
What Is Next After Metformin?
Hanyang University Guri Hospital
Chang Beom Lee

*'Meal prayer', Van Brekelenkam 17th C*

# Introduction

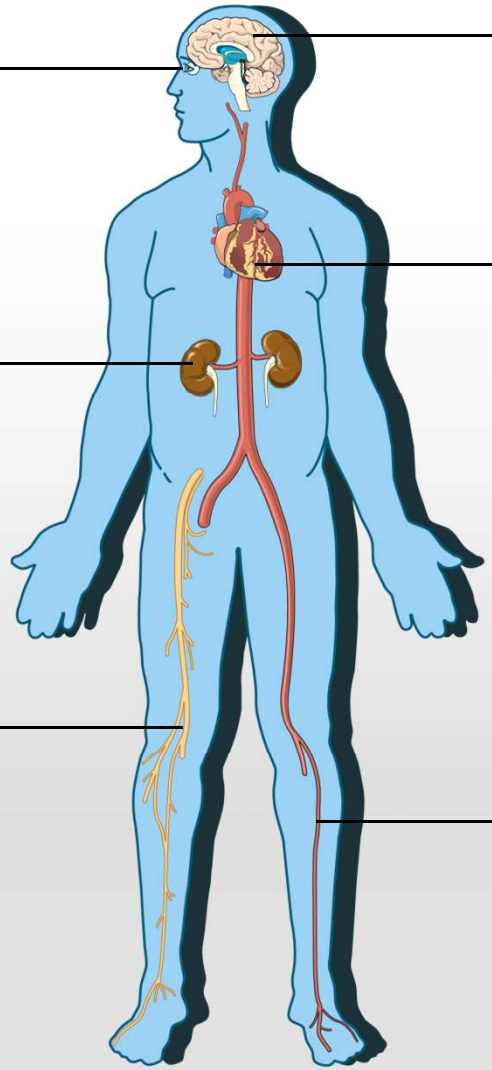
- 2012 ADA/EASD Position Statement
- Proper Patients for Pioglitazone
- β-Cell Preservation by Pioglitazone
- Benefit on CVD by Pioglitazone
- Take Home Messages

# Tissue Damage in Many Organ Systems Leads to Serious Long-Term Complications in T2DM

**Eyes**
**(retinopathy, glaucoma, cataracts)**

**Kidneys**
**(nephropathy, ESRD)**

**Peripheral Nervous System**
**(peripheral neuropathy)**



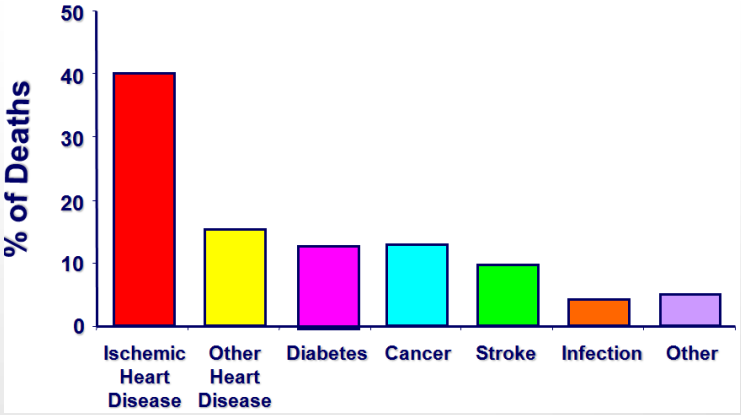
**Brain and Cerebral Circulation**
**(stroke, TIA)**

**Heart and Coronary Circulation**
**(angina, MI, CHF)**

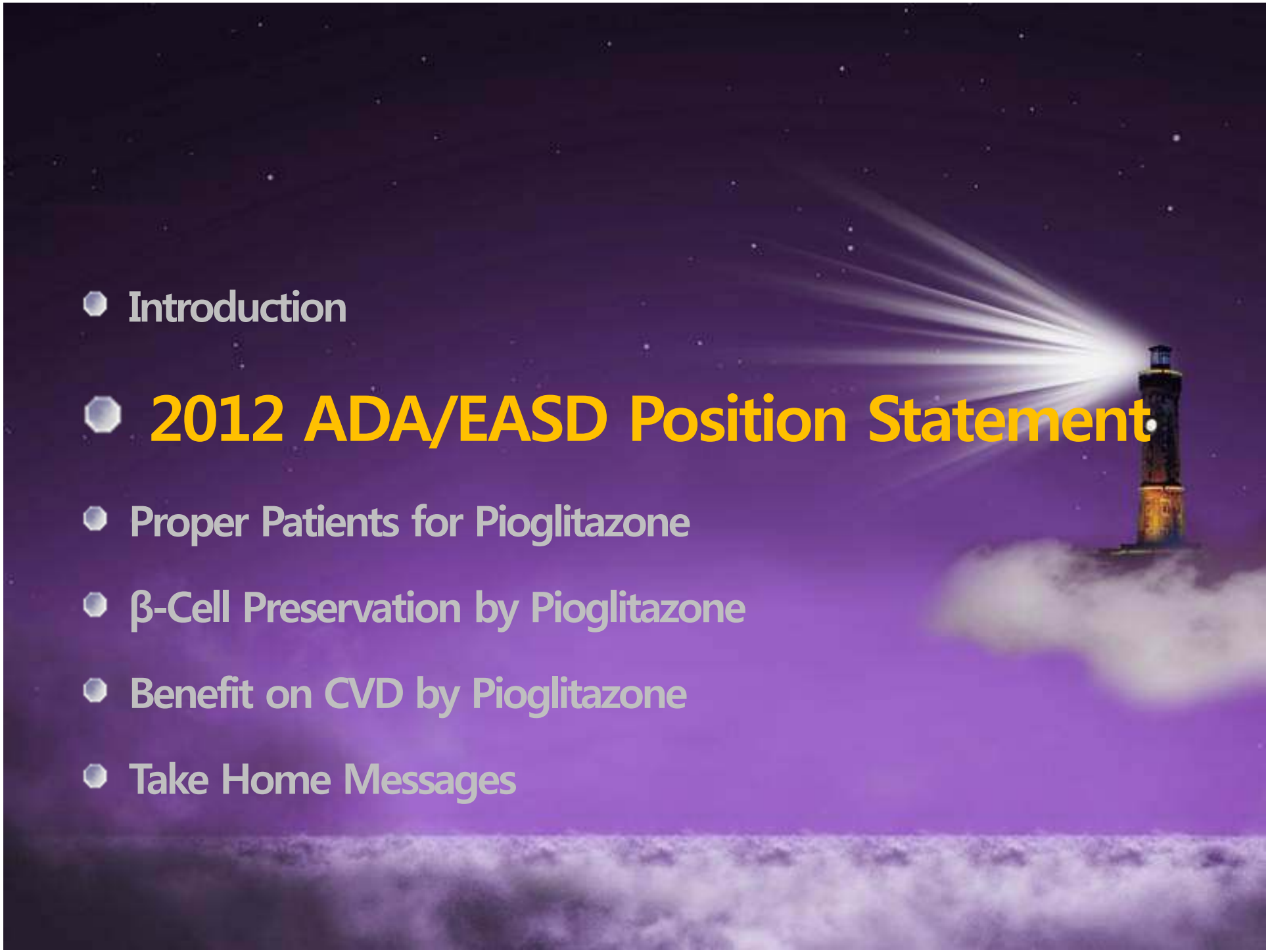
**Peripheral Vascular Tree**
**(peripheral vascular disease, gangrene, amputation)**

# Macrovascular Complications of Diabetes

- **80% of people with T2DM die from cardiovascular disease [1]**
  - **Cerebrovascular disease**
    - **stroke, transient ischemic attacks**
    - **2- to 4-fold increased mortality risk[2]**
  - **Coronary heart disease (CHD)**
    - **Angina, heart attack, heart failure**
    - **2- to 4-fold increased mortality risk[3]**
  - **Peripheral vascular disease**
    - **E.g., intermittent claudication, gangrene, amputations…**




[1] Webster MWI et al, *Lancet*. 1997
[2] Centers for Disease Control and Prevention. National Diabetes Fact Sheet, 2003
[3] Kuusisto J et al, *Eur J Clin Invest*. 1999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# 2012 ADA/EASD Position Statement

Reviews/Consensus Reports/ADA Statements
POSITION STATEMENT

## Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

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Glycemic management in type 2 diabetes mellitus has become increasingly complex and, to some extent, controversial, with a widening array of pharmacological agents now available (1–5), mounting concerns about their potential adverse effects and new uncertainties regarding the benefits of intensive glycemic control on macrovascular complications (6–9). Many clinicians are therefore perplexed as to the optimal strategies for their patients. As a consequence, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) convened a joint task force to examine the evidence and develop recommendations for antihyperglycemic therapy in nonpregnant adults with type 2 diabetes. Several guideline documents have been developed by members of these two organizations (10) and by other societies and federations (2,11–15). However, an update was deemed necessary because of contemporary information on the benefits/risks of glycemic control, recent evidence concerning efficacy and safety of several new drug classes (16,17), the withdrawal/restriction of others, and increasing calls for a move toward more patient-centered care (18,19).

This statement has been written incorporating the best available evidence and, where solid support does not exist, using the experience and insight of the writing group, incorporating an extensive review by additional experts (acknowledged below). The document refers to glycemic control; yet this clearly needs to be pursued within a multifactorial risk reduction framework. This stems from the fact that patients with type 2 diabetes are at increased risk of cardiovascular morbidity and mortality; the aggressive management of cardiovascular risk factors (blood pressure and lipid therapy, antiplatelet treatment, and smoking cessation) is likely to have even greater benefits.

These recommendations should be considered within the context of the needs, preferences, and tolerances of each patient; individualization of treatment is the cornerstone of success. Our recommendations are less prescriptive than and not as algorithmic as prior guidelines. This follows from the general lack of comparative-effectiveness research in this area. Our intent is therefore to encourage an appreciation of the variable and progressive nature of type 2 diabetes, the specific role of each drug, the patient and disease factors that drive clinical decision making (20–23), and the constraints imposed by age and comorbidity (4,6). The implementation of these guidelines will require thoughtful clinicians to integrate current evidence with other constraints and imperatives in the context of patient-specific factors.

**PATIENT-CENTERED APPROACH**—Evidence-based advice depends on the existence of primary source evidence. This emerges only from clinical trial results in highly selected patients, using limited strategies. It does not address the range of choices available, or the order of use of additional therapies. Even if such evidence were available, the data would show median responses and not address the vital question of who responded to which therapy and why (24). Patient-centered care is defined as an approach to "providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions" (25). This should be the organizing principle underlying health care for individuals with any chronic disease, but given our uncertainties in terms of choice or sequence of therapy, it is particularly appropriate in type 2 diabetes. Ultimately, it is patients who make the final decisions regarding their lifestyle choices and, to some degree, the pharmaceutical interventions they use; their implementation occurs in the context of the patients' real lives and relies on the consumption of resources (both public and private).

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This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0413/-/DC1.
S.E. Inzucchi and D.R. Matthews were co-chairs for the Position Statement Writing Group. R.M. Bergenstal, J.B. Buse, A.L. Peters, and R. Wender were the Writing Group for the ADA. M. Diamant, E. Ferrannini, M. Nauck, and A. Tsapas were the Writing Group for the EASD.
This article is being simultaneously published in 2012 in *Diabetes Care* and *Diabetologia* by the American Diabetes Association and the European Association for the Study of Diabetes.




**Glycemic management in type 2 diabetes mellitus has become increasingly complex. As a consequence, ADA and EASD convened a joint task force to examine the evidence and develop recommendations for anti-hyperglycemic therapy in nonpregnant adults with type 2 diabetes.**

***Patient-centered care is defined as an approach to "providing care that is respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions"***

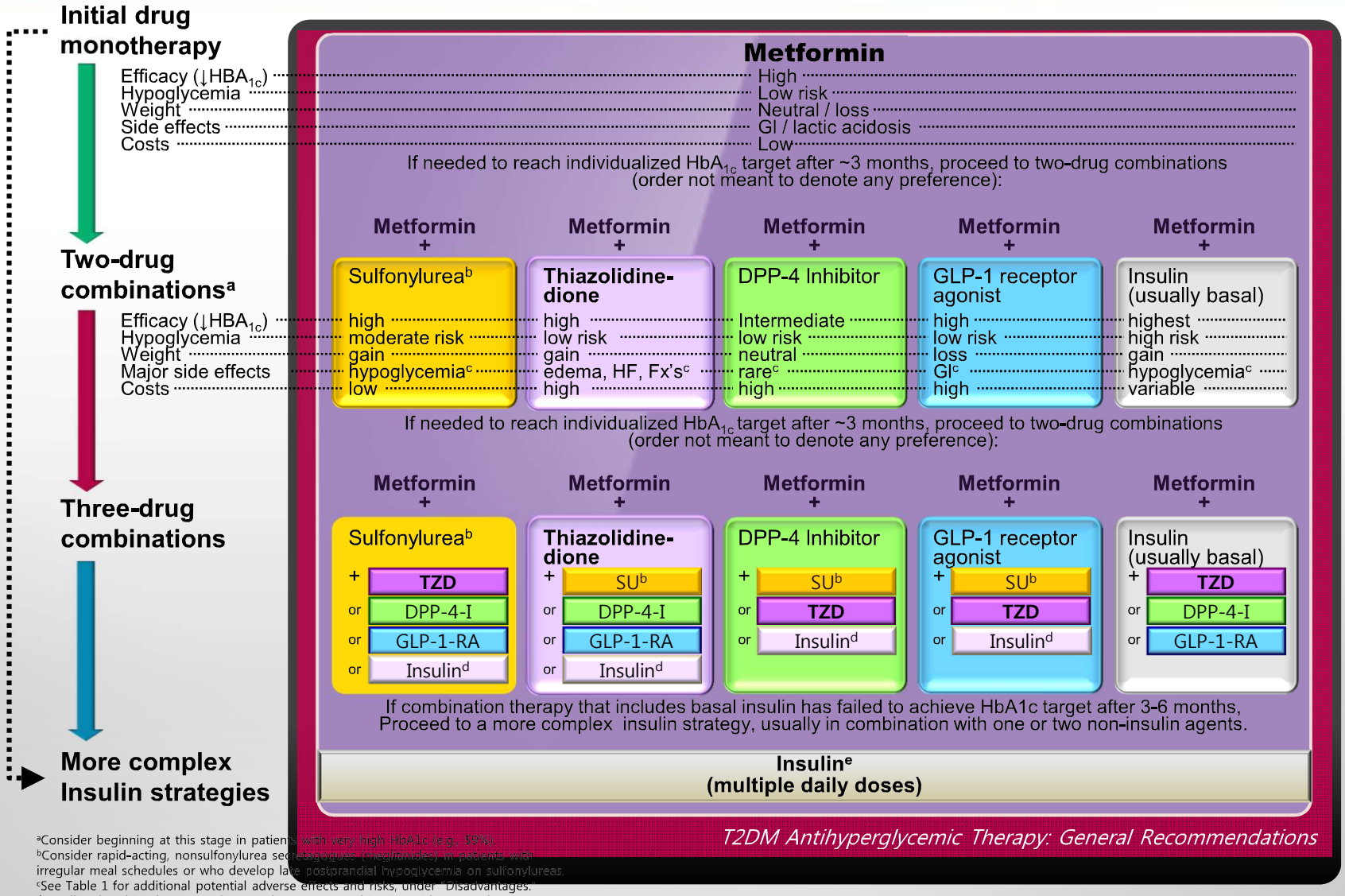
**It means there's no any formulation. Clinicians should know the patients and also pharmaceutical agent completely. Clinician's responsibility is increasing.**

American Diabetes Association.

EASD

Inzucchi SE *et al. Diabetes care* 2012;35:1364-79

# Anti-Hyperglycemic Therapy: General Recommendations




[a]Consider beginning at this stage in patients with very high HbA1c (e.g., 10%).
[b]Consider rapid-acting, nonsulfonylurea secretagogues (meglitinides) in patients with irregular meal schedules or who develop late postprandial hypoglycemia on sulfonylureas.
[c]See Table 1 for additional potential adverse effects and risks, under "Disadvantages."
[d]Usually a basal insulin (NPH, glargine, detemir) in combination with noninsulin agents.
[e]Certain noninsulin agents may be continued with insulin (see text).

Inzucchi SE *et al. Diabetes care* 2012;35:1364-79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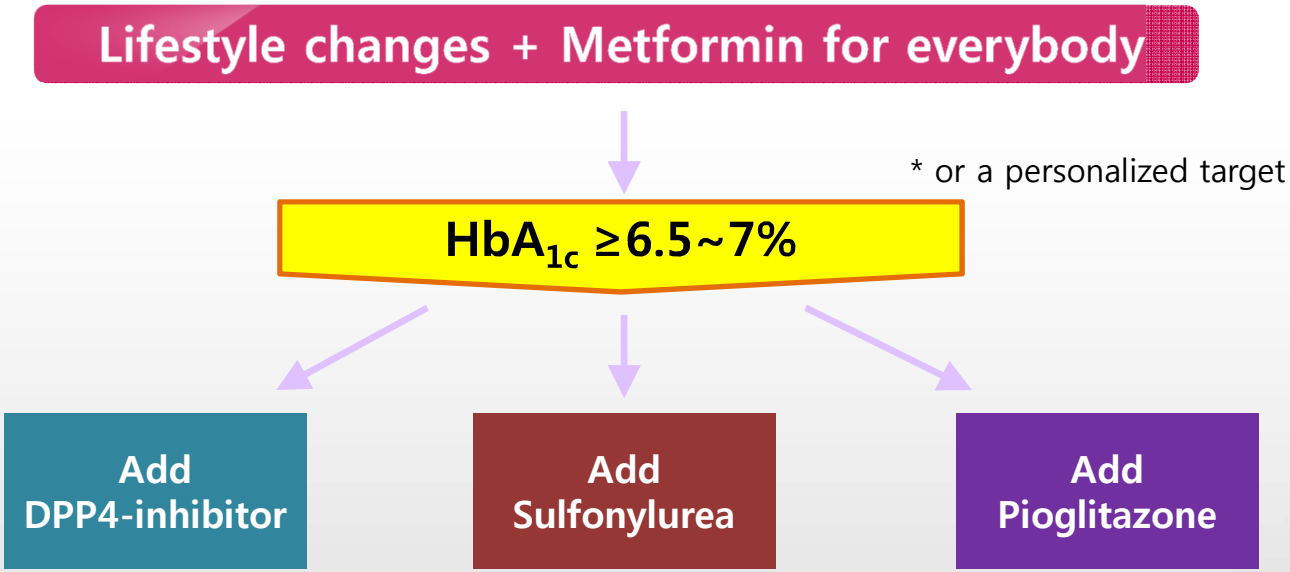
# What should follow metformin

## The 3 options for dual oral therapy



# What should follow metformin

## The 3 options for dual oral therapy

**Lifestyle changes + Metformin for everybody**

* or a personalized target

**$HbA_{1c}$ ≥6.5~7%**

**Add DPP4-inhibitor**

**Add Sulfonylurea**

- Cheap
- Rapid response
- More potent
- Poor durability
- Risk of Hypoglycemia
- Weight gain
- No evidence for a CV benefit

**Add Pioglitazone**

**Often chosen as 2nd line drug for cost rather than medical reasons**

# What should follow metformin

## The 3 options for dual oral therapy

**Lifestyle changes + Metformin for everybody**

* or a personalized target

**$HbA_{1c}$ ≥6.5~7%**

**Add Dpp4-inhibitor**

- Easy to use
- No side effects*
- But expensive

* Pancreatitis

We need a longer follow-up to be quite sure about safety

**Add Sulfonylurea**

A popular 2nd line drug in 2012, When no cost limitation

But all patients do not respond well and need another option

**Add Pioglitazone**

# What should follow metformin

## The 3 options for dual oral therapy

**Lifestyle changes + Metformin for everybody**

* or a personalized target

**$HbA_{1c}$ ≥6.5~7%**

**Add DPP4-inhibitor**

**Add Sulfonylurea**

**Add Pioglitazone**

- Durability
- The most powerful (on the long term)
- No Hypoglycemia
- Possible CV benefit

**Can be beneficial in some patients group such as newly diagnosis patients with insulin resistance, CV risk patients, etc..**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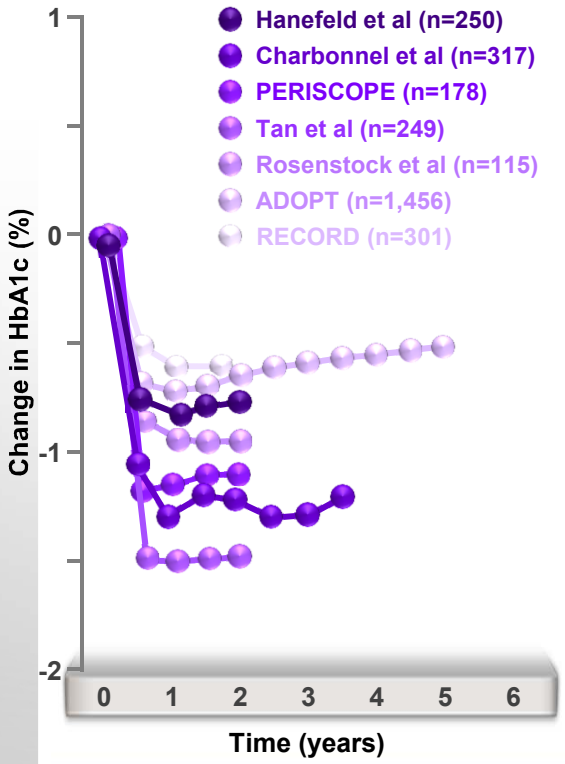
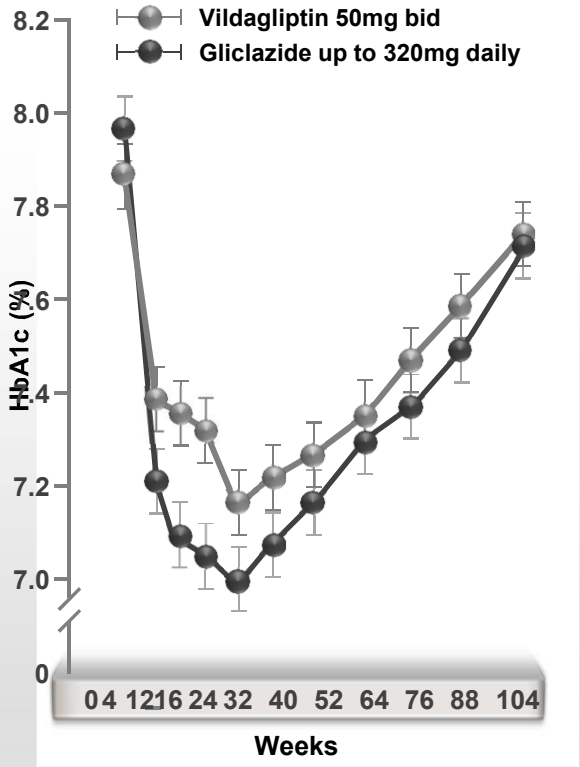
# Sustained Glycemic Control

## TZD



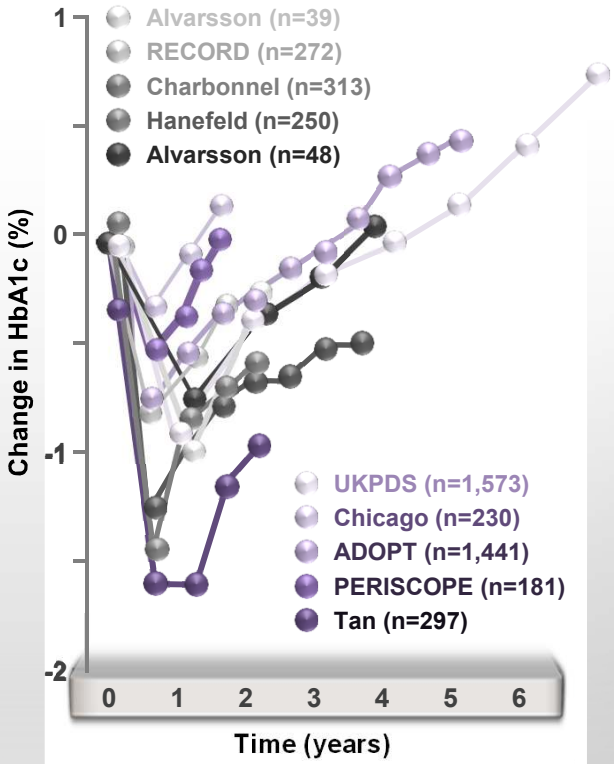

**Most durable option**

## DPP-4i




**The durability of sitagliptin seems to be better than sulfonylureas but less than TZDs**

## SU




**Big drop at the beginning, and then It will goes up significantly**

The NEW ENGLAND JOURNAL of MEDICINE

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

ABSTRACT

BACKGROUND

Impaired glucose tolerance is associated with increased rates of cardiovascular disease 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 impaired glucose tolerance. 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.

RESULTS

Annual incidence rates for type 2 diabetes mellitus were 2.7% in the pioglitazone group and 7.6% in the placebo group, and the hazard ratio for conversion to diabetes in the pioglitazone group was 0.28 (95% confidence interval, 0.16 to 0.49; P<0.001). Conversion to normal glucose tolerance occurred in 48% of the patients in the pioglitazone group and 28% of those in the placebo group (P<0.001). Treatment with pioglitazone as compared with placebo was associated with significantly reduced levels of fasting glucose (a decrease of 11.7 mg per deciliter vs. 8.1 mg per deciliter [0.7 mmol per liter vs. 0.5 mmol per liter], P<0.001), 2-hour glucose (a decrease of 30.5 mg per deciliter vs. 15.6 mg per deciliter [1.6 mmol per liter vs. 0.9 mmol per liter], P<0.001), and $HbA_{1c}$ (a decrease of 0.04 percentage points vs. an increase of 0.20 percentage points, P<0.001). Pioglitazone therapy was also associated with a decrease in diastolic blood pressure (by 2.0 mm Hg vs. 0.0 mm Hg, P=0.05), a reduced rate of carotid intima–media thickening (−1.5%, P=0.047), and a greater increase in the level of high-density lipoprotein cholesterol (by 7.5 mg per deciliter vs. 4.5 mg per deciliter [0.4 mmol per liter vs. 0.3 mmol per liter], P=0.008). Weight gain was greater with pioglitazone than with placebo (5.9 kg vs. 0.77 kg, P<0.001), and edema was more frequent (12.9% vs. 6.4%, P=0.007).

CONCLUSIONS

As compared with placebo, pioglitazone reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes mellitus by 72% but was associated with significant weight gain and edema. (Funded by Takeda Pharmaceuticals and others; ClinicalTrials.gov number, NCT00220961.)

From the Texas Diabetes Institute and University of Texas Health Science Center (R.A.D., D.T., N.M.) and KenAnCo Biostatistics (K.W.) — both in San Antonio; Phoenix Veterans Affairs (VA) Health Care System, Phoenix, AZ (D.C.S., P.D.R.); College of Nursing and Health Innovation, Arizona State University, Phoenix (D.C.S.); SUNY Health Science Center at Brooklyn, Brooklyn, NY (M.B.); Pennington Biomedical Research Center–Louisiana State University, Baton Rouge (G.A.B.); University of Southern California Keck School of Medicine, Los Angeles (T.A.B., H.N.H., W.J.M.); Division of Endocrinology and Metabolism, Georgetown University, Washington, DC (S.C.C.); VA San Diego Healthcare System and University of California at San Diego, San Diego (R.R.H., S.M.); University of Tennessee, Division of Endocrinology, Diabetes, and Metabolism, Memphis (A.E.K., F.B.S.); and Medstar Research Institute, Hyattsville, MD (R.E.R.). Address reprint requests to Dr. DeFronzo at the Diabetes Division, University of Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX 78229, or at albarado@uthscsa.edu.

Drs. DeFronzo and Tripathy contributed equally to this article.

This article (10.1056/NEJMi1010949) was updated on August 31, 2011, at NEJM.org.

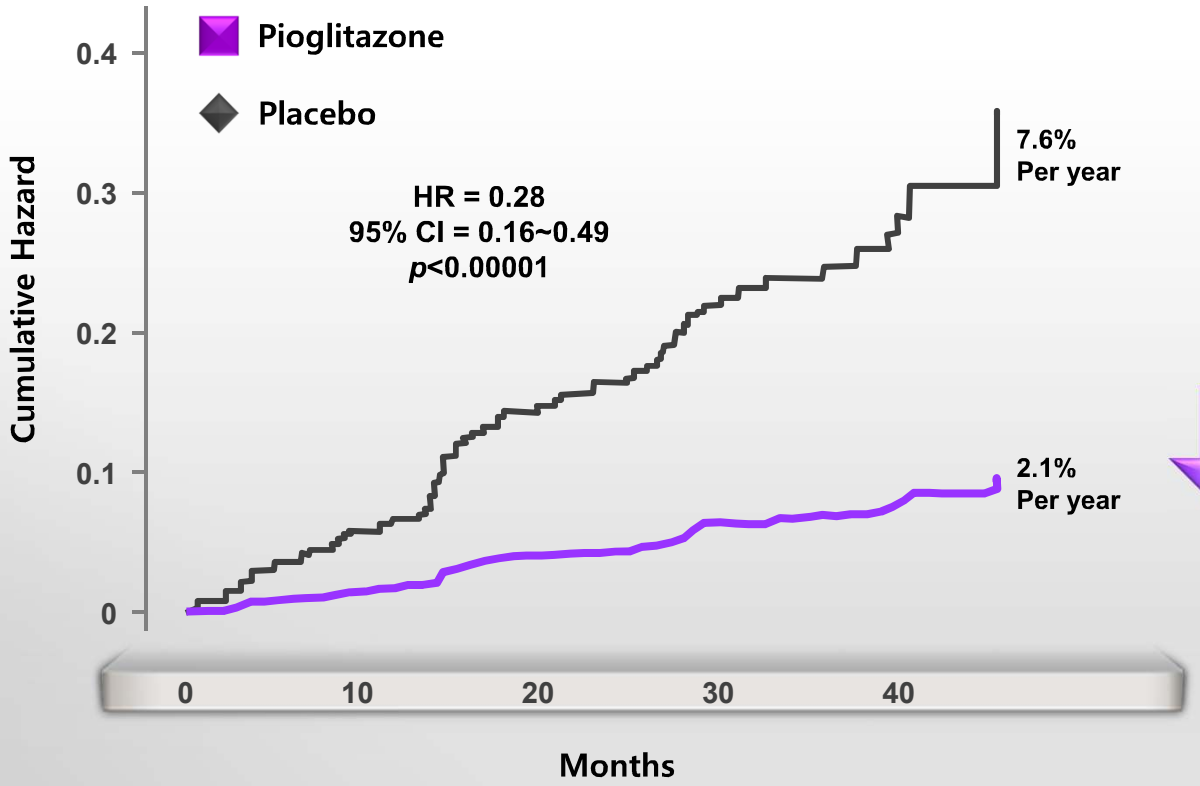
N Engl J Med 2011;364:1104-15.




**They undertook the this study to examine the effect of pioglitazone on prevention of diabetes in IGT pt.**

# ACT NOW: Pioglitazone

## ACTos NOW for the prevention of type 2 diabetes




IGT

\- Pioglitazone 72%

T2DM

As compared with placebo, pioglitazone reduced the risk of conversion of IGT to type 2 diabetes by 72%

DeFronzo RA *et al. N Engl J Med* 2011;364:1104-15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# Benefit on CVD

- **Pioglitazone**
  - **Improves diabetic dyslipidemia**
    - Lowers triglyceride levels
    - Increases size of LDL particles
    - Elevates HDL cholesterol levels
- **Pioglitazone**
  - **Reducing CRP**
  - **Inhibiting smooth muscle cell proliferation**
  - **Decreasing vascular inflammation**
- **Pioglitazone**
  - **Prevented progression of**
    - CIMT (Carotid Intima Media Thickness)
    - IVUS (Intra-Vascular Ultra Sound)

# Benefit on CVD

## Pioglitazone

### - Improves diabetic dyslipidemia

- Lowers triglyceride levels
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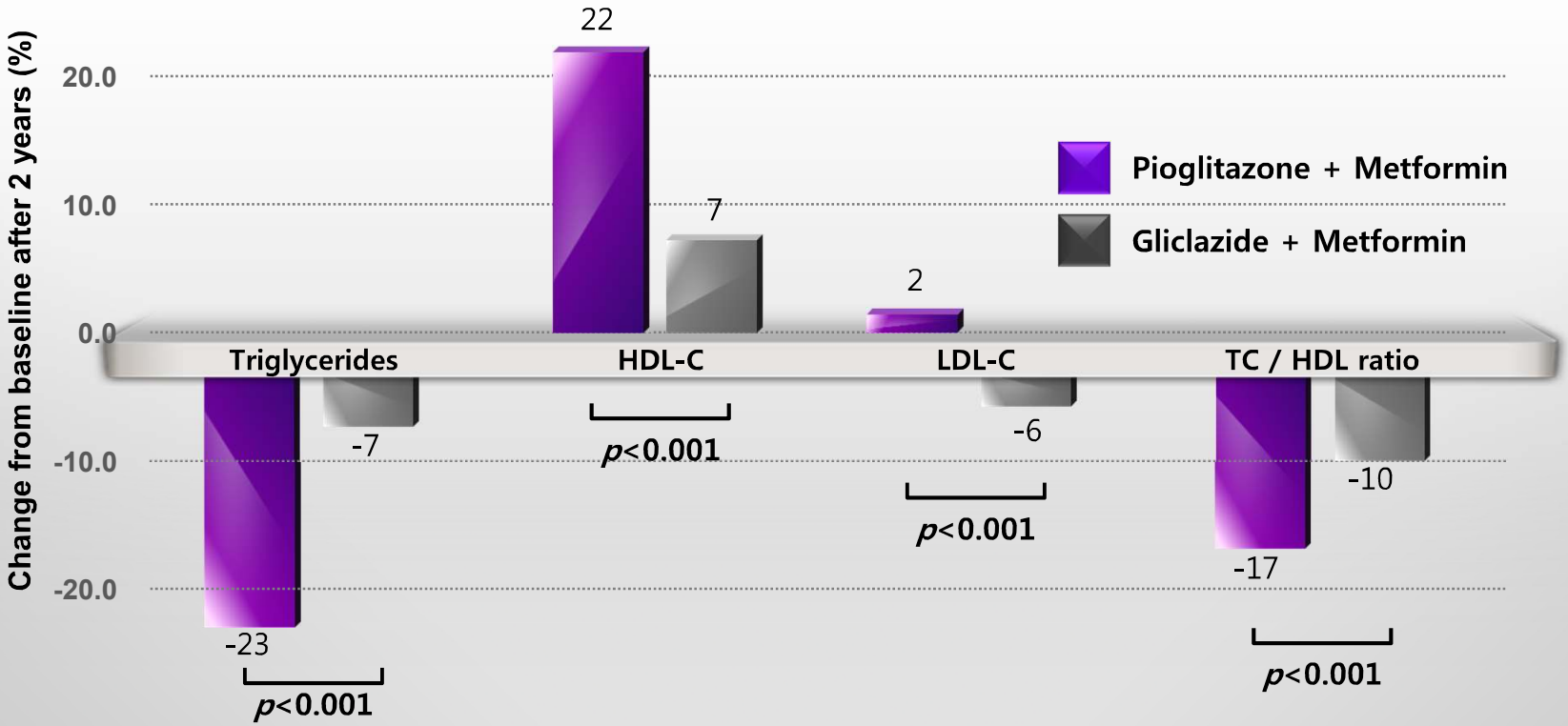
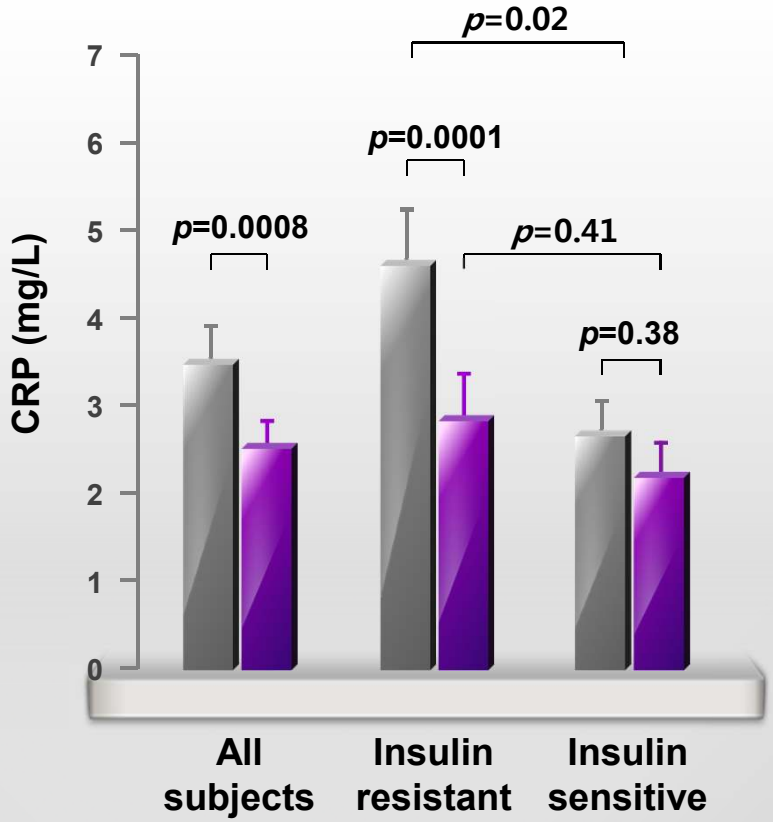


# Benefit on CVD

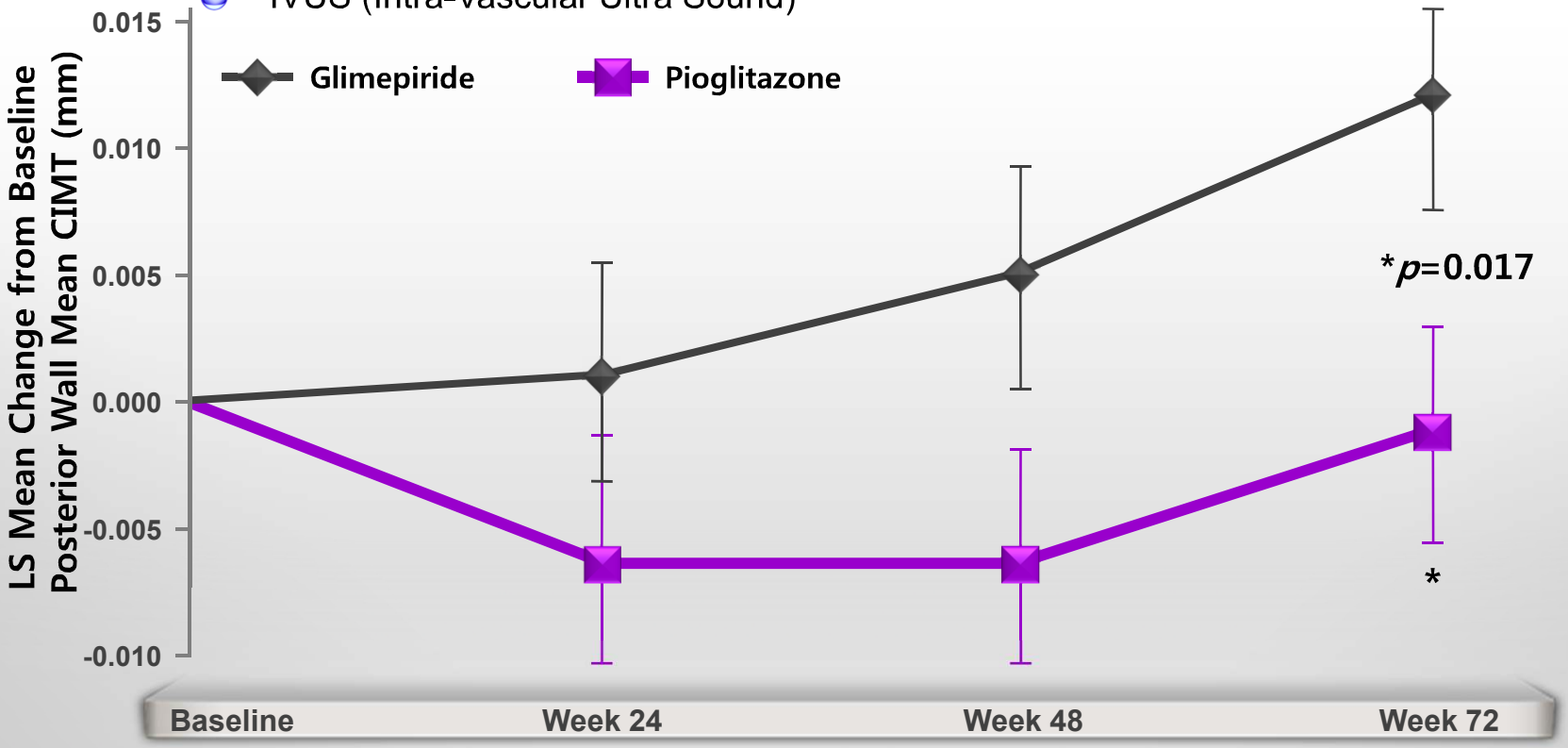
- **Pioglitazone**
  - Reducing CRP
  - Inhibiting smooth muscle cell proliferation
  - Decreasing vascular inflammation



# Benefit on CVD

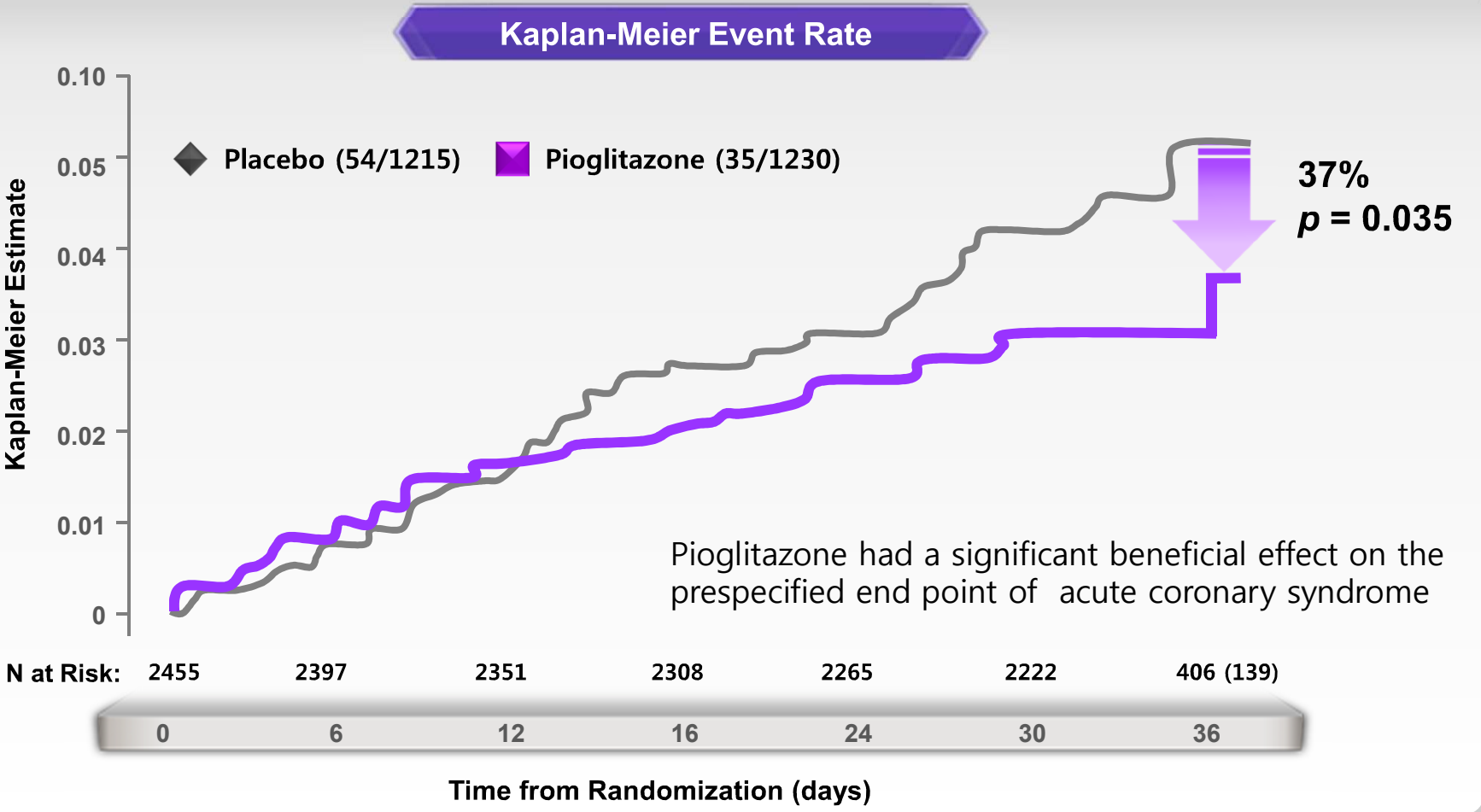
## Pioglitazone

- **Prevented progression of**
  - CIMT (Carotid Intima Media Thickness)
  - IVUS (Intra-Vascular Ultra Sound)



# Benefit on CVD: Acute Coronary Syndrome

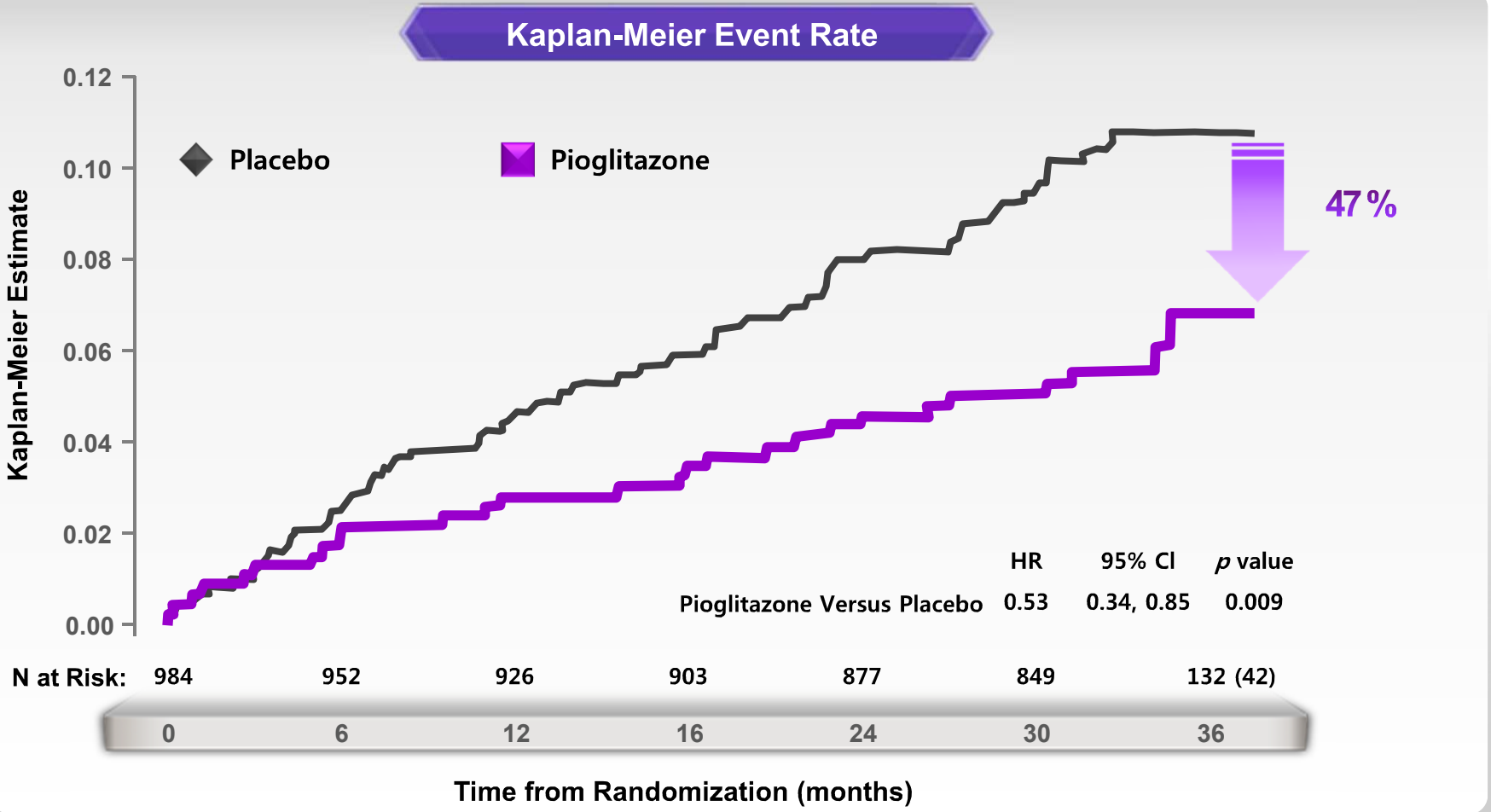
## Pioglitazone's effect on acute coronary syndrome in patients with previous MI




Erdmann E *et al. JACC* 2007;49:1772-1780

# Benefit on CVD: Recurrent stroke

## Pioglitazone's effect on recurrent stroke in patients with previous stroke




Erdmann E *et al. JACC* 2007;49:1772-1780

# Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

| Study | Microvascular | | Macrovascular | | Mortality | |
|---|---|---|---|---|---|---|
| **UKPDS** (Type 2) | ↓ | ↓ | ↔ | ↓ | ↔ | ↓ |
| **DCCT/EDIC** (Type 1) | ↓ | ↓ | ↔ | ↓ | ↔ | ↔ |
| **ACCORD** (Type 2) | ↓ | | ↔ | | ↑ | |
| **ADVANCE** (Type 2) | ↓ | | ↔ | | ↔ | |
| **VADT** (Type 2) | ↓ | | ↔ | | ↔ | |
| **PROactive** | | | ↓ | | ↔ | |

**Initial Trial**

**Long-term Follow-up**


UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854-65
Holman RR. *N Engl J Med* 2008;9;359(15):1577-89
DCCT Research Group. *N Engl J Med* 1993;329;977-86
Nathan DM *et al*. *N Engl J Med* 2005;353:2643-53
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Duckworth W *et al*. *N Engl J Med* 2009;360:129-39

JCEM
THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

ORIGINAL ARTICLE

Endocrine Research

# What Next after Metformin? A Retrospective Evaluation of the Outcome of Second-Line, Glucose-Lowering Therapies in People with Type 2 Diabetes

Christopher LI. Morgan, Chris D. Poole, Marc Evans, Anthony H. Barnett, Sara Jenkins-Jones, and Craig J. Currie

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**Context:** After failure of metformin monotherapy, many second-line, glucose-lowering therapies are available to treat people with type 2 diabetes.

**Objective:** The objective of the study was to compare clinical outcomes using common alternative regimens.

**Design and Setting:** This was a retrospective cohort study using data from the U.K.-based General Practice Research Database.

**Patients:** These were primary care patients with type 2 diabetes who had metformin monotherapy as their first treatment and who then initiated on relevant second-line, glucose-lowering regimens during the study period 2000–2010. A total of 27,457 patients were prescribed a second-line therapy, of whom 26,278 (95.7%) were prescribed a regimen with 1,000 or more observations.

**Main Outcome Measures:** All-cause mortality, major adverse cardiovascular events (MACE), cancer, and a combined end point of any of these were measured. Secondary end points were change in glycosylated hemoglobin between baseline and 12 months. Time to clinical end points was compared using Cox proportional hazards models.

**Results:** Sulfonylurea monotherapy had significantly higher hazard ratios (HRs) for all-cause mortality (HR 1.459, 1.207–1.763); MACE (HR 1.578, 1.187–2.099); stroke (HR 1.444, 1.050–1.987); and the combined end point (HR 1.381, 1.194–1.597). Metformin plus pioglitazone had significantly lower adjusted HRs for all-cause mortality (HR 0.707, 0.515–0.970) and the combined end point (HR 0.747, 0.612–0.911). Mean glycosylated hemoglobin improved between baseline and 12 months for all regimens other than sulfonylurea monotherapy.

**Conclusion:** The combination of metformin plus pioglitazone appears to provide superior clinical outcomes compared with the most commonly used regimen, metformin plus sulfonylurea. Sulfonylurea monotherapy resulted in worse outcome. ***(J Clin Endocrinol Metab* 97: 0000–0000, 2012)**

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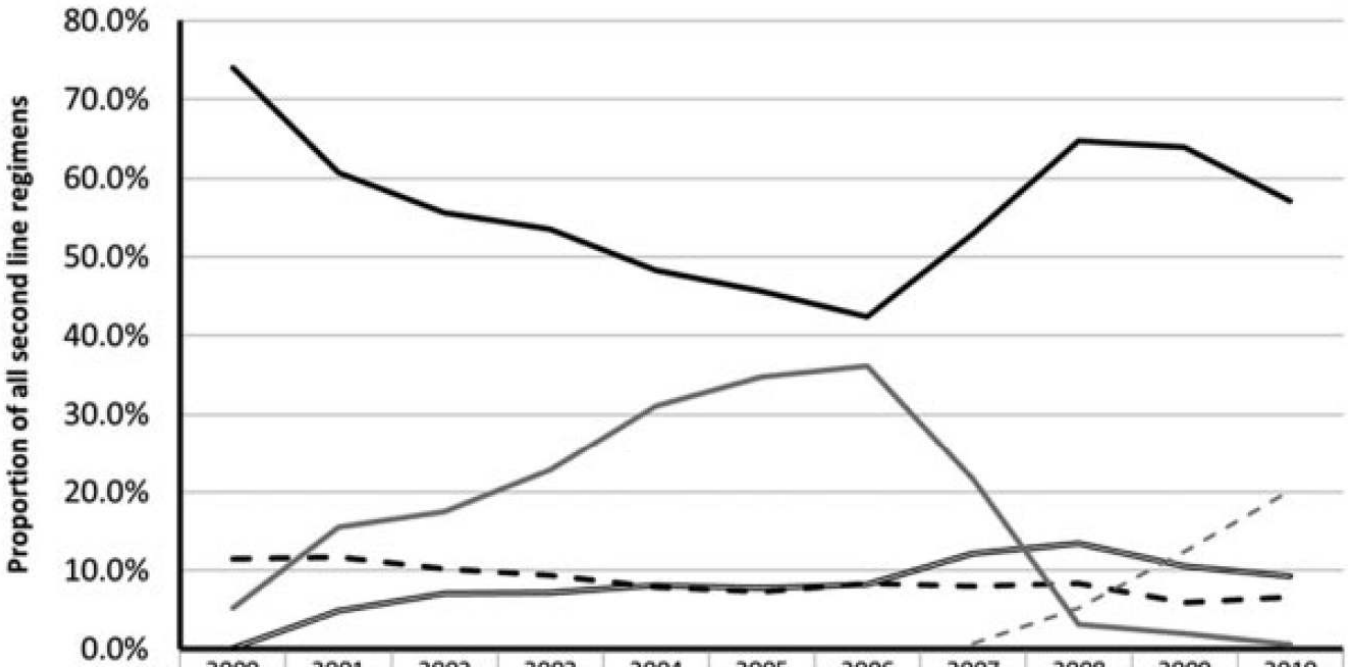
doi: 10.1210/jc.2012–3034 Received August 9, 2012. Accepted September 21, 2012.

Abbreviations: BMI, Body mass index; DPP4, dipeptidyl peptidase 4; GPRD, General Practice Research Database; HbA1c, glycosylated hemoglobin; HR, hazard ratio; MI, myocardial infarction; OAD, oral antidiabetes drug; TZD, thiazolidinedione.

- Retrospective data from the UK General Practice Research Database was used. Patients initiating treatment between 2000 and 2010 were selected
- Its primary objective is to determine the optimal approach after the failure of metformin monotherapy.
- The primary endpoint : all-cause mortality, major adverse cardiovascular event (MACE [MI and stroke]), cancer, and a combined endpoint of the first of any of these.
- A secondary endpoint : change in HbA1c between baseline and 1 year

# Trend for selected second-line regimens as a proportion of all second-line regimens by year




| | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Sulf | 11.5% | 11.7% | 10.2% | 9.4% | 7.9% | 7.3% | 8.4% | 8.0% | 8.3% | 5.9% | 6.6% |
| Met Sulf | 74.1% | 60.7% | 55.6% | 53.5% | 48.3% | 45.6% | 42.4% | 52.9% | 64.7% | 63.9% | 57.1% |
| Met Pio | 0.1% | 4.9% | 7.1% | 7.2% | 8.1% | 7.8% | 8.3% | 12.2% | 13.4% | 10.6% | 9.3% |
| Met Ros | 5.3% | 15.5% | 17.5% | 22.8% | 31.1% | 34.7% | 36.2% | 21.7% | 3.1% | 1.9% | 0.5% |
| Met DPP4 | | | | | | | | 0.7% | 5.2% | 12.4% | 20.2% |

Metformin + sulfonylurea

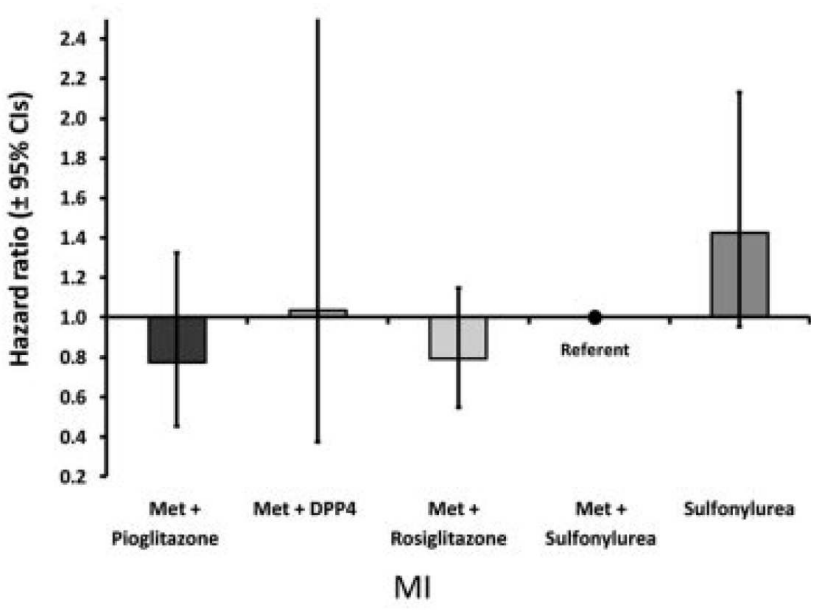
Metformin + DPP4 I

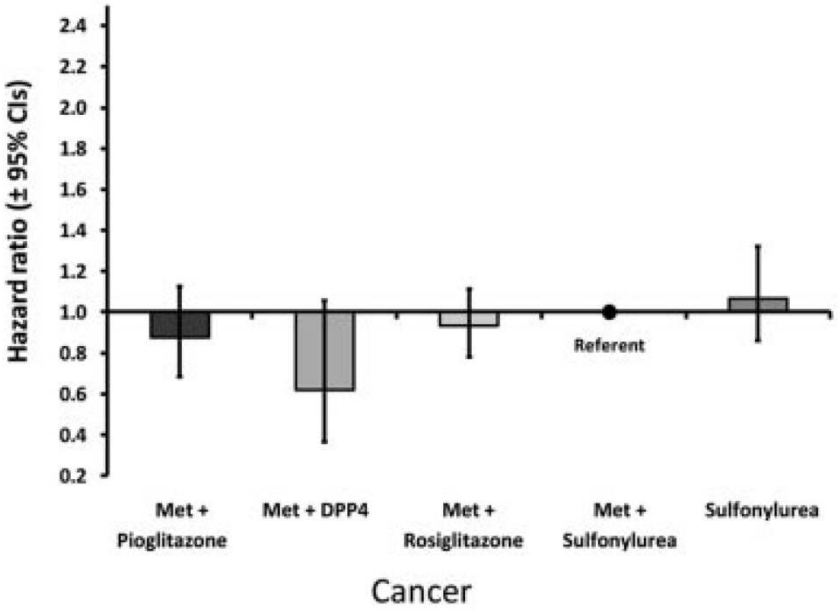
Metformin + pioglitazone

Sulfonylurea

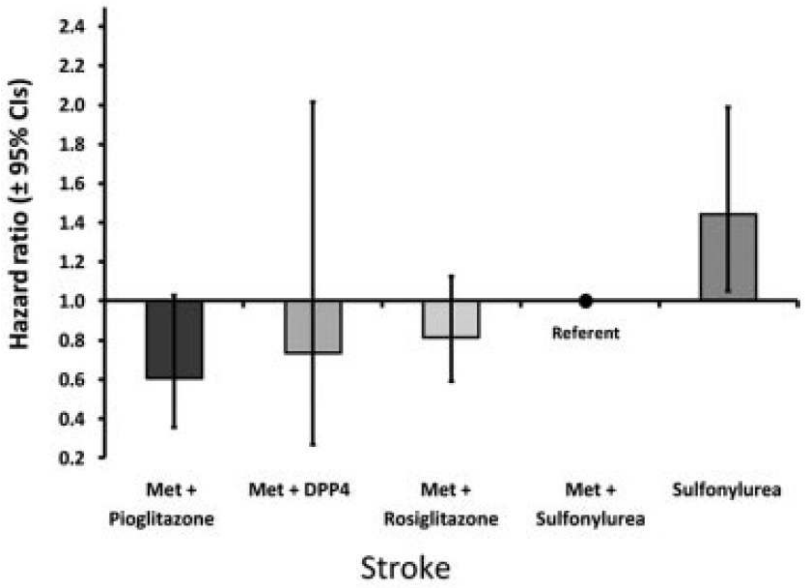
Metformin + rosiglitazone

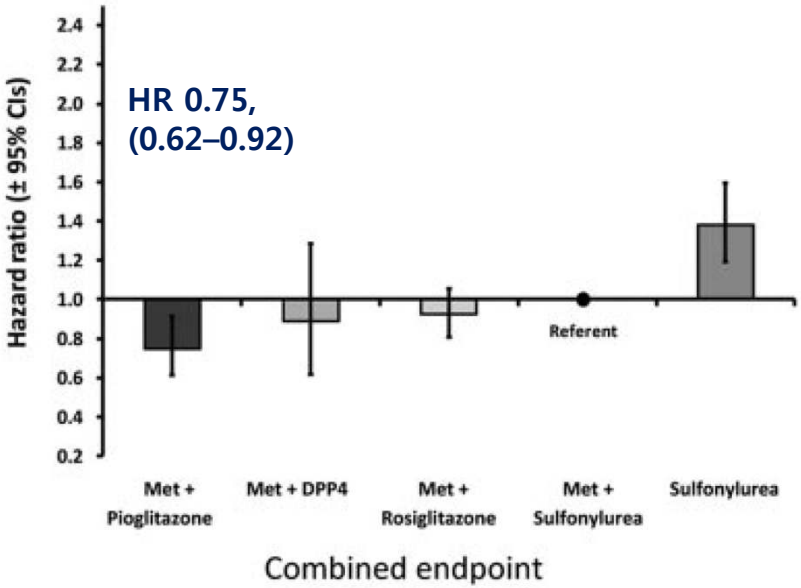
## Summary of clinical outcome showing the general pattern of adjusted hazard across the various end points and end point subcategories by alternative glucose-lowering regimen (II)



## Summary of clinical outcome showing the general pattern of adjusted hazard across the various end points and end point subcategories by alternative glucose-lowering regimen (III)



**Conclusion:**
**The combination of metformin plus pioglitazone appears to provide superior clinical outcomes compared with the most commonly used regimen, metformin plus sulfonylurea.**


Introduction
2012 ADA/EASD Position Statement
Proper Patients for Pioglitazone
β-Cell Preservation by Pioglitazone
Benefit on CVD by Pioglitazone
Take Home Messages

# Take Home Messages

## Rosiglitzone

- Reduces insulin resistance
- Higher durability (Prolonged potent lowering of HbA1C)
- Decrease cardiovascular risk (PROactive: secondary prevention of MI, stroke)
- Strongest effect on prevention of diabetes (ACT Now: associated with decrease in IMT)
- Good effect on diabetic dyslipidemia