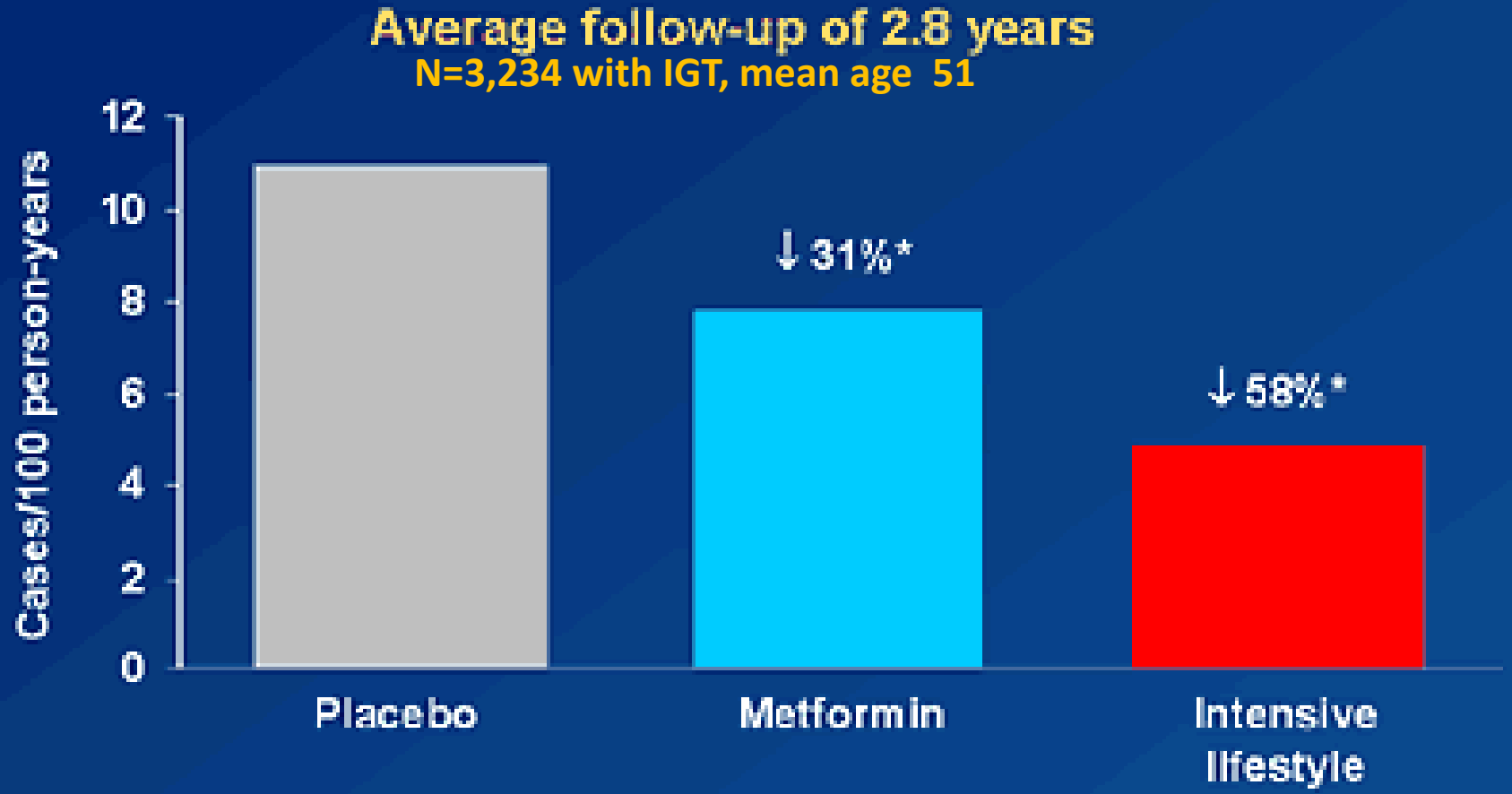
Li G, et al. *Lancet*. 2008;371:1783-1789.

Finnish Diabetes Prevention Study: Effect of Lifestyle Intervention



Toumilehto J et al. *N Engl J Med.* 2001;344:1343-1350.

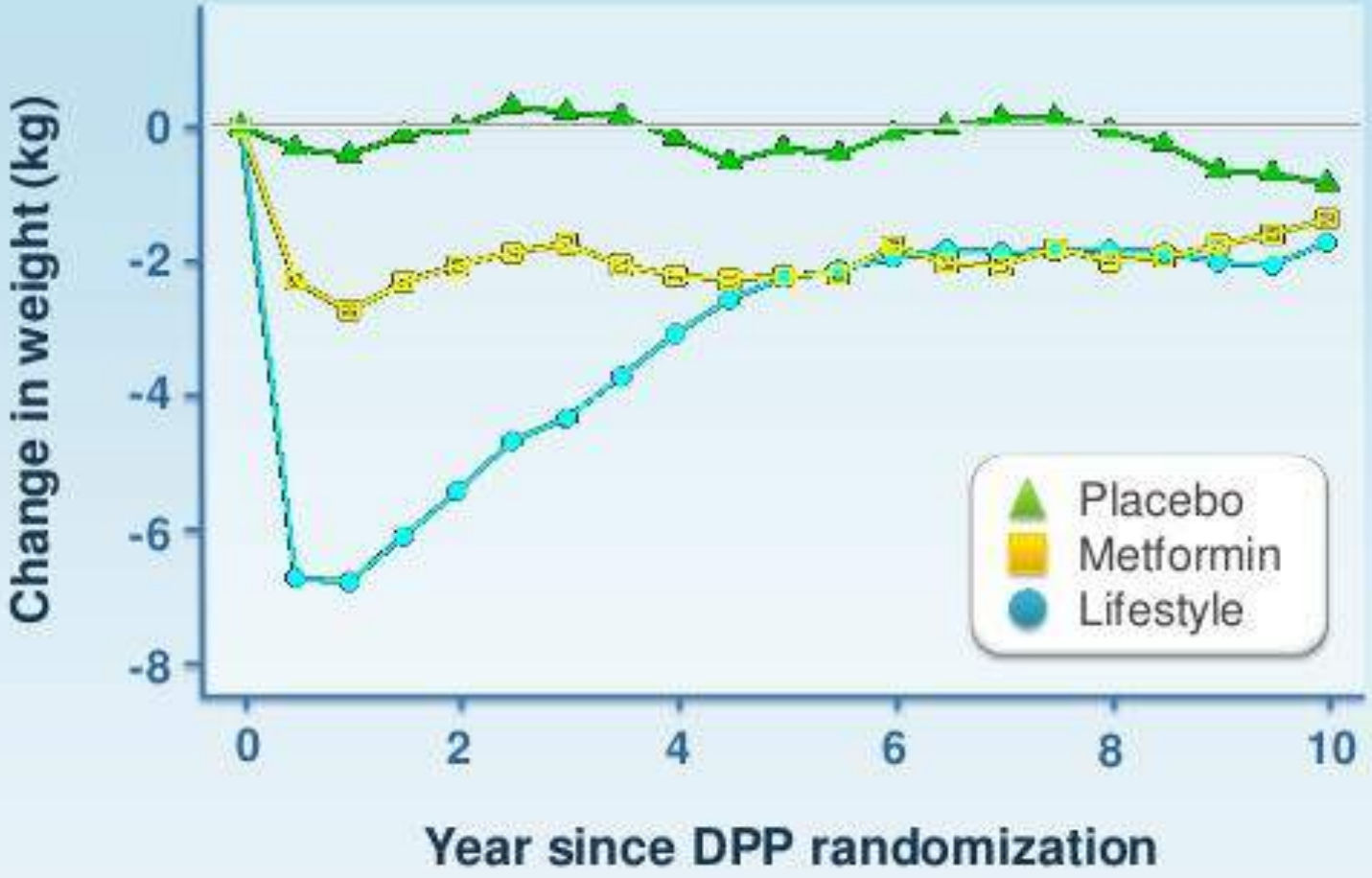
Diabetes Prevention Program: Progression to Type 2 Diabetes



*All pairwise comparisons significanty different by group; sequential log-rank test.

The Diabetes Prevention Program Research Group. *N Engl J Med.* 2002;346:393.

Weight Change Over Time

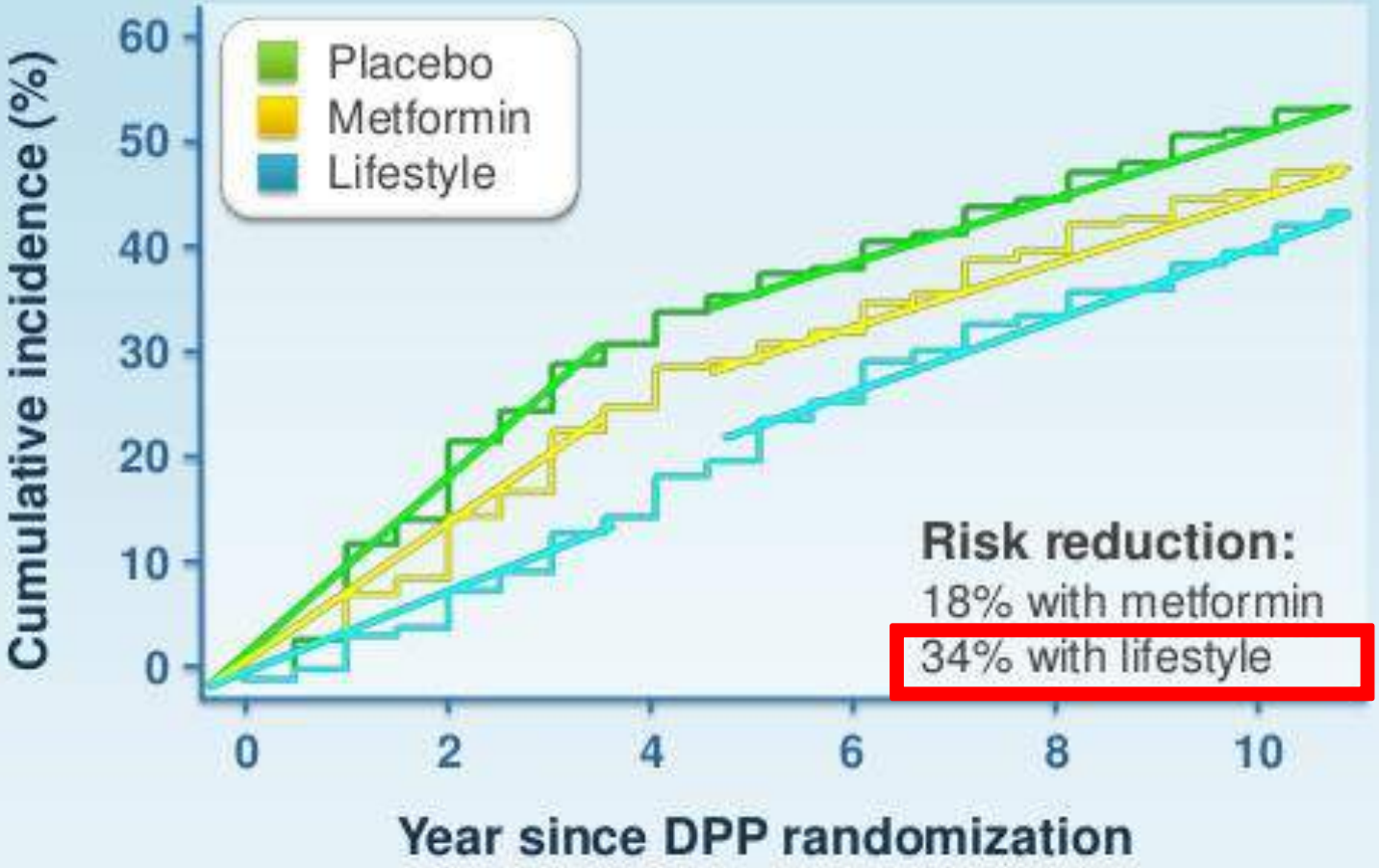


Produced by the International Chair on Cardiometabolic Risk

Adapted from Diabetes Prevention Program Research Group Lancet 2009;374:1677-86

Source: www.myhealthywaist.org

Diabetes Prevention Program Outcomes Study (DPPOS)
Incidence of Diabetes



Produced by the International Chair on Cardiometabolic Risk

Adapted from Diabetes Prevention Program Research Group Lancet 2009;374:1677-86

Source: www.myhealthywaist.org

Komplikasyonlar yavaşlatılabilir veya engellenebilir mi?

- Çalışmaların çoğu sağlanan faydanın diyabet ortaya çıkışının engellenip engellenemediği ile ilişkili
- İstatistiksel olarak diyabete bağlı mikrovasküler ve özellikle de makrovasküler komplikasyonlarla ilgili karar verecek şekilde dizayn edilmemişler veya olgu sayısı yeterli değil.

Articles

Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study

Diabetes Prevention Program Research Group†

† Members listed in the appendix

Published: 13 September 2015

- **Findings**
- During a mean follow-up of 15 years, diabetes incidence was reduced by 27% in the lifestyle intervention group (hazard ratio 0·73, 95% CI 0·65–0·83; p<0·0001) and by 18% in the metformin group (0·82, 0·72–0·93; p=0·001), compared with the placebo group, with declining between-group differences over time. At year 15, the cumulative incidences of diabetes were 55% in the lifestyle group, 56% in the metformin group, and 62% in the placebo group. The prevalences at the end of the study of the aggregate microvascular outcome were not significantly different between the treatment groups in the total cohort (placebo 12·4%, 95% CI 11·1–13·8; metformin 13·0%, 11·7–14·5; lifestyle intervention 11·3%, 10·1–12·7). However, in women (n=1887) the lifestyle intervention was associated with a lower prevalence (8·7%, 95% CI 7·4–10·2) than in the placebo (11·0%, 9·6–12·6) and metformin (11·2%, 9·7–12·9) groups, with reductions in the lifestyle intervention group of 21% (p=0·03) compared with placebo and 22% (p=0·02) compared with metformin. Compared with participants who developed diabetes, those who did not develop diabetes had a 28% lower prevalence of microvascular complications (relative risk 0·72, 95% CI 0·63–0·83; p<0·0001).

OPEN ACCESS Freely available online PLoS one

Ten-Year Mortality and Cardiovascular Morbidity in the Finnish Diabetes Prevention Study—Secondary Analysis of the Randomized Trial

Matti Uusitupa[1]*, Markku Peltonen[2], Jaana Lindström[2,3], Sirkka Aunola[4], Pirjo Ilanne-Parikka[5,6], Sirkka Keinänen-Kiukaanniemi[7,8,9,10], Timo T. Valle[2], Johan G. Eriksson[2,11,12], Jaakko Tuomilehto[2,3,13] for the Finnish Diabetes Prevention Study Group

1 School of Public Health and Clinical Nutrition, Food and Health Research Centre, University of Kuopio, Kuopio, Finland, **2** Diabetes Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland, **3** Department of Public Health, University of Helsinki, Helsinki, Finland, **4** Population Studies Unit, Department of Welfare and Health Promotion, National Institute for Health and Welfare, Turku, Finland, **5** Diabetes Center, Finnish Diabetes Association, Tampere, Finland, **6** Science Center, Pirkanmaa Hospital District, Tampere University Hospital, Tampere, Finland, **7** Institute of Health Sciences, University of Oulu, Oulu, Finland, **8** Health Centre of Oulu, Oulu, Finland, **9** Unit of General Practice, Oulu University Hospital, Oulu, Finland, **10** Oulu Deaconess Institute Research Centre, Oulu, Finland, **11** Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland, **12** Vasa Central Hospital, Vasa, Finland, **13** South Ostrobothnia Central Hospital, Seinäjoki, Finland

Conclusions: Lifestyle intervention among persons with IGT did not decrease cardiovascular morbidity during the first 10 years of follow-up. However, the statistical power may not be sufficient to detect small differences between the intervention and control groups. Low total mortality among participants of the DPS compared with individuals with IGT in the general population could be ascribed to a lower cardiovascular risk profile at baseline and regular follow-up.

5. Prevention or Delay of Type 2 Diabetes

American Diabetes Association

Diabetes Care 2017;40(Suppl. 1):S44–S47 | DOI: 10.2337/dc17-S008

- %7 kilo kaybı (mümkünse ilk 6 ay içinde)
- Haftada 500-1000 gr
- Günlük alınan total kalorinin 500-1000 kcal altı
- Yağın miktarından çok kalitesi önemli
- Tam tahıllı gıdalar, fındık, yoğurt ve kahvenin koruyuculuğu bildirilmiş.
- Fazla kırmızı et tüketimi, fruktoz ve tatlandırıcılı gıdalar artmış risk ile ilişkili

Ann Intern Med 2016;165:491–500
Am J Clin Nutr 2003;77:622–629
Am J Clin Nutr 2014;100:278–288
BMC Med 2014;12:215

İnsülin direncinde diyet vs egzersiz

DİYET

Adipoz doku azalması üzerinden

Adipositokin düzenlenmesi
Kronik inflamasyonun azalması
Plazma SYA azalması

EGZERSİZ

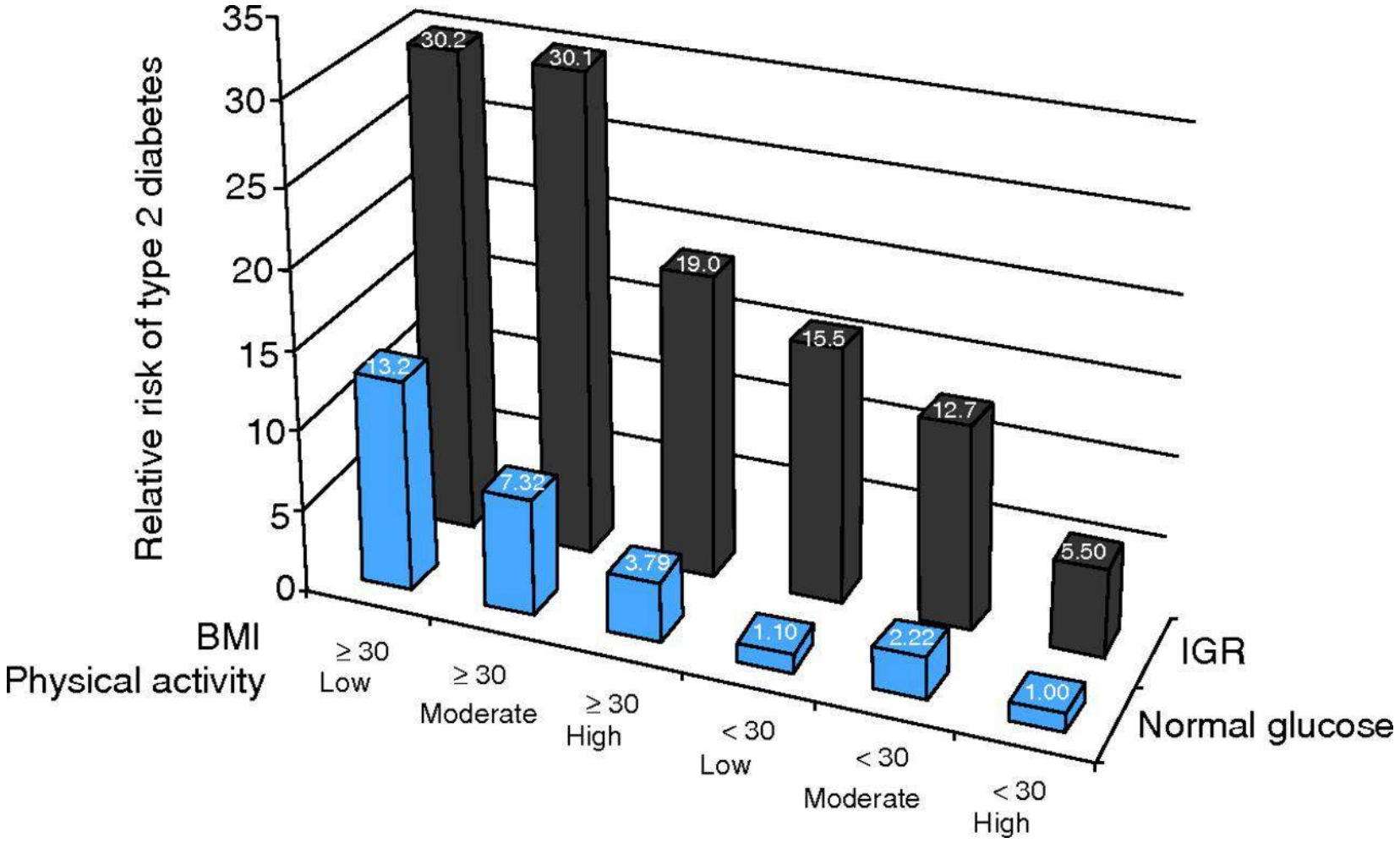
Kas metabolizması üzerinden

Mitokondriyal fonksiyonlarda düzelme
Artmış enerji harcanması
Miyositlerde AMP-kinaz bağımlı glukoz kullanımı artışı

Artmış insülin duyarlılığı

J Obes Weight Loss Ther. 2015 Jul; 5(0 5): S5-003

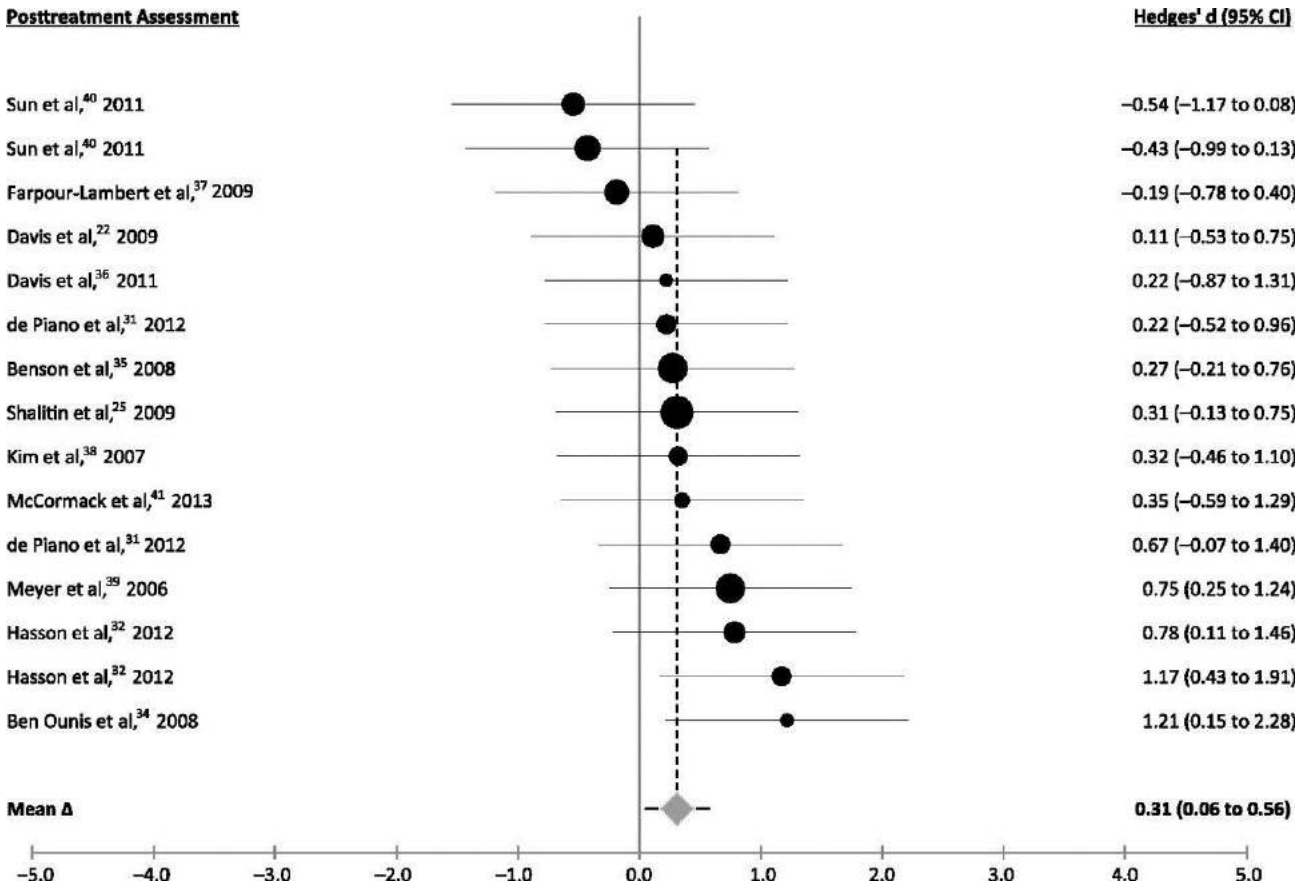
Relative risks of type 2 diabetes according to joint levels of physical activity, BMI and glucose homoeostasisAdjusted for age, sex, study year, systolic blood pressure, smoking status and education.



Gang Hu et al. Essays Biochem. 2006;42:177-192

Pediatrics
January 2014, VOLUME 133 / ISSUE 1

Exercise and Insulin Resistance in Youth: A Meta-Analysis



Based on the cumulative results from these studies, a small to moderate effect was found for exercise training on fasting insulin and improving insulin resistance in youth (Hedges' d effect size = 0.48 [95% confidence interval: 0.22–0.74], $P < .001$ and 0.31 [95% confidence interval: 0.06–0.56], $P < .05$, respectively).

Egzersiz önerileri

- ADA= 150 dk/hafta orta yoğunluklu fiziksel aktivite (arada en fazla 1 gün boşluk)- direnç egzersizleri de eklenebilir.
- Prediyabet çalışma grubu=Egzersiz türü için (Aerobik veya direnç egzersizler) özel bir öneri bulunmamaktadır.
- İdeal olarak ana öğünlerden 1 saat sonra yapılmalıdır.
- 24 saat içerisinde en az 8000-10000 adım aktivite önerilmektedir.

FARMAKOTERAPİ

- Metformin
- Akarboz
- Glitazonlar
- Orlistat
- İnkretin bazlı tedaviler
- İnsülin sekretogogları
- İnsülin

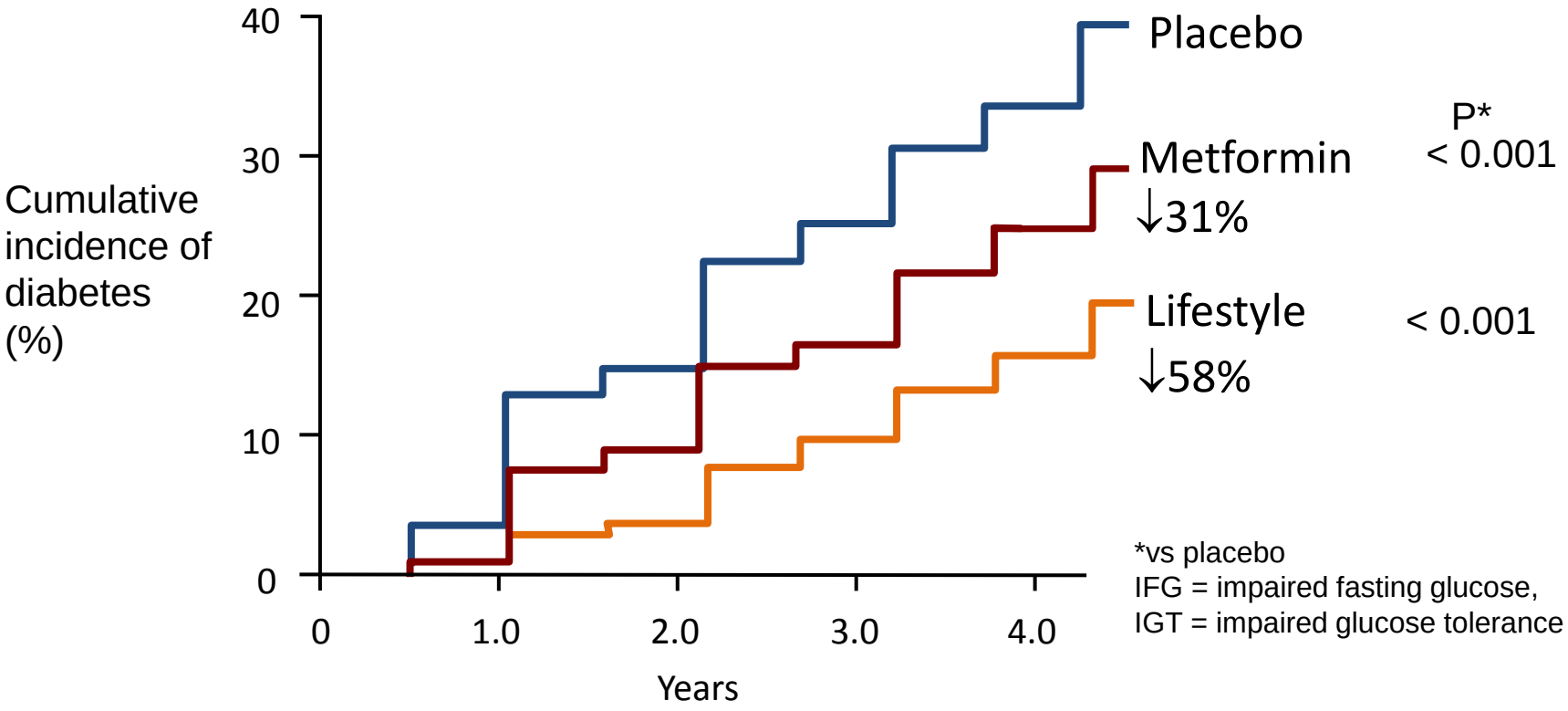
Prevansiyon: Metformin

Table 3 Overview of principal diabetes prevention trials with and without evaluation of metformin

Trial	Design	Subjects	*N*; duration (years)	Control group	Active treatments	% change in diabetes risk
Principal diabetes prevention trials that evaluated metformin						
DPP (US) [19]	RCT	IGT and high-normal glucose	3234; 3	Placebo plus standard lifestyle advice	Metformin plus standard lifestyle advice	−31
					Intensive lifestyle intervention	−58
DPP Outcome Study (US) [69]	O	Epidemiological follow-up to DPP	2766; 5.7	Placebo plus intensive lifestyle advice	Metformin 1700 mg/day + intensive lifestyle advice	−13
					Intensive lifestyle advice	+5
IDPP (India) [20, 65]	RCT	IGT	531; 2.5	Standard lifestyle advice	Metformin plus standard lifestyle advice	−26
					Metformin plus intensive lifestyle intervention	−28
					Intensive lifestyle intervention	−29
Wenying et al. (China) [68]	NR	IGT	321; 3	Standard lifestyle advice	Metformin	−88
					Acarbose	−87
					Intensive lifestyle intervention	−43
Li et al. (China) [66]	RCT	IGT	70; 1	Placebo	Metformin	−66[a]
Iqbal Hydrie et al. (Pakistan) [67]	RCT	IGT	317; 1.5	Standard lifestyle advice	Metformin	−76.5
					Intensive lifestyle intervention	−71
CANOE (Canada) [64]	RCT	IGT	207; 3.9	Placebo	Metformin 500 mg plus rosiglitazone 2 mg twice daily	−66

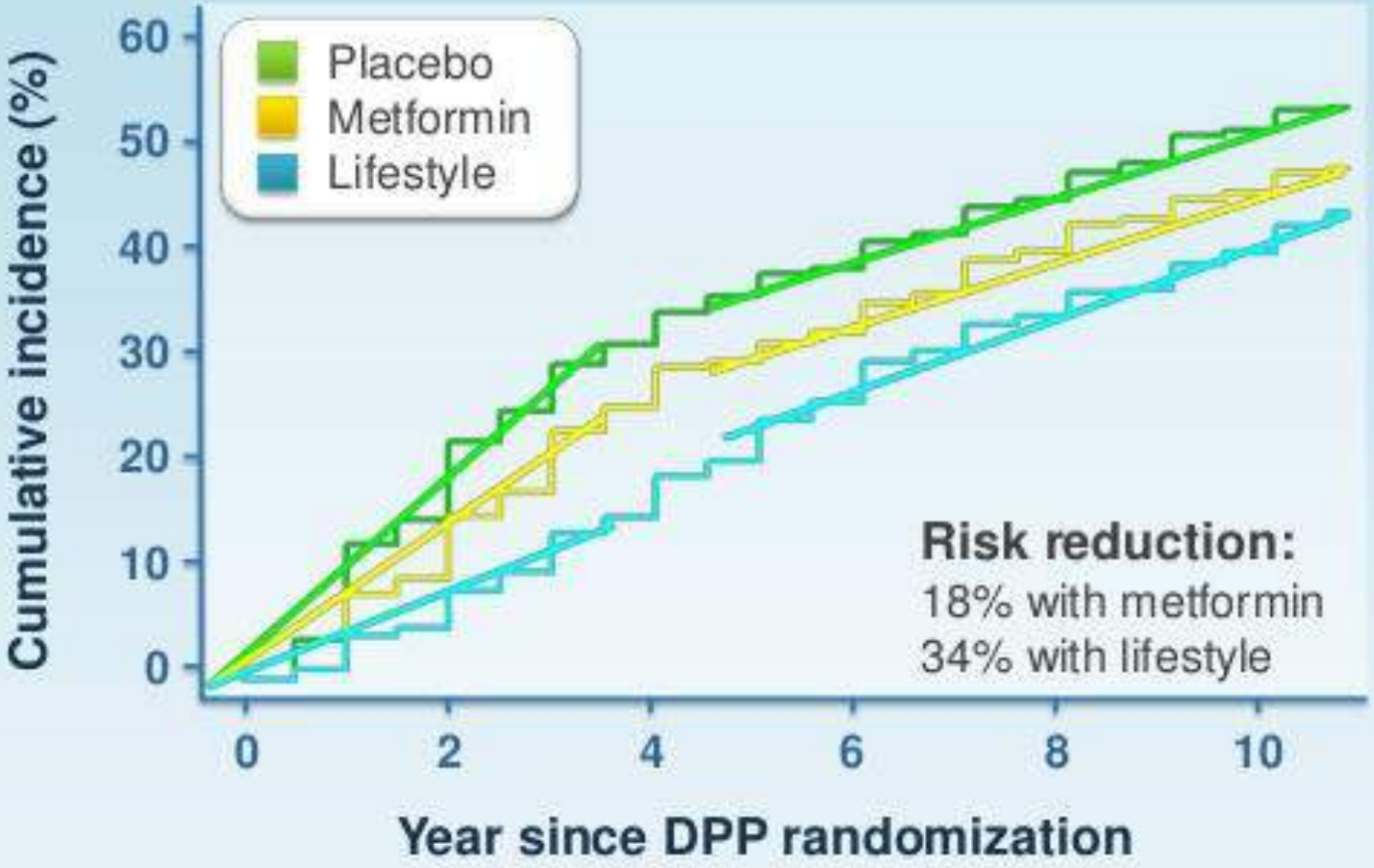
Diabetes Prevention Program (DPP)

- N = 3234 with IFG and IGT, without diabetes



Diabetes Prevention Program (DPP) Research Group. *N Engl J Med* 2002;346:393-403.

Diabetes Prevention Program Outcomes Study (DPPOS)
Incidence of Diabetes

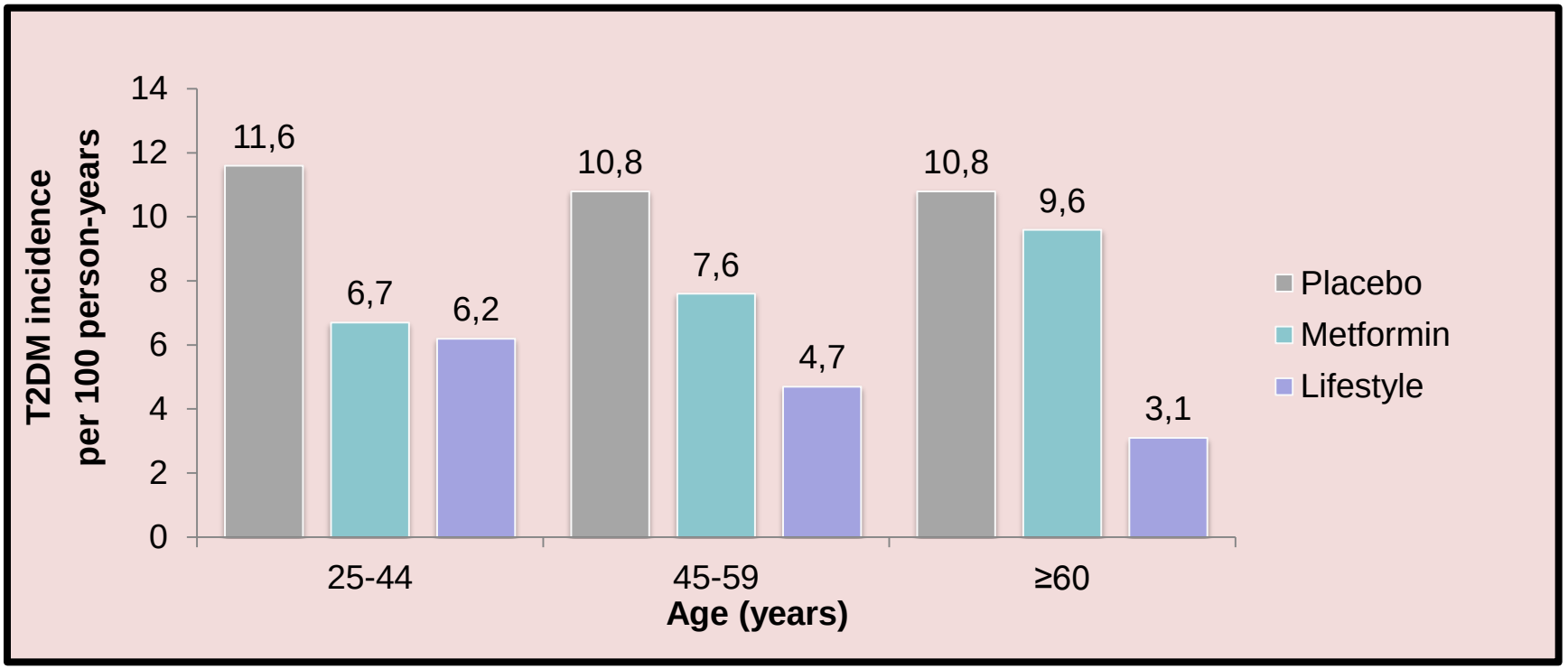


Produced by the International Chair on Cardiometabolic Risk

Adapted from Diabetes Prevention Program Research Group Lancet 2009;374:1677-86

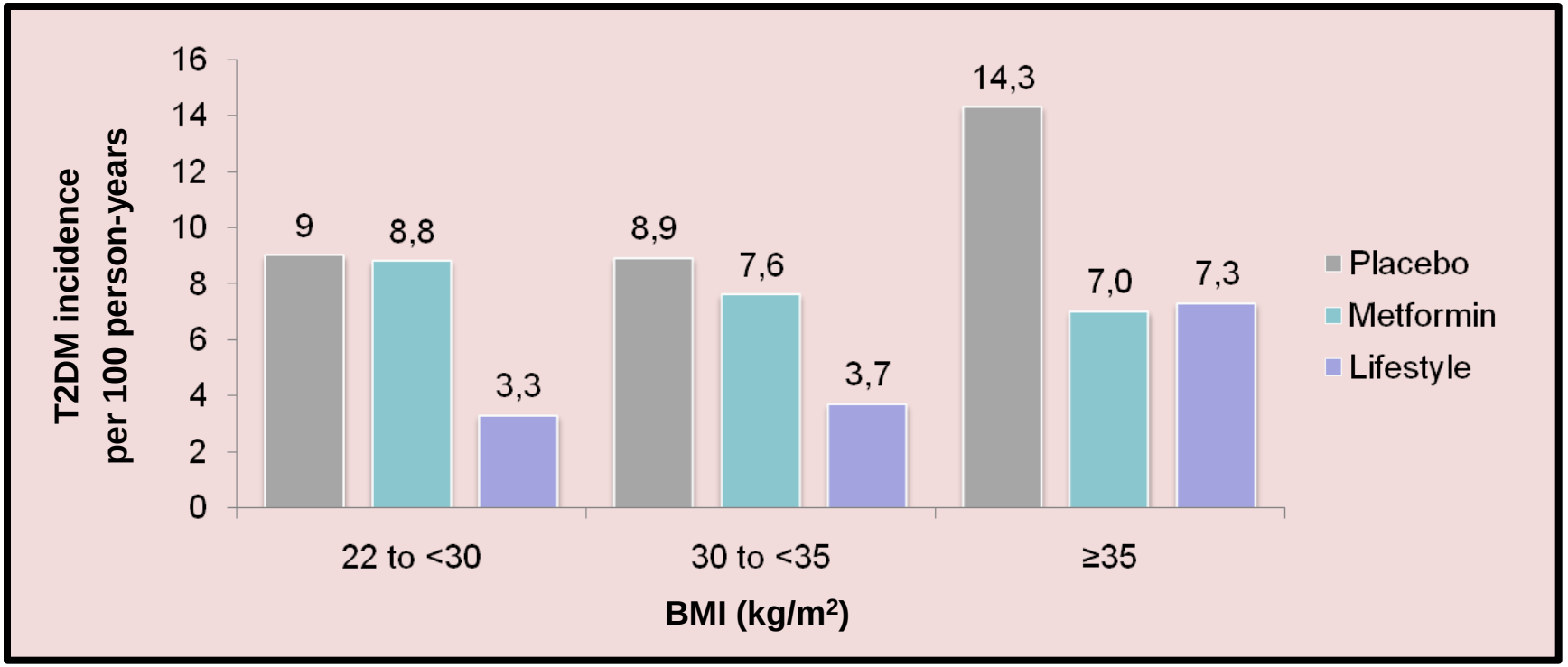
Source: www.myhealthywaist.org

DPP Çalışması: Yaş – Tip 2 Diyabet İnsidansı



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

DPP Çalışması: Kilo – Tip 2 Diyabet İnsidansı



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

Diyabet Önleme Programı (DPP) - GDM

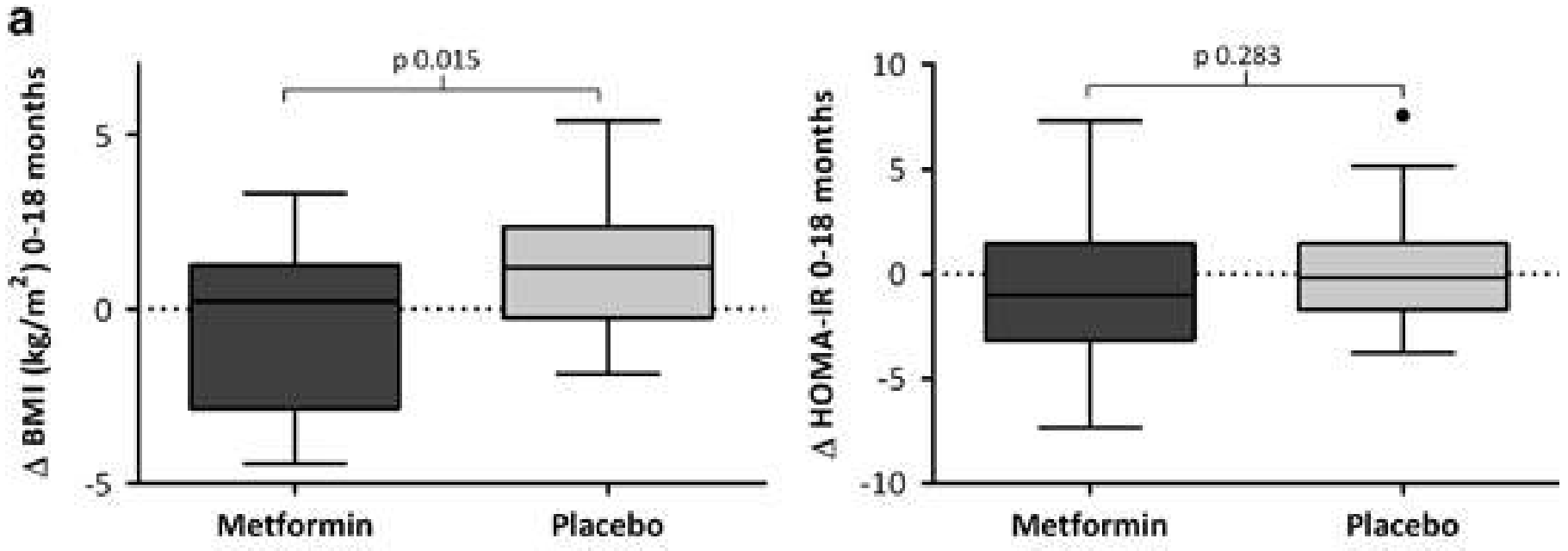
- GDM öyküsü olan BGT'li kadınlarda plaseboya göre; yaşam tarzı değişimi (%53) ve Metformin (%50) benzer oranda diyabet riskini azaltmış.
- Daha önce doğum yapmış, GDM öyküsü olmayan, BGT'li kadınlarda diyabet için risk azalması:
  - Yaşam tarzı değişimi: %49
  - Metformin: %14

Ratner RE et al. JCEM 2008;93:4774-9

METFORMİN ve İNSÜLİN DİRENCİ

Long-term treatment with metformin in obese, insulin-resistant adolescents: results of a randomized double-blinded placebo-controlled trial

Effect of metformin on primary end points BMI and HOMA-IR after 18 months.

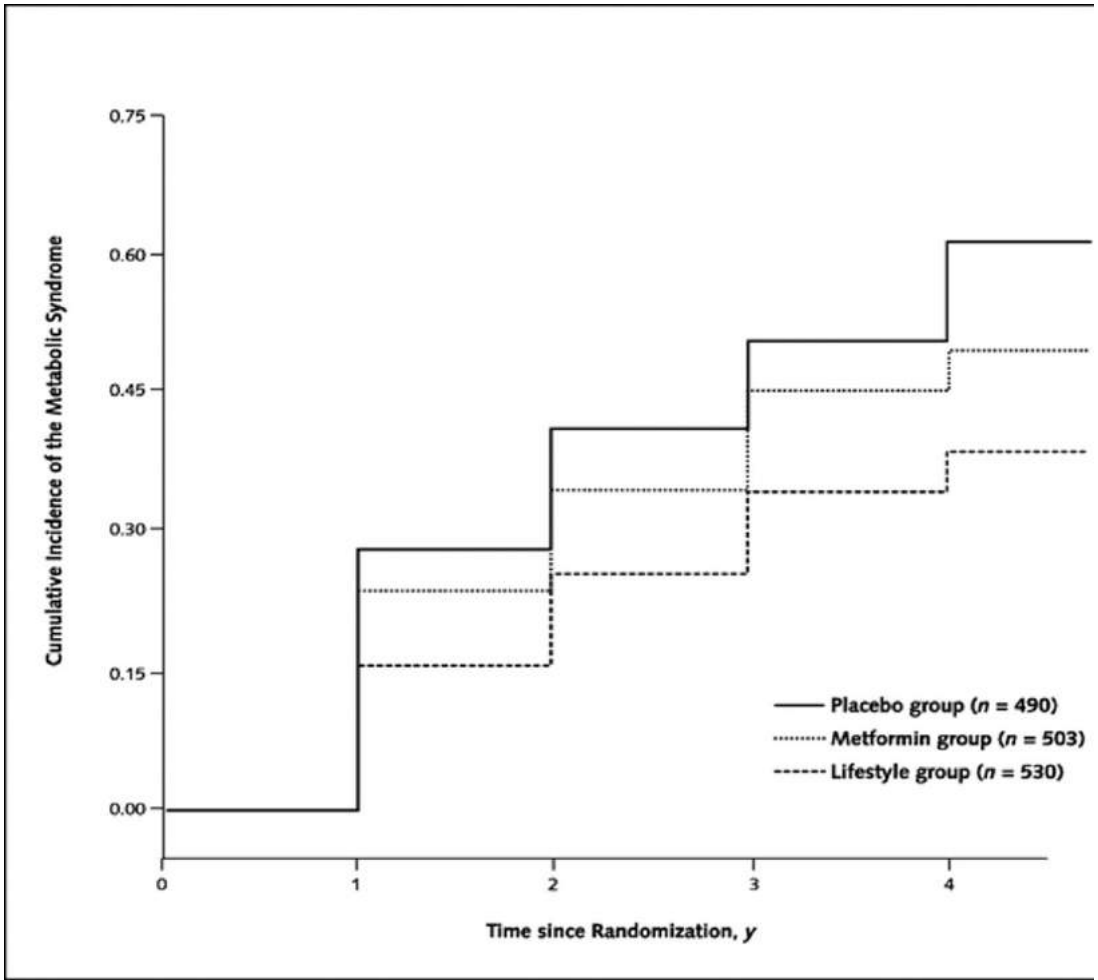


Nutrition & Diabetes (2016) **6**, e228

The Effect of Metformin and Intensive Lifestyle Intervention on the Metabolic Syndrome: The Diabetes Prevention Program Randomized Trial

Ann Intern Med. 2005;142:611-619

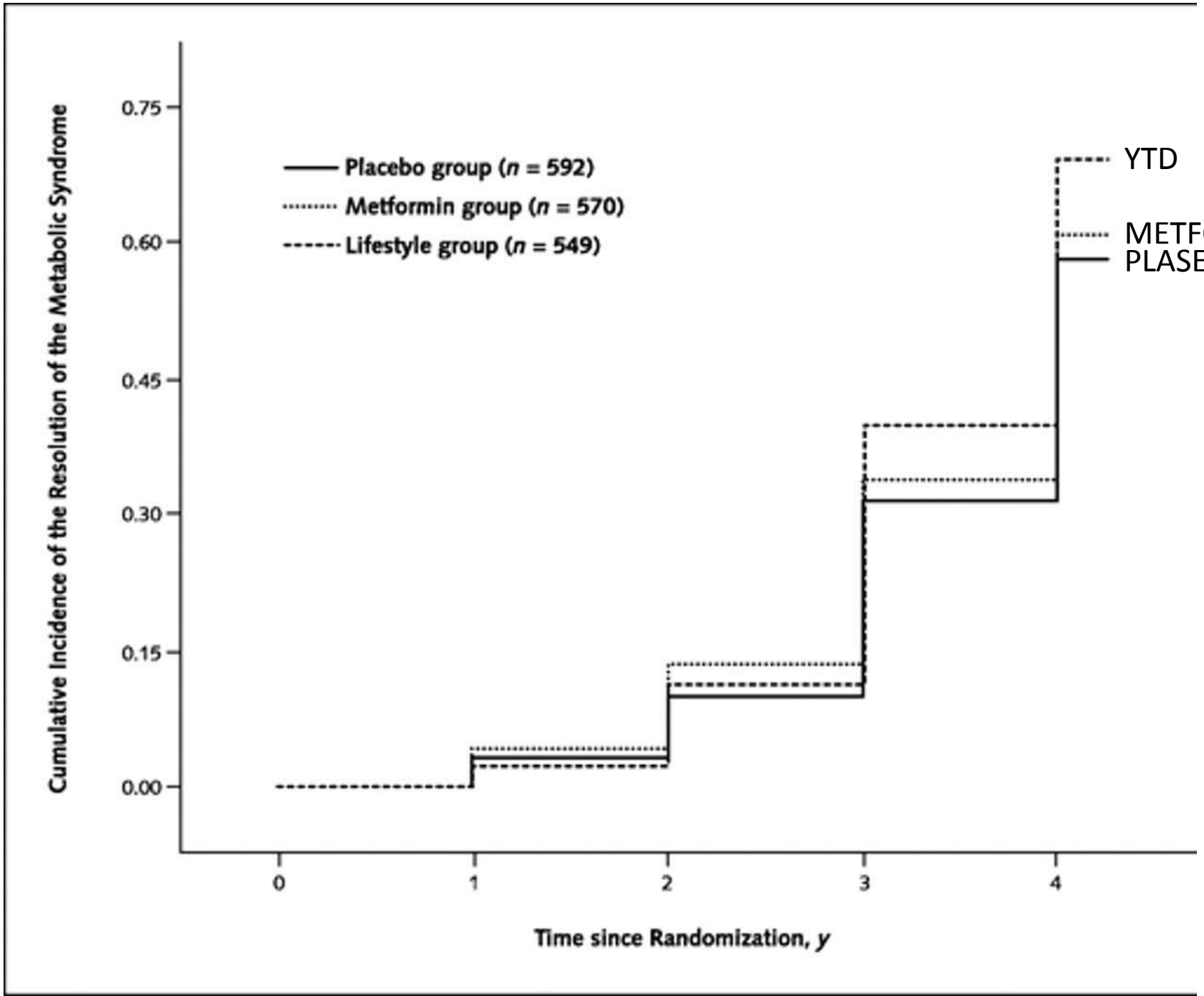
3 yıllık izlemde yeni Met. Sendrom tanısı alan hastalar



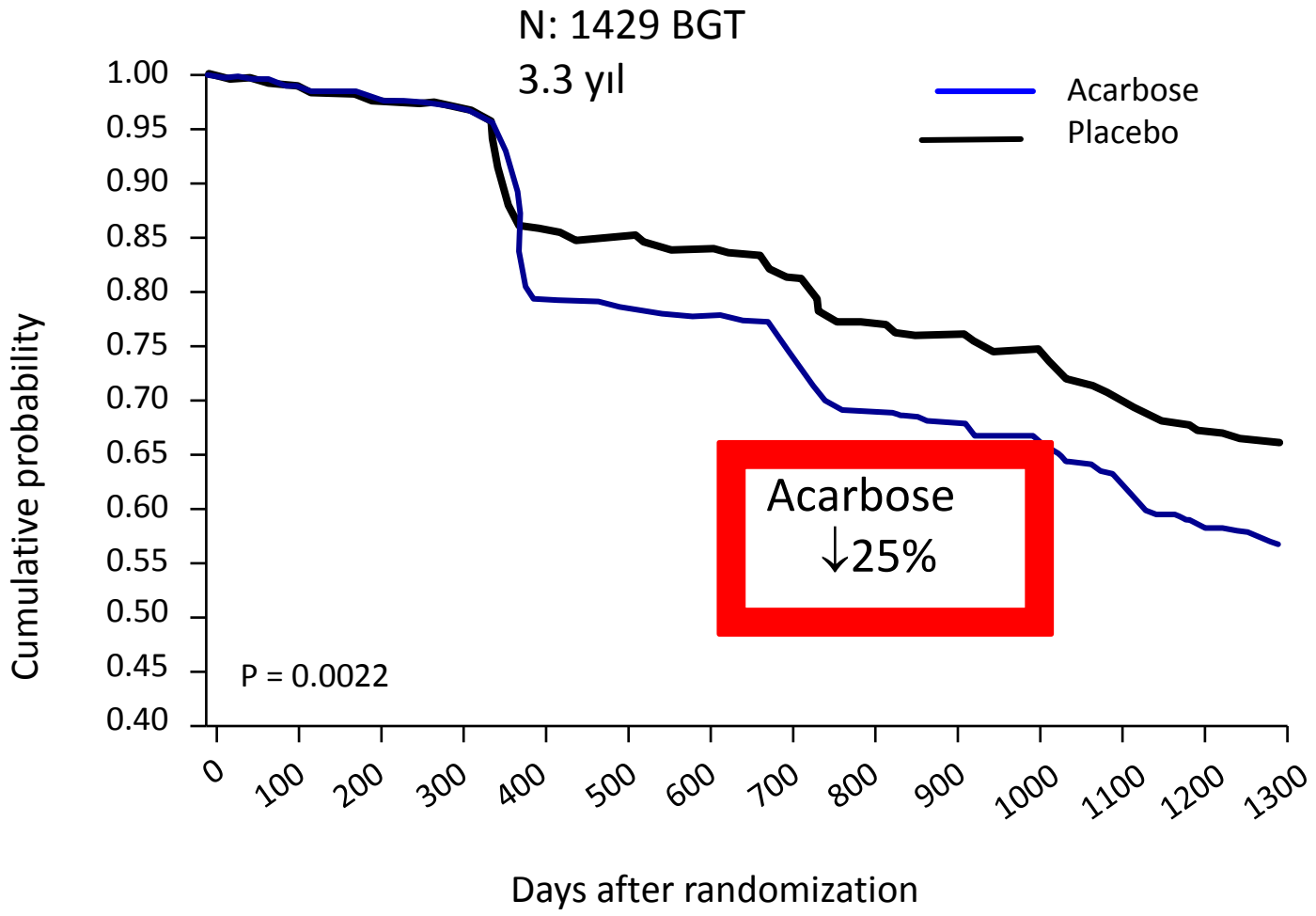
%40

%33

%27


Cumulative Incidence of the Resolution of the Metabolic Syndrome
0.75
0.60
0.45
0.30
0.15
0.00
Placebo group (n = 592)
Metformin group (n = 570)
Lifestyle group (n = 549)
0
1
2
3
4
Time since Randomization, y
YTD
METFORMİN
PLASEBO

STOP-NIDDM Çalışması: Akarbozun Tip 2 Diyabet Riskine Etkisi



Chiasson JL, et al. *Lancet* 2002;359:2072-77.

STOP-NIDDM: Alt Gruplar

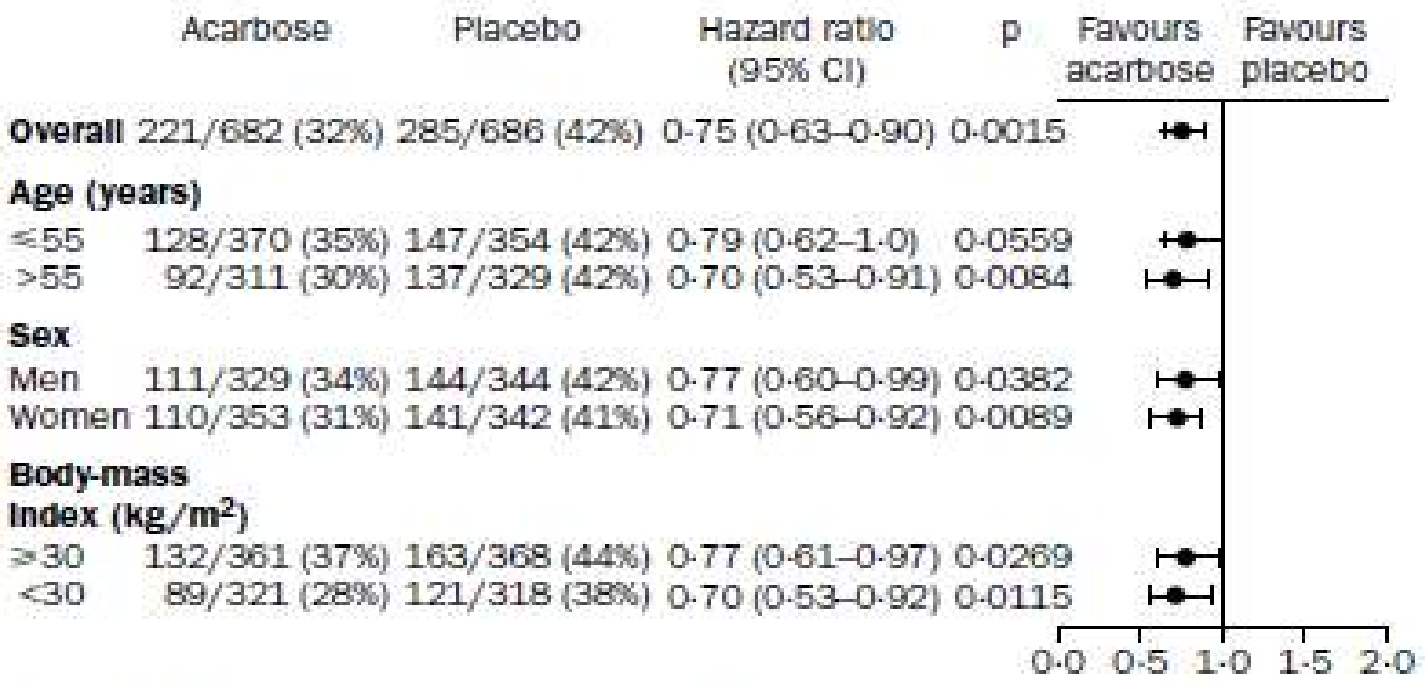


Figure 2: **Effect of acarbose on development of diabetes**

Data were calculated with Cox's proportional-hazard model adjusted for age, sex, and body-mass index.

Pioglitazon: ACT-NOW Çalışması

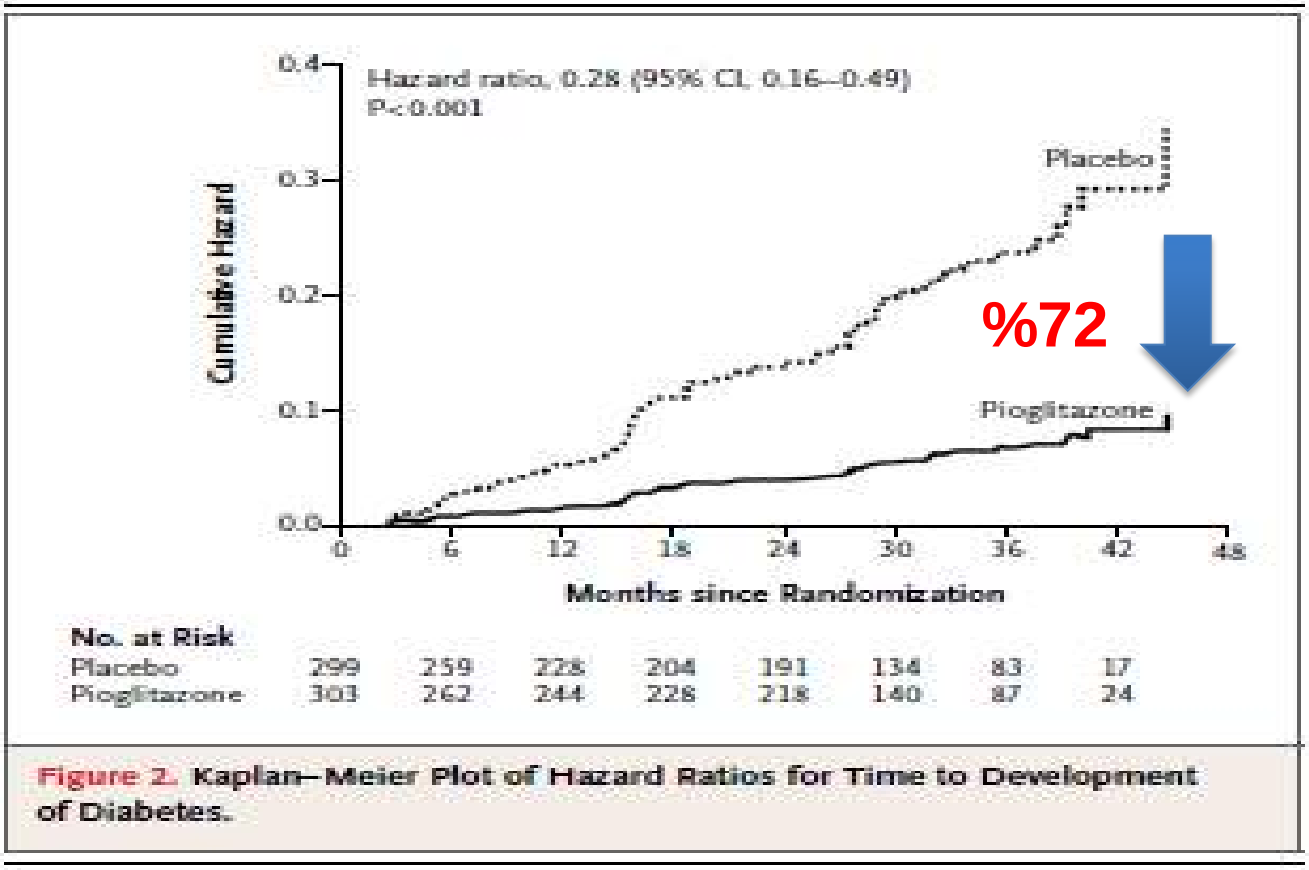


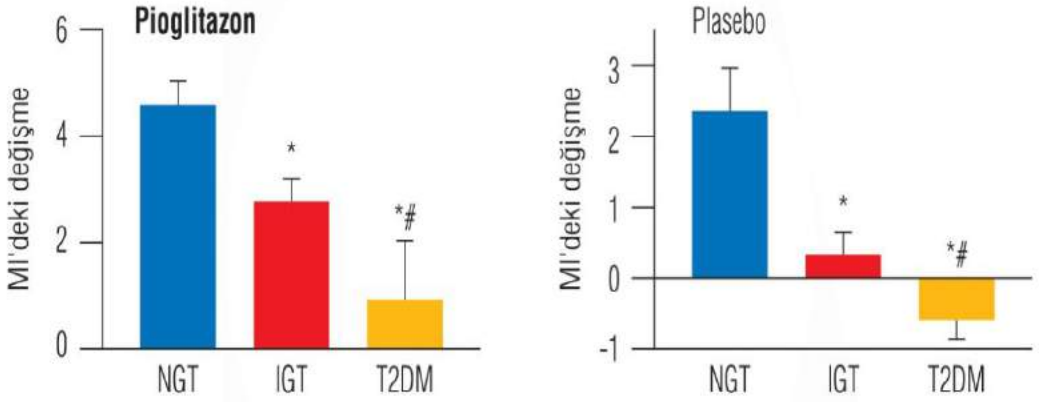
Figure 2. Kaplan–Meier Plot of Hazard Ratios for Time to Development of Diabetes.

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

DeFronzo RA, et al. NEJM 2011;364:1104-15

ACT-NOW - İnsülin Duyarlılığı (Matsuda İndeksi)

Matsuda İndeksindeki Değişmeler



İnsülin duyarlılığı indeksi (Matsuda indeksi [MI]):

İnsulin sekresyonu (IS) / İnsulin direnci (IR; $\Delta I_{0\text{-}120}$ / $\Delta G_{0\text{-}120}$ / ΔIS oranı $[ISR]_{0\text{-}120}$ / $\Delta G_{0\text{-}120}$)

*P < 0.05 , NGT için, IGT veya T2DM'ye göre; #P < 0.05 IGT için, T2DM'ye göre.

NGT: Normal glukoz toleransı, **IGT:** Bozulmuş glukoz toleransı, **T2DM:** Tip 2 diyabet

REF: Ralph A. DeFronzo and ar. Prevention of diabetes with pioglitazone in Act NOW Psysiologic Correlates, Diabetes, Vol.62, November 2013

İskelet kasında Pioglitazon tedavisi ile insülin duyarlılığı Metformin'e göre %65 artmaktadır.

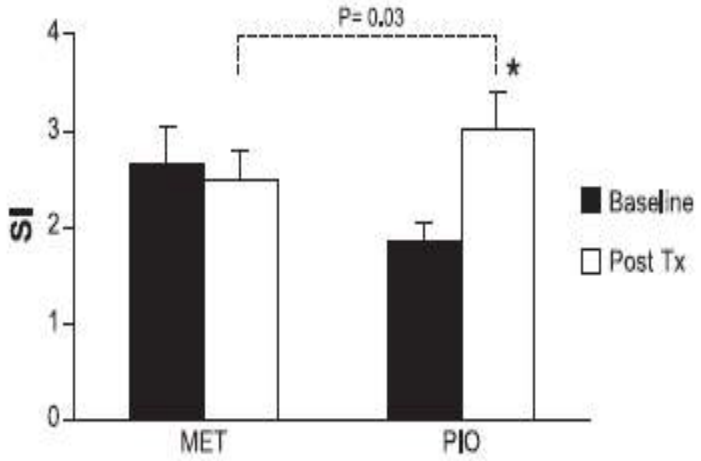
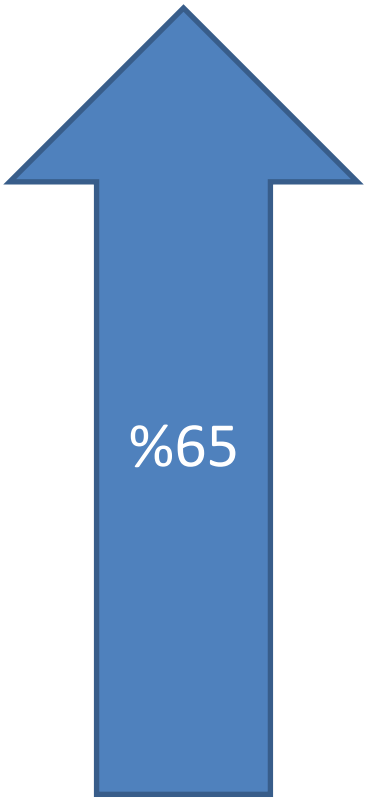


Fig. 2. Insulin sensitivity index (S_I) did not change after treatment (Post Tx) with metformin. S_I improved from 1.84×10^{-5} min^{-1}/pM to 3.02×10^{-5} min^{-1}/pM after pioglitazone (*$P = 0.002$ vs. baseline). Posttreatment S_I values were significantly higher in pioglitazone compared with metformin group ($P = 0.03$). To convert S_I from min^{-1}/pM to $min^{-1}/(\mu U/ml)$, multiply by 6.



- İnsülin duyarlılık endeksi(S1) metformin tedavisi sonrası değişmemiştir.
- Tedavi sonrası insülin duyarlılık değerleri Pioglitazon grubunda Metformine göre anlamlı derecede yüksektir

S1:İnsülin Duyarlılık Endeksi

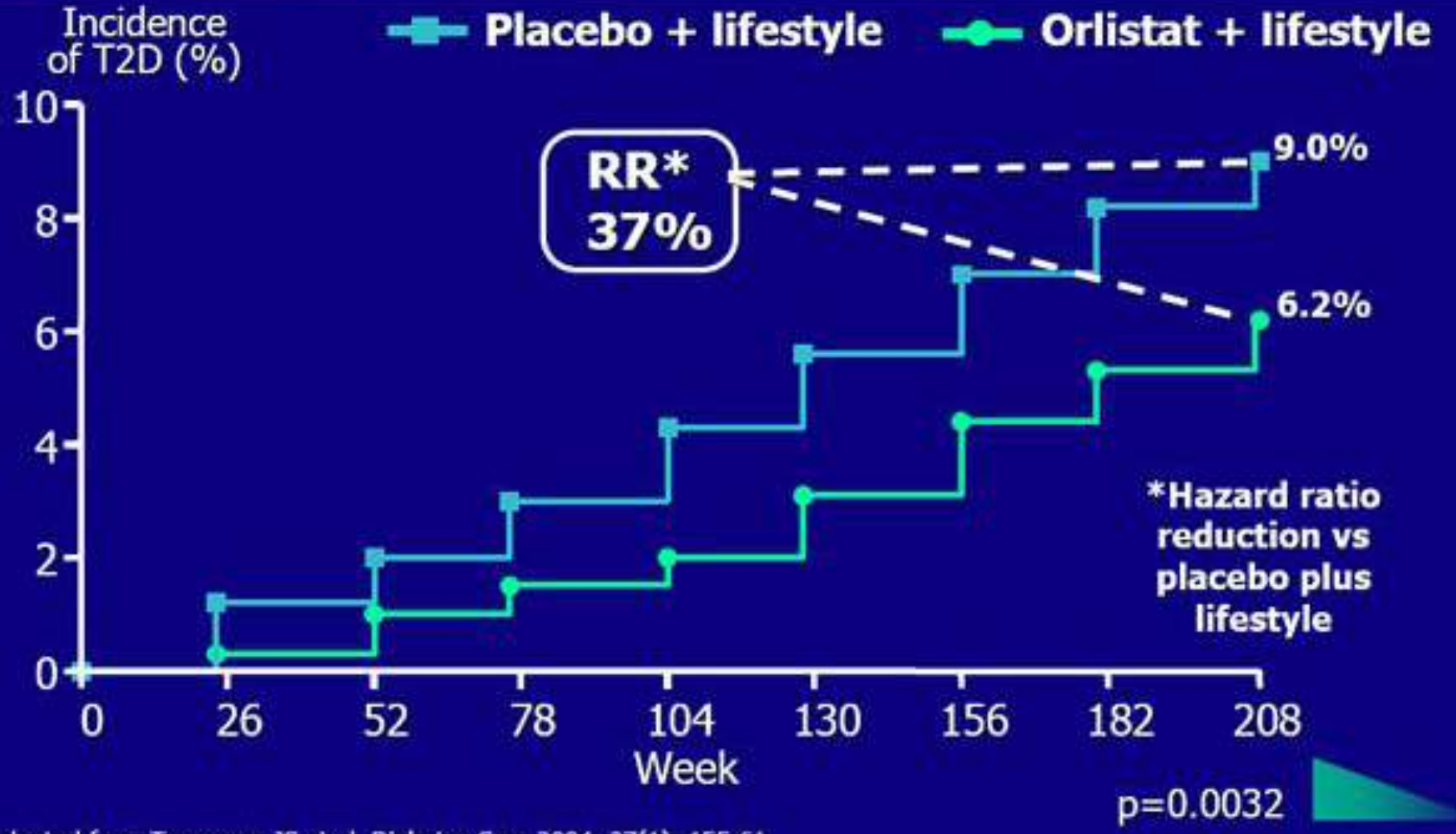
**Am J Physiol Endocrinol Metab* 288: E930–E934, 2005.
Pioglitazone improves insulin sensitivity through reduction in muscle lipid and redistribution of lipid into adipose tissue.

İNSÜLİN DİRENCİ ÇALIŞTAYI SONUÇ RAPORU

5. Ülkemizde diyabet tedavisinde kullanım onayı olan ilaçlardan, **sadece pioglitazon insülin duyarlılığını artırmaktadır.**

- Pioglitazonun, yüksek kardiyovasküler riske sahip **insülin dirençli olan fakat diyabeti olmayan hastalarda** kardiyovasküler riski azalttığı **(IRIS trial, KV risk azaltımı %24)**,
- Prediyabetik hastalarda insülin direncini azaltarak diyabet insidansını azalttığı **(ACT-NOW study; diyabet gelişme riski azaltımı %72)** ve
- Diyabetlilerde olumlu kardiyovasküler ve pleotropik etkiler gösterdiği **(PROACTIVE study; KV risk azaltımı %16)** kanıtlanmıştır.
- Ülkemizde diyabet tedavisinde kullanım onayı olan ilaçlardan, **sadece pioglitazon insülin duyarlılığını artırmaktadır** (ADA-EASD kılavuzu, 2016).
- Yan etkileri dikkate alınarak kullanılabilir.
- Ülkemizde diyabeti olmayanlarda ruhsatı yoktur.

Effect of orlistat on development of type 2 diabetes (XENDOS)



Adapted from Torgerson JS et al, Diabetes Care 2004; 27(1): 155-61

Cochrane: Insulin secretagogues for prevention of type 2 diabetes mellitus

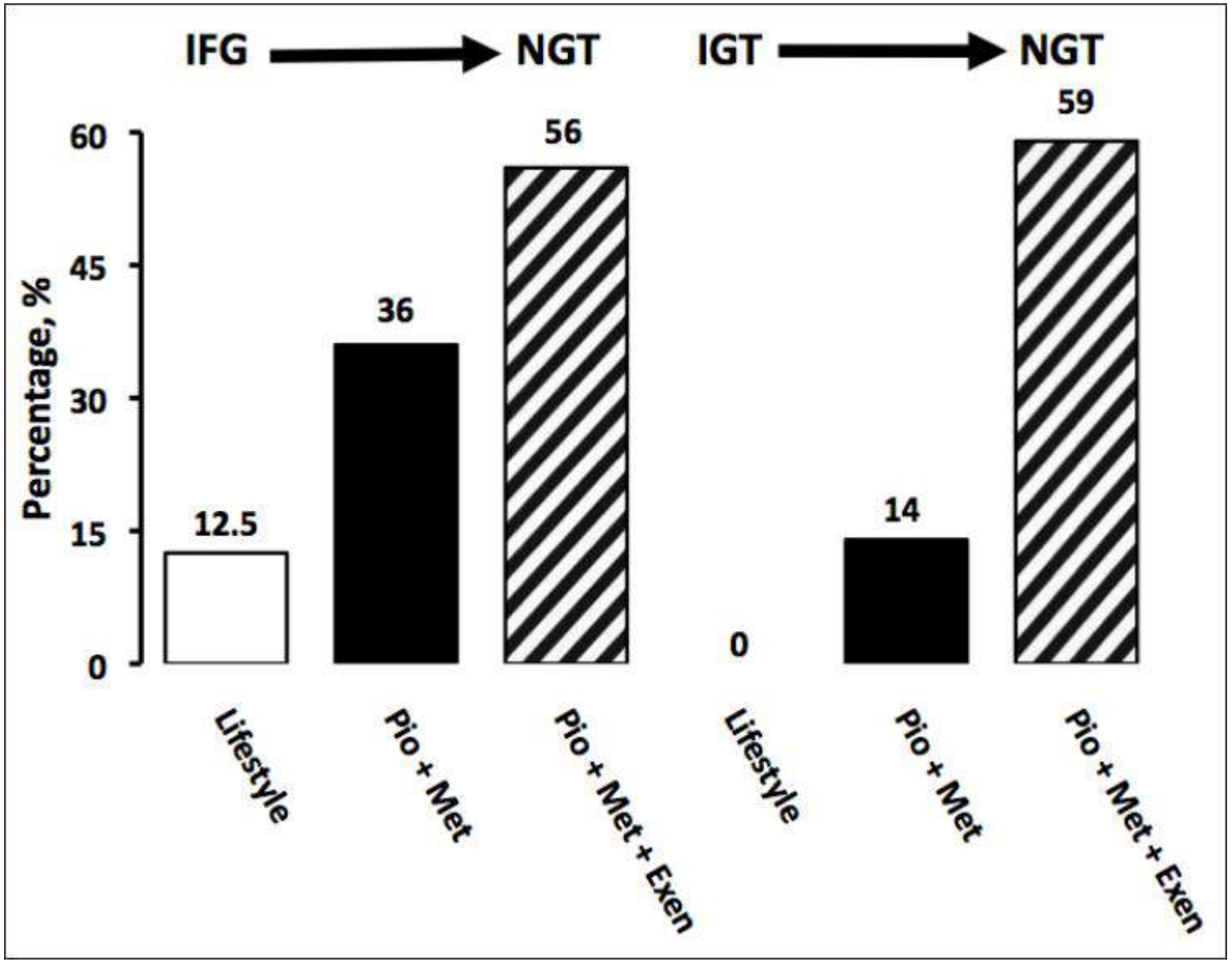
- NAVIGATOR (Nateglinid vs pls)
  - Diyabet insidansı %36.0 vs %33.9; HR 1.07, p=0.05

- Glimeprid vs pls (çok düşük kalitede kanıt)
  - RR 0.75%95 CI 0.54-1.04; p=0.08

Hemmingsen B, et al. Cochr Dat Sys Rev 2016;10:

EXENATİDE ve DİYABET PREVANSİYONU

n=105 prediyabetik hasta, 5.5 -8.9 ay takip



Endocr Pract. 2012 May-Jun;18(3):342-50

Prediyabette İnkretin Temelli Tedaviler
Liraglutid

564 non-diyabetik obez (%31 prediyabetik)
Liraglutid (1.2-1.8-2.4-3.0 mg) / Pls / Orlistat

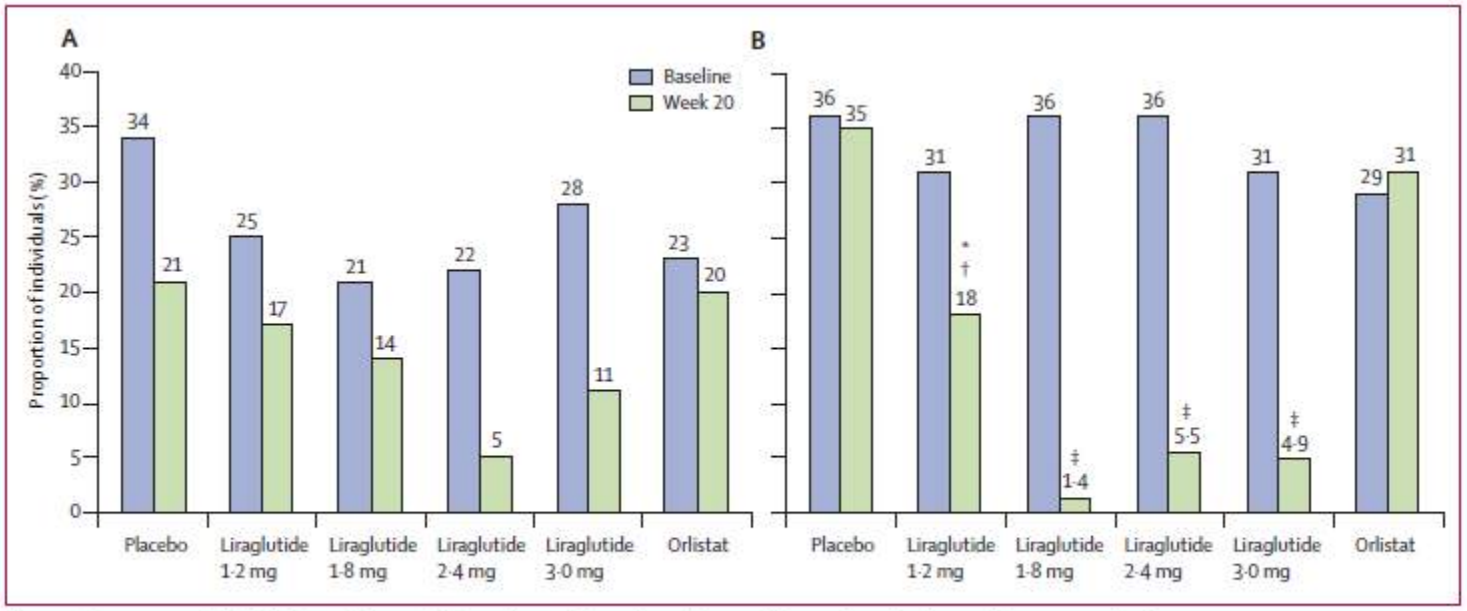
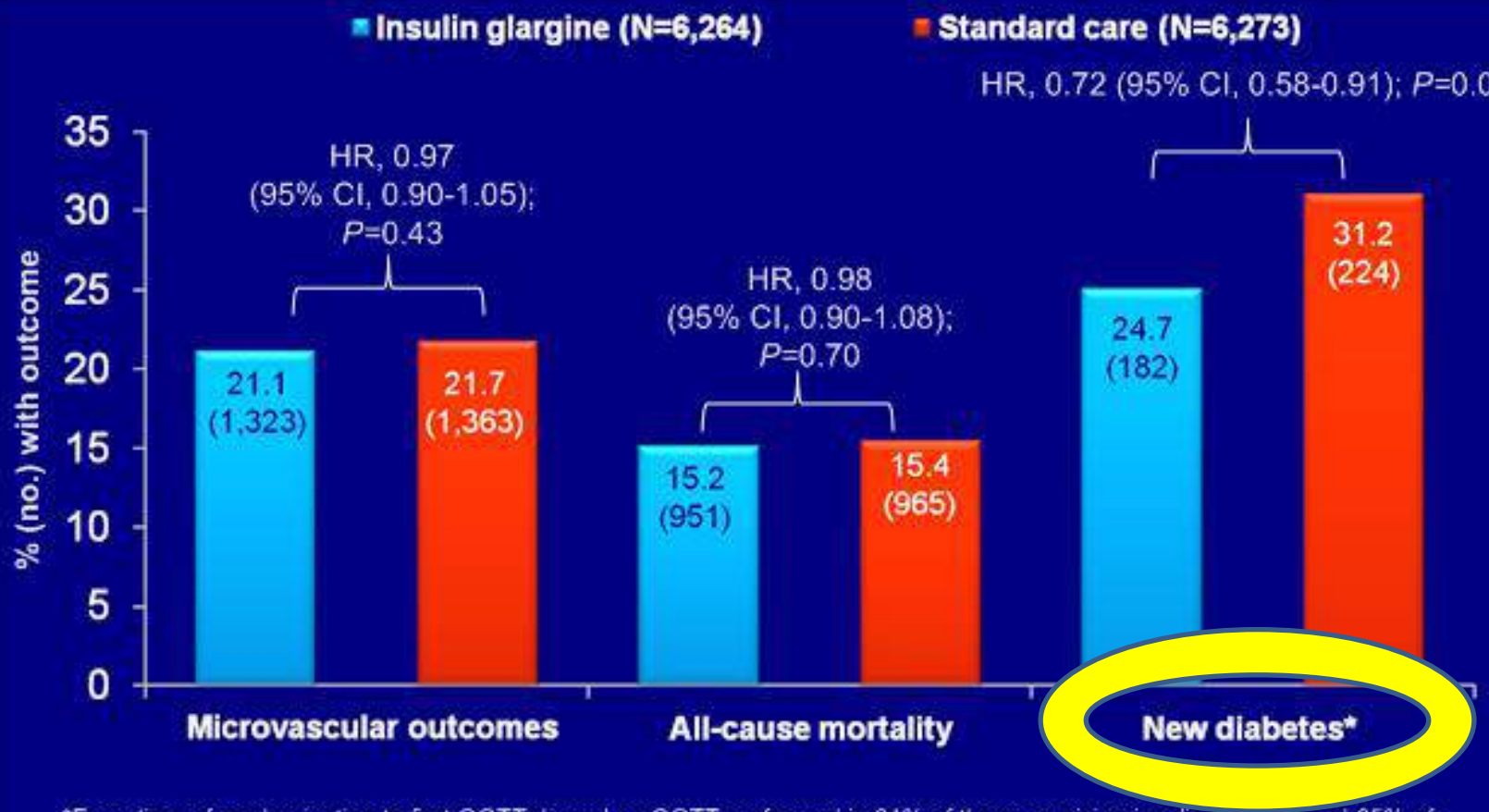


***Figure 4*: Percentage of individuals with metabolic syndrome (A) and prediabetes (B) at randomisation and after 20 weeks of treatment**
Individuals included are those with valid assessment at the start and the end of the 20-week trial period. *p=0·007 *vs* placebo. †p=0·008 *vs* orlistat. ‡p≤0·0001 *vs* placebo or orlistat.

Continuous coverage of the American Diabetes Association 72nd Scientific Sessions

ORIGIN Glargine Trial: Secondary Outcomes



*From time of randomization to first OGTT; based on OGTT performed in 64% of those receiving insulin glargine and 65% of those receiving standard care

ORIGIN=Outcome Reduction with Initial Glargine Intervention

The ORIGIN Trial Investigators. *N Engl J Med*. 2012; Jun 11. Epub ahead of print.

Tanıda YTD ek direkt ilaç başlama kriterleri

- YTD yetersiz yada uygulamaya rağmen glisemik parametrelerde gerileme olmayan yada ilerleyen hastalar
- VKİ> 35 kg/m2 ve <60 yaş
- BAG ve BGT kombine durum
- HbA1C >%6 olanlar
- GDM öyküsü olan prediyabetik kadınlar

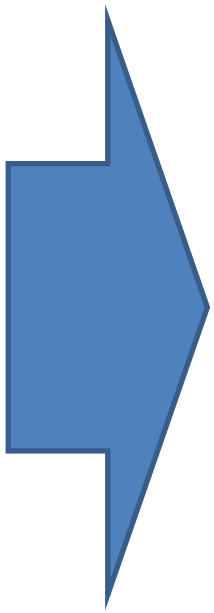
TÜRKDİAB Prediyabet Tanı ve Tedavi Rehberi 2017

Ucuz, etkili, uzun dönemde güvenli ve güçlü kanıtlara sahip olması nedeniyle prediyabetli hastalarda ilk basamak tedavi olarak metformin tercih edilmelidir.

VKİ >35
YAŞ<60
GDM ÖYKÜSÜ OLAN KADIN

Metformin

NASH
BAG ve BGT birlikte
Güçlü aile öyküsü
Dislipidemi
HT
PKOS
Akantosis Nigrikans
Metformin intoleransı
Metformin etkisizliği



PİOGLİTAZON*

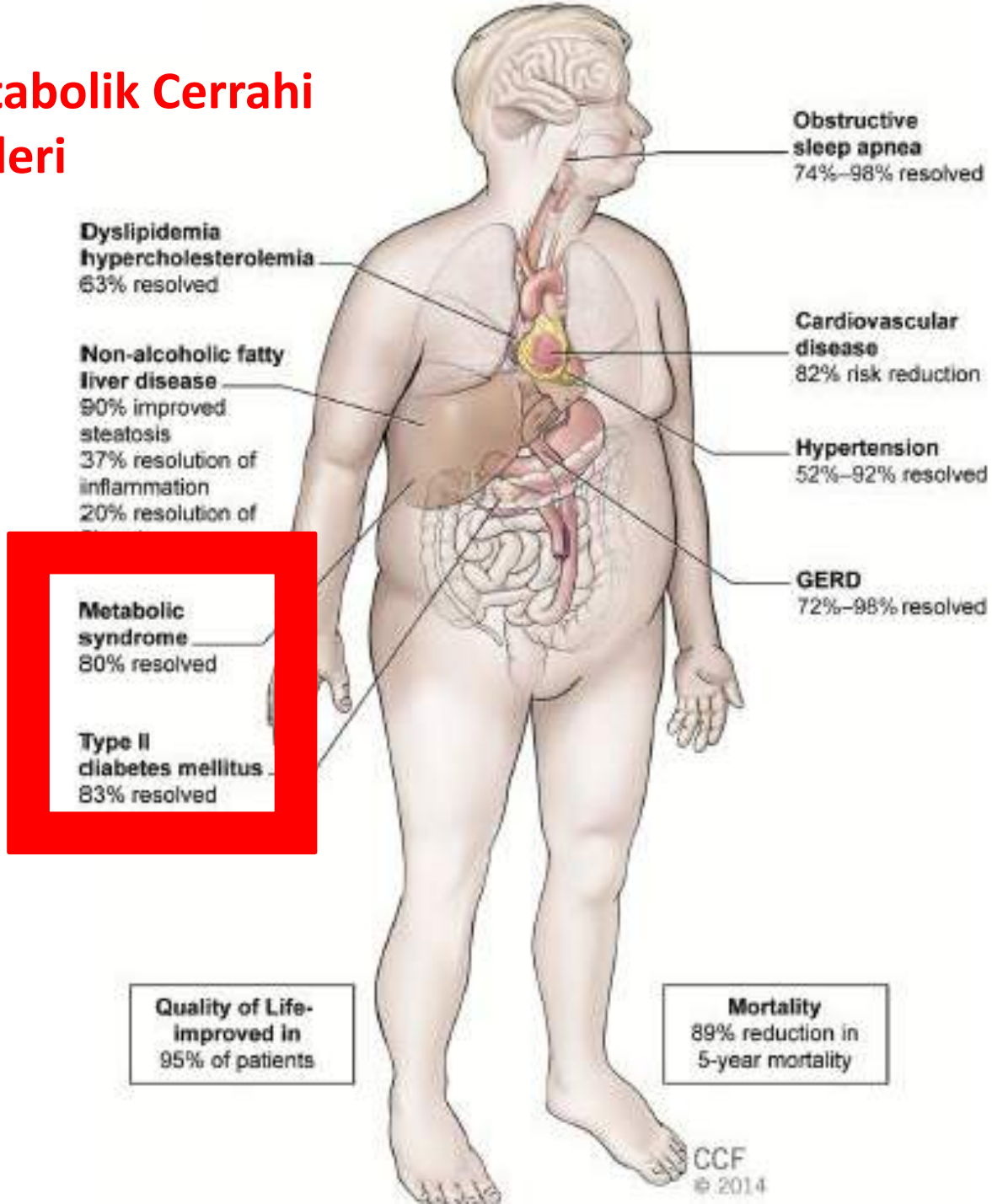
Ödem
Kilo artışı
KKY
Kırık riski

* **Bu endikasyonda henüz onay almamıştır**.

BKI 35 kg/m2 olup metformin tedavisinden fayda görmeyen prediyabetli hastalarda GLP-1 agonistleri veya bir lipoprotein lipaz inhibitörü olan orlistat düşünülebilir.

BKI düşük veya yaş ileri hastalarda farmakolojik tedavi başlanacaksa birinci basamakta akarboz tercih edilebilir

Metabolik Cerrahi Etkileri



Surg Clin N Am 96 (2016) 717–732

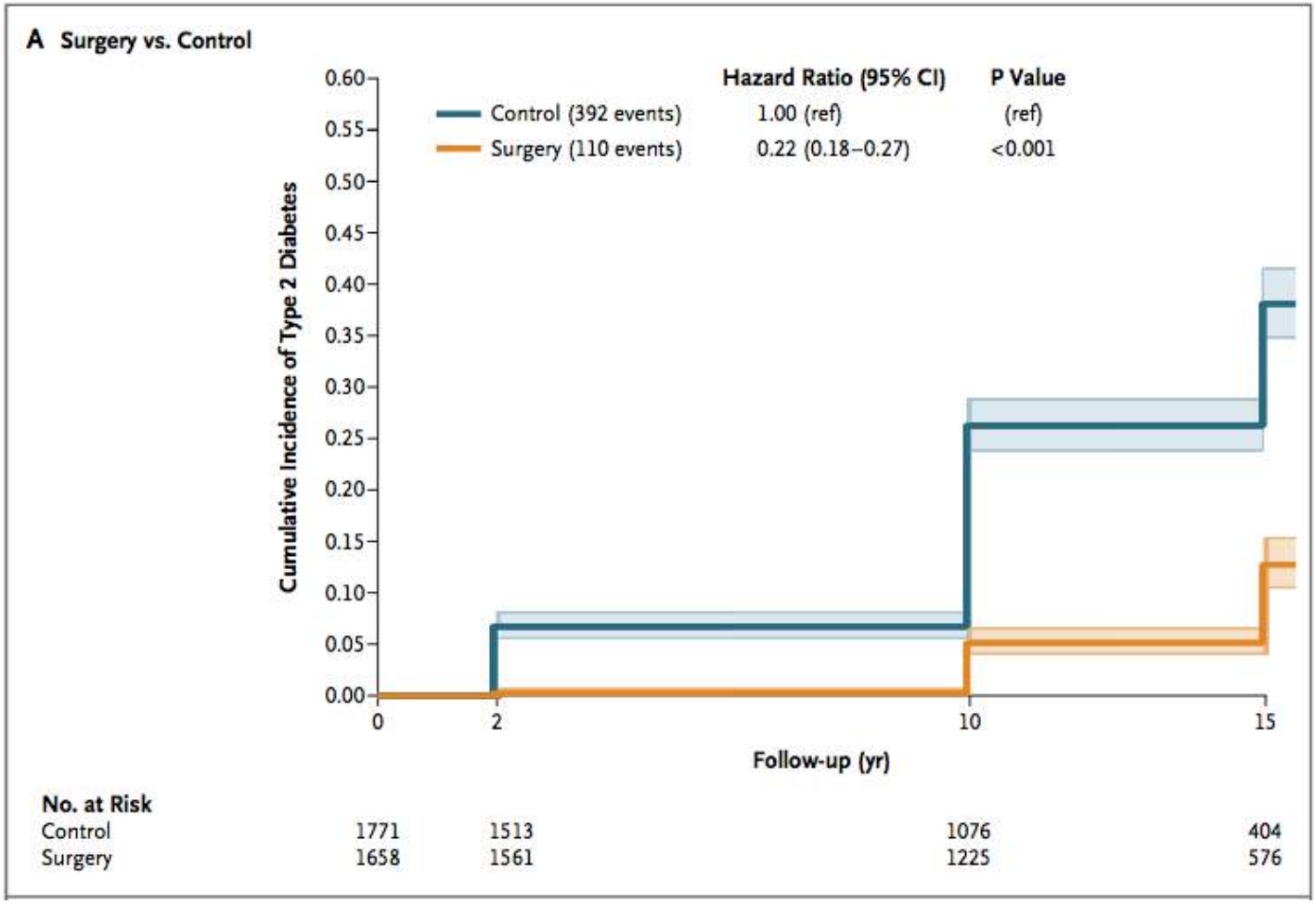
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bariatric Surgery and Prevention of Type 2 Diabetes in Swedish Obese Subjects

Lena M.S. Carlsson, M.D., Ph.D., Markku Peltonen, Ph.D., Sofie Ahlin, M.D., Åsa Anveden, M.D., Claude Bouchard, Ph.D., Björn Carlsson, M.D., Ph.D., Peter Jacobson, M.D., Ph.D., Hans Lönroth, M.D., Ph.D., Cristina Maglio, M.D., Ingmar Näslund, M.D., Ph.D., Carlo Pirazzi, M.D., Stefano Romeo, M.D., Ph.D., Kajsa Sjöholm, Ph.D., Elisabeth Sjöström, M.D., Hans Wedel, Ph.D., Per-Arne Svensson, Ph.D., and Lars Sjöström, M.D., Ph.D.

N Engl J Med 2012; 367:695-704 | August 23, 2012 | DOI: 10.1056/NEJMoa1112082



%87

SONUÇ

- İnsülin direnci ve prediyabet sadece diyabete gidiş sürecinde kilometre taşları değildir. Tedavi edilmesi gereken durumlardır.
- Nonfarmakolojik tedavi tüm olgulara önerilmelidir.
- Farmakolojik tedavi ve metabolik cerrahi seçilmiş olgularda kanıta dayalı bilgiler doğrultusunda uygulandığında etkin olabilir.