
بسم الله

Primary prevention in pre-diabetes: The role of Pharmacotherapy

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Introduction

- More than 8% of adults worldwide have either IFG/IGT. Every year about 5–10% of these people will develop diabetes and acquire the disease burden related to its diagnosis, symptoms, need for surveillance for chronic consequences, and associated costs.(1)

- Prevention of T2D among those with prediabetes is a public health priority. Just as excess body weight is strongly associated with insulin resistance and hyperglycemia, improved glycemia is readily noticeable when individuals with overweight/obesity lose weight; however, the health benefits of weight loss may persist only when the initial weight loss persists over the long-term.(2)

1. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. Lancet.2006

2. Long-term Weight Loss with Metformin or Lifestyle Intervention in the Diabetes Prevention Program Outcomes Study. Ann Intern Med. 2019

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

Diabetes Prevention Program Research Group*

N Engl J Med.
2002 Feb 7
346(6):
393–403.

Mechanism of Metformin Action

- Metformin has several mechanisms and sites of action in humans. Its beneficial effects include inhibition of gluconeogenesis with a consequent decrease in HGO and increased insulin sensitivity, increased glucose utilization in the gut and enhanced insulin sensitivity in skeletal muscle, and effects on the gut microbiota and the immune system.

- However, the mechanisms that contribute to its effects on body weight are not well understood. Decreases in appetite and food intake have been reported with metformin in several but not all studies. Metformin is not known to significantly alter energy expenditure.

❖ Background

We hypothesized that modifying these factors with a lifestyle-intervention program or the administration of metformin would prevent or delay the development of diabetes.

❖ Methods

We randomly assigned 3234 nondiabetic persons with elevated FPG and PLG concentrations to placebo, metformin (850 mg twice daily), or a lifestyle-modification program with the goals of **at least a 7 %** weight loss and at least 150 minutes of physical activity per week. The mean age of the participants was 51 years, and the mean BMI was 34.0; 68 % were women.

Results

- The lifestyle intervention reduced the incidence by **58%** and metformin by **31%**, as compared with placebo; the lifestyle intervention was significantly more effective than metformin.
- **To prevent one case of diabetes during a period of three years, 6.9 % would have to participate in the lifestyle-intervention program, and 13.9% would have to receive metformin**.

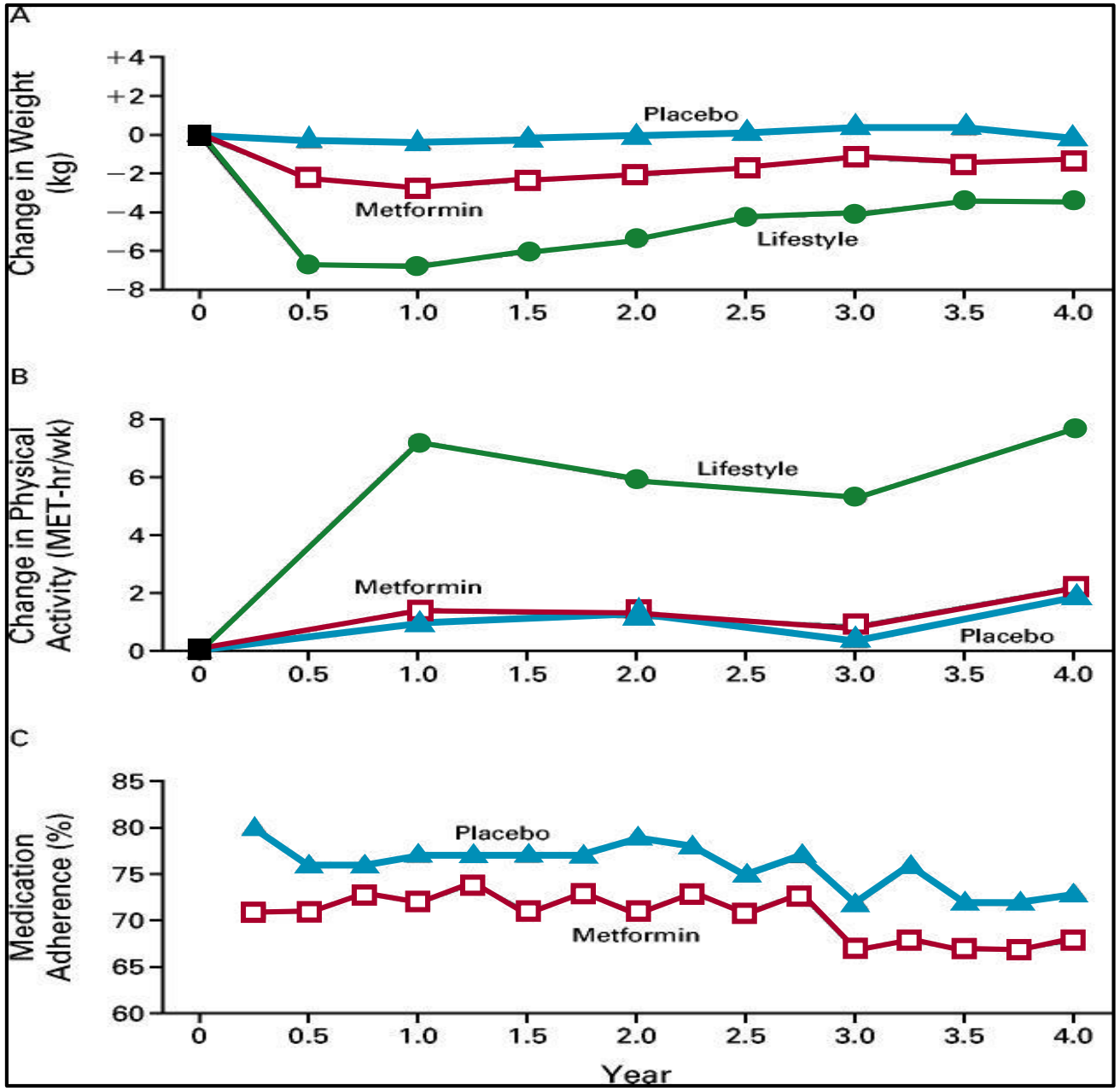
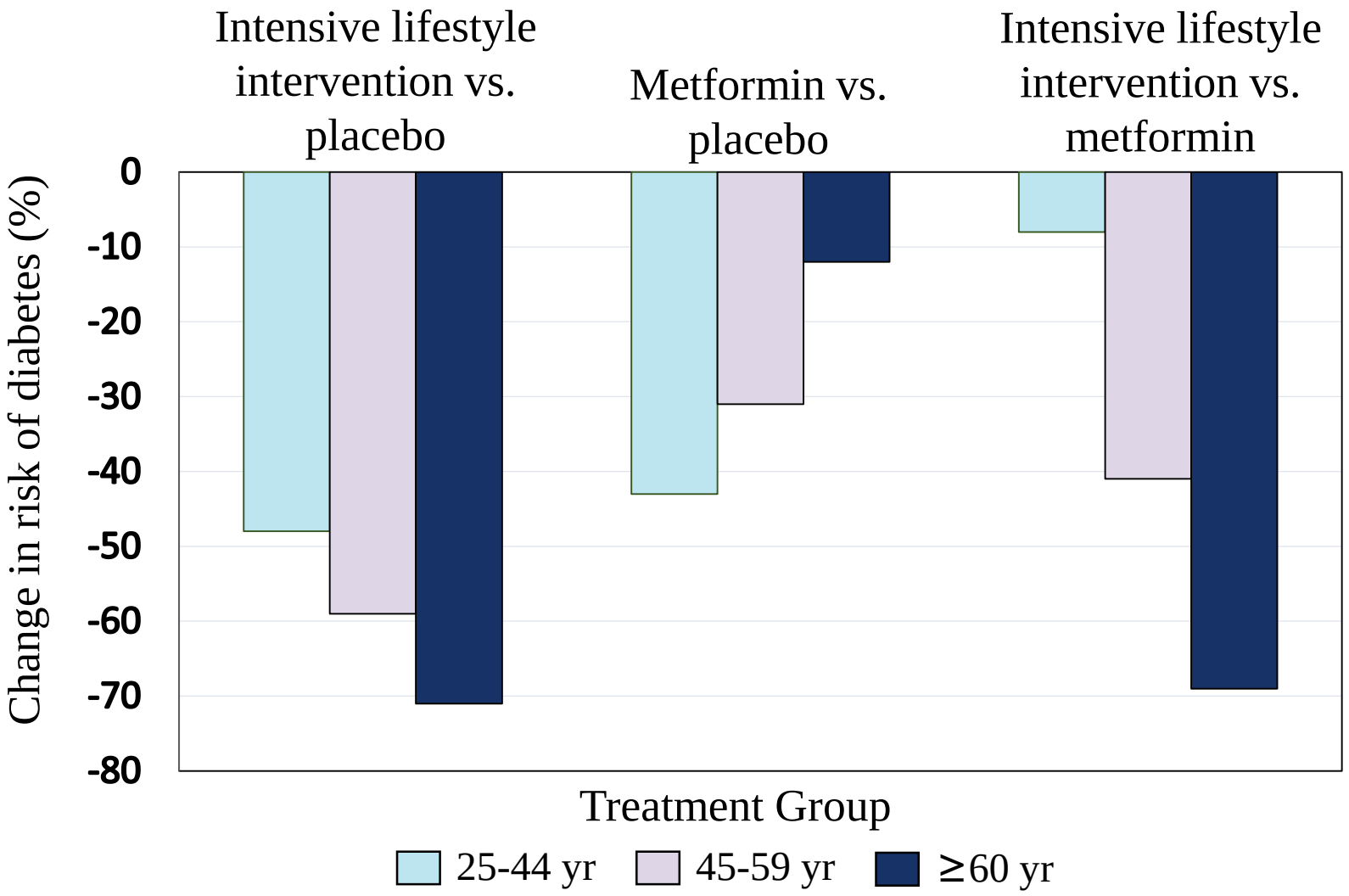


Figure 1.

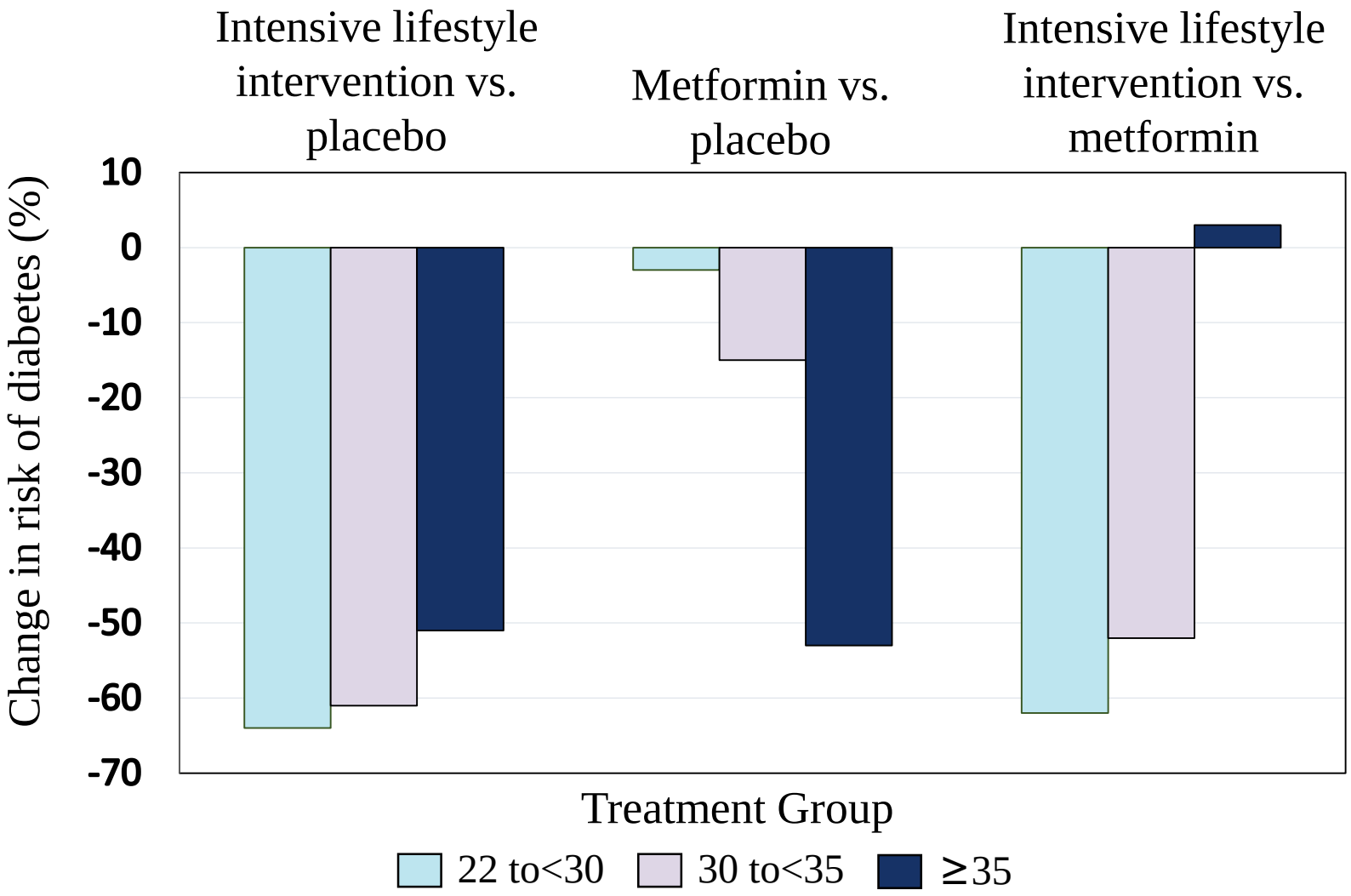
Changes in Body Weight (Panel A) and Leisure Physical Activity (Panel B) and Adherence to Medication Regimen (Panel C) According to Study Group.

In the DPP, metformin and ILS were associated with average weight losses over 2.8 years of 2.1 kg and 5.6 kg, respectively vs 0.1 kg with placebo.

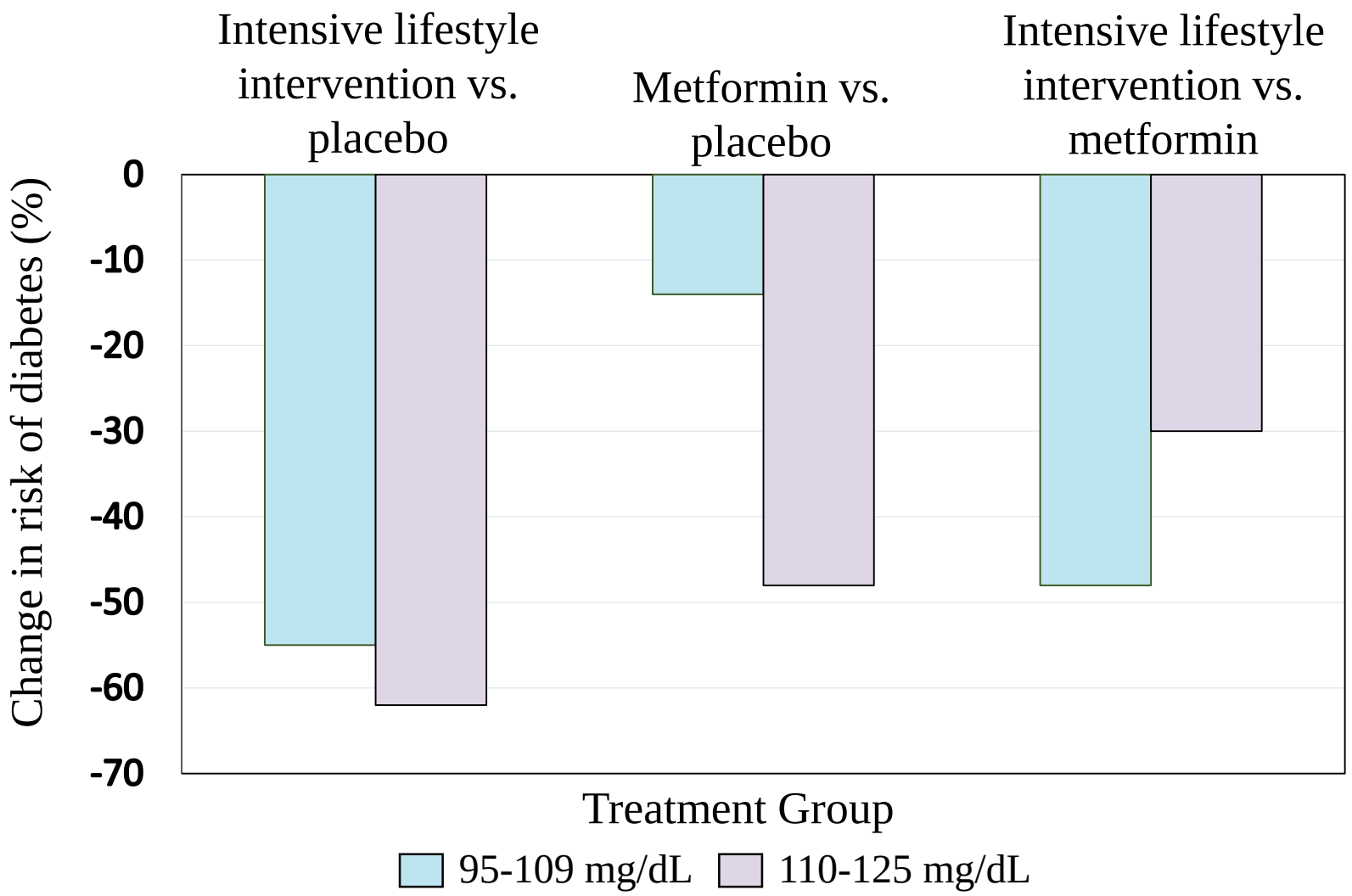
Effects of treatment on diabetes risk with population stratified by age at baseline



Effects of treatment on diabetes risk with population stratified by BMI at baseline



Effects of treatment on diabetes risk with population stratified by FPG at baseline



ADA 2021

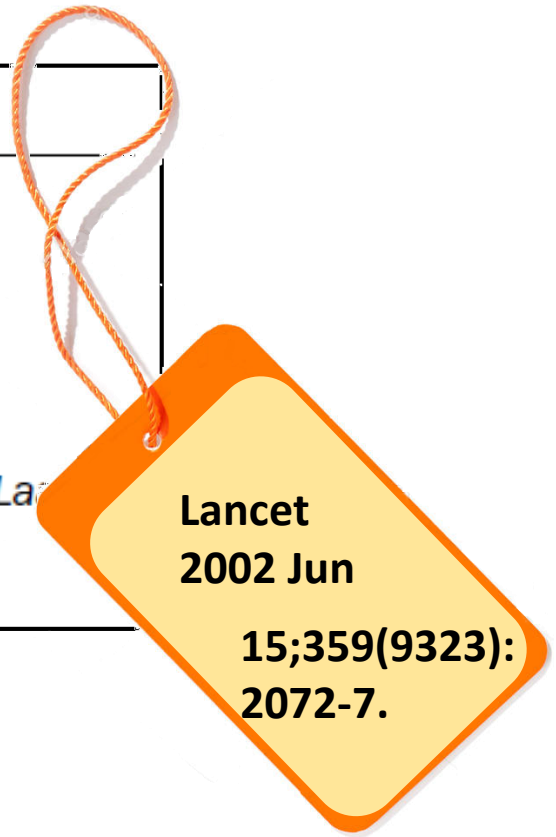
Recommendations

- 3.6 Metformin therapy for prevention of type 2 diabetes should be considered in those with prediabetes, especially for those with BMI≥35 kg/m2, those aged < 60 years, and women with prior gestational diabetes mellitus. A
- 3.7 Long-term use of metformin may be associated with biochemical vitamin B12 deficiency; consider periodic measurement of vitamin B12 levels in metformin treated patients, especially in those with anemia or peripheral neuropathy. B

ARTICLES

Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial

Jean-Louis Chiasson, Robert G Josse, Ramon Gomis, Markolf Hanefeld, Avraham Karasik, Markku La
*for The STOP-NIDDM Trial Research Group**



❖ **Background**

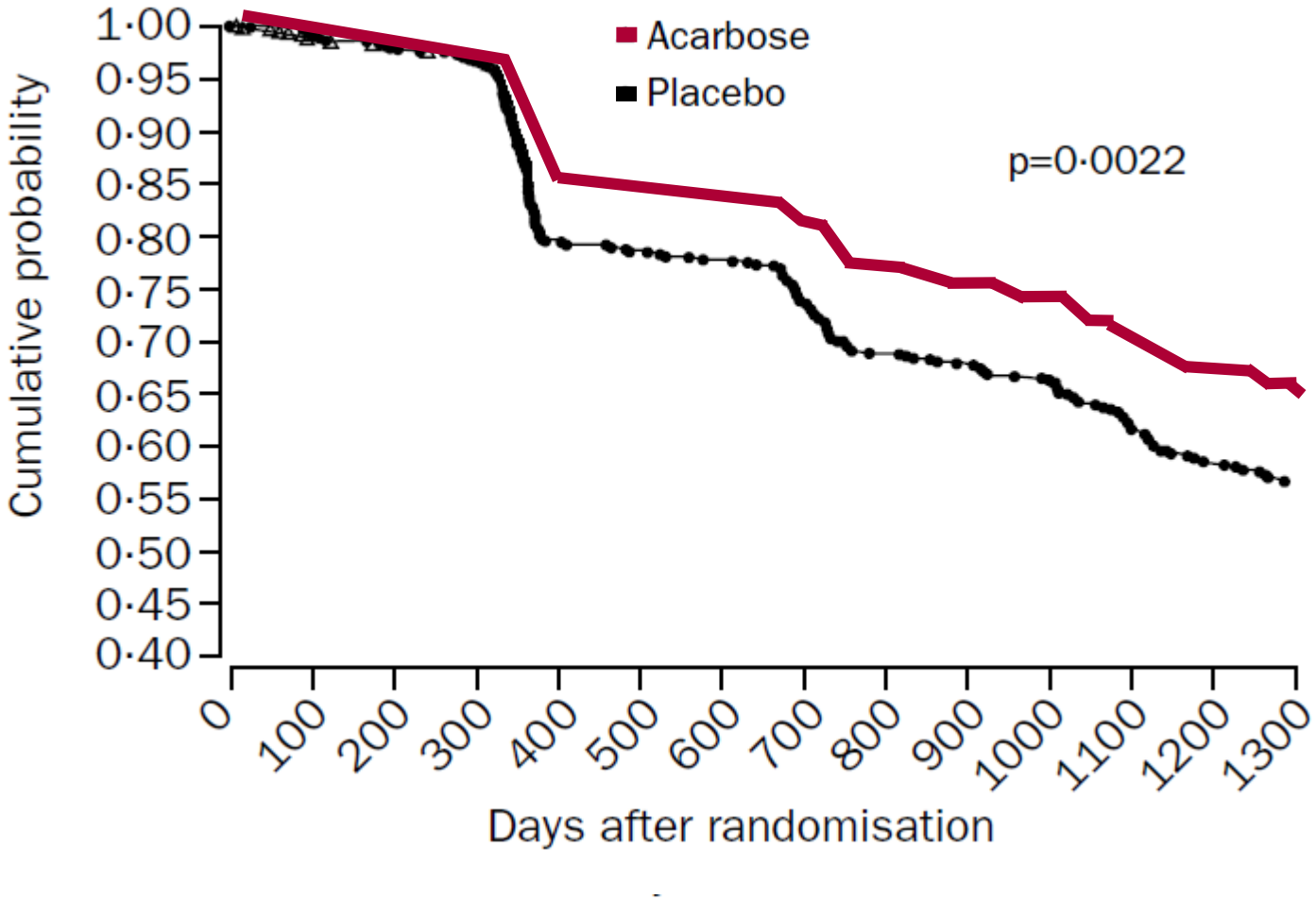
We aimed to assess the effect of acarbose in preventing or delaying conversion of IGT to type 2 diabetes.

❖ **Methods**

In a multicentre, placebo-controlled randomized trial, we randomly allocated patients with IGT to 100 mg acarbose(714) or placebo(715) three times daily. The primary endpoint was development of diabetes on the basis of a yearly OGTT. Analyses were by intention to treat.

❖ **Findings**

32% patients randomised to acarbose and **42%** randomised to placebo developed diabetes (relative hazard 0·75 [95% CI 0·63–0·90]; p=0·0015). Furthermore, acarbose significantly increased reversion of IGT to NGT (p<0·0001).



Patients at risk

Acarbose	682	655	628	612	531	523	515	497	463	447	432	349	268	212
Placebo	686	671	655	640	512	505	497	470	434	427	414	331	255	208

Figure 3.

Effect of acarbose and placebo on cumulative probability of remaining free of diabetes over time

Conclusion

Acarbose could be used, either as an alternative or in addition to changes in lifestyle, to delay development of type 2 diabetes in patients with impaired glucose tolerance.

NNT for prevention of diabetes:

1/11 among IGTT cases for 3.3 years follow up

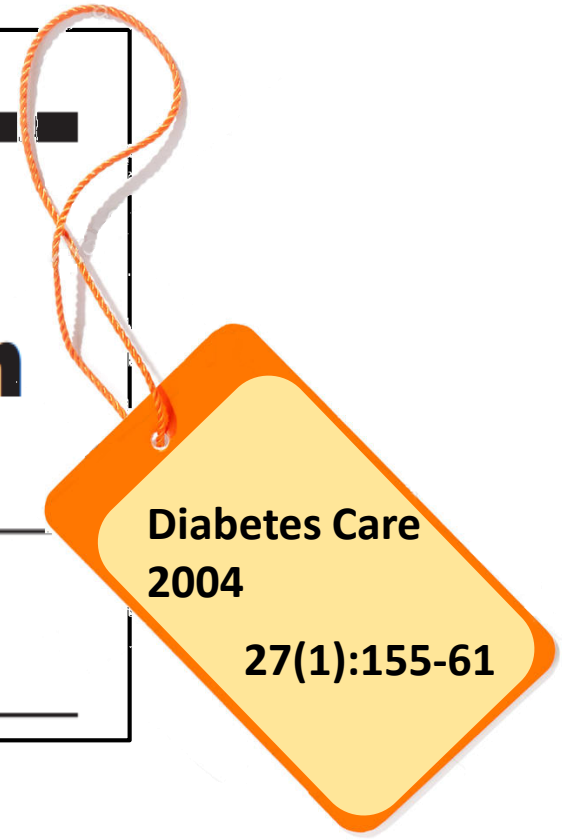
Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet. 2002

Emerging Treatments and Technologies

ORIGINAL ARTICLE

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



❖ OBJECTIVE

We hypothesized that adding a weight-reducing agent to lifestyle changes may lead to an even greater decrease in body weight, and thus the incidence of type 2 diabetes, in obese patients.

❖ RESEARCH DESIGN AND METHODS

In a 4-year, double-blind, prospective study, we randomized 3,305 patients to lifestyle changes plus either orlistat 120 mg or placebo, three times daily. **Participants had a BMI ≥30 kg/m2 and normal (79%) or IGT (21%)**. Primary endpoints were time to onset of type 2 diabetes and change in body weight. Analyses were by intention to treat.

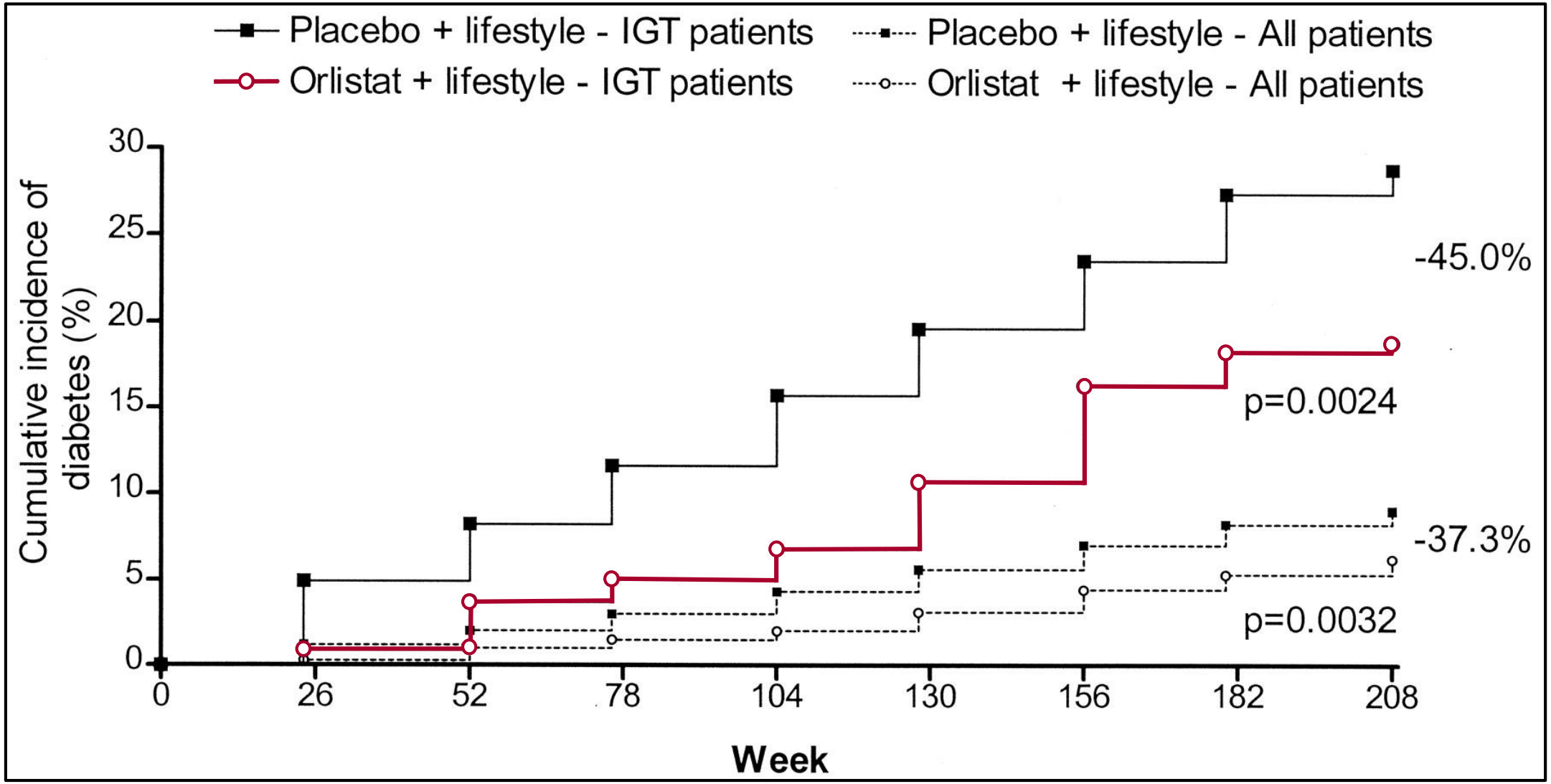


Figure 1 **Cumulative incidence of diabetes by study group in all obese patients (IGT or NGT at baseline) and only in obese patients with IGT at baseline. The decrease in the risk of developing diabetes with orlistat plus lifestyle compared with placebo plus lifestyle is indicated. P values shown are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

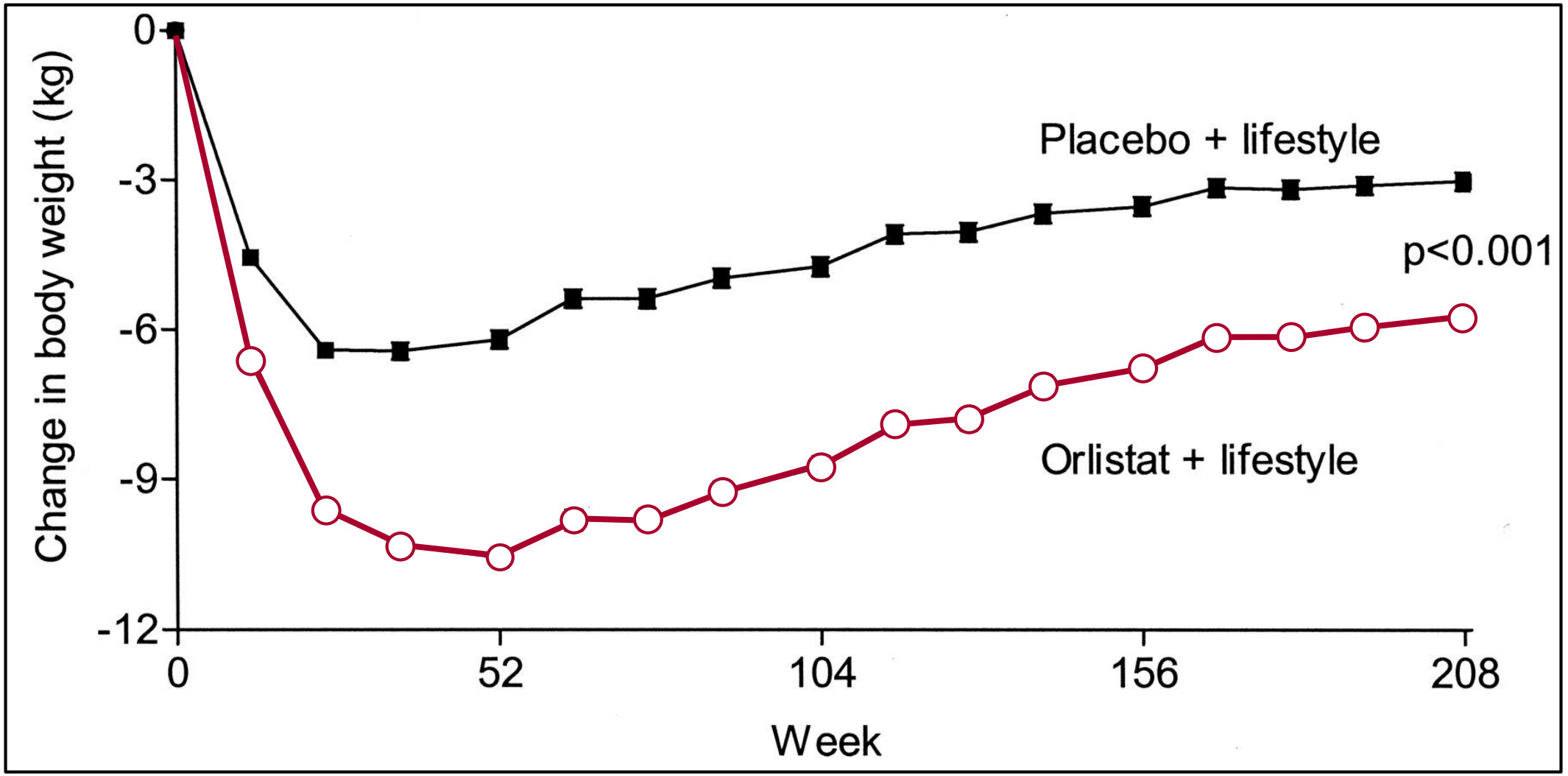


Figure 2 **Weight loss (means ± SEM) during 4 years of treatment with orlistat plus lifestyle changes or placebo plus lifestyle changes in obese patients (LOCF data).**

Conclusion

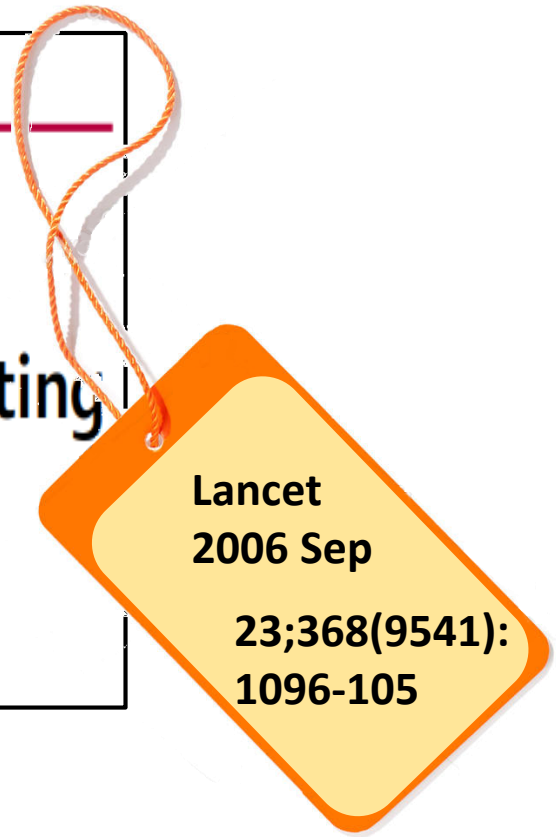
In summary, the addition of orlistat to lifestyle changes significantly reduces the incidence of type 2 diabetes in obese subjects. **With our study design, reduction was only apparent in the IGT subgroup**. Adding orlistat also significantly increases weight loss in obese patients with either IGT or NGT and improves other cardiovascular risk factors. Orlistat treatment is safe and well tolerated over 4 years of treatment.

NNT for prevention of diabetes:

1/36 for 4 years follow up

Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial

The DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators*



❖ Background

Rosiglitazone is a thiazolidinedione that reduces insulin resistance and might preserve insulin secretion. The aim of this study was to assess prospectively the drug's ability to prevent type 2 diabetes in individuals at high risk of developing the condition.

❖ Methods

5269 adults aged 30 years or more **with IFG or IGT, or both, and no previous CVD** were recruited from 191 sites in 21 countries and randomly assigned to receive rosiglitazone (8 mg daily; n=2365) or placebo (2634) and followed for a median of 3 years.

The primary outcome was a composite of incident diabetes or death. Analyses were done by intention to treat.

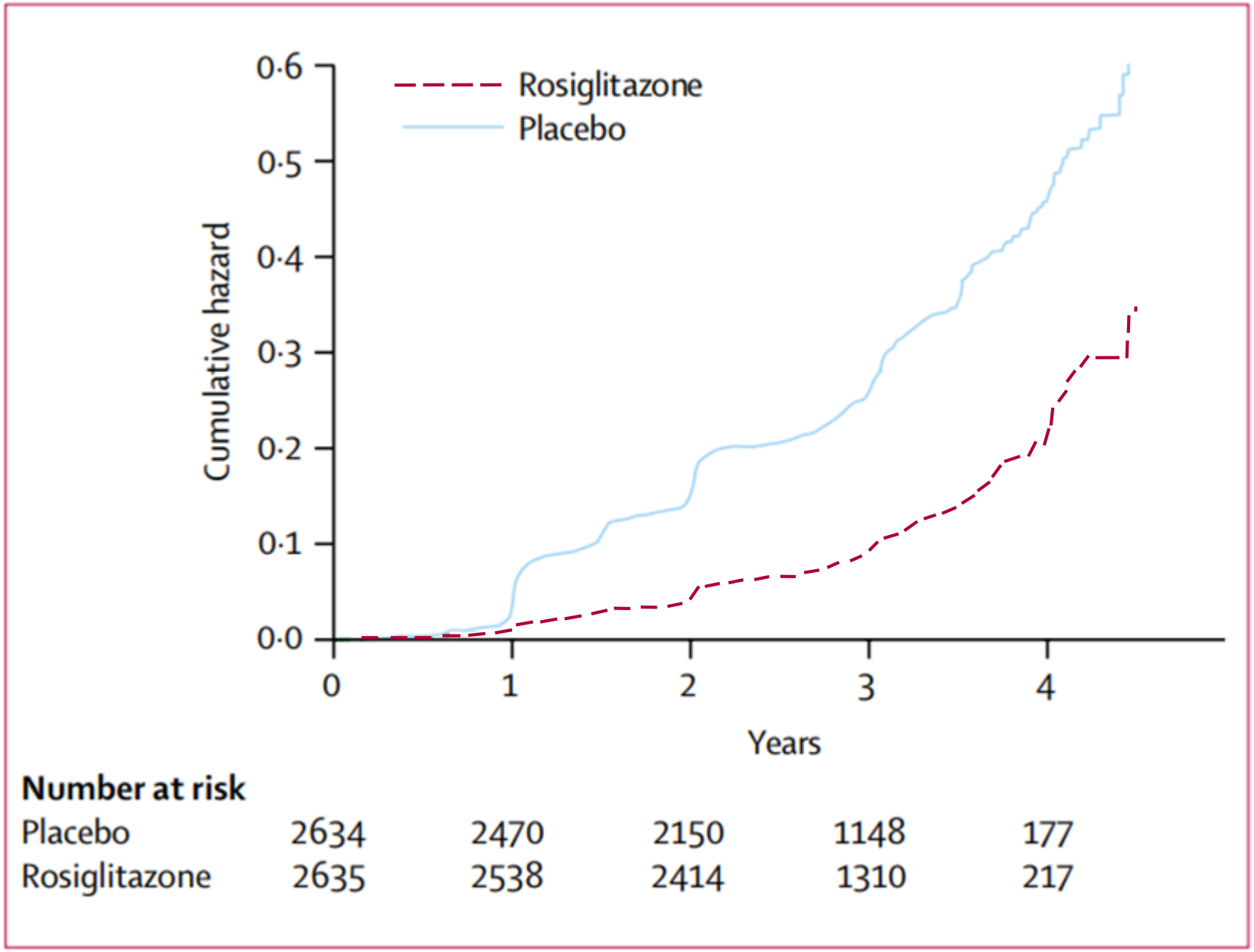


Figure 2.

Time to occurrence of primary outcome.

306 (11.6%) individuals given rosiglitazone and 686 (26.0%) given placebo developed the composite primary outcome (hazard ratio 0.40, 95% CI 0.35-0.46; p<0.0001); 1330 (50.5%) individuals in the rosiglitazone group and 798 (30.3%) in the placebo group became normoglycaemic (1.71, 1.57-1.87; p<0.0001).

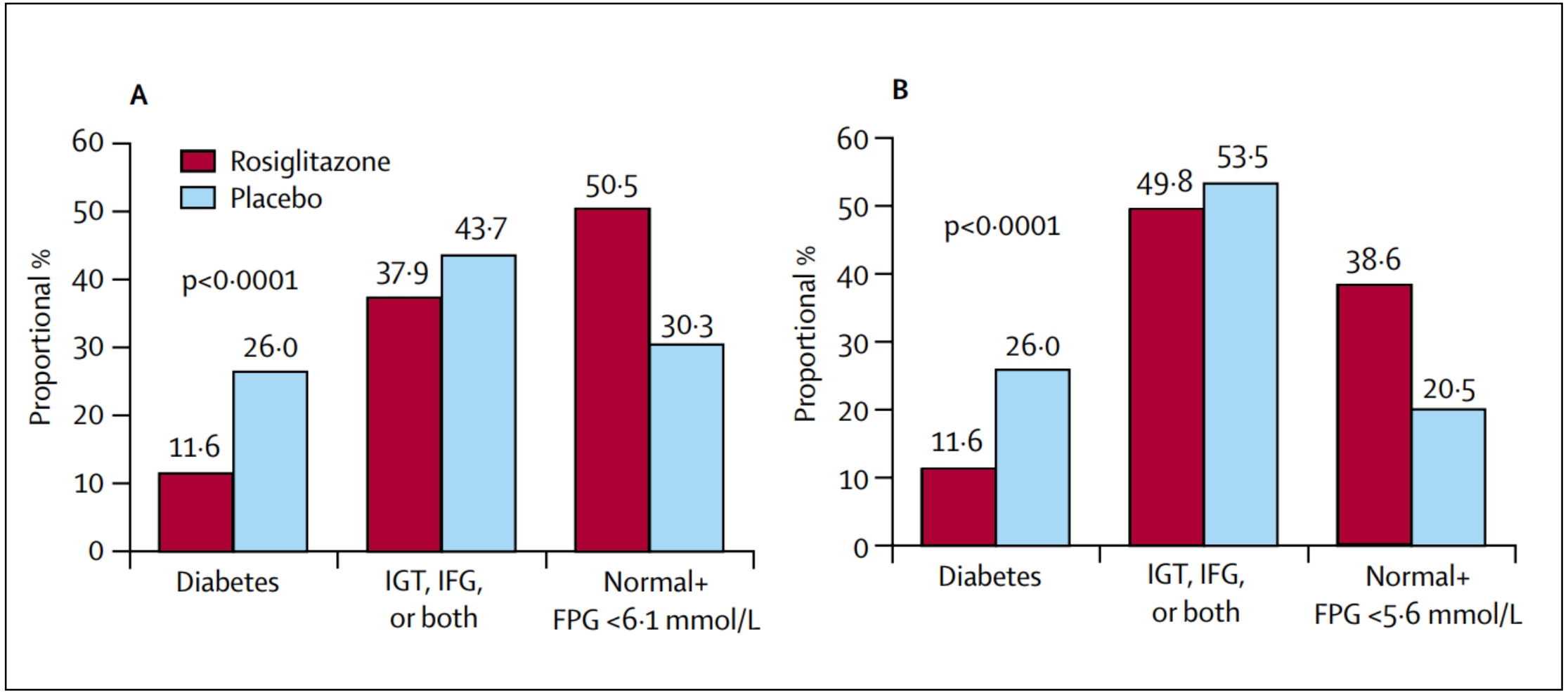


Figure 4. Proportion of participants who either developed diabetes, regressed to normal, or had impaired fasting glucose or impaired glucose tolerance, or both, at the last assessment

(A) FPG defined as concentration <6·1 mmol/L or **(B)** <5·6 mmol/L. The p value for the likelihood that the distribution across categories would have occurred by chance using both FPG cutoff s was <0·0001.

Conclusion

- This large, prospective, blinded international clinical trial shows that 8 mg of rosiglitazone daily, together with lifestyle recommendations, substantially reduces the risk of diabetes or death by 60% in individuals at high risk for diabetes.
- Mean SBP and DBP were 1·7 mm Hg and 1·4 mm Hg lower, respectively, in the rosiglitazone group than in the placebo group ($p<0·0001$).
- Mean hepatic ALT concentrations during the first year of therapy were 4·2 U/L lower in patients treated with rosiglitazone than those in the placebo group ($p<0·0001$).

NNT for prevention of diabetes:

1/7 among IGTT/IFG cases for 3 years follow up

Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. Lancet.2006

Conclusion

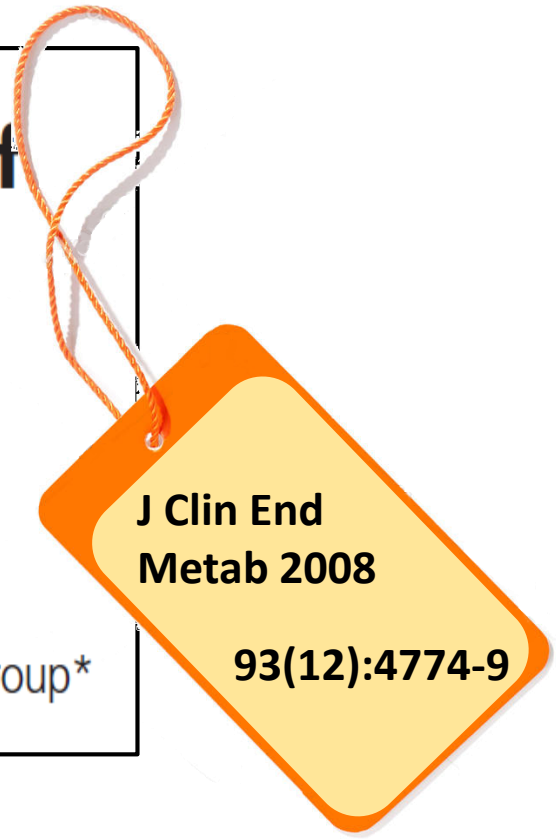
For every 1000 people treated with rosiglitazone for 3 years

Rosiglitazone was also increased the likelihood of regression to normoglycaemia by about 70–80% suggests that it is treating dysglycaemia as well as reducing the frequency of diabetes.

Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. Lancet.2006

Prevention of Diabetes in Women with a History of Gestational Diabetes: Effects of Metformin and Lifestyle Interventions

Robert E. Ratner, Costas A. Christophi, Boyd E. Metzger, Dana Dabelea, Peter H. Bennett, Xavier Pi-Sunyer, Sarah Fowler, Steven E. Kahn, and The Diabetes Prevention Program Research Group*



- **Objective:** The DPP sought to identify individuals with IGT and intervene in an effort to prevent or delay their progression to diabetes. This analysis examined the differences between women enrolled in DPP with and without a reported history of GDM.
- **Design:** The DPP was a randomized, controlled clinical trial.
- **Setting:** The study was a multicenter, National Institutes of Health-sponsored trial carried out at 27 centers including academic and Indian Health Services sites.
- **Patients:** A total of 2190 women were randomized into the DPP and provided information for past history of GDM. This analysis addressed the differences between those 350 women providing a past history of GDM and those 1416 women with a previous live birth but no history of GDM.
- **Main Outcomes:** The primary outcome was the time to development of diabetes ascertained by semiannual FPG and annual OGTT.

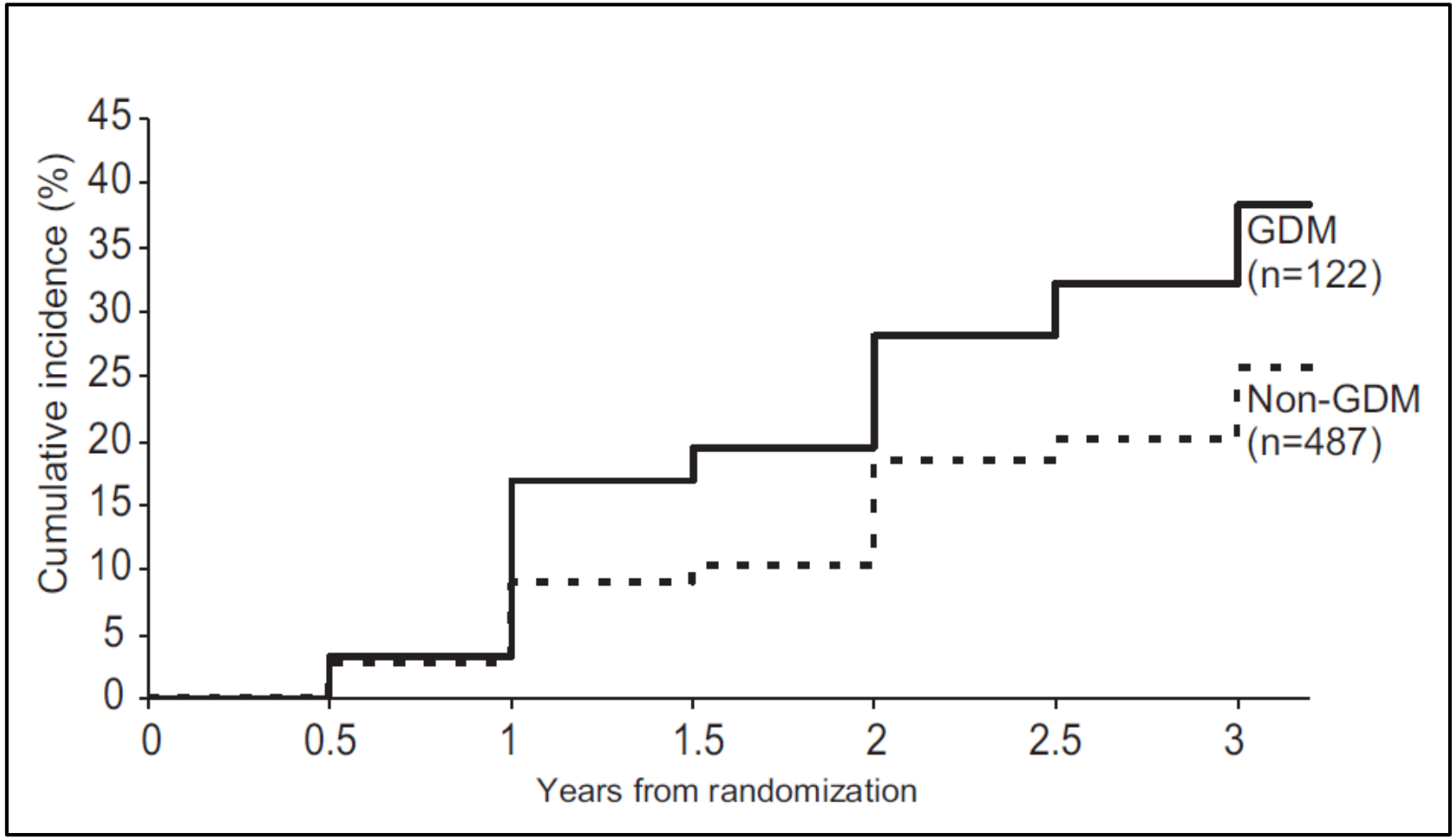


Figure 2
Cumulative incidence of diabetes mellitus among the placebo group by history of GDM.

Without History of GDM

With History of GDM

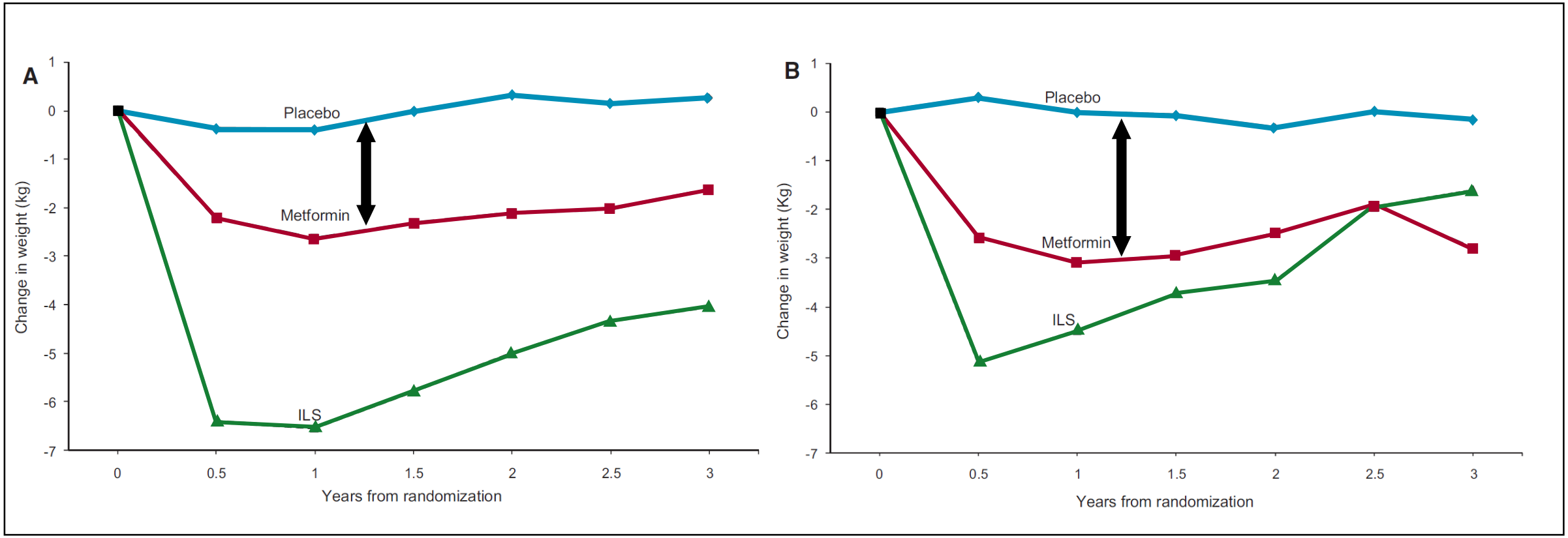


Figure 3

Change in weight during DPP by randomized treatment group.

Without History of GDM

With History of GDM

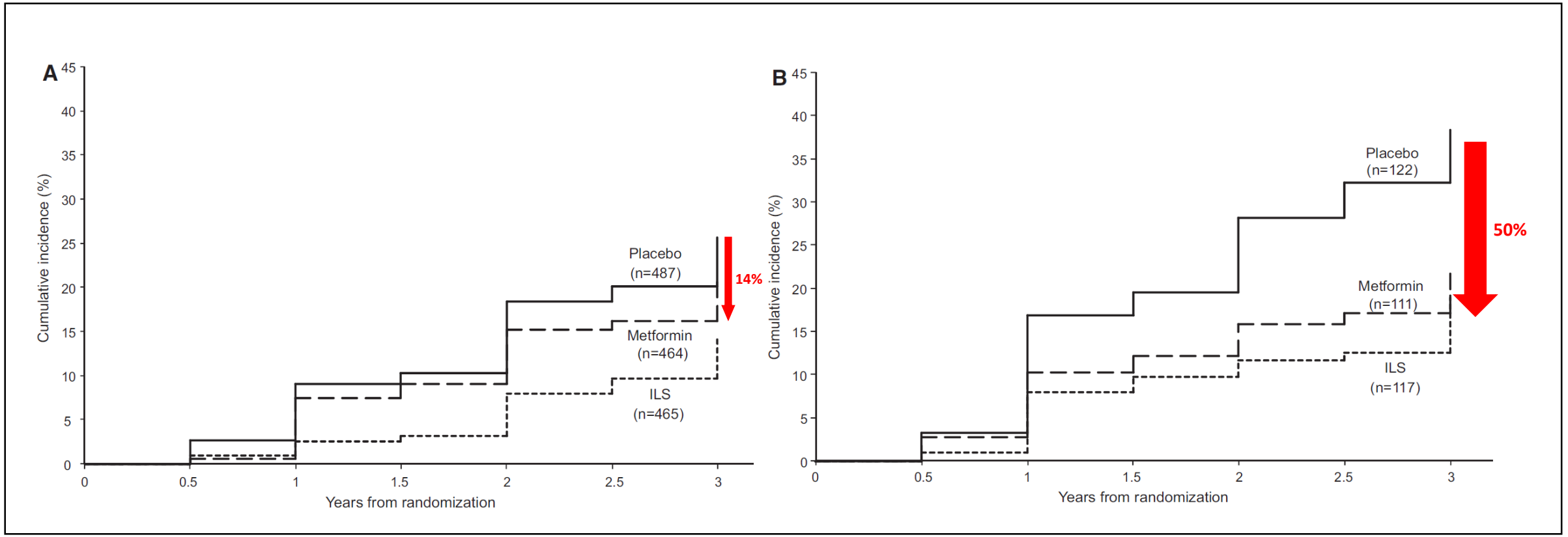


Figure 4

Cumulative incidence of diabetes in DPP by randomized treatment group.

TABLE 2. Effect of DPP treatment on incidence of diabetes

	Placebo		Metformin		ILS	
	GDM (n = 122)	No GDM (n = 487)	GDM (n = 111)	No GDM (n = 464)	GDM (n = 117)	No GDM (n = 465)
Incidence of diabetes (number of cases per 100 person-years)[a]	15.2[b]	8.9	7.8	7.8	7.4	4.7
Reduction in incidence (compared with placebo)[a]			50.4[c]	14.4	53.4[c]	49.2[c]
Number needed to treat (to prevent one case in 3 yr compared with placebo)[a]			6.1	24.0	5.3	9.0

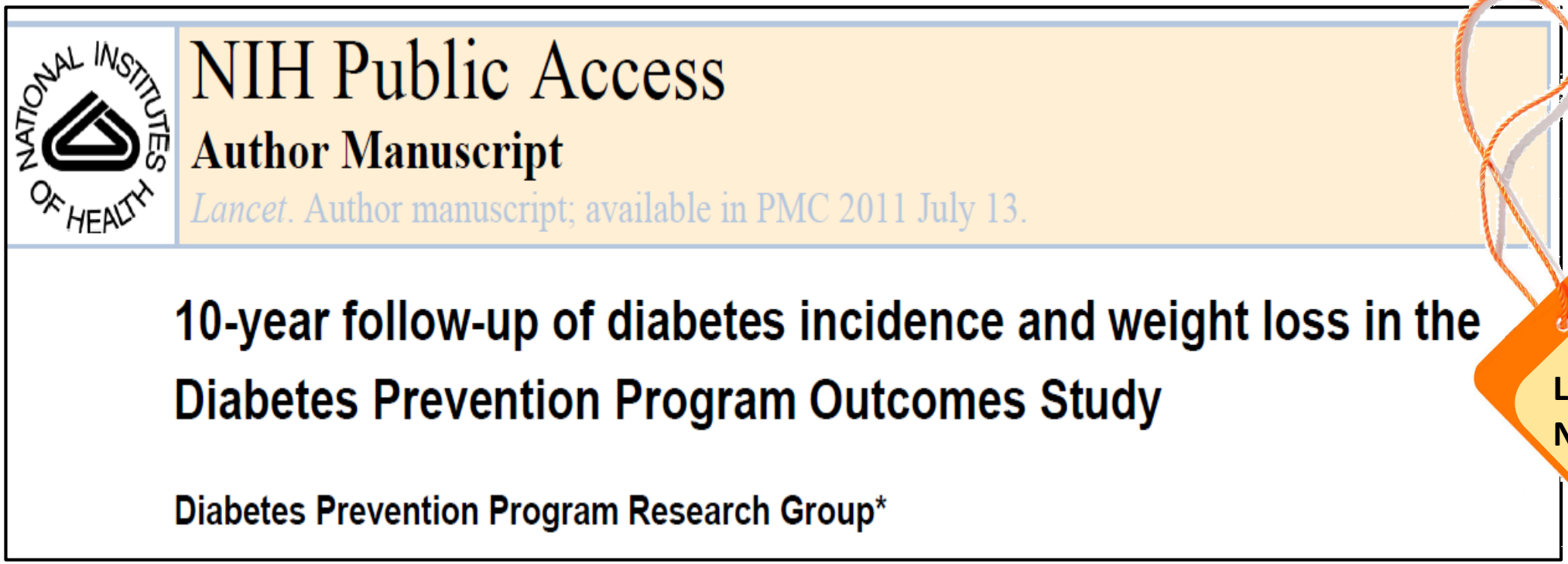
[a] Adjusted for age.

[b] $P < 0.05$ compared with non-GDM group.

[c] $P < 0.05$ compared with placebo.

NNT for prevention of diabetes:

1/6 among GDM cases for 3 years follow up



NIH Public Access

Author Manuscript

Lancet. Author manuscript; available in PMC 2011 July 13.

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

Diabetes Prevention Program Research Group*

Lancet. 2009 November 14; 374(9702): 1677–1686

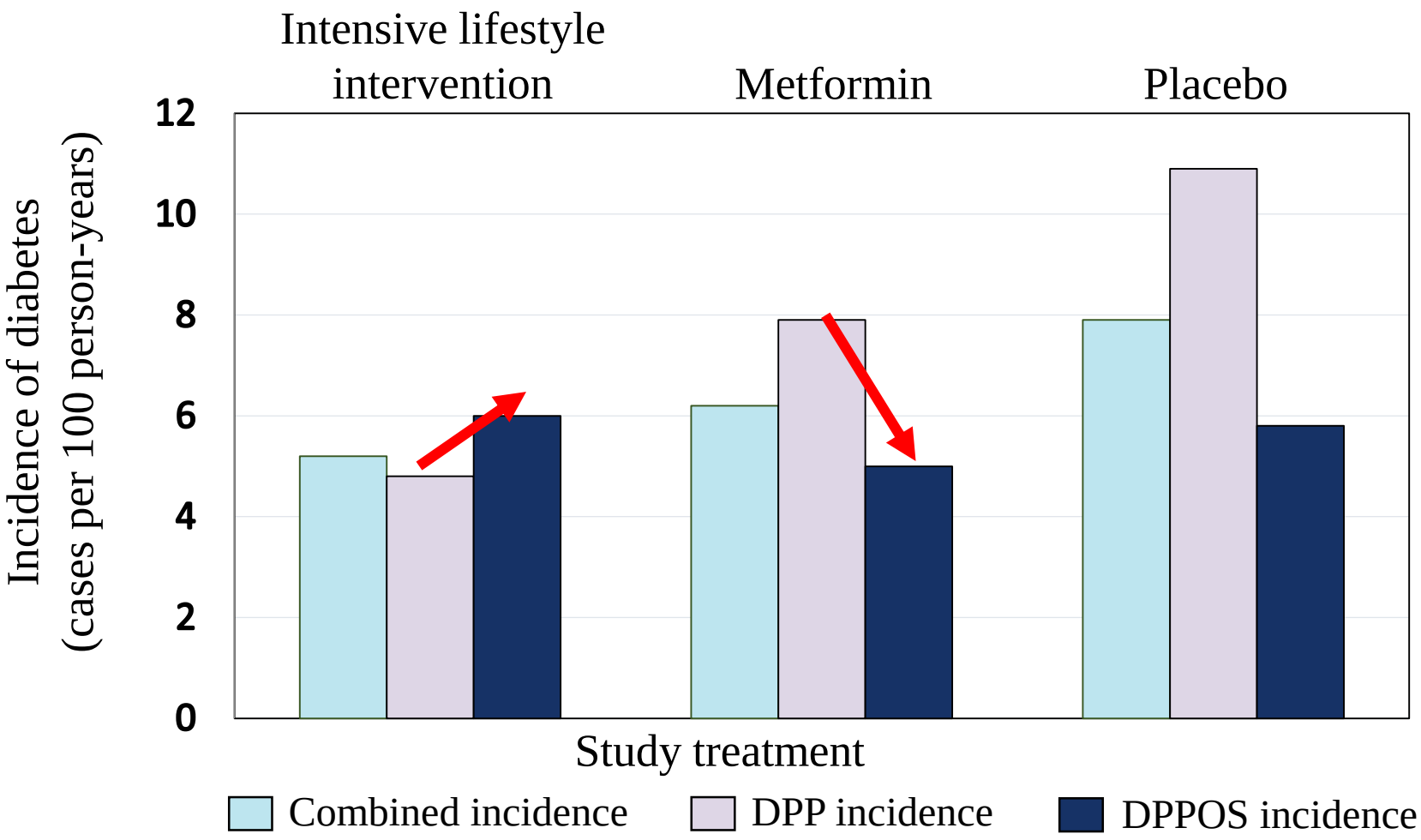
❖ BACKGROUND

In the 2·8 years of the DPP trial, diabetes incidence in high-risk adults was reduced by 58% with intensive lifestyle intervention and by 31% with metformin, compared with placebo.

❖ METHODS

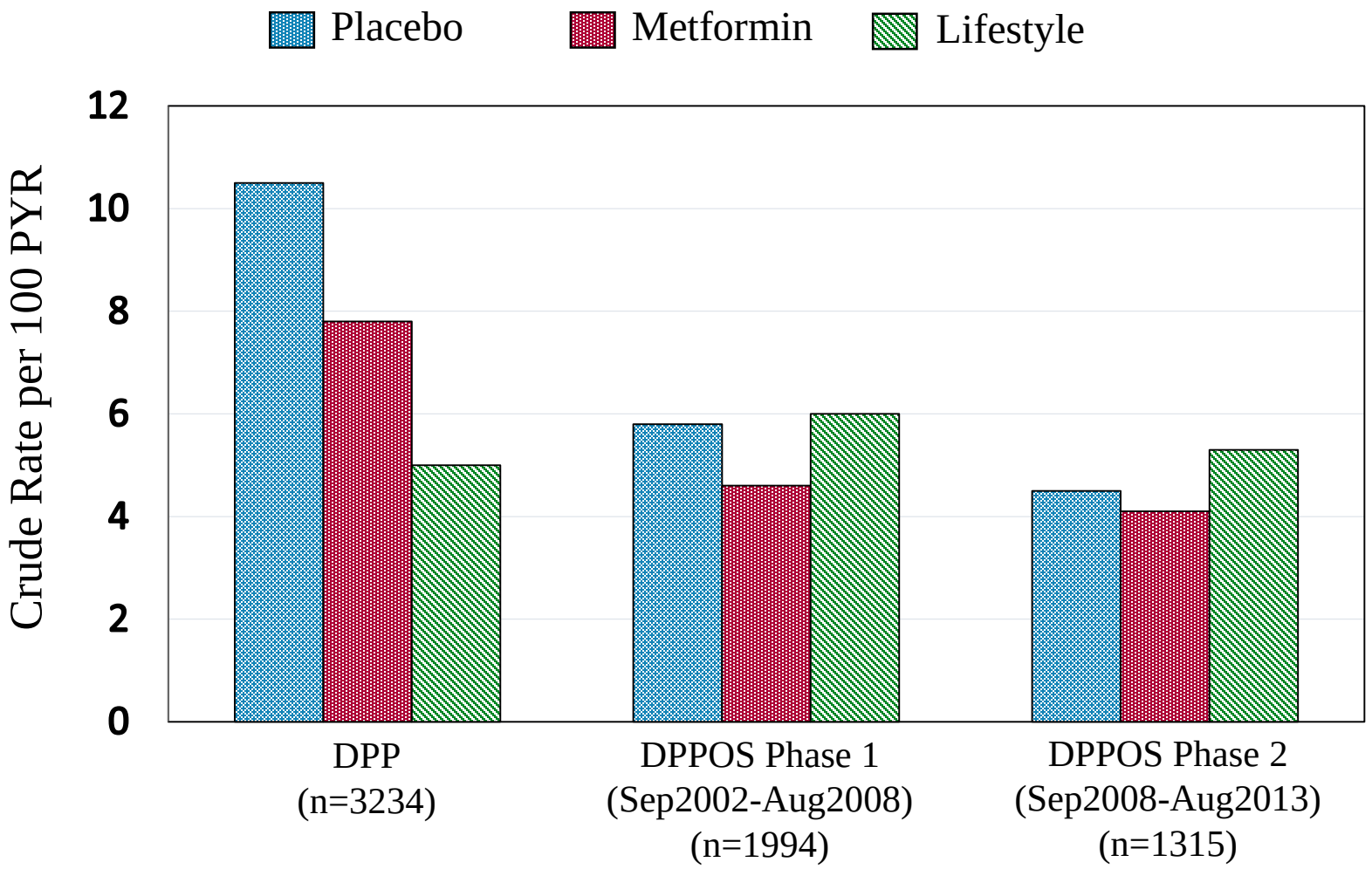
All active DPP participants were eligible for continued follow-up. 2766 of 3150 (88%) enrolled for a median additional follow-up of 5·7 years. 910 participants were from the lifestyle, 924 from the metformin, and 932 were from the original placebo groups. On the basis of the benefits from the intensive lifestyle intervention in the DPP, all three groups were offered group-implemented lifestyle intervention. Metformin treatment was continued in the original metformin group **(850 mg twice daily as tolerated)**, with **participants unmasked to assignment**, and the original lifestyle intervention group was offered additional lifestyle support.

Incidence of diabetes during DPP and DPPOS



- 10 year effects on diabetes incidence and weight loss were evaluated in 2,766 subjects.
- Diabetes incidence rate was reduced by **34% for the original intensive lifestyle intervention group and by 18% for the original metformin group** compared with placebo.
- **Metformin decreased the incidence of overt diabetes by 13% compared with the original placebo group**, whereas in the original intensive lifestyle group the incidence of overt diabetes was 5% higher than that in the placebo group.

Incidence rates of diabetes in DPP/DPPOS according to study phase

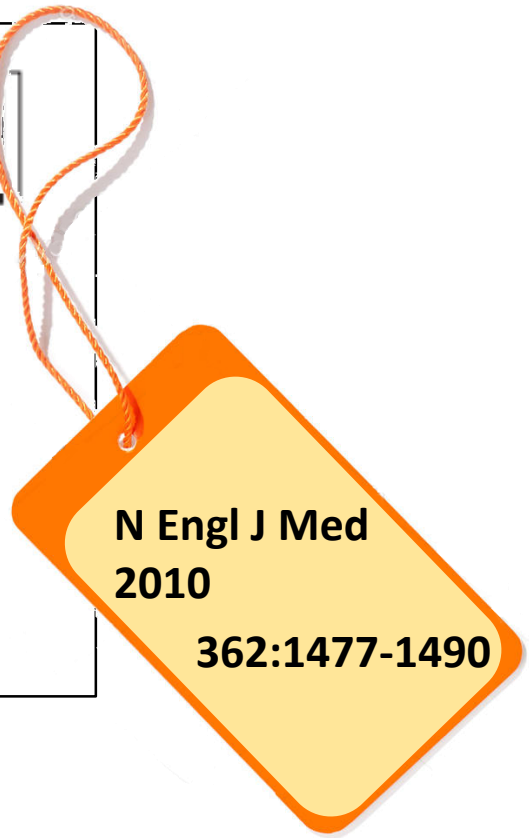


- The reduction in the cumulative incidence of diabetes by either lifestyle intervention or metformin therapy persists for at least 10 years.
- **The risk of developing diabetes was lowest for patients who had reverted from IGT to normal glucose regulation, irrespective of the original treatment assignment.**
- During the longer-term evaluation alone, metformin was more effective than intensive lifestyle change in reducing the risk of onset of overt diabetes.

ORIGINAL ARTICLE

Effect of Valsartan on the Incidence of Diabetes and Cardiovascular Events

The NAVIGATOR Study Group*



❖ BACKGROUND

It is not known whether drugs that block the renin–angiotensin system reduce the risk of diabetes and CVD in patients with IGT.

❖ METHODS

In this double-blind, randomized clinical trial with a 2-by-2 factorial design, we assigned 9306 patients with IGT and established CVD or CVD risk factors to receive valsartan (up to 160 mg daily) or placebo (and nateglinide or placebo) in addition to lifestyle modification. We then followed the patients for a median of 5.0 years for the development of diabetes (6.5 years for vital status).

We studied the effects of valsartan on the occurrence of three coprimary outcomes: the development of diabetes; an extended composite outcome of death from CVD, nonfatal MI, nonfatal stroke, hospitalization for CHF, arterial revascularization, or hospitalization for ACS; and a core composite outcome that excluded ACS and revascularization.

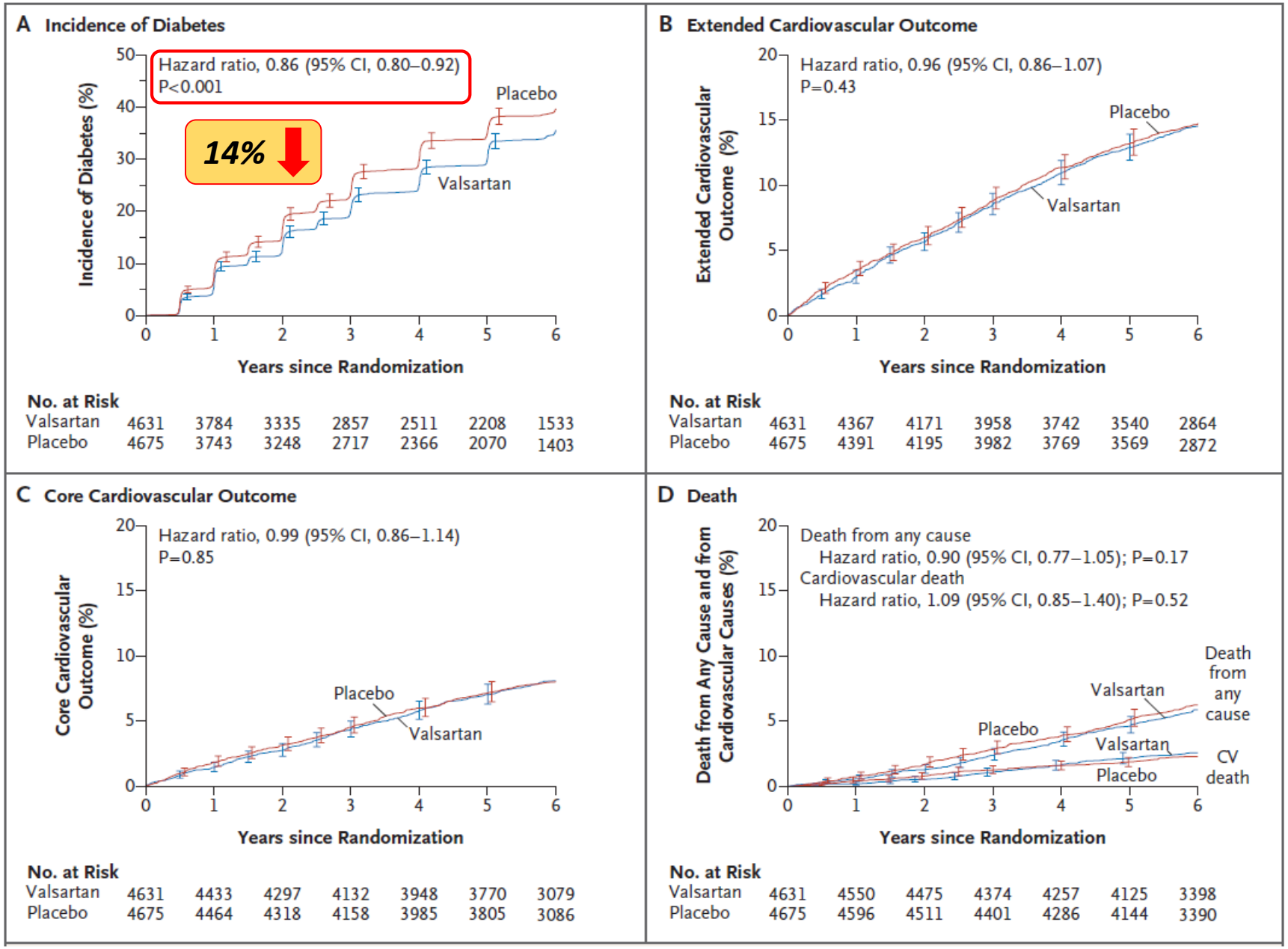


Figure 3

Kaplan–Meier Curves for Three Coprimary Outcomes and Death. Panel A shows the incidence of diabetes, the coprimary outcome. Panel B shows the coprimary extended cardiovascular outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, arterial revascularization, or hospitalization for unstable angina. Panel C shows the coprimary core cardiovascular outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Panel D shows the outcomes of death from any cause and from cardiovascular (CV) causes. All P values are two-sided. The I bars indicate 95% confidence intervals.

Conclusion

- When added to lifestyle intervention, a single daily dose of valsartan (up to 160 mg) reduced the risk of diabetes but not of cardiovascular events in patients with impaired glucose tolerance and established cardiovascular disease or risk factors.

- The relative reduction of 14% in the risk of diabetes in the valsartan group would translate into **38 fewer cases of diabetes per 1000 patients treated for 5 years, a reduction that was consistent across all subgroups that we examined**.

ORIGINAL ARTICLE

Pioglitazone for Diabetes Prevention in Impaired Glucose Tolerance

Ralph A. DeFronzo, M.D., Devjit Tripathy, M.D., Ph.D., Dawn C. Schwenke, Ph.D., MaryAnn Banerji, M.D., George A. Bray, M.D., Thomas A. Buchanan, M.D., Stephen C. Clement, M.D., Robert R. Henry, M.D., Howard N. Hodis, M.D., Abbas E. Kitabchi, M.D., Ph.D., Wendy J. Mack, Ph.D., Sunder Mudaliar, M.D., Robert E. Ratner, M.D., Ken Williams, M.Sc., Frankie B. Stentz, Ph.D., Nicolas Musi, M.D., and Peter D. Reaven, M.D., for the ACT NOW Study

N Engl J Med
2011 Mar
24;364(12):
1104-15

❖ BACKGROUND

Impaired glucose tolerance is associated with increased rates of CVD and conversion to type 2 diabetes mellitus. Interventions that may prevent or delay such occurrences are of great clinical importance.

❖ METHODS

We conducted a randomized, double-blind, placebo-controlled study to examine whether pioglitazone can reduce the risk of type 2 diabetes mellitus in adults with **IGT**. A total of 602 patients were randomly assigned to receive pioglitazone or placebo. The median follow-up period was 2.4 years. Fasting glucose was measured quarterly, and oral glucose tolerance tests were performed annually. Conversion to diabetes was confirmed on the basis of the results of repeat testing.

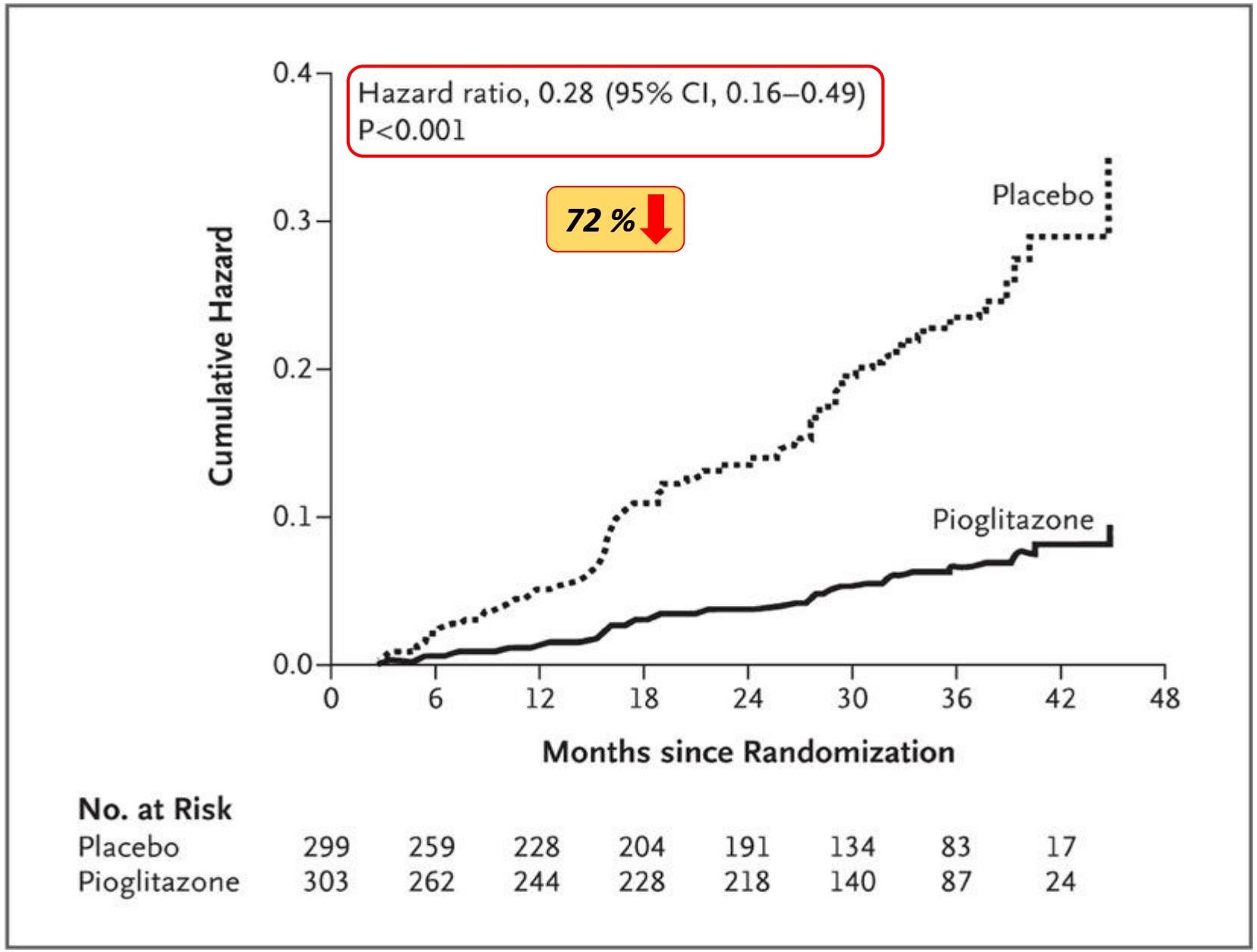


Figure 2.
Kaplan–Meier Plot of Hazard Ratios for Time to Development of Diabetes.

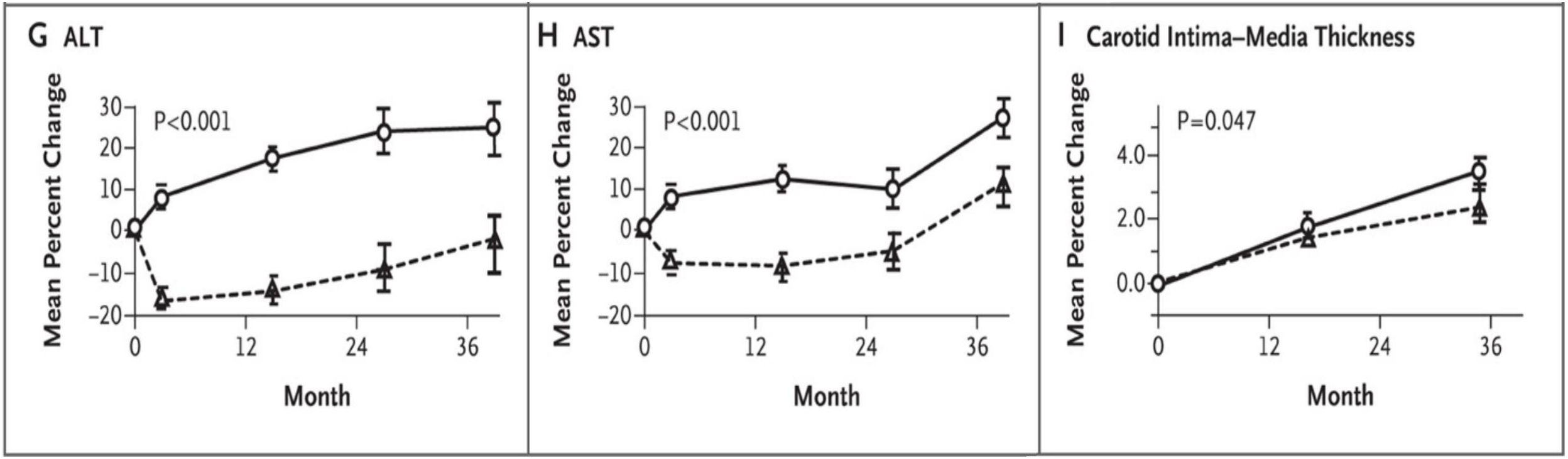


Figure 4. Effects of Pioglitazone as Compared with Placebo.

Over the course of the study, mean percentage changes and standard errors in continuous measures were calculated with the use of a linear, mixed-repeated-measures model fit to all available data for each measure. As compared with placebo, treatment with pioglitazone (dashed lines) had beneficial effects on fasting plasma glucose levels (Panel A), 2-hour plasma glucose levels (Panel B), and HbA1c levels (Panel C) and on systolic and diastolic blood pressure (Panels E and F, respectively), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (Panels G and H, respectively), and carotid intima–media thickness (Panel I). Weight gain was greater with pioglitazone than with placebo (Panel D).

Table 2. Number and Type of Adverse Events.*

Adverse Event	Pioglitazone (N = 303)	Placebo (N = 299)
	no. of events	
Cancer	3	8
Cardiovascular system	26	23
Central nervous system	6	5
Death	3	1
Digestive system	13	12
Edema†	39	19
Elective surgery	22	16
Endocrine system	1	3
Immune system	2	4
Musculoskeletal system	12	13
Ophthalmologic system	0	1
Respiratory system	9	6
Reproductive system	4	4
Skin	6	3
Urogenital system	5	3
Weight gain‡	205	128
Total	356	249

* For the comparison of placebo and pioglitazone regarding frequency of edema, cardiovascular events, and total events, P = 0.007, P = 0.80, and P = 0.03, respectively. The total number of adverse events — excluding edema — did not differ significantly between groups (P = 0.52).
† Edema was defined as an increase above baseline by two or more grades on one or more distinct study visits.
‡ Weight gain was defined as a gain of more than 1 kg.

Conclusion

Treatment with pioglitazone in patients with IGT reduced the risk of diabetes, although pioglitazone was associated with significant weight gain and edema. Use of pioglitazone improved DBP, HDL-C and serum levels of ALT and AST, and it slowed progression of carotid intima–media thickening. The influence of these effects on long-term diabetic complications remains to be determined.

NNT for prevention of diabetes:

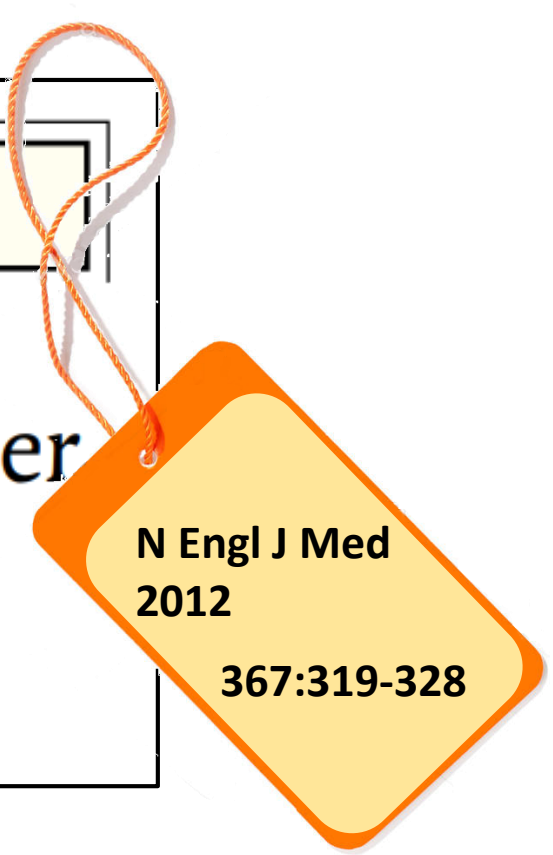
1/18 among IGT cases for 2.4 years follow up

Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med. 2011 Mar

ORIGINAL ARTICLE

Basal Insulin and Cardiovascular and Other Outcomes in Dysglycemia

The ORIGIN Trial Investigators*



❖ Background

The provision of sufficient basal insulin to normalize fasting plasma glucose levels may reduce cardiovascular events, but such a possibility has not been formally tested.

❖ Methods

- We randomly assigned 12,537 people (mean age, 63.5 years) with CVD risk factors plus IFG, IGT, or type 2 diabetes to receive insulin glargine (with a target FBS ≤95 mg per deciliter) or standard care and to receive n–3 fatty acids or placebo with the use of a 2-by-2 factorial design.
- The median follow-up was 6.2 years (interquartile range, 5.8 to 6.7).

Main Findings

- When persons without diabetes after the first OGTT underwent a second test a median of 100 days after insulin was stopped, additional cases of diabetes were detected in both groups (i.e., 30% and 35% with diabetes, on the basis of OGTT performed in 44% and 47% of eligible participants, respectively; odds ratio, 0.80; 95% CI, 0.64 to 1.00; P=0.05).
- Moreover, when cases of diabetes that could not be confirmed by the predefined adjudication criteria (i.e., uncertain diabetes) were added to those that met the adjudication criteria after both OGTT, the incidence of diabetes was reduced by 31% (i.e., 35% vs. 43%; odds ratio, 0.69; 95% CI, 0.56 to 0.86; P=0.001).

Conclusion

In summary, therapy with basal insulin glargine for more than 6 years had a neutral effect on cardiovascular outcomes and cancers.

Moreover, this therapy maintained near-normal glycemic control and slowed progression of dysglycemia, but it was associated with a modest increase in hypoglycemic episodes and in weight.

Long-term Effects of Lifestyle Intervention or Metformin on Diabetes Development and Microvascular Complications: the DPP Outcomes Study

Diabetes Prevention Program Research Group*, D. M. Nathan, M.D.[1] [(Chair)], E. Barrett-Connor, M.D.[2], J.P. Crandall, M.D.[3], S. L. Edelstein, Sc.M.[4], R.B. Goldberg, M.D.[5], E. S. Horton, M.D.[6], W.C. Knowler, M.D., Dr.P.H.[7], K. J. Mather, M.D.[8], T. J. Orchard, M.D.[9], X. Pi-Sunyer, M.D.[10], D. Schade, M.D.[11], and M. Temprosa, Ph.D.[4]

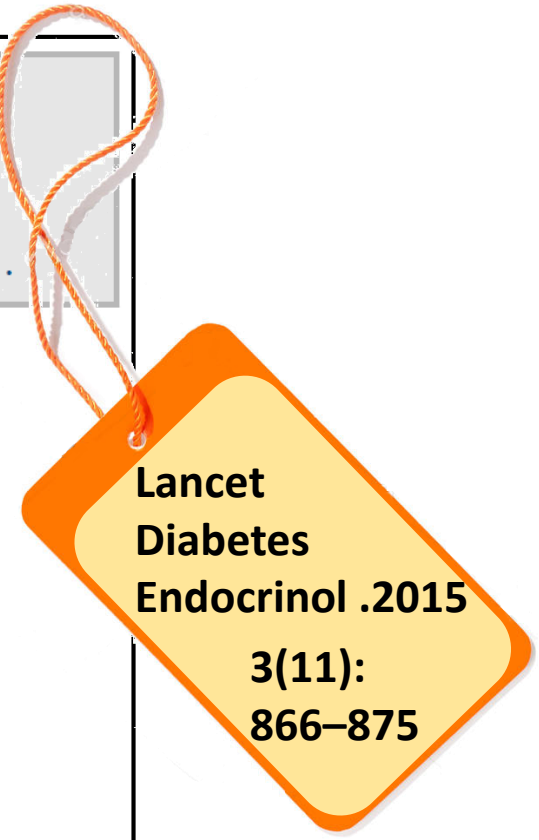
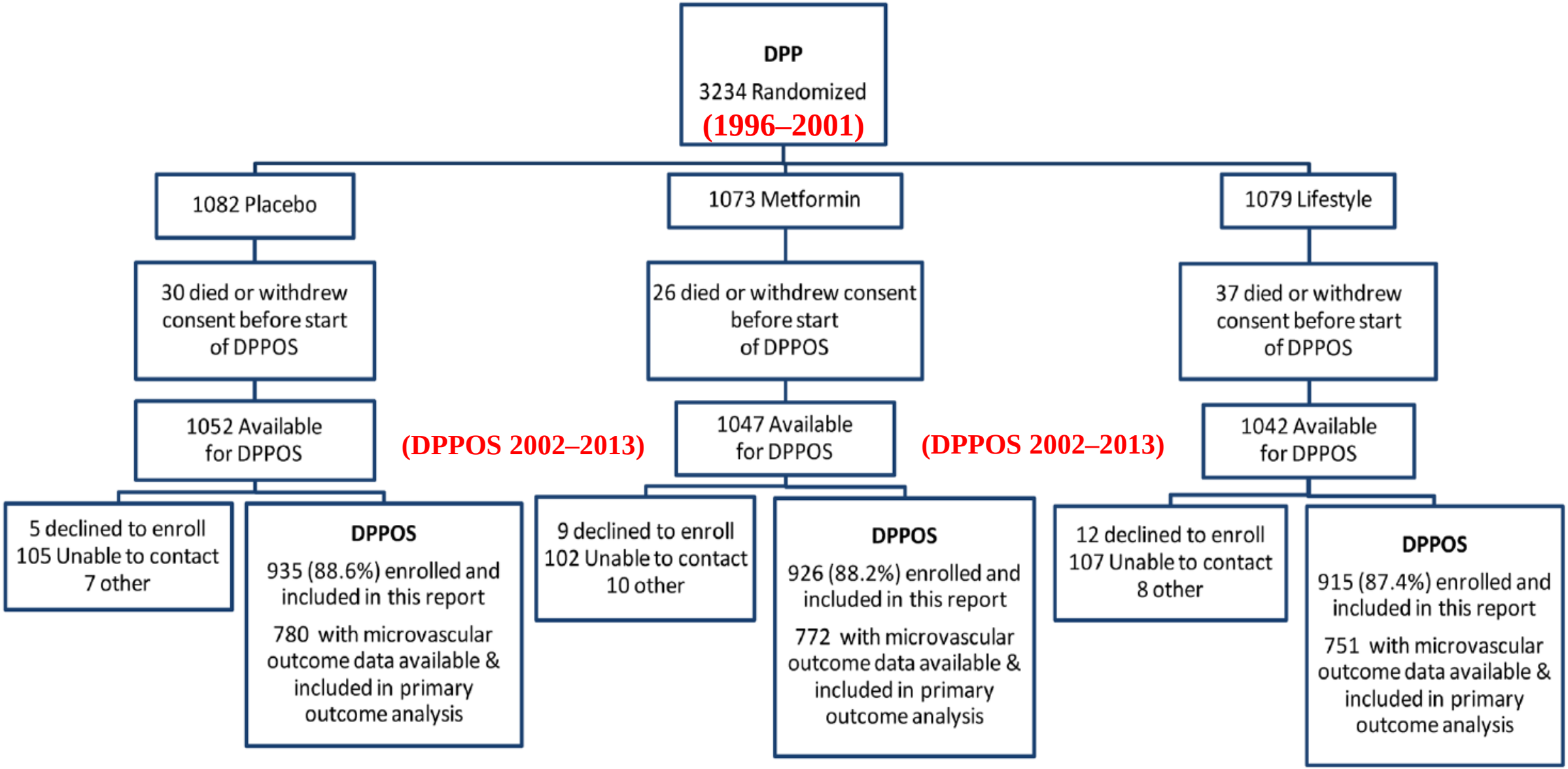


Figure 2: **Diabetes Prevention Program Outcomes Study consort diagram.**



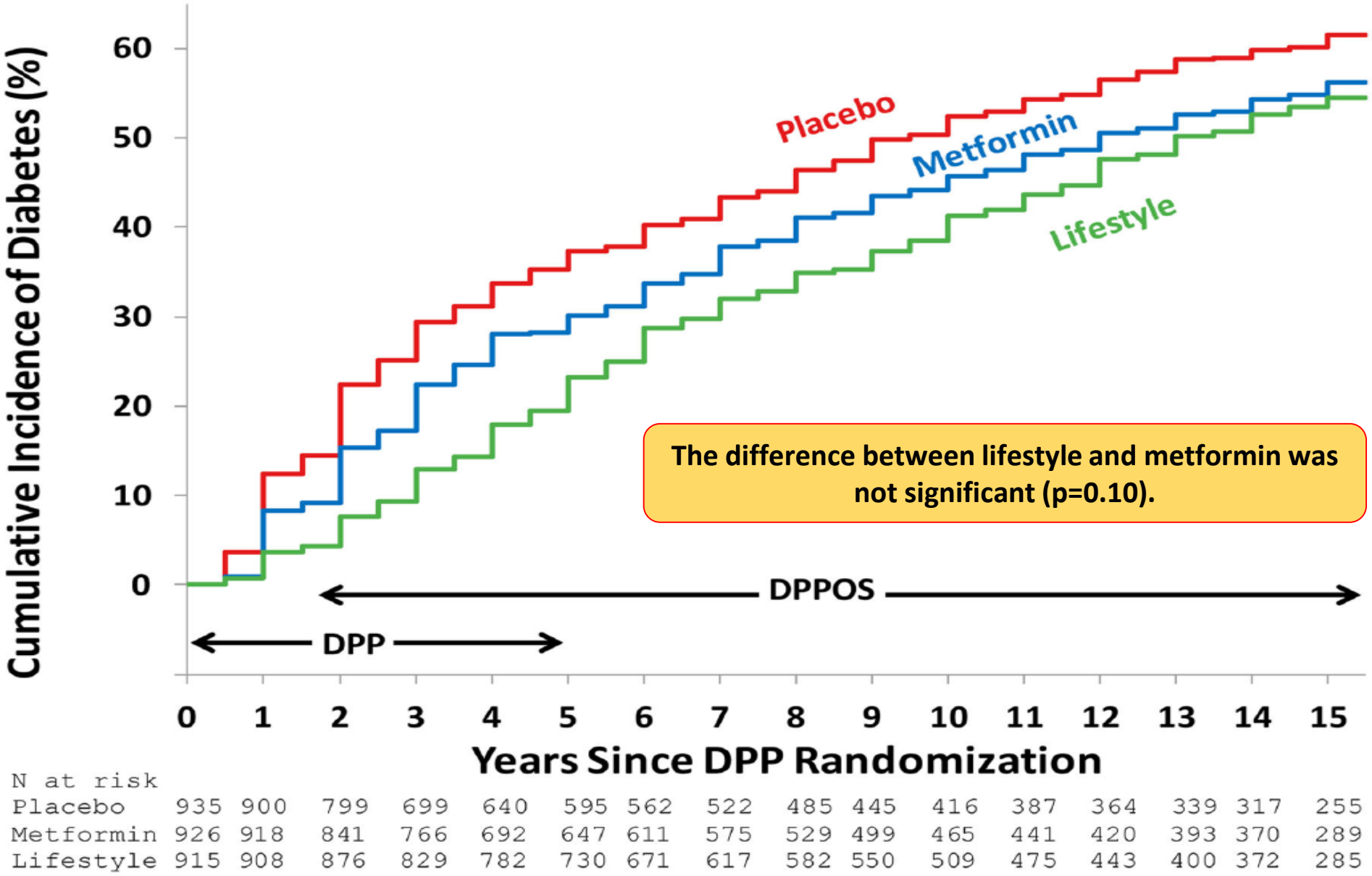


Figure 2:
Cumulative incidence of diabetes by treatment group among the 2776 DPPOS participants. The DPP and DPPOS periods, and the overlap between them, are indicated.

Over the entire study, the incidence rates for participants were 7.0%, 5.7% and 5.2% per year for placebo, metformin and lifestyle, respectively,

Articles

3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial

*Carel W le Roux, Arne Astrup, Ken Fujioka, Frank Greenway, David C W Lau, Luc Van Gaal, Rafael Violante Ortiz, John P H Wilding, Trine V Skjøth, Linda Shapiro Manning, Xavier Pi-Sunyer, for the SCALE Obesity and Prediabetes NN8022-1839 Study Group**

Lancet
2017 Apr8
389(10077): 1399-1409

❖ Background

Liraglutide 3·0 mg was shown to reduce bodyweight and improve glucose metabolism after the 56-week period of this trial, one of four trials in the SCALE programme. In the 3-year assessment of the SCALE Obesity and Prediabetes trial we aimed to evaluate the proportion of individuals with prediabetes who were diagnosed with type 2 diabetes.

❖ Methods

In this randomised, double-blind, placebo-controlled trial, adults with prediabetes and a **BMI of at least 30 kg/m2, or at least 27 kg/m2 with comorbidities**, were randomised 2:1, using a telephone or web-based system, to once-daily subcutaneous liraglutide 3·0 mg or matched placebo, as an adjunct to a reduced-calorie diet and increased physical activity. Time to diabetes onset by 160 weeks was the primary outcome, evaluated in all randomised treated individuals with at least one post-baseline assessment.

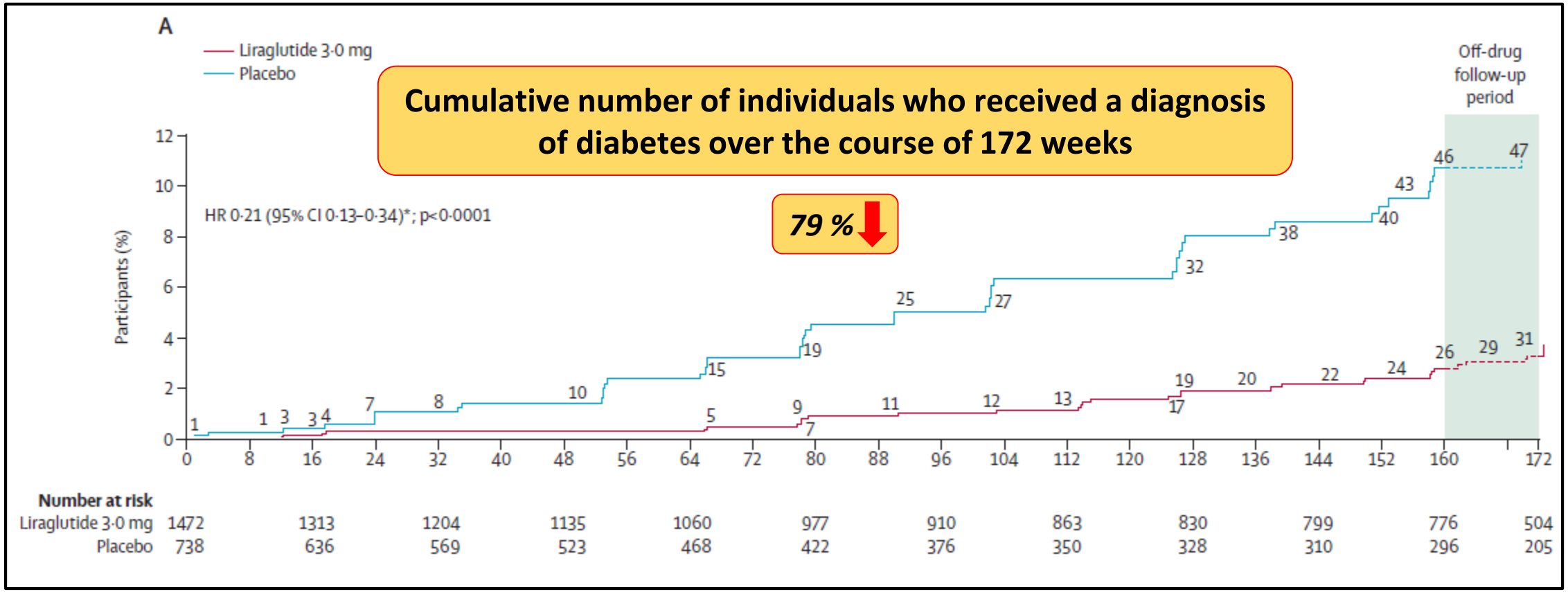


Figure 2: Liraglutide 3·0 mg and glycaemic status

LOCF=last-observation-carried-forward. OR=odds ratio. *Derived from the primary Weibull analysis. **(A)** Kaplan-Meier estimates of the proportion of participants who received a diagnosis of type 2 diabetes during the course of the trial. Glycaemic status was defined according to American Diabetes Association 2010 criteria.17 All individuals for whom diabetes was diagnosed had prediabetes at screening, except for one in the placebo group, who had normoglycaemia. The numbers along the graph lines show the cumulative number of individuals who received a diagnosis of diabetes over the course of 172 weeks. The time until 1% were diagnosed with diabetes was 90 weeks with liraglutide 3·0 mg and 24 weeks with placebo (post-hoc analysis). Participants were off treatment during the 12-week observational follow-up period, but still on diet and exercise.

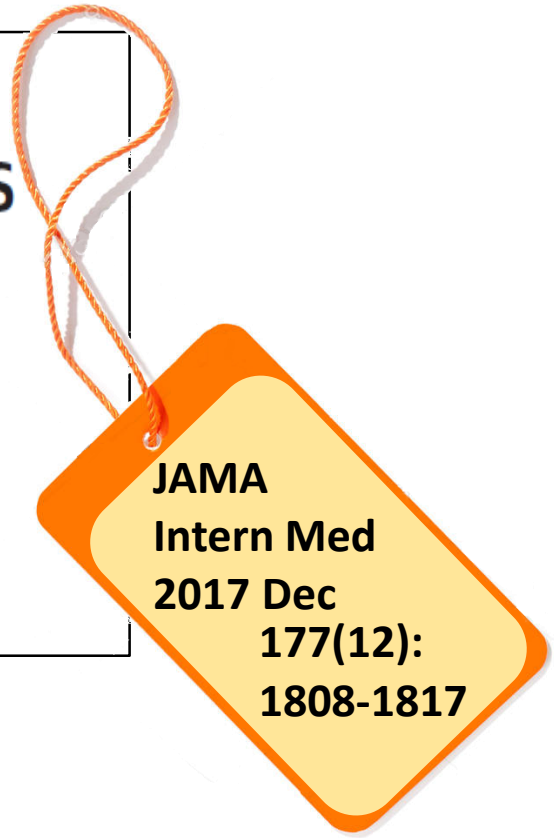
However !

The need for daily injections and high cost are key limitations of liraglutide for longterm weight management and T2D prevention. Therefore, other interventions that could promote LTWL are needed.

3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet. 2017

Long-term Sustainability of Diabetes Prevention Approaches
A Systematic Review and Meta-analysis of Randomized Clinical Trials

J. Sonya Haw, MD; Karla I. Galaviz, PhD; Audrey N. Straus, MSN; Alysse J. Kowalski, MPH; Matthew J. Magee, PhD; Mary Beth Weber, PhD; Jingkai Wei, MPH; K. M. Venkat Narayan, MD; Mohammed K. Ali, MD



❖ **Importance**

Diabetes prevention is imperative to slow worldwide growth of diabetes-related morbidity and mortality. Yet the long-term efficacy of prevention strategies remains unknown.

❖ **Objective**

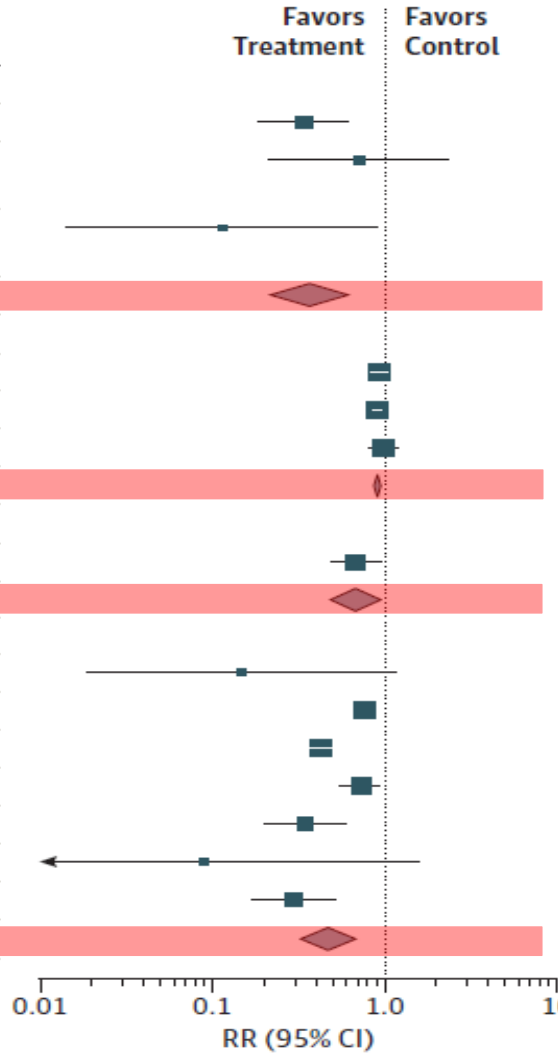
To estimate aggregate long-term effects of different diabetes prevention strategies on diabetes incidence.

❖ **Data Sources**

Systematic searches of MEDLINE, EMBASE, Cochrane Library, and Web of Science databases. The initial search was conducted on January 14, 2014, and was updated on February 20, 2015. Search terms included prediabetes, primary prevention, and risk reduction.

Figure 3. Relative Risks (RRs) and Diabetes Incidence Rates Among Medication Studies Stratified by Drug Class at the End of the Active Intervention Period

Source	Drug	Incidence per Person-year		Diabetes Cases, No.		RR (95% CI)
		Treatment	Control	Treatment	Control	
Weight loss						
XENDOS,[55] 2004	Orlistat	0.21	1.0	14.0	41	0.34 (0.19-0.62)
SEQUEL,[56] 2014	Phentermine-topiramate ER (7.5/46 mg)	2.40	3.4	4.0	7	0.71 (0.21-2.34)
SEQUEL,[56] 2014[a]	Phentermine-topiramate ER (15/92 mg)	0.40	3.4	1.0	7	0.11 (0.01-0.91)
Subgroup RR						0.37 (0.22-0.62)
RAS blockade						
DREAM,[57] 2006	Ramipril	6.00	6.0	449.0	489	0.93 (0.82-1.04)
NAVIGATOR,[58] 2010	Valsartan	6.60	7.4	1532.0	1722	0.90 (0.85-0.95)
TRANSCEND,[59] 2011	Telmisartan	4.30	4.4	157.0	165	0.98 (0.81-1.19)
Subgroup RR						0.91 (0.86-0.95)
Lipid lowering						
BIP,[60] 2005	Bezafibrate	4.00	6.0	42.0	56	0.68 (0.48-0.95)
Subgroup RR						0.68 (0.48-0.95)
Insulin sensitizers						
Li et al,[61] 1999	Metformin	3.00	18.0	1.0	6	0.15 (0.02-1.17)
DPP,[33] 2002	Metformin	7.80	11.0	236.0	313	0.76 (0.66-0.88)
DREAM,[72] 2006	Rosiglitazone	4.00	8.0	280.0	658	0.43 (0.37-0.48)
IDPP,[44] 2006	Metformin	16.00	22.0	51.0	73	0.73 (0.56-0.94)
CANOE,[62] 2010	Metformin plus rosiglitazone	3.00	10.0	14.0	41	0.34 (0.20-0.59)
Lu et al,[63] 2011	Metformin	0.50	6.1	0.5	5	0.09 (0.01-1.58)
ACT NOW,[64] 2011	Pioglitazone	2.10	7.6	15.0	50	0.30 (0.17-0.52)
Subgroup RR						0.47 (0.32-0.68)



63%

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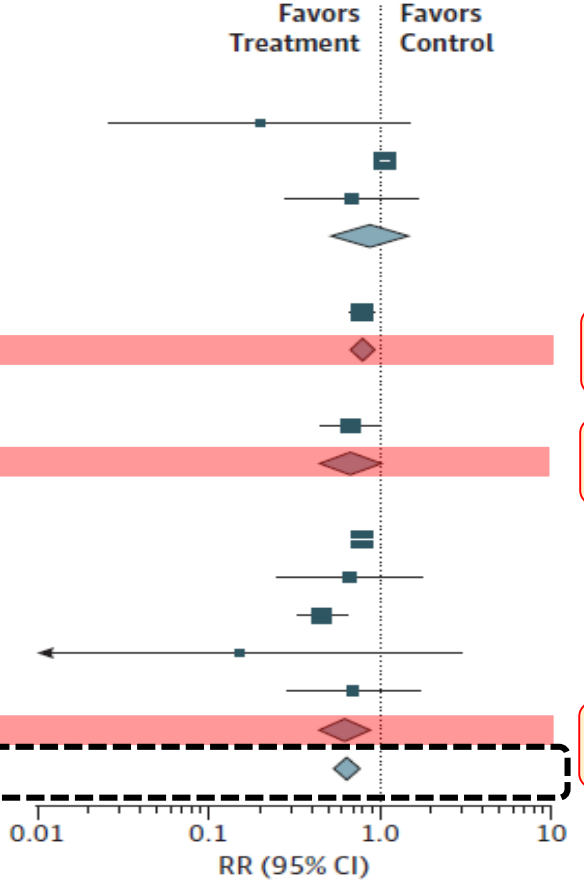
Figure 3. Relative Risks (RRs) and Diabetes Incidence Rates Among Medication Studies Stratified by Drug Class at the End of the Active Intervention Period

Source	Drug	Incidence per Person-year		Diabetes Cases, No.		RR (95% CI)
		Treatment	Control	Treatment	Control	
Insulin secretagogues						
Eriksson et al,[65] 2006	Glipizide	4.0	20.0	1.0	5	0.20 (0.03-1.53)
NAVIGATOR,[73] 2010	Nateglinide	7.2	6.8	1674.0	1580	1.06 (1.01-1.12)
DIANA,[66] 2012	Nateglinide	12.0	17.0	7.0	10	0.69 (0.28-1.68)
Subgroup RR						0.87 (0.52-1.46)
Insulin						
ORIGIN,[67] 2012	Insulin glargine	2.0	3.0	182.0	224	0.79 (0.67-0.94)
Subgroup RR						0.79 (0.67-0.94)
Hormone therapy						
HERS,[68] 2003	Estrogen/progestin	6.0	9.0	24.0	46	0.68 (0.45-1.02)
Subgroup RR						0.68 (0.45-1.02)
Alpha-glucosidase inhibitors						
STOP-NIDDM,[69] 2002	Acarbose	10.0	13	221.0	285	0.78 (0.68-0.90)
DAISI,[70] 2008	Acarbose	6.0	8.0	5.0	9	0.67 (0.25-1.78)
Kawamori et al,[71] 2009	Voglibose	2.0	4.0	50.0	106	0.46 (0.34-0.64)
Lu et al,[63] 2011[a]	Acarbose	0.3	4.7	0.5	3	0.15 (0.01-2.97)
DIANA,[66] 2012[a]	Voglibose	12.0	17.0	7.0	10	0.70 (0.29-1.71)
Subgroup RR						0.62 (0.44-0.88)
Overall RR						0.64 (0.54-0.76)



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Twenty-one studies including 24 comparisons were analyzed. Active treatment mean (S… l RR is the pooled effect for all studies; subgroup RR is the pooled effect for a subgroup of studies. ACE indicates angiotensin-converting enzyme; ACT NOW, Actos Now for Prevention … ANOE, Canadian Normoglycemia Outcomes Evaluation; DAISI, Dutch Acarbose Intervention Study in Persons With Impaired Glucose Tolerance; DIANA, Diabetes and Diffuse Coro… M, Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication; ER, extended release; HERS, Heart and Estrogen/progestin Replacement Study; IDPP, Indian Diabete… lsartan in Impaired Glucose Tolerance Outcomes Research; ORIGIN, Outcome Reduction With Initial Glargine Intervention; RAS, renin-angiotensin system; STOP-NIDDM, Study to Pr… SCEND, Telmisartan Randomised Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease; and XENDOS, Xenical in the Prevention of Diabetes in Obese Subjects.

Efficacy of Medication Interventions

- During the active intervention period (mean [SD], 3.1 [1.5] years; range, 1.0-6.3 years), medication trials (n = 21; 18 medication and 3 LSM plus medication trials) achieved an RR reduction of **36% (RR, 0.64; 95% CI, 0.54-0.76).**
- Diabetes incidence rates in intervention participants were 5.4 cases per 100 person-years compared with 9.4 cases per 100 person-years in control participants (RD, 4.0; 95% CI, 2.3-5.7).

NNT for prevention of diabetes:

1/25 for 3 years follow up

Long-term Sustainability of Diabetes Prevention Approaches: A Systematic Review and Meta-analysis of Randomized Clinical Trials. JAMA Intern Med.2017

Table. Random-Effects Meta-analyses Exploring RR for Diabetes Among LSM and Medication Studies After Treatment Withdrawal

Source	Intervention	Active Intervention, y	End of Active Intervention, RR (95% CI)	Follow-up[a]	End of Follow-up, RR (95% CI)
LSM Trials					
Swinburn et al,[40] 2001	Reduced-fat diet	1.0	0.76 (0.25-2.34)	5.0 y	0.70 (0.26-1.88)
DPP,[33,34] 2002, 2009[b]	Diet and physical activity	2.8	0.48 (0.41-0.58)	5.7 y	0.68 (0.63-0.73)
DPS,[35,36] 2001, 2013	Diet and physical activity	4.0	0.44 (0.29-0.68)	9.0 y	0.63 (0.54-0.73)
Da Qing,[37,38] 1997, 2008	Diet and physical activity	6.0	0.68 (0.54-0.85)	9.4 y	0.86 (0.81-0.92)
Pooled estimate			0.55 (0.43-0.70)		0.72 (0.60-0.86)
Medication Trials					
Eriksson et al,[65] 2006	Glipizide	0.5	0.41 (0.01-11.3)	52 wk	0.20 (0.03-1.53)
DREAM,[22,72] 2006, 2011	Rosiglitazone	3.0	0.43 (0.37-0.48)	10 wk	1.07 (0.88-1.32)
DREAM,[22,57] 2006, 2011[b]	Ramipril	3.0	0.93 (0.82-1.04)	10 wk	1.08 (0.89-1.33)
DPP,[21,33] 2002, 2003	Metformin	2.8	0.76 (0.66-0.88)	2 wk	0.76 (0.68-0.85)
STOP-NIDDM,[69] 2002	Acarbose	3.0	0.78 (0.68-0.90)	12 wk	1.46 (0.90-2.36)
ORIGIN,[67] 2012	Insulin glargine	6.2	0.79 (0.67-0.94)	14 wk	0.86 (0.74-0.99)
Pooled estimate			0.71 (0.55-0.92)		0.95 (0.79-1.14)

The mean observation periods for washouts across these studies was **17 weeks**. Compared with those receiving placebo, participants receiving the study drug had a 29% lower diabetes risk at the end of the active intervention, while no significant RR reductions were observed at the end of the washout period.

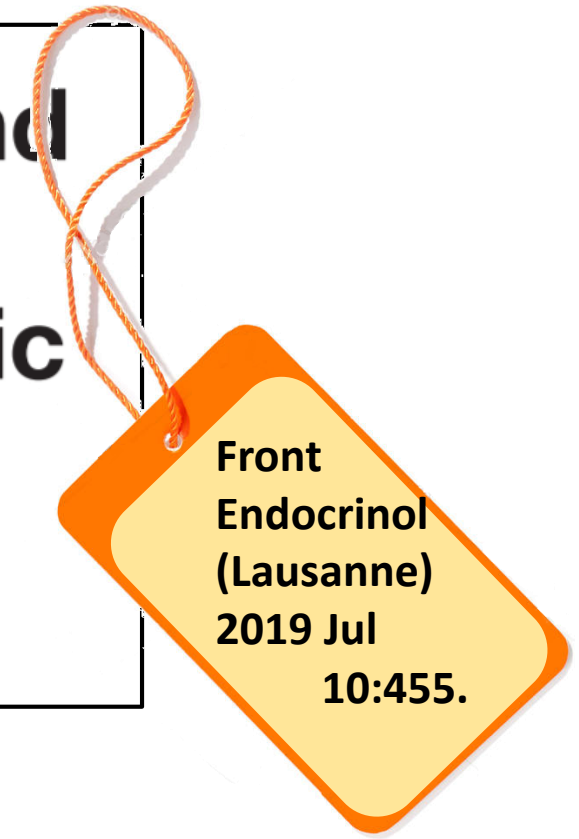
We found that participants receiving LSM interventions had lower risk for diabetes than control participants 5 to 9 years after completing the intervention, although the effects decreased over time.

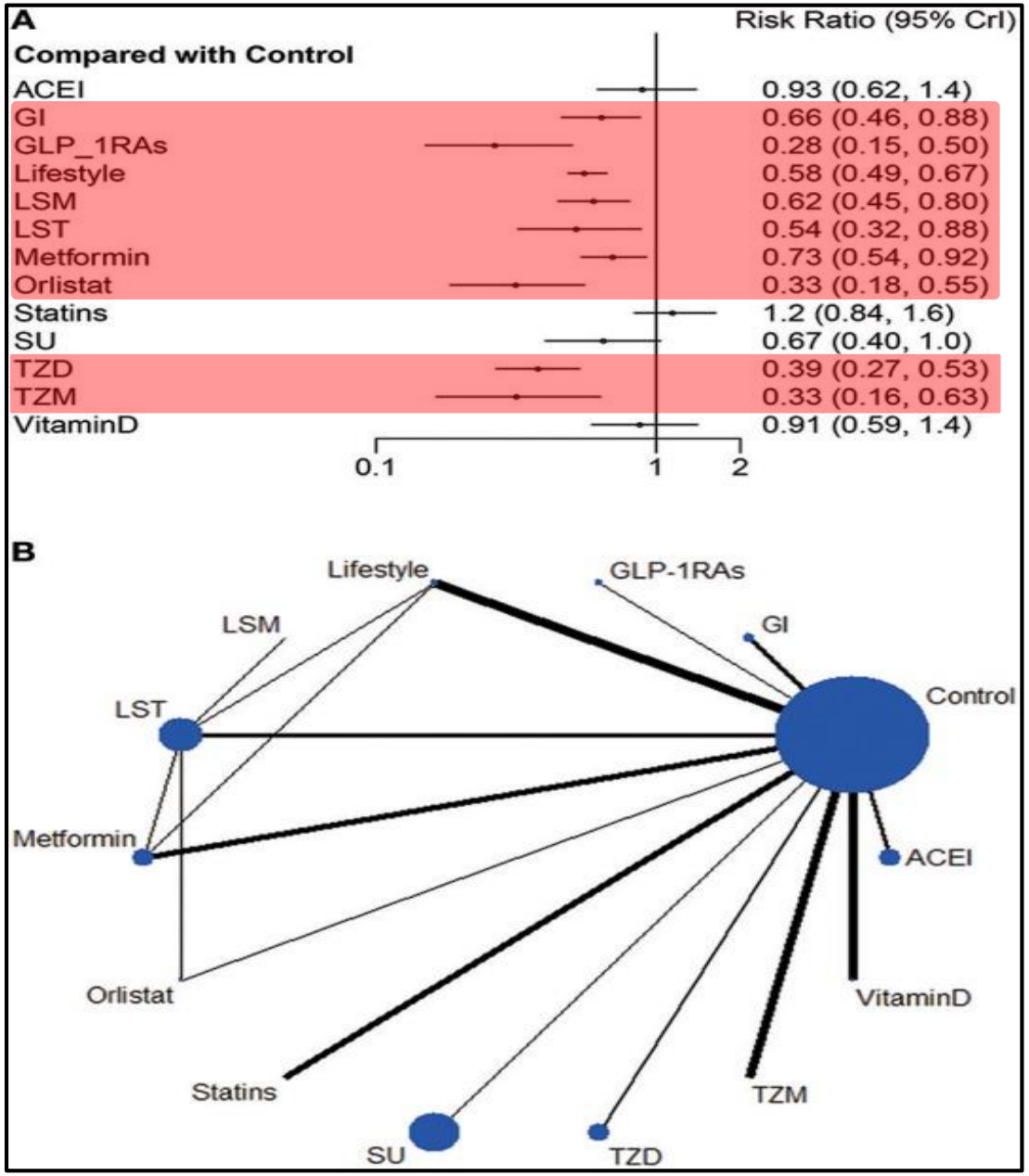
Heterogeneity and Study Quality

- Studies were heterogeneous, leading to a high proportion of variability between study effects.
- In a multivariate meta-regression, amount of weight lost, participant mean age, and proportion of male participants accounted for 59% of the heterogeneity ($P < .01$).
- In which every kilogram lost explained an additional 7% decrease in diabetes relative risk

Effects of Lifestyle Modification and Anti-diabetic Medicine on Prediabetes Progress: A Systematic Review and Meta-Analysis

*Zhi Sheng[1], Jia-Yu Cao[1], Ying-Chang Pang[1], Hang-Cheng Xu[1], Jing-Wen Chen[1], Jun-Hua Yuan[2], Rui Wang[2], Cai-Shun Zhang[2], Liu-Xin Wang[2] and Jing Dong[2,3]**





(A) Relative risk ratio and 95% credible interval of strategy interventions compared to control group in Bayesian random effect model of network meta-analysis.

(B) Network plot: Weight the nodes according to the number of patients that have received each treatment; calculate the control group risk for studies including the control and weight the edges according to the mean control group risk for all comparisons vs. control.

- Compared to placebo, GLP-1RAs ***72%*** ↓ , TZD Plus Metformin ***67%*** ↓ and TZD ***61%*** ↓ significantly delayed the progression of diabetes; however, the limited sample size and the small quantity of studies caused instability of this inference.
- The data of both GLP-1RAs and orlistat were captured from severely obese people (mean BMI = 39 and 37 respectively), contributing to potential inconsistency. **Metformin is less effective in people with lower baseline BMIs or lower FPG concentrations than in those with higher values for these variables**; the drug works by inhibiting endogenous glucose production.
- It was suggested that the differences in insulin sensitivity and insulin secretion between IGT and IFG, and the greater severity of the abnormalities when both coexist might predict different rates of progression to diabetes, and different pharmacological agents might be needed to treat the pathophysiology.
- Therefore, more relevant trials are needed to reinforce or further complement this review, especially for endpoints of clinical complications, such as cardiovascular events/death and data on cost-effectiveness.

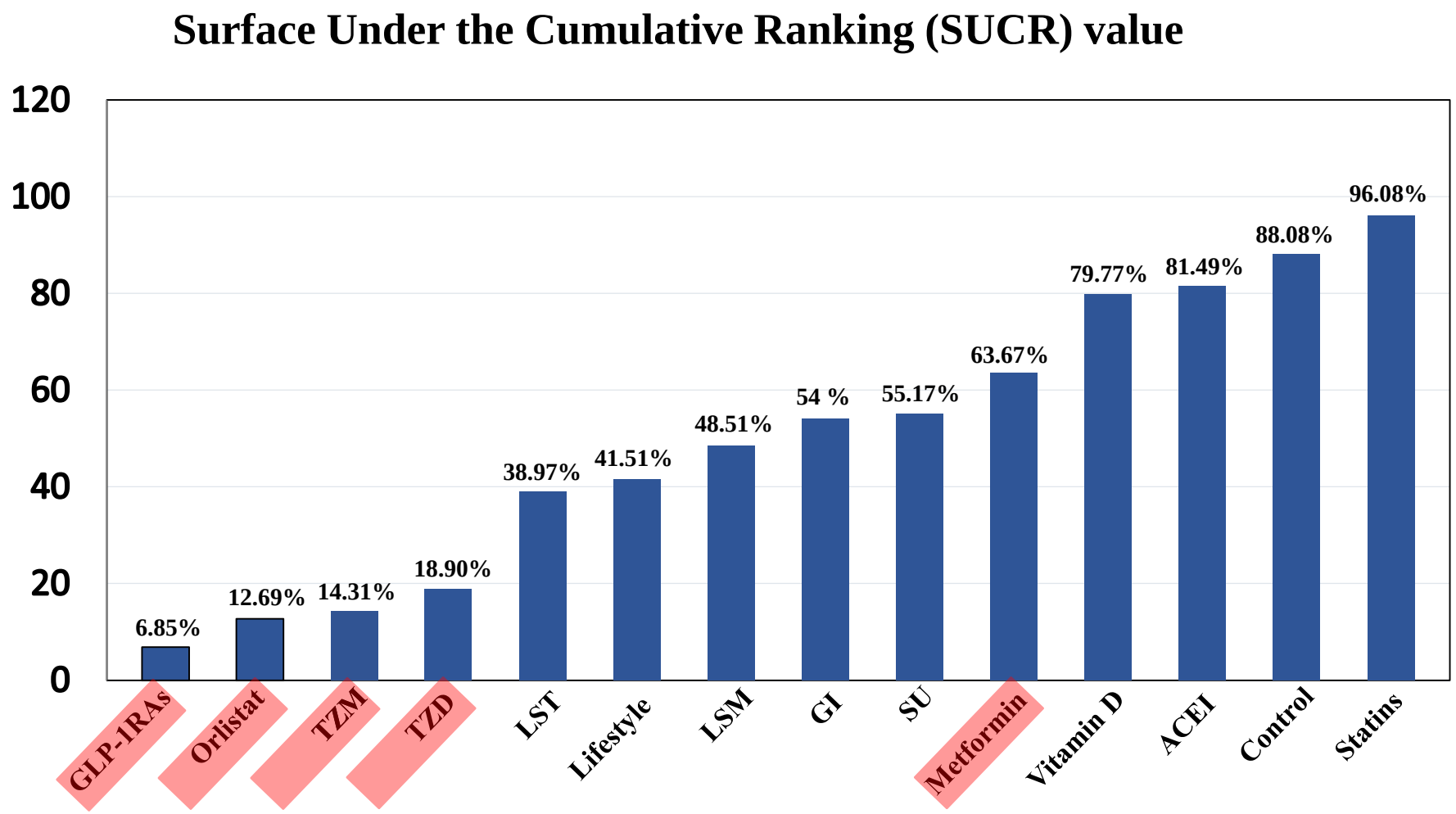


Figure 3

SUCRA Value of Diabetic Incidence. We ranked all fourteen intervention strategies based on their probabilities of prediabetes leading to diabetes and calculated SUCRA to obtain a more precise sorted consequence. The lower the SUCRA value, the more likely this measure is to prevent the progression of the diabetes process.

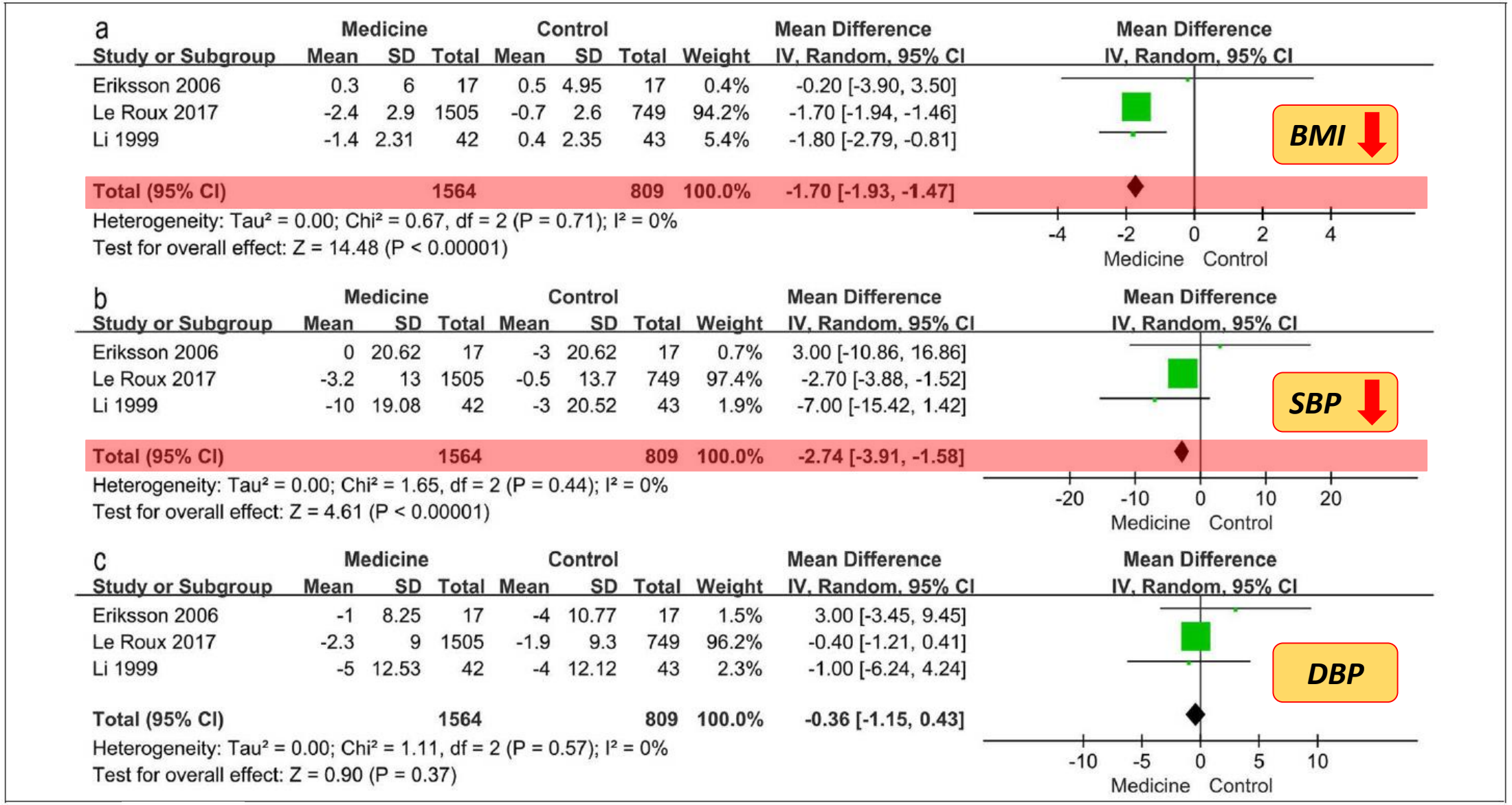


Figure 5 Traditional meta-analysis of the effect on physical conditions: Medicine vs. Control. **(a–f)** BMI (kg/m^2), systolic pressure (mmHg), diastolic pressure (mmHg), fasting blood glucose (mg/dL), 2 h postprandial blood glucose (mg/dL), total cholesterol (mmol/L, mg/dL).

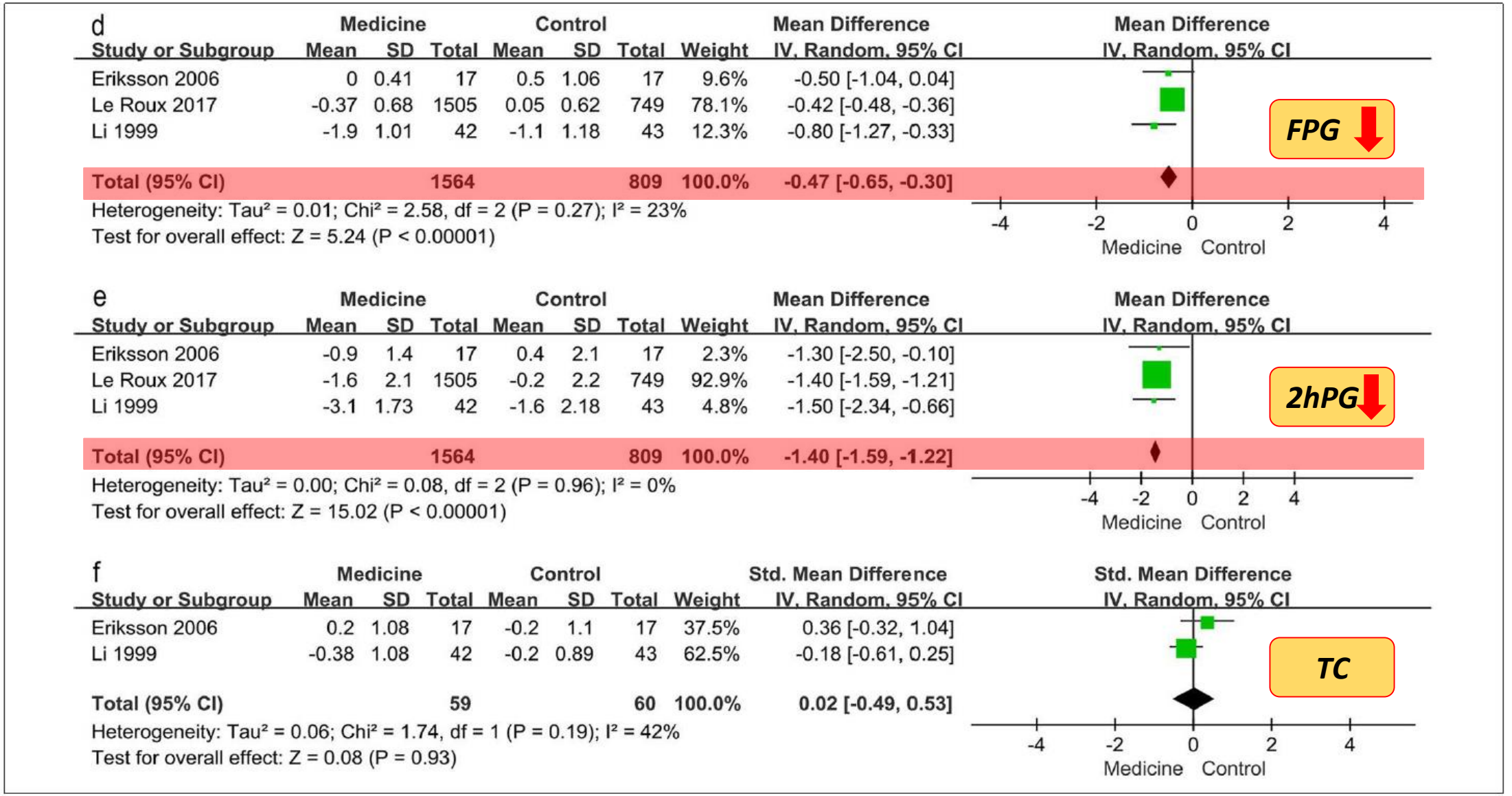
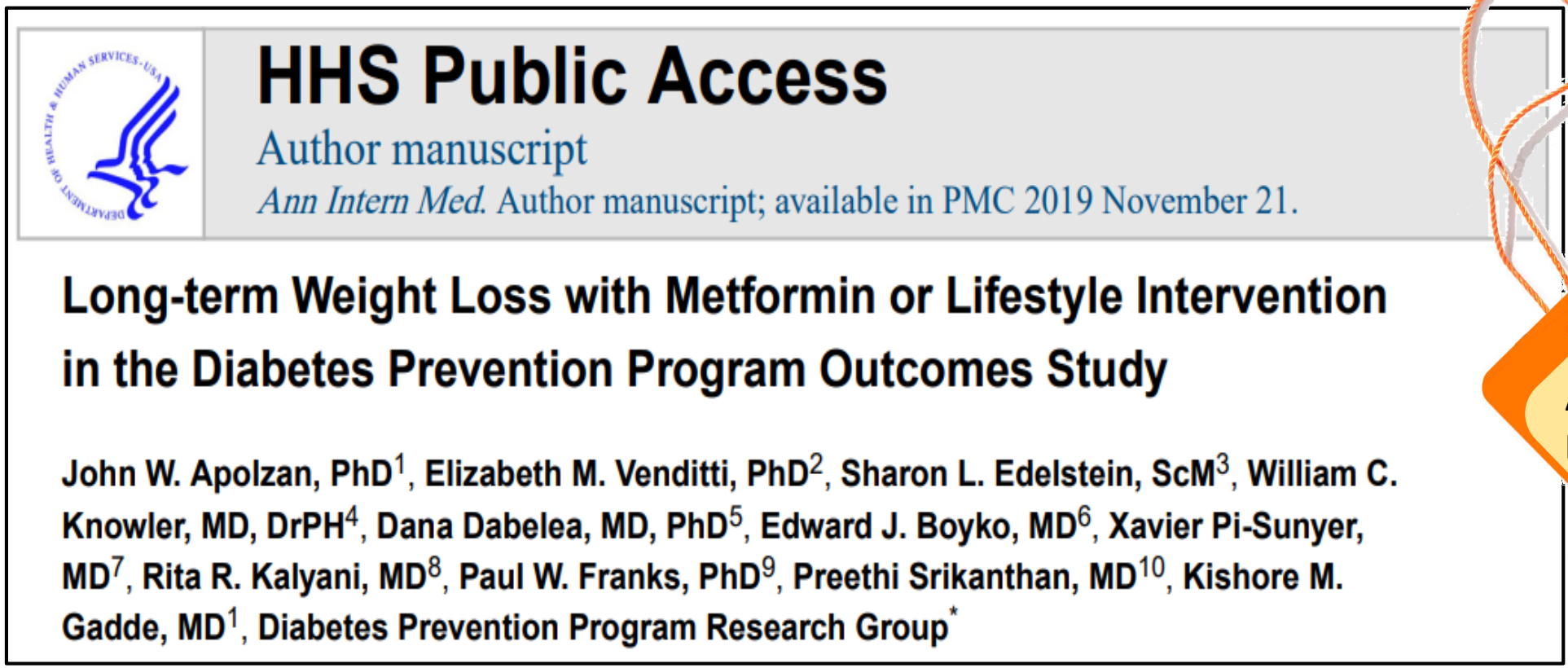


Figure 5 Traditional meta-analysis of the effect on physical conditions: Medicine vs. Control. **(a–f)** BMI (kg/m^2), systolic pressure (mmHg), diastolic pressure (mmHg), fasting blood glucose (mg/dL), 2 h postprandial blood glucose (mg/dL), total cholesterol (mmol/L, mg/dL).

Conclusion

In adults with pre-diabetes, firm evidence supports the notion that lifestyle modifications and metformin reduces the incidence of diabetes with an average of 20% relative risk reduction, while statins increase the relative risk 20%.

Effects of Lifestyle Modification and Anti-diabetic Medicine on Prediabetes Progress: A Systematic Review and Meta-Analysis. Front Endocrinol.2019



HHS Public Access

Author manuscript

Ann Intern Med. Author manuscript; available in PMC 2019 November 21.

Long-term Weight Loss with Metformin or Lifestyle Intervention in the Diabetes Prevention Program Outcomes Study

John W. Apolzan, PhD[1], Elizabeth M. Venditti, PhD[2], Sharon L. Edelstein, ScM[3], William C. Knowler, MD, DrPH[4], Dana Dabelea, MD, PhD[5], Edward J. Boyko, MD[6], Xavier Pi-Sunyer, MD[7], Rita R. Kalyani, MD[8], Paul W. Franks, PhD[9], Preethi Srikanthan, MD[10], Kishore M. Gadde, MD[1], Diabetes Prevention Program Research Group*

Ann Intern Med. 2019
170(10): 682-690

❖ **Background**

Identifying reliable predictors of long-term weight loss could lead to improved weight management.

❖ **Objective**

To identify predictors.

❖ **Design**

The DPP was a randomized controlled trial that compared weight loss using placebo, intensive lifestyle intervention, or metformin, and its Outcomes Study (DPPOS) observed patients after the masked treatment phase ended.

❖ **Participants**

Of the 3234 randomized participants, 1066 lost ≥ 5% of their baseline weight during the first year and have been followed for 15 years.

❖ Primary aims

To compare among participants who achieved clinically significant 1-year weight loss of ≥5%, differences in long-term weight loss maintenance according to originally randomized intervention group, and to examine baseline factors that predicted success in maintaining weight loss for up to 15 years.

❖ Results

- After 1 year, 28.5% metformin participants, 62.6% intensive lifestyle participants, and 13.4% placebo participants, achieved ≥ 5% weight loss.
- After the masked treatment phase ended, the mean amount of weight loss relative to baseline that was maintained between years 6 and 15 was 6.2% for metformin participants, 3.7% for intensive lifestyle participants, and 2.8% for placebo participants.

Predictors of long-term weight loss ; Metformin

For years 5,10, and 15 and overall, **only older** age at baseline (per 10 years; odds ratios [ORs], 1.74, 2.25, 2.37, and 1.74, respectively; overall P < 0.001), **greater weight loss at year 1** (per 5% loss; ORs, 2.08, 1.97, 1.14, and 1.70, respectively; overall P < 0.001), and **active use of study metformin** (use vs. nonuse; ORs, 4.83, 4.02, 2.17, and 1.91, respectively; overall P < 0.001) independently predicted LTWL.

Figure 1. Patterns of mean weight change over 15 years.

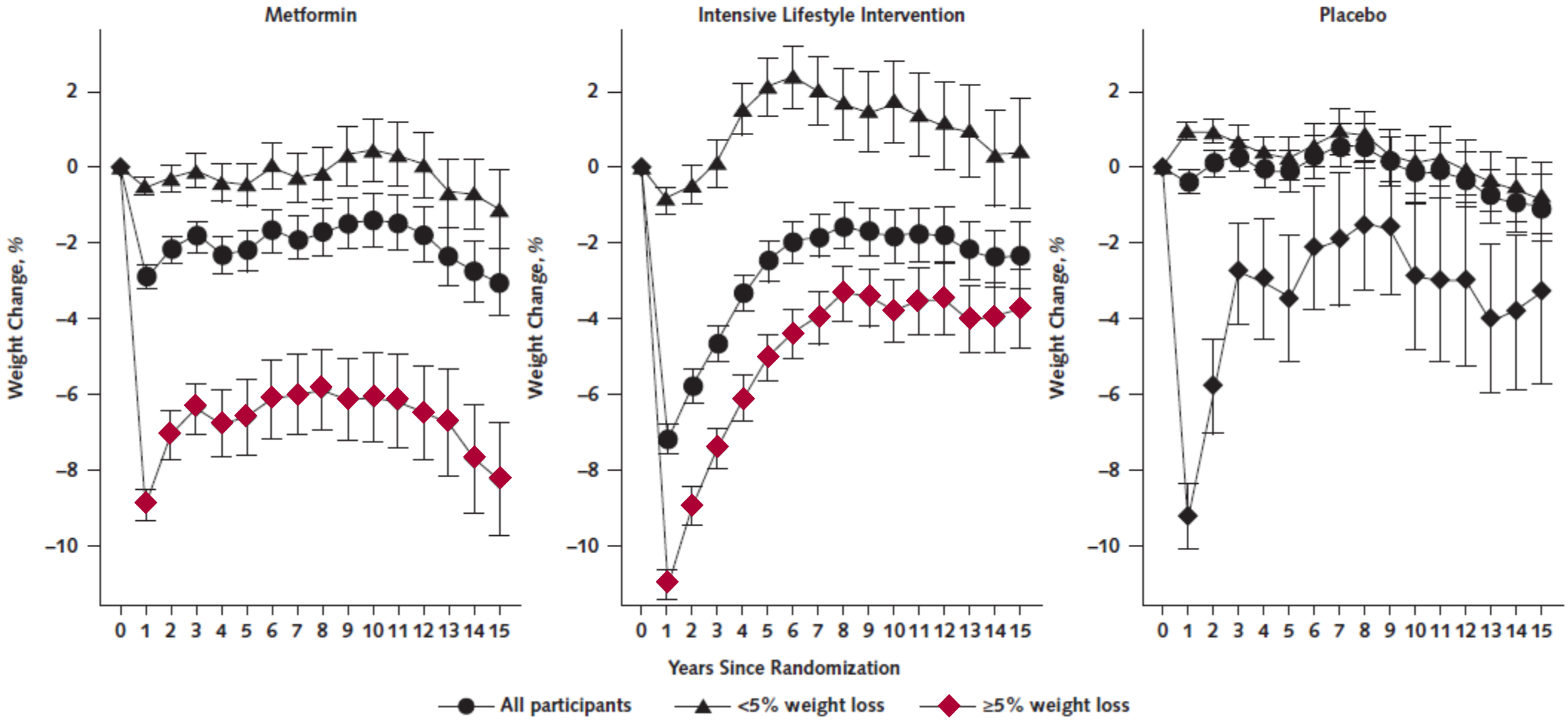
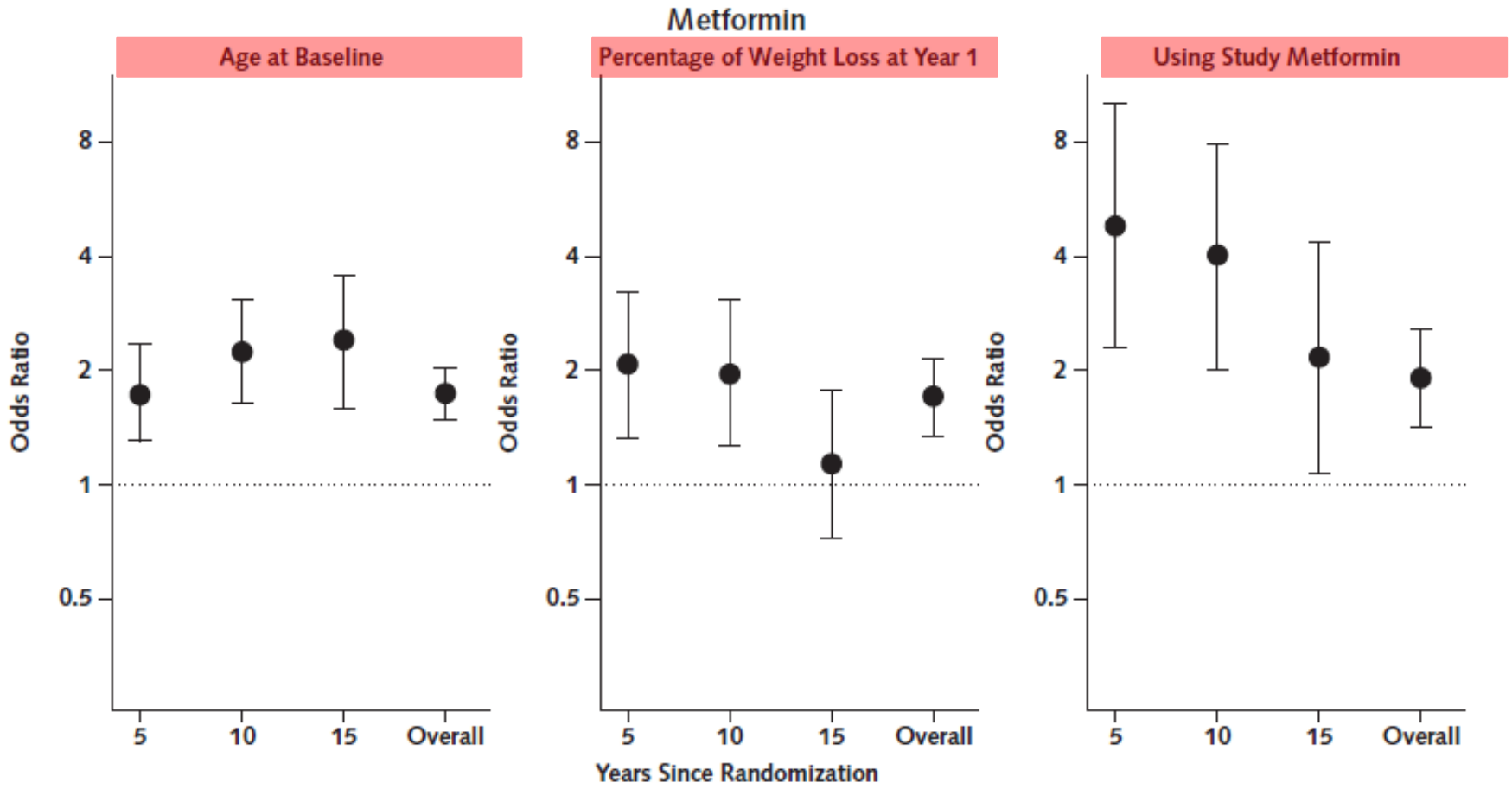


Figure 2. Predictors of long-term weight loss.



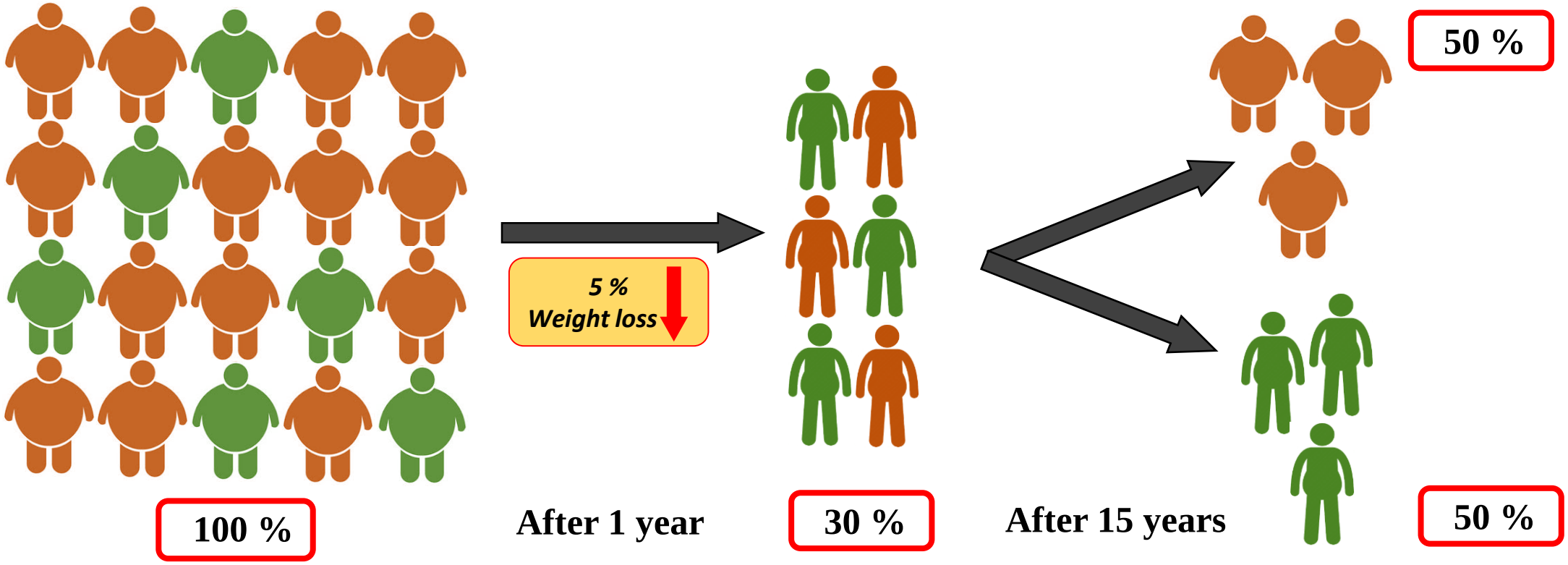
For Years 5, 10, 15 and overall, only older age at baseline (per 10 years; odds ratios [ORs] 1.74, 2.25, 2.37 and 1.74, respectively; overall p<0.001), greater Year 1 weight loss (per 5% weight loss; ORs 2.08, 1.97, 1.14 and 1.70, respectively, overall p<0.001), and active use of study-metformin (taking vs not taking metformin; ORs 4.83, 4.02, 2.17 and 1.91; overall p<0.001) independently predicted LTWL.

Conclusion

We examined body weight changes over 15 years among overweight or obese subjects at risk for T2D who enrolled in the DPP and continued in the DPPOS, and elucidated characteristics of those achieving LTWL. Our key findings are:

1) Although twice as many participants in the ILS group versus the metformin group lost at least 5% of their weight in the first year, **those who were originally assigned to metformin had greater success in maintaining LTWL**.
2) Greater 1-year weight loss predicted LTWL in all groups. Other independent predictors of LTWL were **older age and current use of metformin in the metformin group**, older age and absence of either diabetes or a family history of diabetes in the ILS group.
3) Cumulative diabetes incidence rates over 15 years were lower among those who lost at least 5% of their weight in the first year.

Metformin



Future investigations should focus on whether metformin could be a useful intervention for LTWL after initial weight loss with lifestyle interventions, antiobesity drugs or devices, or bariatric surgery.

Long-term Weight Loss with Metformin or Lifestyle Intervention in the Diabetes Prevention Program Outcomes Study. Ann Intern Med. 2019

کلام آخر؛

- شناخت صحیح پاتوفیزیولوژی اختلالات تحمل گلوکز از قند ناشتای مختل تا اختلالات تحمل گلوکز و یا حضور همزمان هر دو میتواند در مداخلات دارویی پیشگیری کننده از دیابت کمک بسزایی نماید.
- هدف نهایی در مداخلات دارویی لازم است نه تنها پیشگیری از دیابت بلکه کاهش ریسک حوادث قلبی– عرقی و مرگ و میر را نیز لحاظ نماید. البته لازم است در طی این مداخلات، هزینه درمان را مد نظر قرار داد.
- با توجه به تجربه بیش از دو دهه استفاده از داروی متفورمین و مطالعات اخیر و نقش آن در تداوم کاهش وزن، استفاده از آن در مبتلایان به اضافه وزن توام با وضعیت پیش دیابتی خصوصاً در افراد سن پایین تر و با سطوح بالاتر قند به عنوان یک مداخله مقرون به صرفه میتواند به شکل گسترده تری مدنظر قرار گیرد.