

Introduction

Gabriele Riccardi
Department of Clinical Medicine and Surgery,
Federico II University, Naples, Italy

Diabete Ricerca

SID fondata nel 1964 Società Italiana di Diabetologia

Disclosures

Participation in sponsored clinical trials:

Boehringer Ingelheim, MSD, Sanofi

Travel support:Takeda

Research grant to the Department: Guidotti

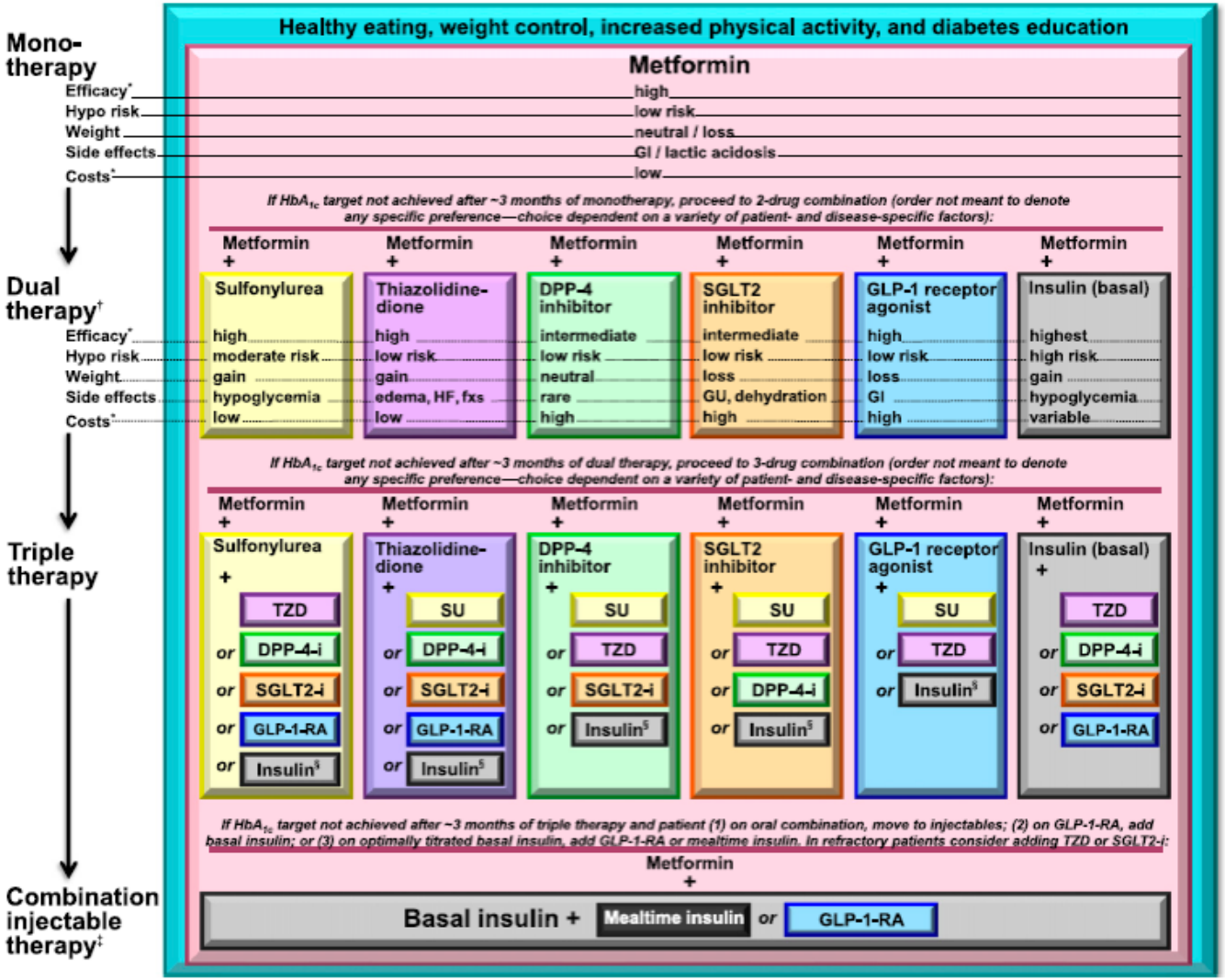
Speaking fees: Lilly, Sanofi

Proportion of patients randomized to diet, sulfonylureas or insulin, respectively, who attained an HbA1c value of less than 7% at different times during the intervention

	3 years	6 years	9 years
Diet	25%	12%	9%
Sulfonylureas	50%	34%	24%
Insulin	47%	37%	28%

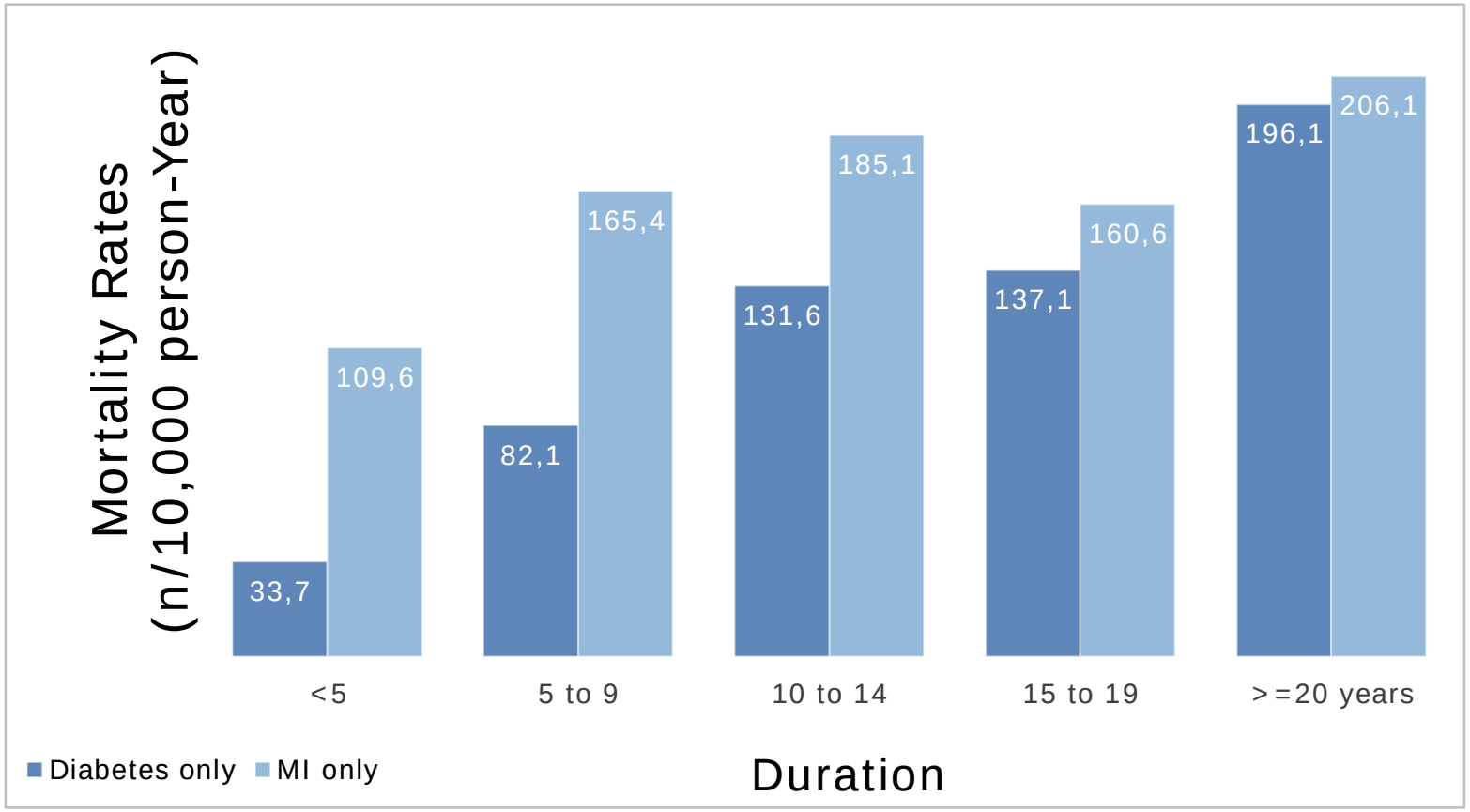
UKPDS
Turner RC et al, JAMA 1999

Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach



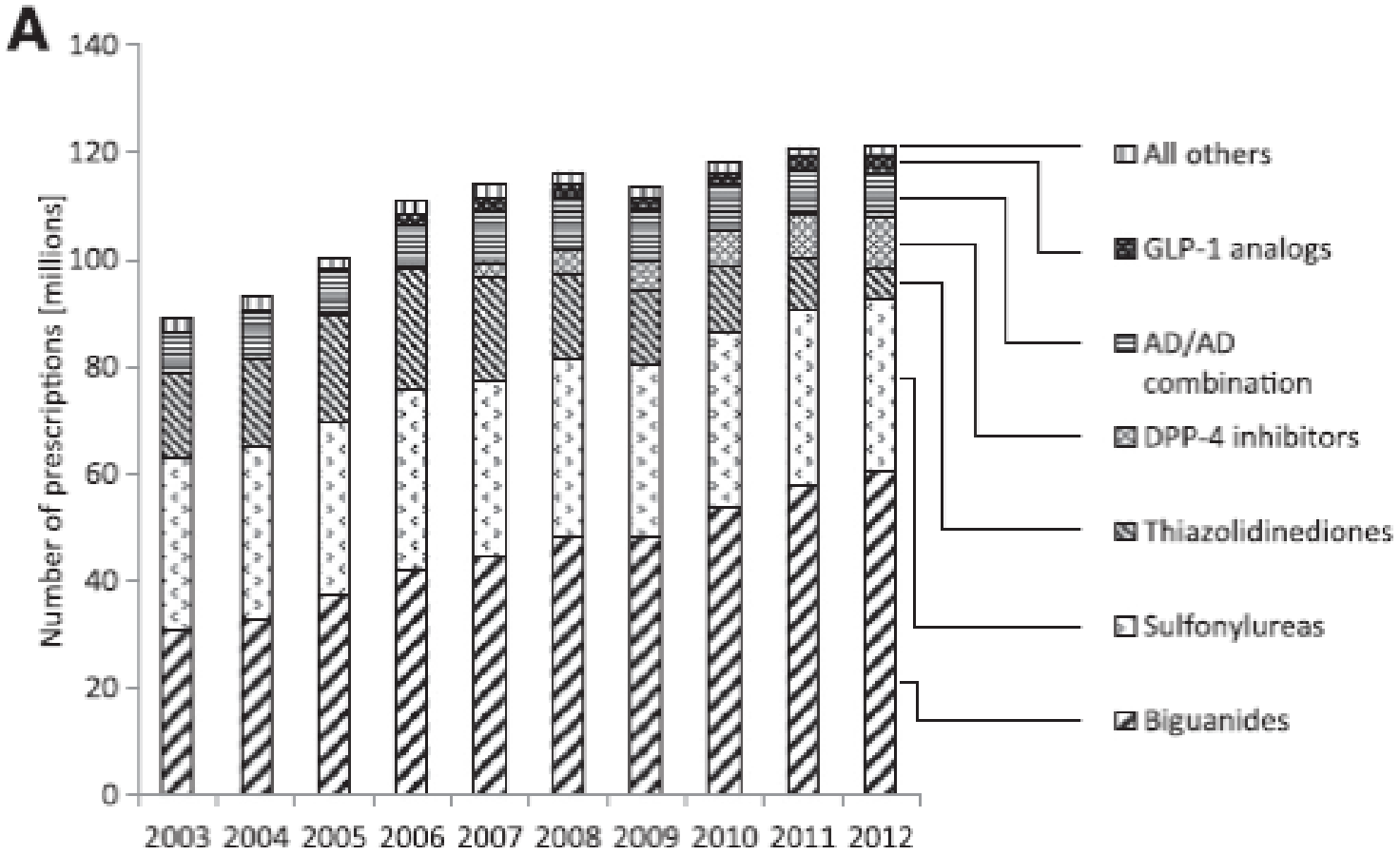
ADA-EASD
Inzucchi S et al,
Diabetes Care 2015

CHD mortality (n/10,000 person-years) by duration of follow-up for men with Diabetes or Myocardial Infarction



MRFIT
Vaccaro O et al,
Arch Intern Med 2004

Trends in the use of antidiabetes drugs in USA over 10 years



IMS Health Databases
Hampp C et al
Diabetes Care 2014

Published metanalyses of observational studies and RCT on sulfonylureas and CVD

Meta-analysis, authors and year	Type of studies included (n)	Sulphonylurea vs comparator	Outcome	Pooled point estimates (95% CI)
Selvin et al., 2008 [33]	RCT (5)	SU vs no SU	Cardiovascular morbidity	0.89 (0.71–1.11)
	RCT (5)	SU vs no SU	Cardiovascular mortality	0.92 (0.68–1.26)
	RCT (6)	SU vs no SU	All-cause mortality	0.90 (0.70–1.15)
Rao et al., 2008 [32]	Observational (5)	SU + MET vs diet, MET monotherapy, SU monotherapy	Cardiovascular mortality or hospitalization	1.43 (1.10–1.85)
	Observational (4)	SU + MET vs diet, MET monotherapy, SU monotherapy	Cardiovascular mortality	1.29 (0.73–2.27)
	Observational (7)	SU + MET vs diet, MET monotherapy, SU monotherapy	All-cause mortality	1.19 (0.88–1.62)
Phung et al., 2013 [29]	Observational (9)	SU vs no SU	Cardiovascular mortality	1.27 (1.18–1.34)
	RCT (7)	SU vs no SU	Cardiovascular mortality	1.22 (0.63–2.39)
Monami et al., 2013 [35]	RCT (30)	SU vs no SU	MACE	1.08 (0.86–1.36)
	RCT (37)	SU vs no SU	All-cause mortality	1.22 (1.01–1.49)
Hemmingsen et al., 2013*[31]	RCT (3)	SU monotherapy vs MET	Cardiovascular morbidity	0.67 (0.48–0.93)
	RCT (6)	SU monotherapy vs MET	Cardiovascular mortality	1.47 (0.54–4.01)
	RCT (6)	SU monotherapy vs MET	All-cause mortality	0.98 (0.61–1.58)
Forst et al., 2013 [30]	Observational (4)	SU vs no SU	Cardiovascular mortality	2.72 (1.95–3.79)
	Observational (12)	SU vs no SU	All-cause mortality	1.92 (1.48–2.49)
Zhang et al., 2014 [34]	RCT (4)	DDP-4 inhibitors vs SU	Cardiovascular events	0.53 (0.32–0.87)
Simpson et al., 2015 [36]	RCT (7), observational (17)	Chlorpropamide vs glyburide	All-cause mortality	1.34 (0.98–1.86)
		Tolbutamide vs glyburide		1.13 (0.90–1.42)
		Glipizide vs glyburide		0.98 (0.80–1.19)
		Glimepiride vs glyburide		0.83 (0.68–1.00)
		Gliclazide vs glyburide		0.65 (0.53–0.79)

Abdelmoneim A et al, Diabetes, Obesity and Metabolism 2015

Observational studies with no major biases assessing the cardiovascular safety of sulfonylureas

Author	Study design	Comparison	Outcome(s)	Relative risk[a] (95% CI)
Cardiovascular events				
McAfee et al. (21)	Cohort	Sulfonylureas vs. metformin	MI and coronary revascularization	1.30 (1.04–1.61)
Schramm et al. (38)	Cohort	Glimepiride vs. metformin	MACE	1.32 (1.24–1.40)
		Glyburide vs. metformin	MACE	1.19 (1.11–1.28)
		Glipizide vs. metformin	MACE	1.27 (1.17–1.38)
		Tolbutamide vs. metformin	MACE	1.28 (1.17–1.39)
Roumie et al. (43)	Cohort	Sulfonylureas vs. metformin	MACE	1.16 (1.08–1.25)
All-cause mortality				
Gulliford et al. (11)	Cohort	Sulfonylureas + metformin vs. metformin	All-cause mortality	0.95 (0.64–1.40)
Azoulay et al. (29)	Nested case-control	Sulfonylureas vs. metformin	All-cause mortality	1.43 (1.33–1.56)
Wheeler et al. (46)	Cohort	Glyburide vs. metformin	All-cause mortality	1.38 (1.27–1.50)
		Glipizide vs. metformin	All-cause mortality	1.55 (1.43–1.67)

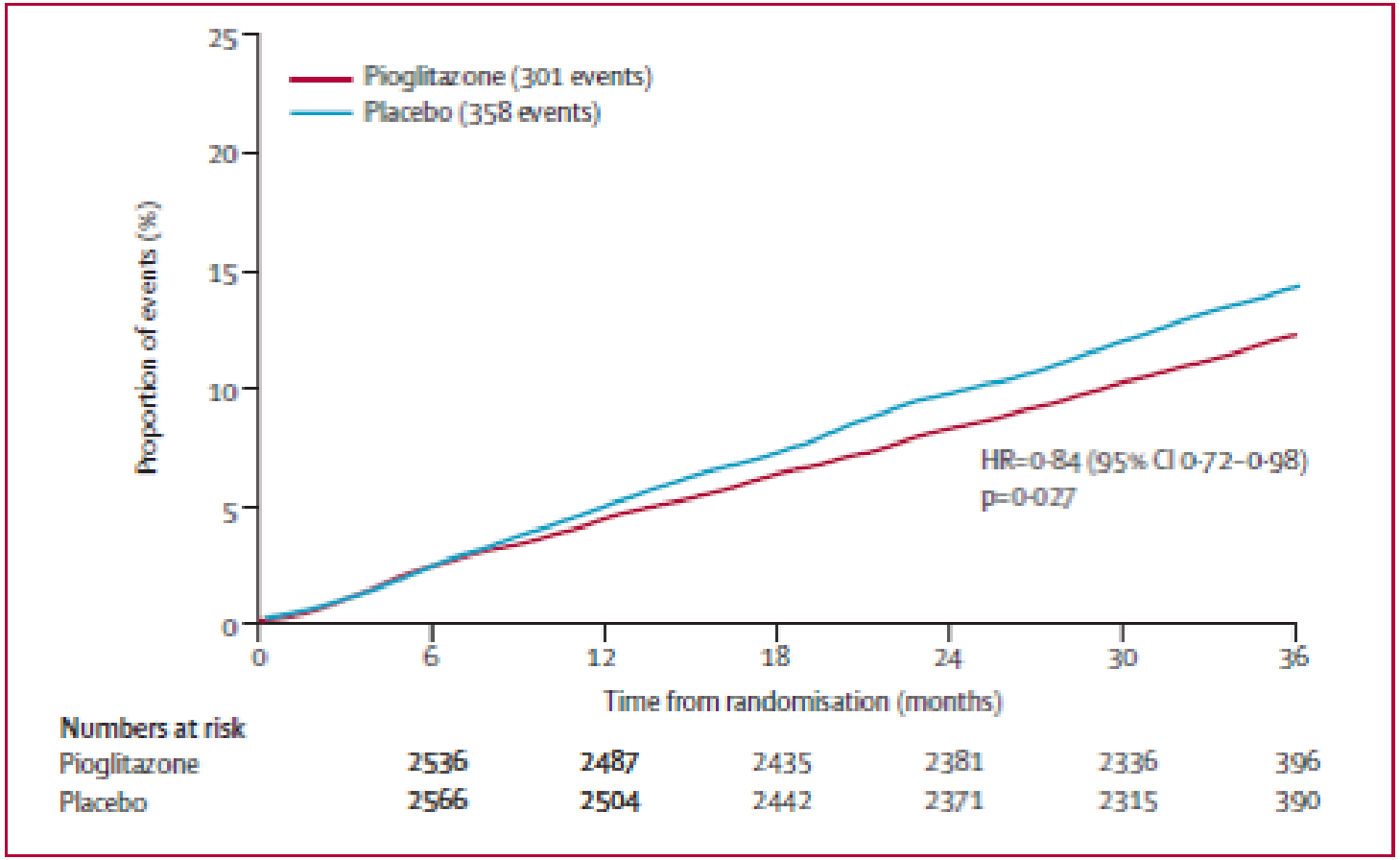
Azoulay L and Suissa S, Diabetes Care 2017

Relevant characteristics of Sulfonylureas and Pioglitazone

	Advantages	Disadvantages
SULFONYLUREAS	↓Microvascular risk	Hypoglycemia
	Extensive experience	Weight gain
	Low cost	Low durability
		Blunts myocardial ischemic preconditioning ?
PIOGLITAZONE	No hypoglycemia	Edema/heart failure
	Durability (?)	Weight gain
	↑HDL-C	Bone fractures
	↓Triglycerides	↑Bladder cancer
	↓CVD events	

ADA-EASD
Inzucchi S et al,
Diabetes Care 2015

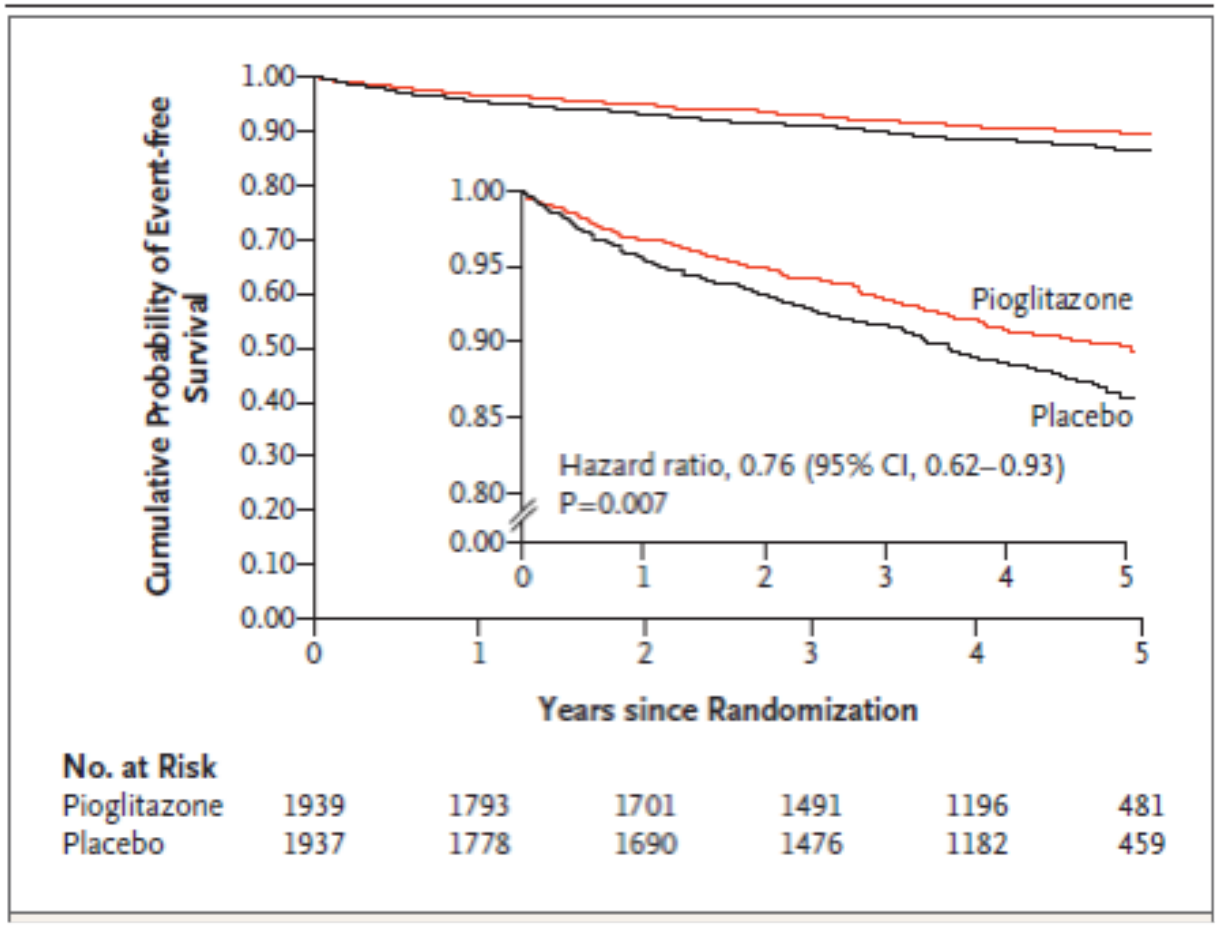
Secondary prevention of macrovascular events with pioglitazone vs placebo in patients with type 2 diabetes in the PROactive Study



PROACTIVE
Dormandy JA et al,
Lancet 2005

Key secondary endpoint: Death from any cause, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke

Effects of Pioglitazone on ischemic cardiovascular events in non-diabetic people with a recent Ischemic Stroke or TIA



IRIS
Kernan W.N. et al,
NEJM 2016

The primary outcome was fatal or nonfatal stroke or myocardial infarction.

Background

The Italian Diabetes Society, a non-profit organization devoted to the dissemination of science and to physicians' education, has promoted a pragmatic trial to compare, in usual clinical practice conditions, the long-term effects of a sulfonylurea or pioglitazone as add-on therapy to metformin in the treatment of T2DM patients poorly controlled with metformin monotherapy.

Aims

To compare the long-term effects of pioglitazone or a sulfonylurea as add-on to metformin with regard to

1) Incidence of CV events and mortality
2) Glucose control and its durability
3) Safety

TOSCA.IT
Thiazolidinediones Or Sulfonylureas and Cardiovascular Accidents Intervention Trial

Thank you for your attention

Diabete Ricerca

SID fondata nel 1964
Società Italiana di Diabetologia



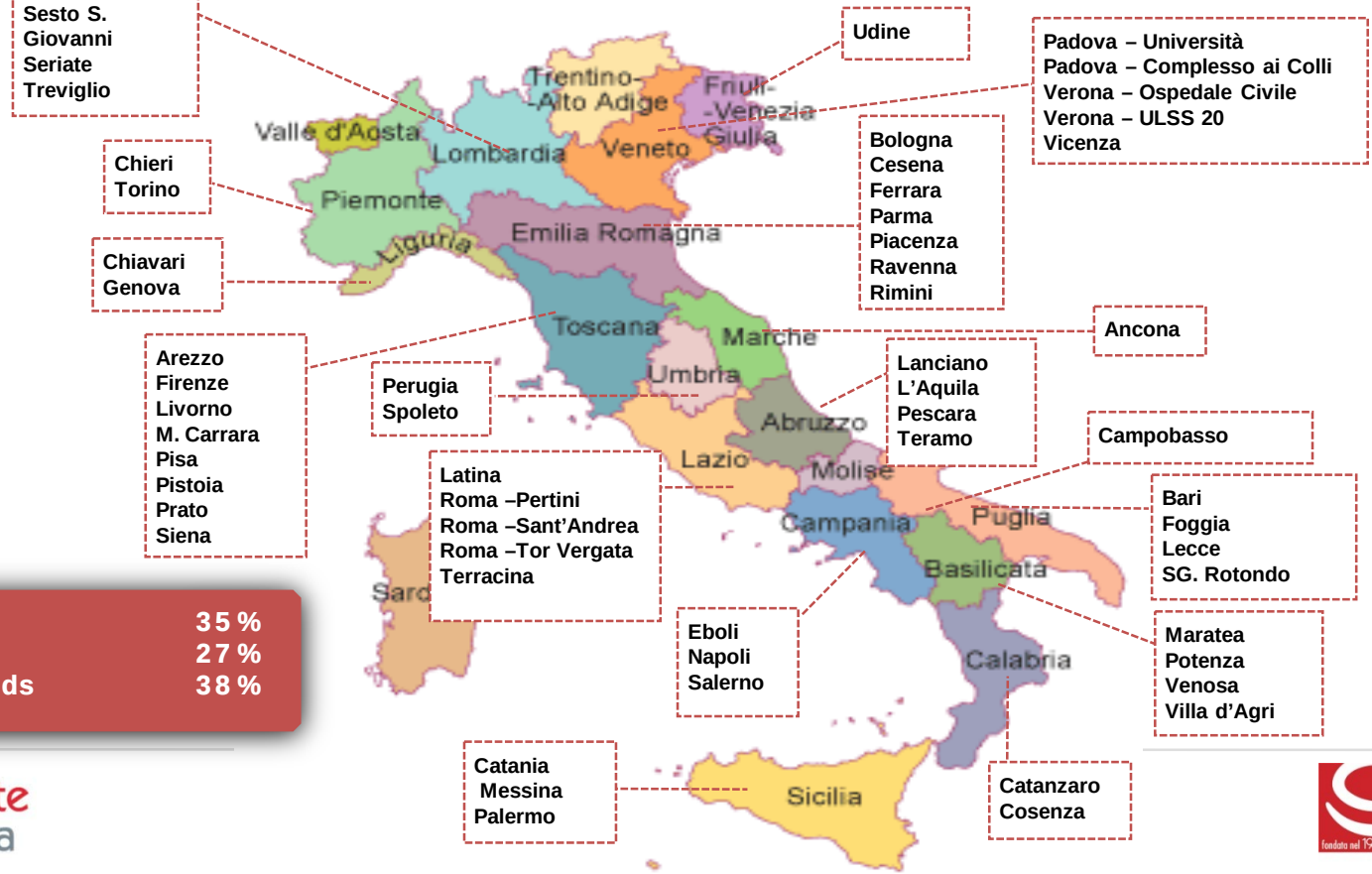
Study Design and Baseline data

Olga Vaccaro
Department of Clinical Medicine and Surgery, Federico II University, Naples, Italy

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fondata nel 1964

Participating centres



North	35 %
Center	27 %
South - islands	38 %

Key inclusion and exclusion criteria

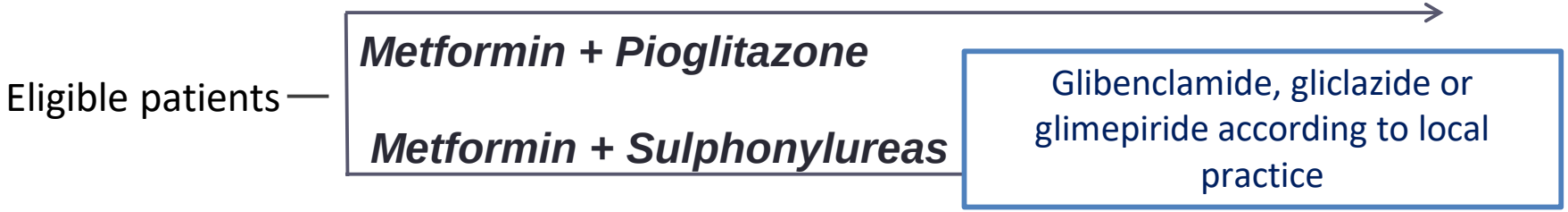
INCLUSION CRITERIA

- Type 2 diabetes
- Age 50-75 years
- BMI 20-45 Kg/m^2
- Metformin monotherapy full dosage (2-3g/day)
- HbA1c 7.0-9.0% (53-75 mmol/mol)

EXCLUSION CRITERIA

- Plasma creatinine ≥ 1.5 mg/dl
- Heart failure (NYHA class 1 or higher)
- Documented cardiovascular events in the prior 6 months
- Liver cirrhosis or severe hepatic dysfunction

Randomization and Masking



Prospective, randomized, open label, blinded end point design

- Participants and investigators were aware of treatment group assignment
- An external Adjudication Committee, blind with regard to treatment, reviewed and adjudicated:

- Components of the primary end point
- Safety end points of interest in relation to the study drugs

Trial procedures

- Permuted block randomization was done centrally and was stratified by centre and prior CVD
- Follow-up visits were scheduled at 1, 3, 6 months from randomization and every 6 months thereafter
- Biochemical measurements were performed at a central laboratory
- There were no pre-specified goals for HbA1c, the investigators were to follow the current recommendations
- In case of HbA1c ≥ 8% (64 mmol/mol) an extra-visit was scheduled three months apart

Study Drug Titration

Metformin dosage constant throughout the study (2-3 g/day)

Add-on drugs were titrated according to HbA1c and home glucose monitoring

- Glibenclamide 5-15 mg/day
- Gliclazide 30-120 mg/day
- Glimepiride 2-6 mg/day
- Pioglitazone 15-45 mg/day

As deemed appropriate by the investigator

Study conduct

Failure of treatment: defined as HbA1c ≥ 8% (64 mmol/mol) on two consecutive occasions three months apart

Rescue insulin treatment: introduced in case of failure of treatment. Basal and subsequently prandial boluses of insulin analogues were added to the study drugs

CV risk factors: Investigators were encouraged to treat major CV risk factors according to targets recommended by current guidelines

Primary and Secondary Cardiovascular Outcomes

Primary outcome:

A composite of all-cause death, non-fatal myocardial infarction (MI) - including silent MI, non-fatal stroke, urgent coronary revascularization

Key secondary outcome:

A composite of sudden death, fatal and non-fatal MI (including silent MI), fatal and non-fatal stroke, leg amputation above the ankle, any revascularizations

Expanded secondary outcome:

A composite of the primary outcome plus heart failure, any revascularization, angina confirmed by new ECG abnormalities, intermittent claudication with an ankle/brachial index <0.90.

Other Secondary Outcomes

Glucose control

- Failure of treatment
- HbA1c

Body weight, Waist circumference

CV risk factors

- Plasma lipids
- Blood pressure
- Microalbuminuria
- C-reactive protein

New or worsening nephropathy

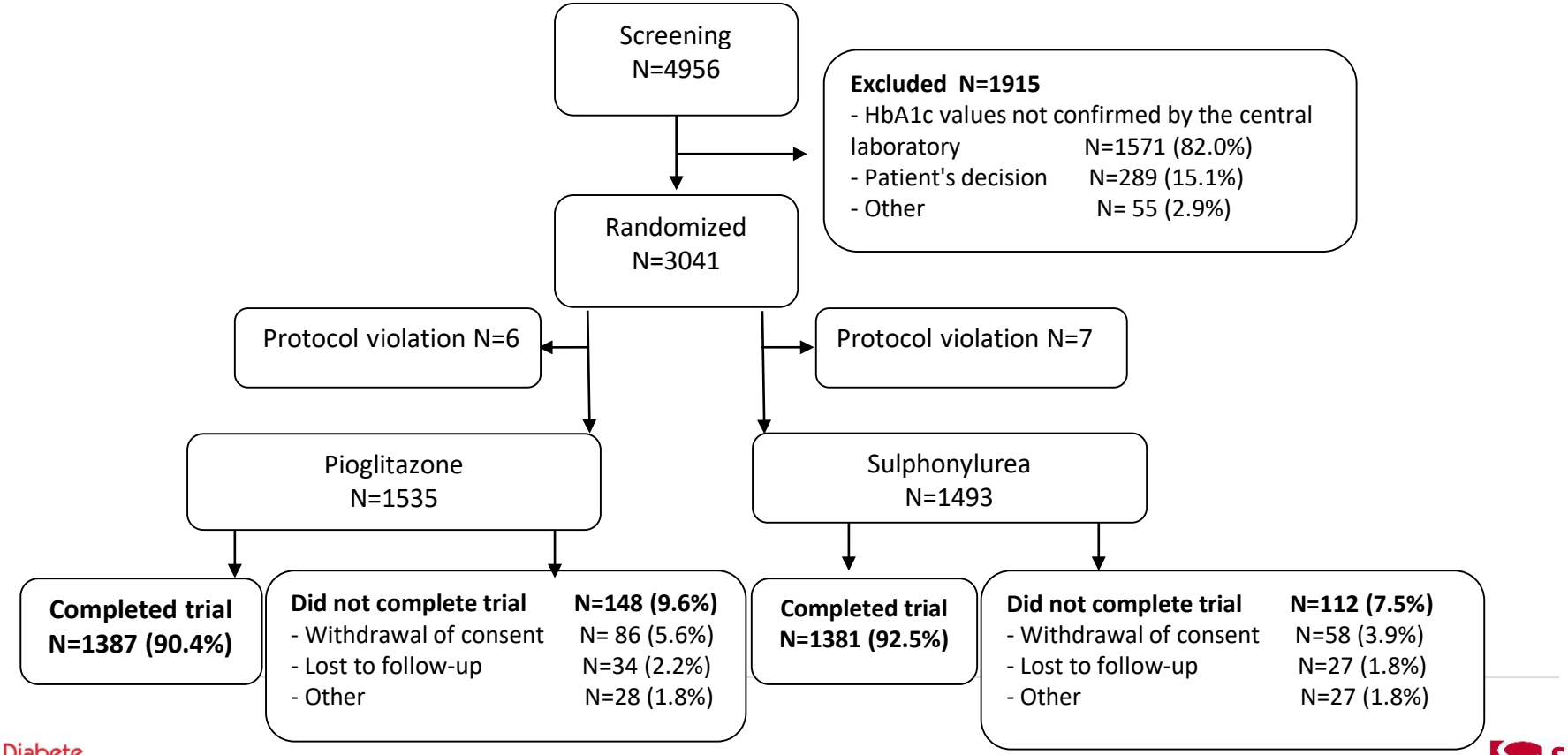
- New onset macroalbuminuria
- Doubling of baseline creatinine
- Permanent dialysis

Safety Outcomes

- Hypoglycemia
- Heart failure*
- Neoplasms*
- Pathological fractures*
- Macular edema*

*Confirmed by the adjudication committee

Study Participant Disposition



Study Timeline

- September 18, 2008: First patient entered
- January 15, 2014: Last patient entered

The efficacy analysis was event driven
The study was to be continued until 498 end point events had occurred

Futility analysis, performed per recommendation of the Data Safety Monitoring Board due to low event rate, was the reason of premature study discontinuation on May 2017.

Follow-up

	Pioglitazone N (%)	Sulphonylureas N (%)
Intention-to-treat population	1535	1493
Median follow-up-months (IQ range)	57.6 (42.0 - 60.2)	57.1 (42.4 - 60.2)
Discontinued study drug prematurely	432 (28.1)	238 (15.9)*

* p<0.001

Diabete Ricerca

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Baseline Characteristics

	Pioglitazone (n=1535)	Sulfonylurea (n=1493)
Age - years	62.3 (6.5)	62.2 (6.5)
Male sex - no. (%)	909 (59.2)	865 (57.9)
BMI - kg/m^2	30.2 (4.4)	30.4 (4.5)
Duration of diabetes - years	8.4 (5.6)	8.5 (5.8)
HbA1c - %	7.7 (0.5)	7.7 (0.5)
HbA1c - mmol/mol	60.3 (5.4)	60.5 (5.6)

Prevalent CV disease at baseline

	Pioglitazone (n=1535)	Sulphonylurea (n=1493)
Prior CVD≠	187 (12.2)	148 (9.9)
Prior myocardial infarction	109 (7.1)	86 (5.8)
Prior stroke	28 (1.8)	13 (0.9)
Prior acute coronay syndrome	39 (2.5)	40 (2.7)
Prior coronary revascularization	105 (6.8)	101 (6.8)
Prior extra-coronary revascularization	14 (0.9)	12 (0.8)

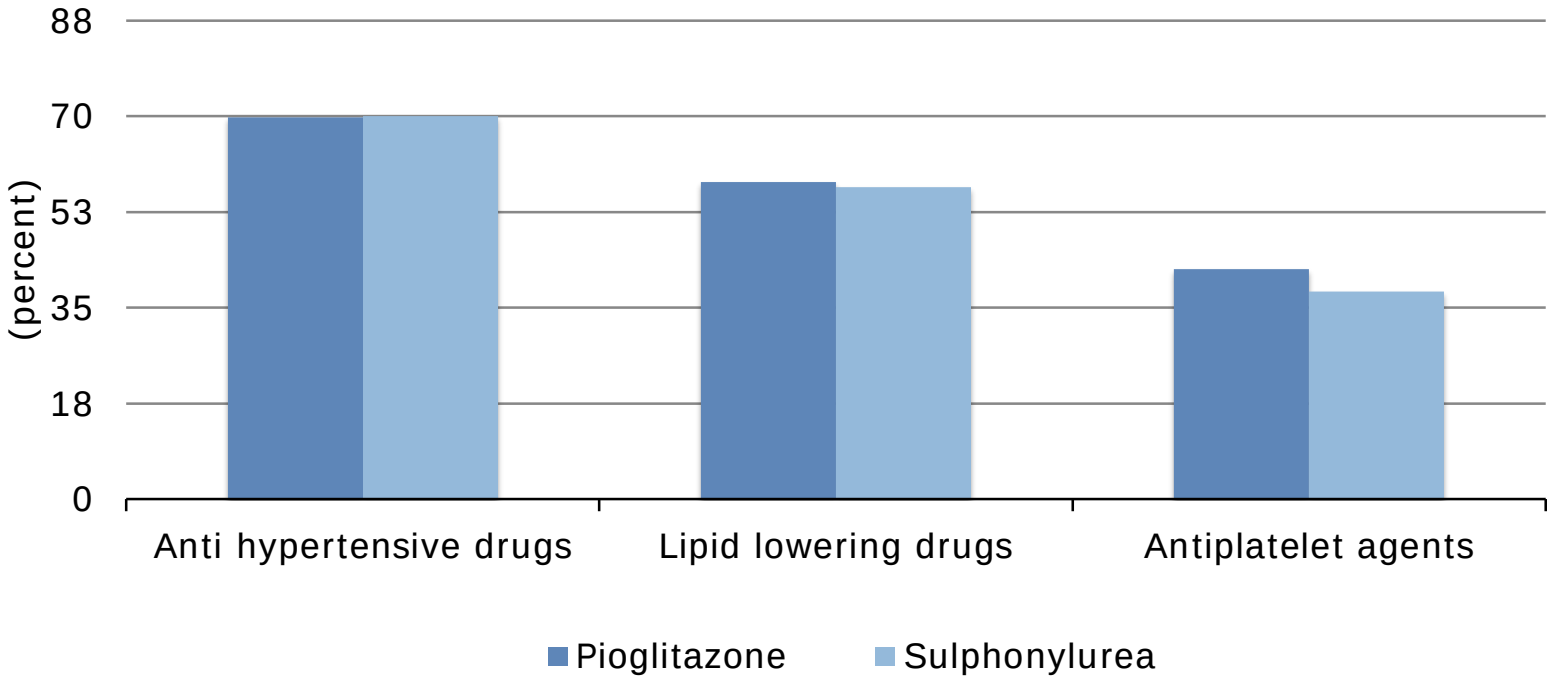
≠ Some patiens had more than one condition

Cardiovascular risk factors at baseline

	Pioglitazone (n=1535)	Sulfonylurea (n=1493)
LDL Cholesterol – (mmol/l)	2.67 (0.81)	2.66 (0.82)
HDL Cholesterol - (mmol/l)	1.20 (0.34)	1.20 (0.33)
Triglycerides - (mmol/l)	1.72 (1.04)	1.73 (0.93)
Systolic BP - mmHg	134.3 (15.1)	133.7 (14.2)
Diastolic BP- mmHg	79.5 (8.7)	79.7 (8.1)
Microalbuminuria – no. (%)	321 (22.1)	312 (21.9)
Smokers –no. (%)	281 (18.3)	252 (16.9)

Data is mean (SD) or N (%)

Treatment of CV risk factors at baseline



Summary

TOSCA.IT is a pragmatic trial with:

- Head to head comparison of two active, inexpensive and widely available treatments
- Open label design
- Blind adjudication of cardiovascular end points
- Blind adjudication of safety endpoints (heart failure, pathological fractures, cancers, macular edema)
- Centralized biochemical measurements
- Long term follow-up
- Population at low cardiovascular risk

    11% prevalence of prior CVD

    Optimal control of major cardiovascular risk factors



Efficacy on Blood Glucose Control and Cardiovascular Risk Factors Profile

Stefano Del Prato

Dept. of Clinical & Experimental Medicine University of Pisa, Italy

Diabete Ricerca

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Disclosures

Consultant - AstraZeneca, Boehringer Ingelheim, Eli Lilly & Company, GlaxoSmithKline, Hanmi Pharmaceuticals, Intarcia Therapeutics, Janssen Pharmaceuticals, Merck Sharp & Dohme, Novartis Pharmaceuticals, Novo Nordisk, Sanofi, Servier,

Takeda Pharmaceuticals

Research support - AstraZeneca, Boehringer Ingelheim,

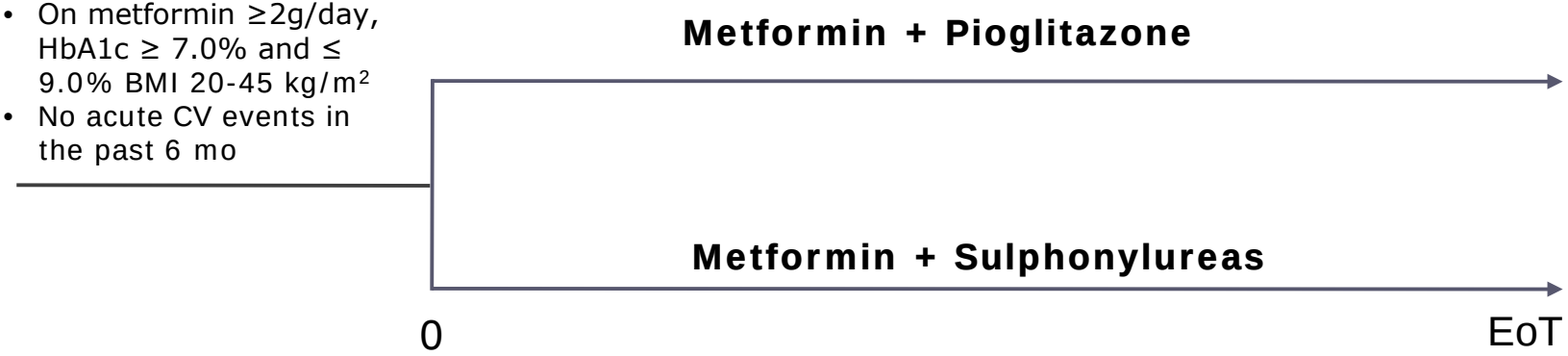
Merck Sharp & Dohme, Novartis Pharmaceuticals

Study Design

Multicenter, randomized, active-controlled, single-blind CV outcome trial (NCT00700856)

Screening period	Randomized, double-blind short-term treatment period

- T2DM for at least 2 year,
- Age 50 to 75 years,
- On metformin ≥2g/day, HbA1c ≥ 7.0% and ≤ 9.0% BMI 20-45 kg/m^2
- No acute CV events in the past 6 mo

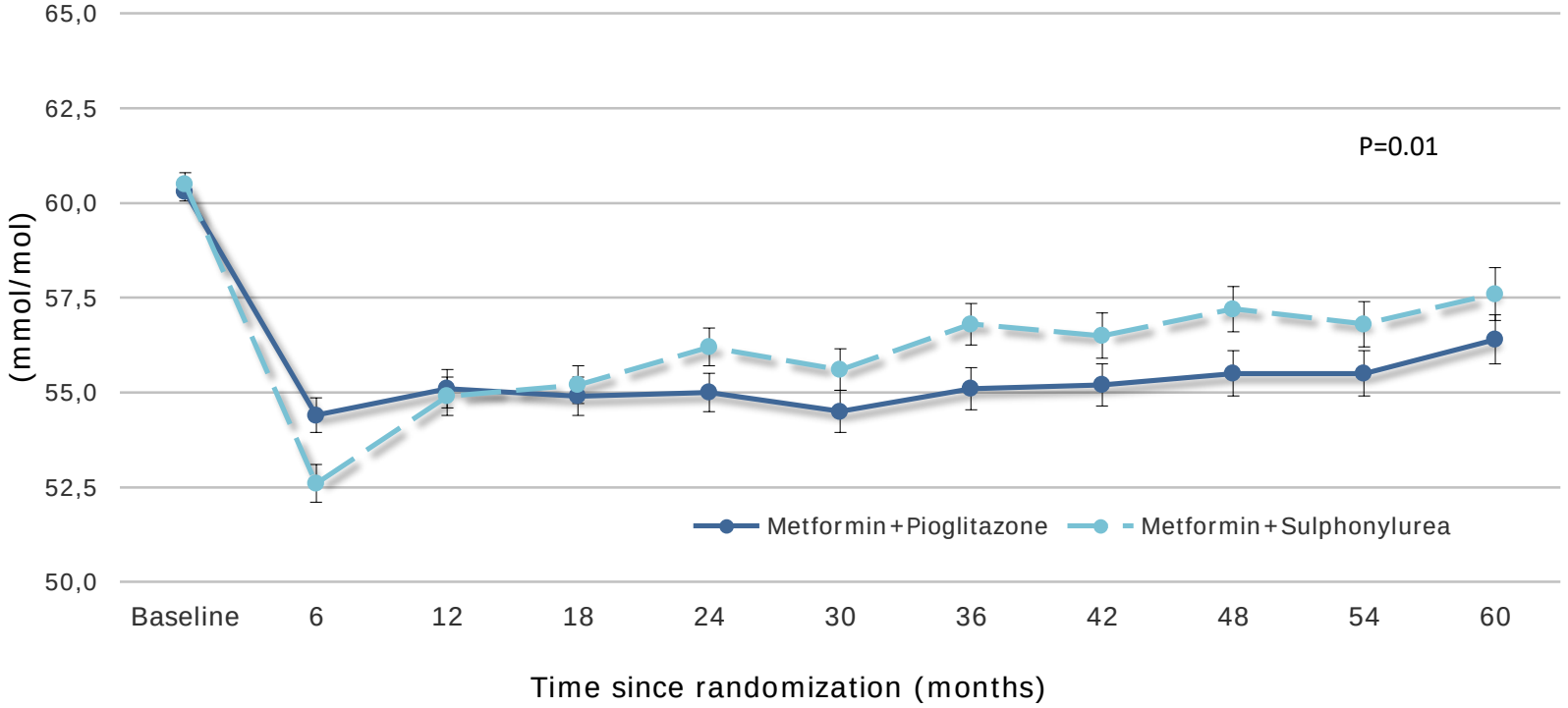


HbA_{1c}, glycated haemoglobin; BMI, body mass index; DAPA, dapagliflozin; FPG, fasting plasma glucose; MET, metformin; SAXA, saxagliptin; SITA, sitagliptin

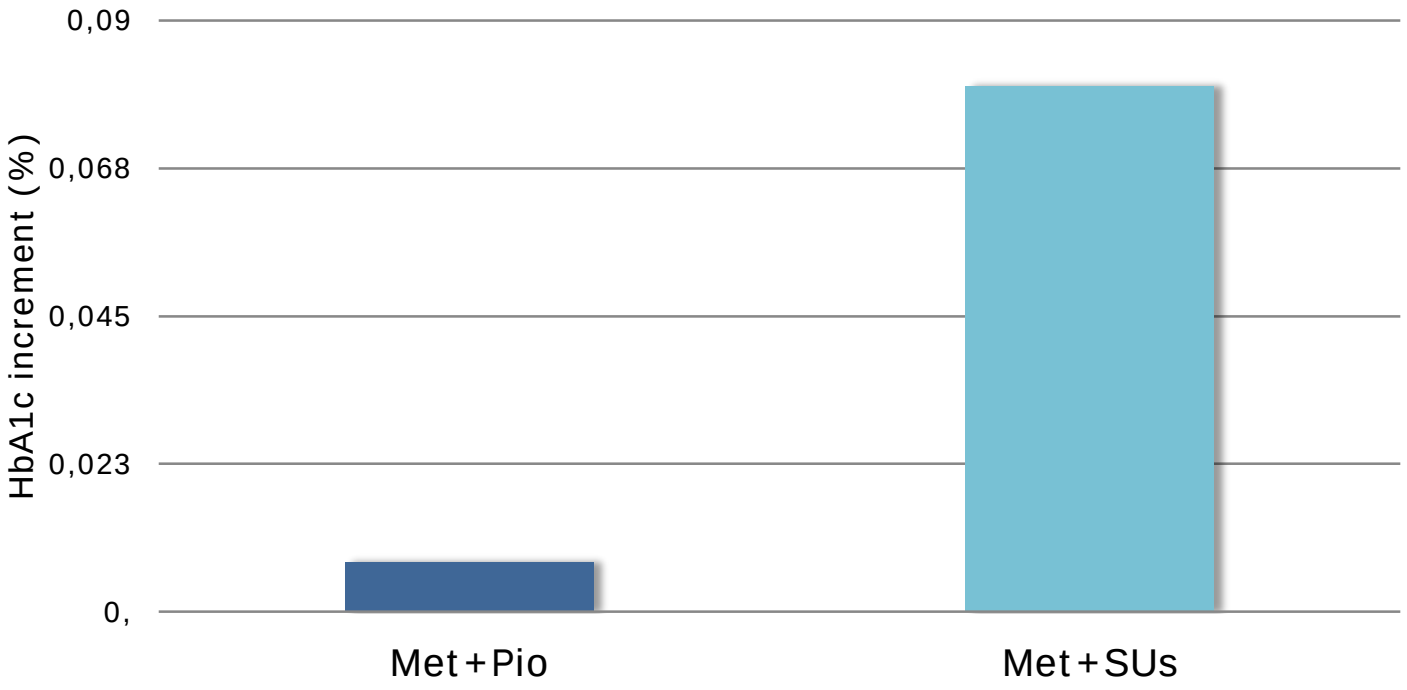
Study Medications

	Metformin + Pioglitazone (average dose, mg)	Metformin + Sulphonylurea (average dose, mg)
Pioglitazone	23.0±8.6	---
Glibenclamide (1.6%)	---	7.6±4.0
Glimepiride (49.9%)	---	2.5±0.9
Gliclazide (48.5%)	---	42.0±18.6

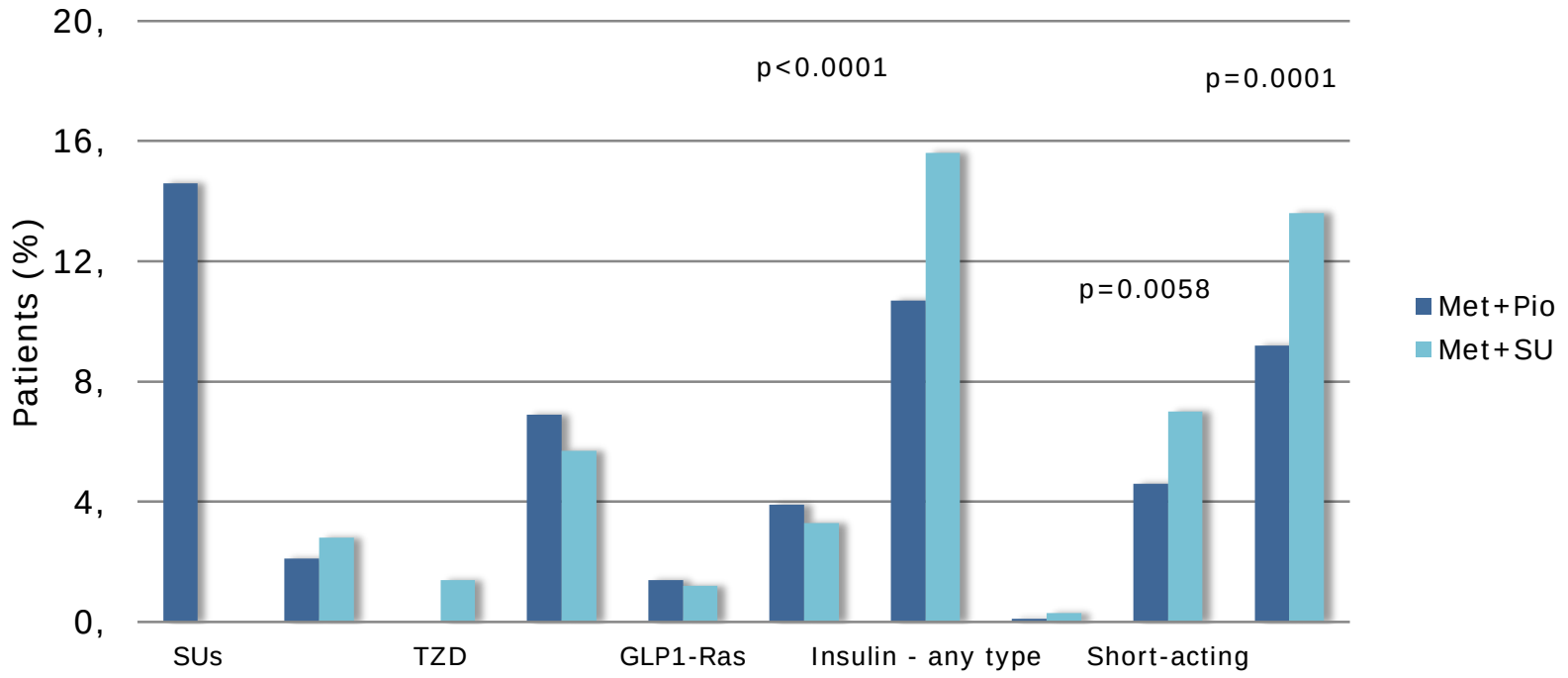
HbA1c


65,0
62,5
60,0
57,5
55,0
52,5
50,0
(mmol/mol)
P=0.01
Metformin+Pioglitazone
Metformin+Sulphonylurea
Baseline
6
12
18
24
30
36
42
48
54
60
Time since randomization (months)

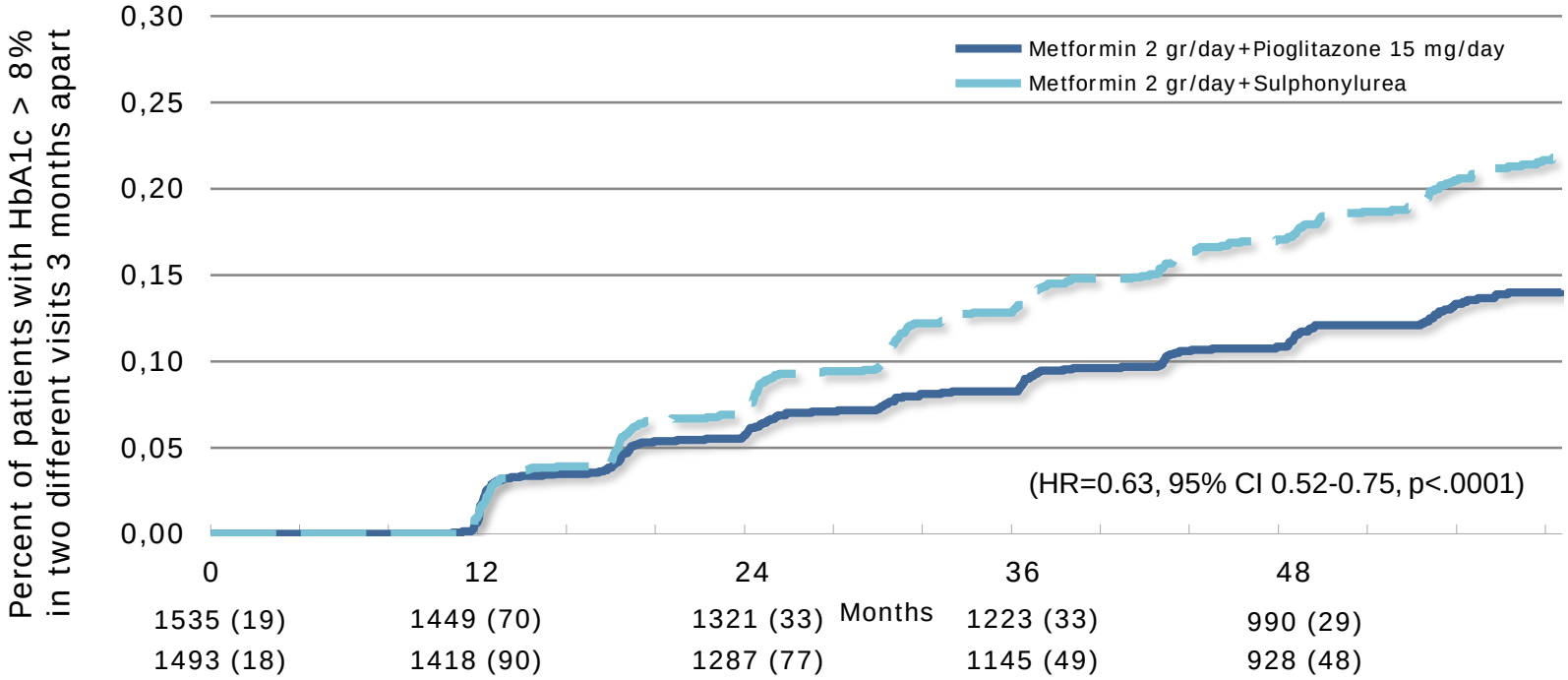
Annual HbA1c Increment



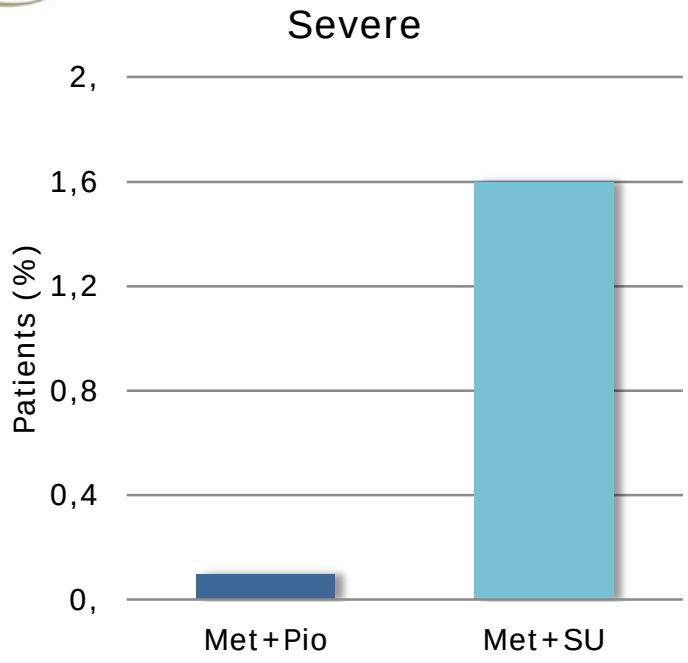
Introduction of Glucose-lowering Medications during the Trial

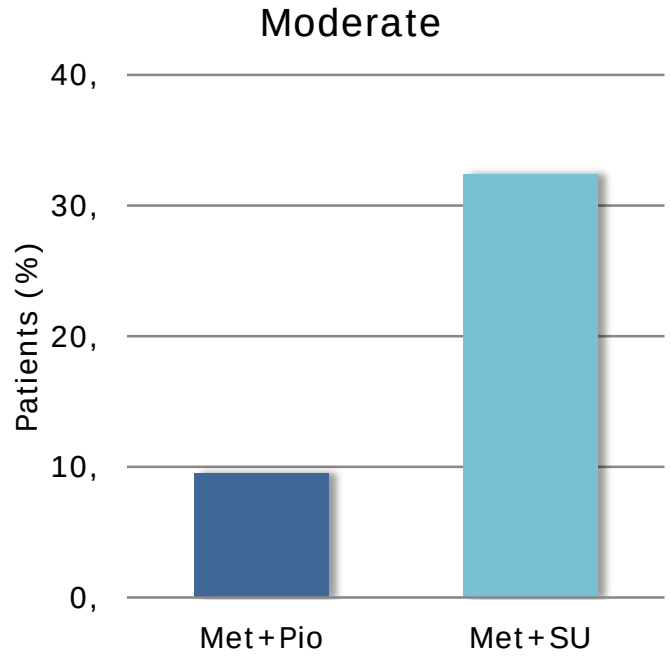


Time to Failure of Study Treatments



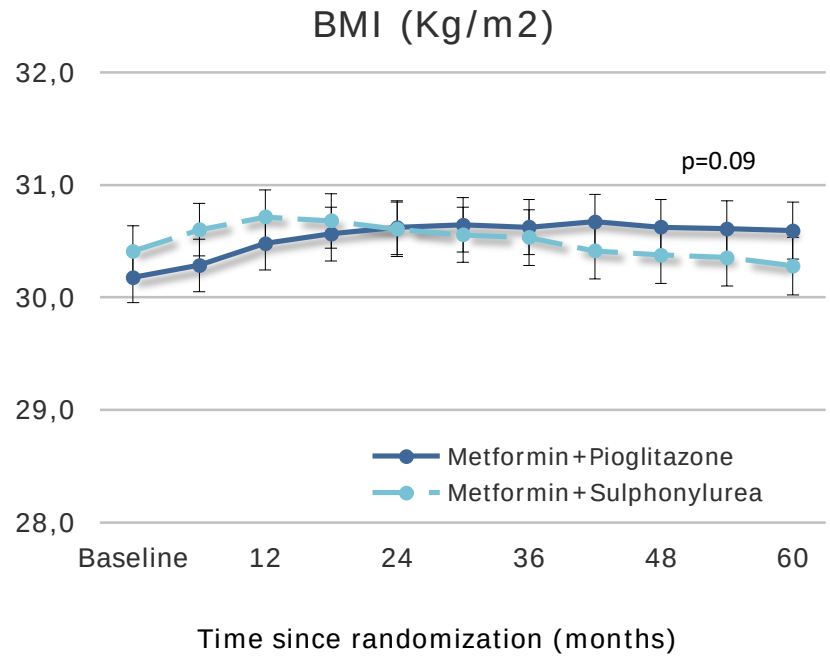
Hypoglycaemia*

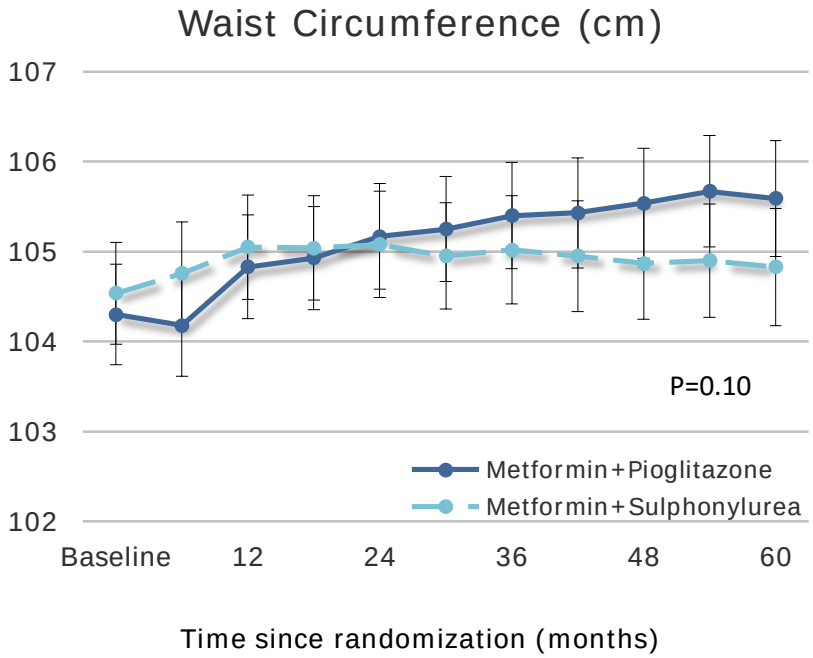




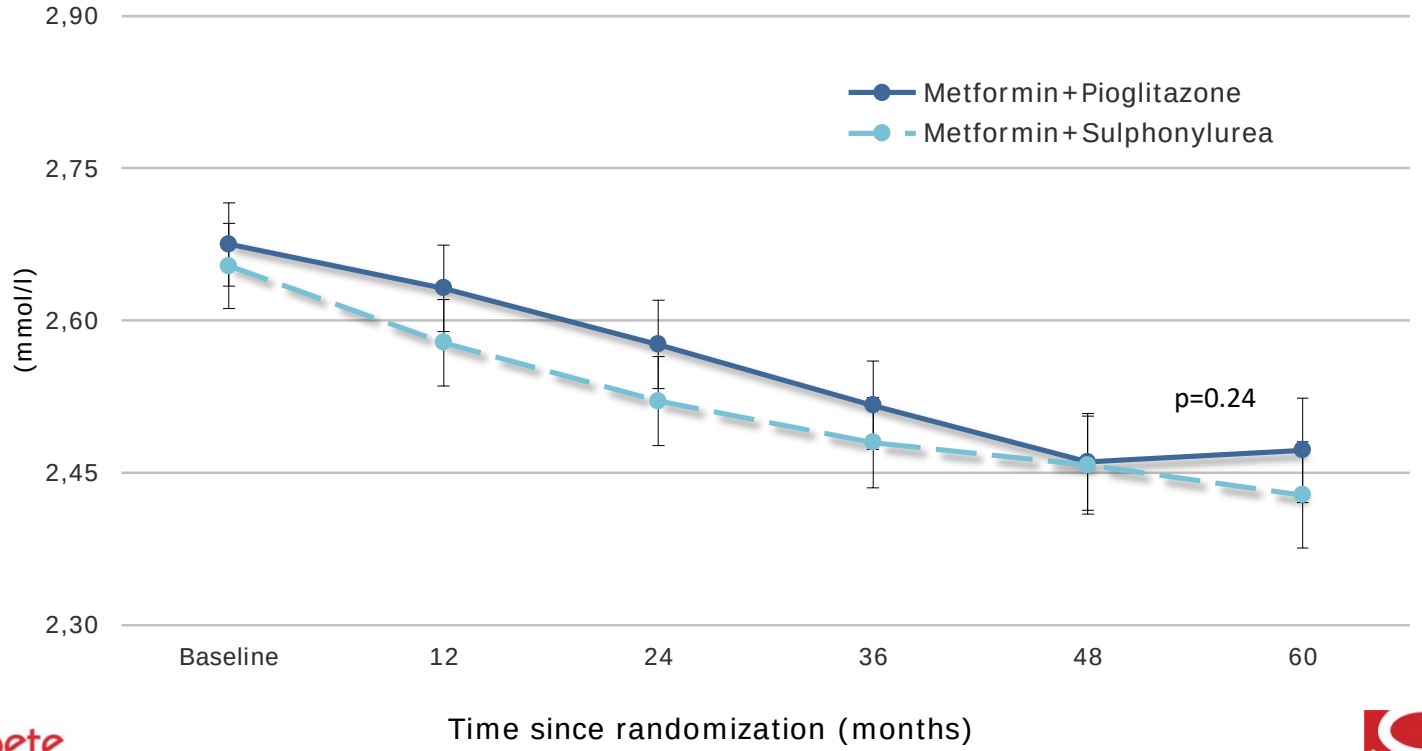
*Plasma glucose <60mg/dl; moderate: not requiring assistance; severe: requiring assistance

Body Weight Related Measurements

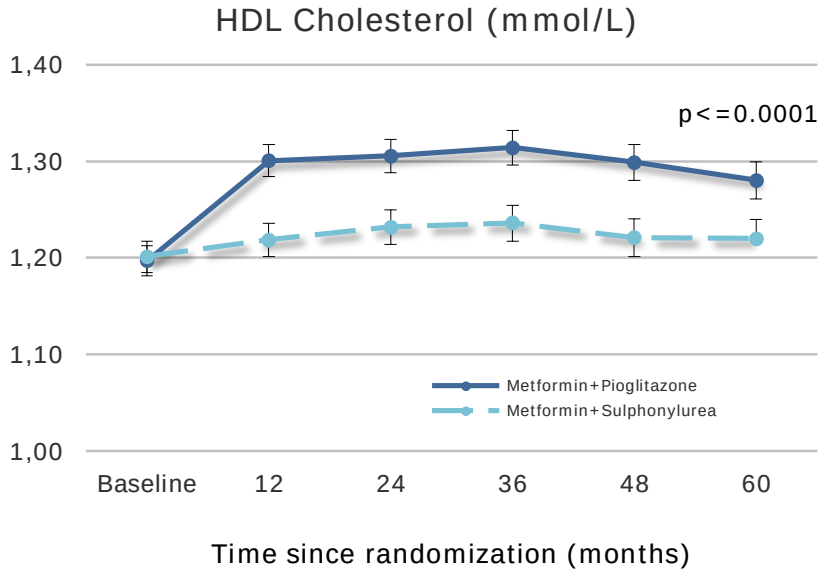


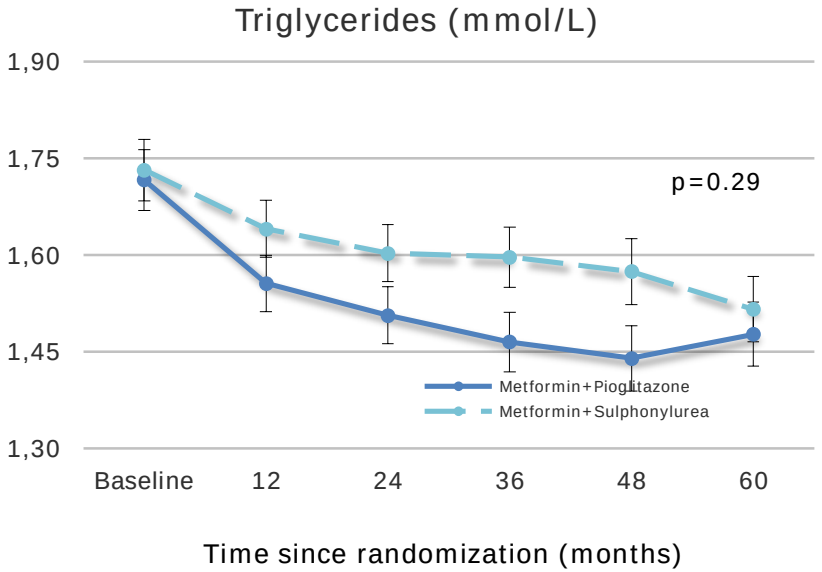


Lipid Parameters: LDL-Cholesterol

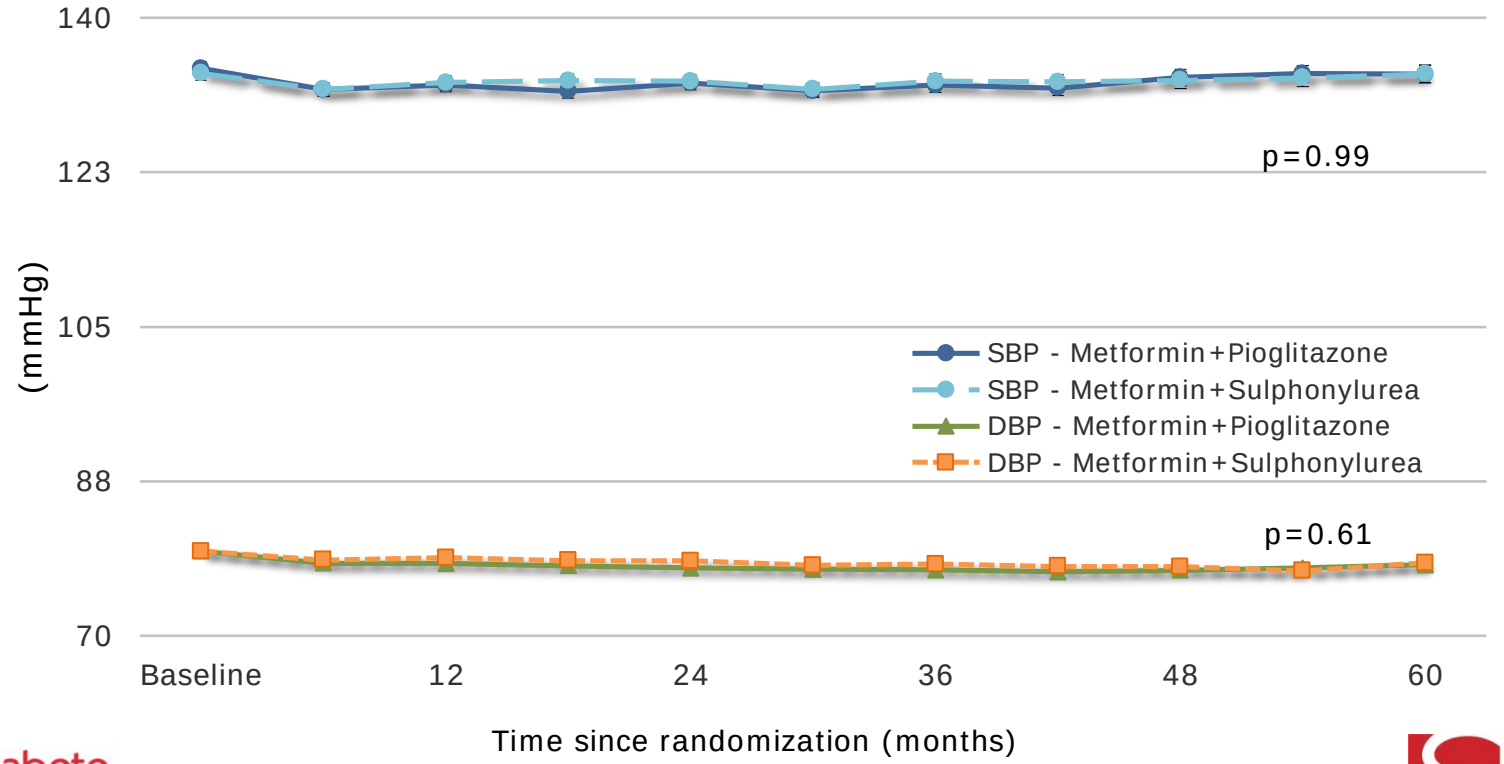


Lipid Parameters: HDL-Cholesterol and Triglycerides

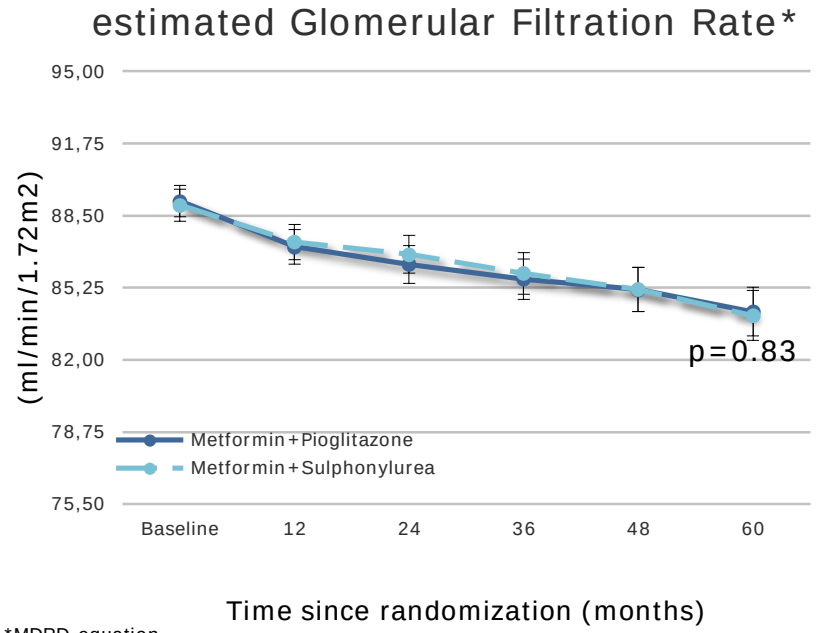


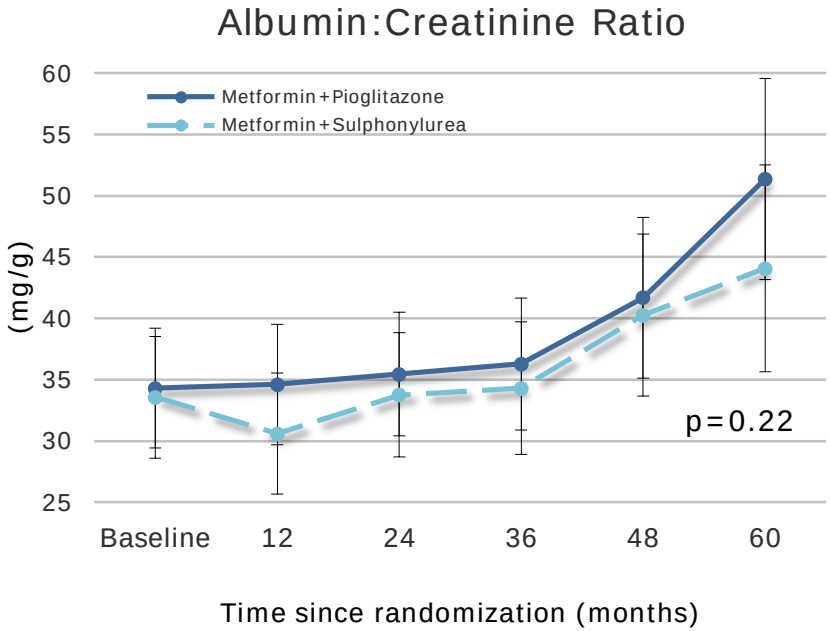


Systolic & Diastolic Blood Pressure



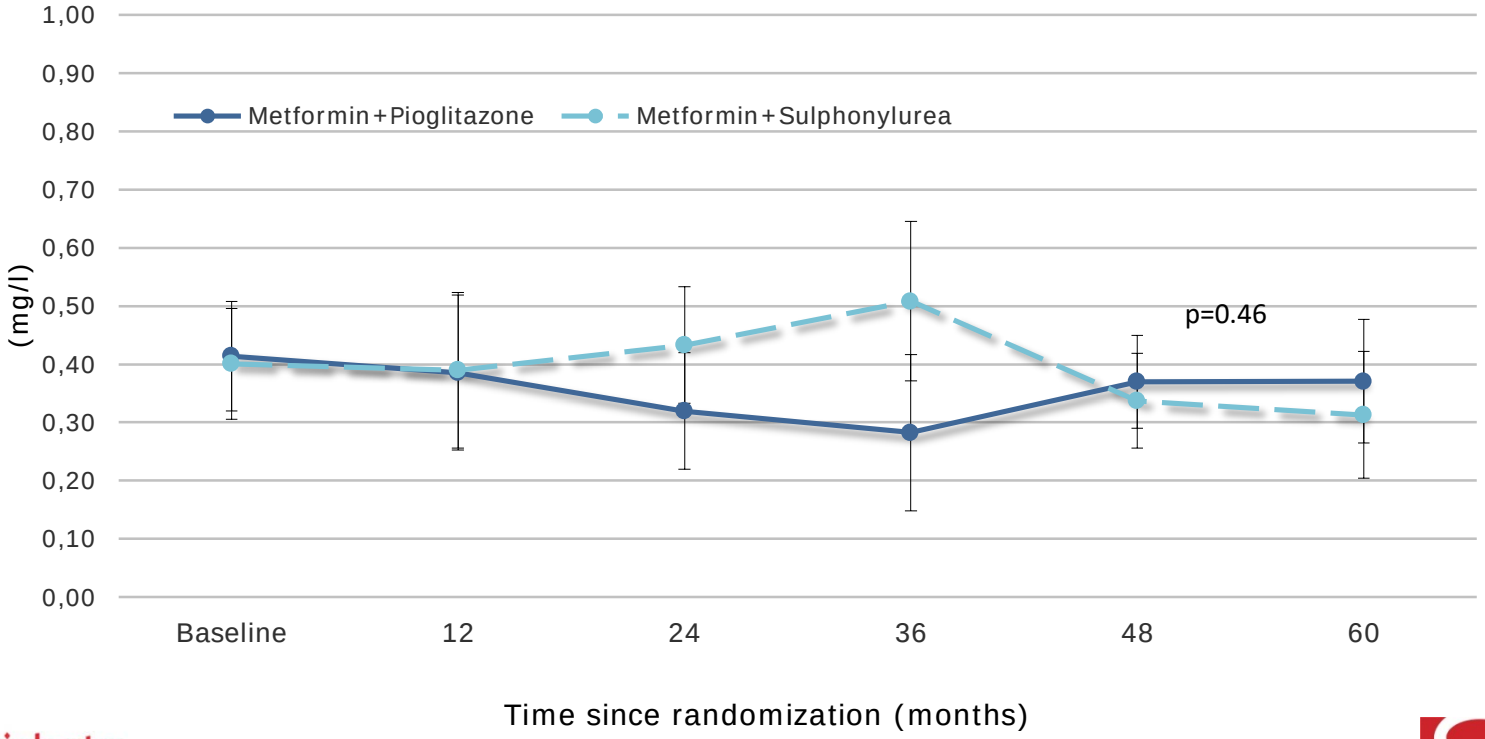
Renal Function Parameters





*MDRD equation

hs-C-Reactive Protein



Summary

- Slightly though significantly better glycemic control was maintained with pioglitazone than with sulphonylureas
- Insulin rescue therapy was more common in the SU treatment arm
- Hypoglycemic events of moderate intensity were more frequent in SU patients; severe hypoglycemic events were rare, although more frequent with SUs
- There were no differences between treatments with respect to LDL-cholesterol and triglycerides, though PIO was associated with higher level of HDL-cholesterol
- There were no differences with respect to body weight, waist circumference, blood pressure, ACR, eGFR, and hs-PCR



Cardiovascular outcomes

Antonio Nicolucci

Center for Outcomes Research and Clinical Epidemiology - Pescara, Italy

Disclosures

No conflict of interest in the field covered by the lecture

Primary outcome

Time to first MACE composed of:

- all-cause death
- non-fatal myocardial infarction (MI) - including silent MI
- non-fatal stroke
- urgent coronary revascularization

MACE: major adverse cardiovascular event

Statistical analysis

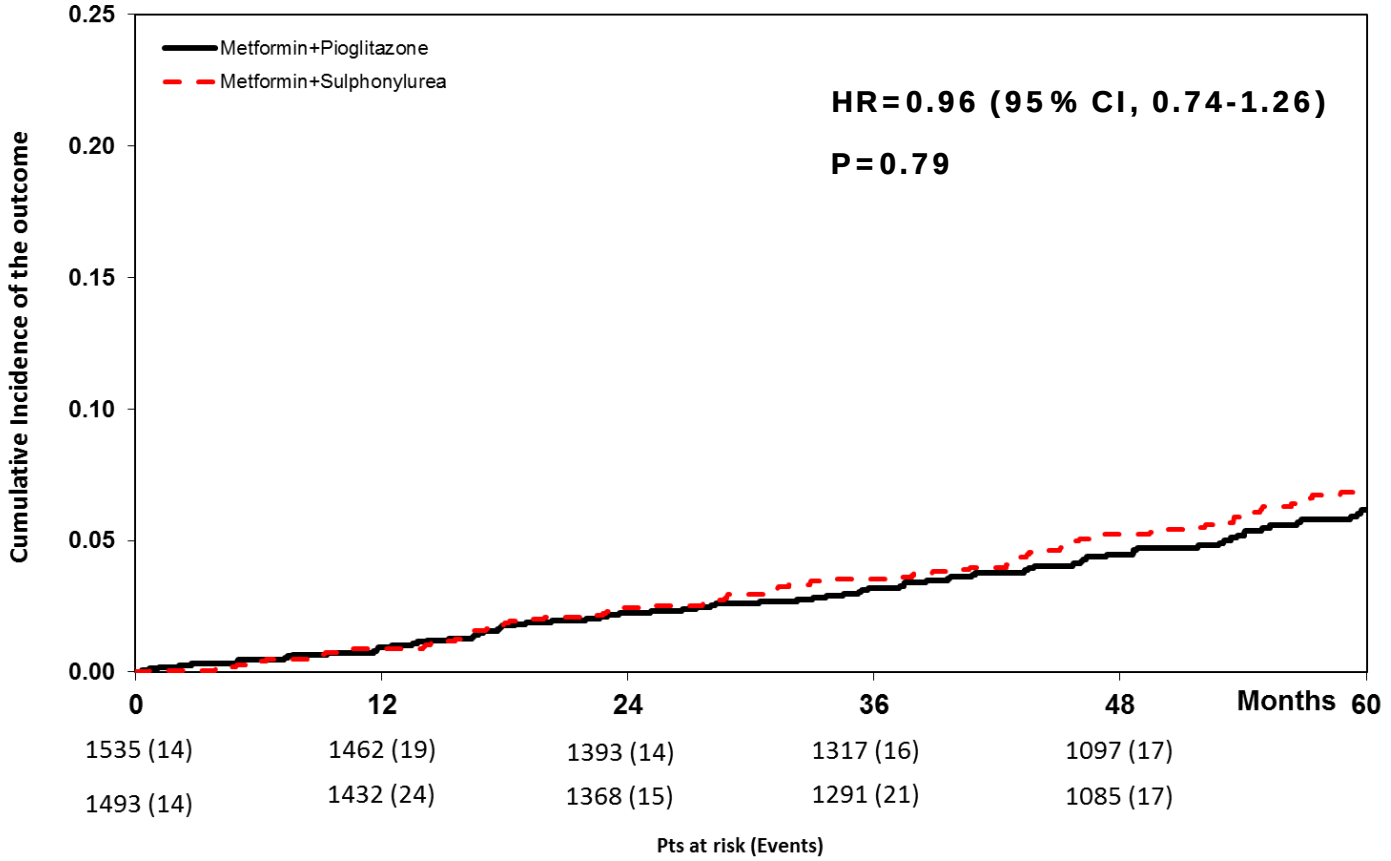
Primary statistical analysis:	Cox proportional hazards model with treatment as a covariate
Test for the primary outcome:	Superiority (HR=0.80; α=0.05; 1-β=0.80)

Statistical analysis

Timing for primary statistical analysis:	Event driven (498 events)
Final analysis:	Based on the results of futility analysis, the trial was closed after the adjudication of 213 events (5% residual probability of showing an HR=0.80)

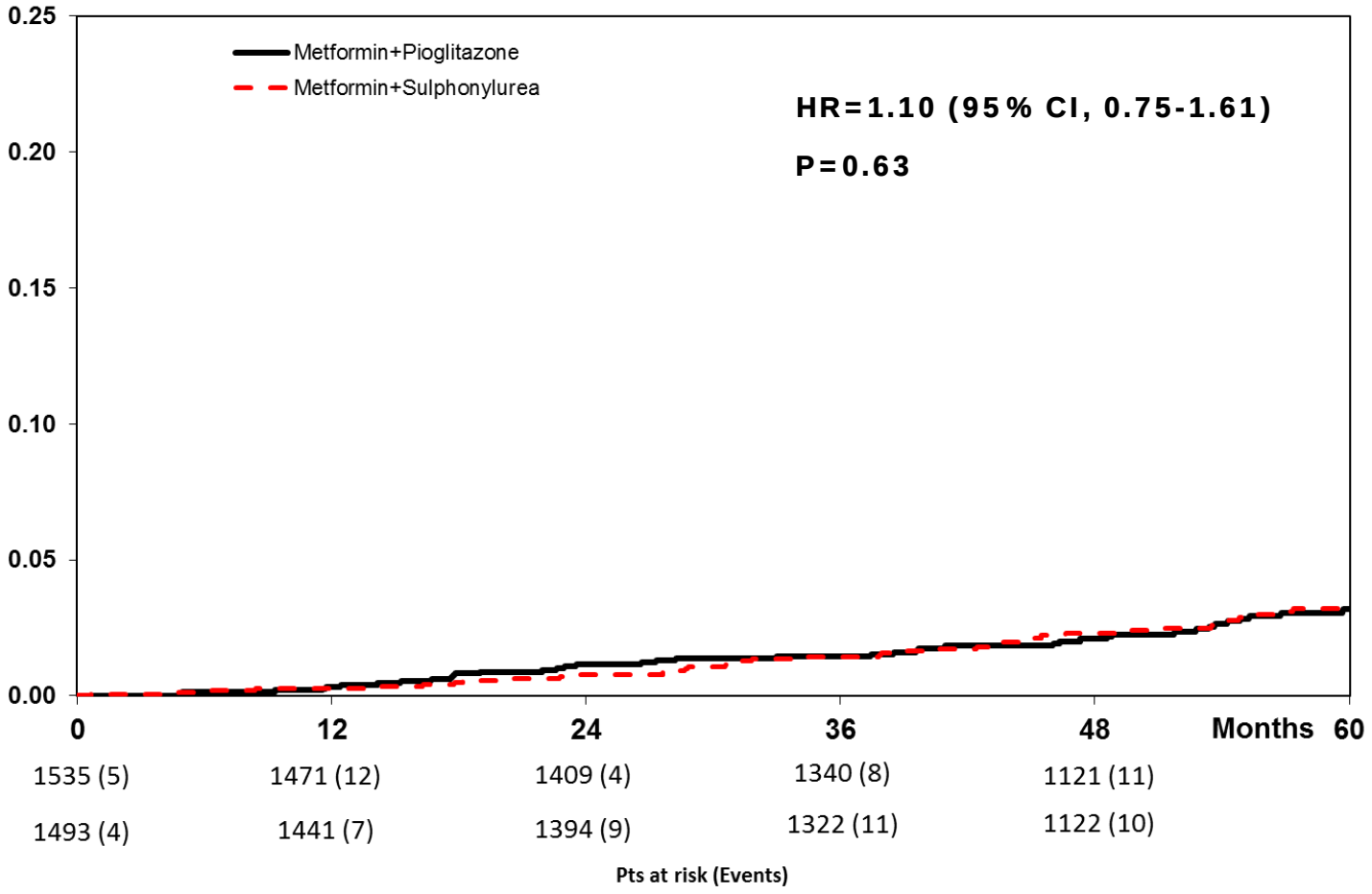
Primary outcome

All-cause death, non-fatal MI - including silent MI, non-fatal stroke, urgent coronary revascularization

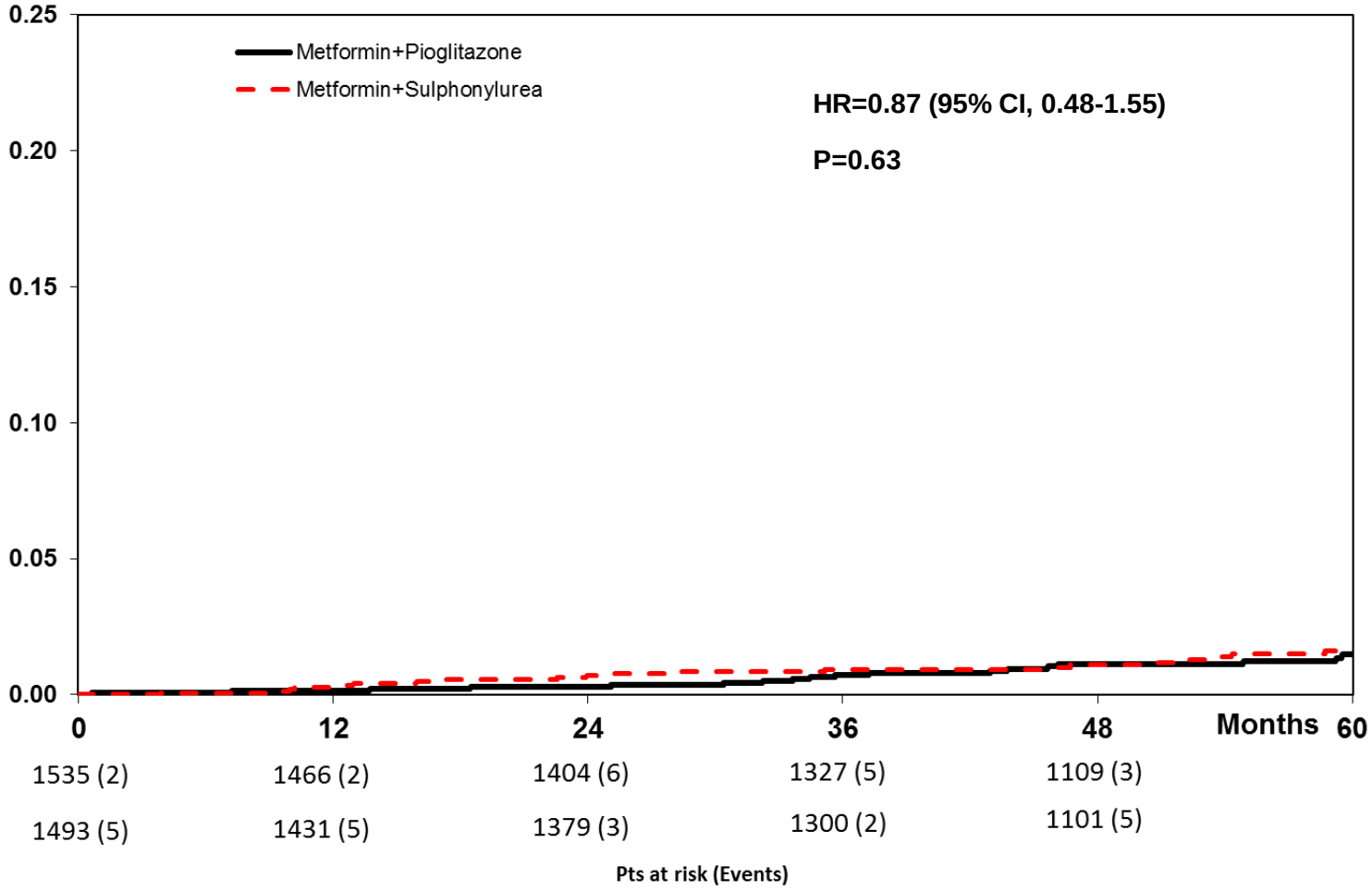


The cumulative incidences were estimated with the use of the Kaplan –Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. CI: confidence interval; HR: hazard ratio.

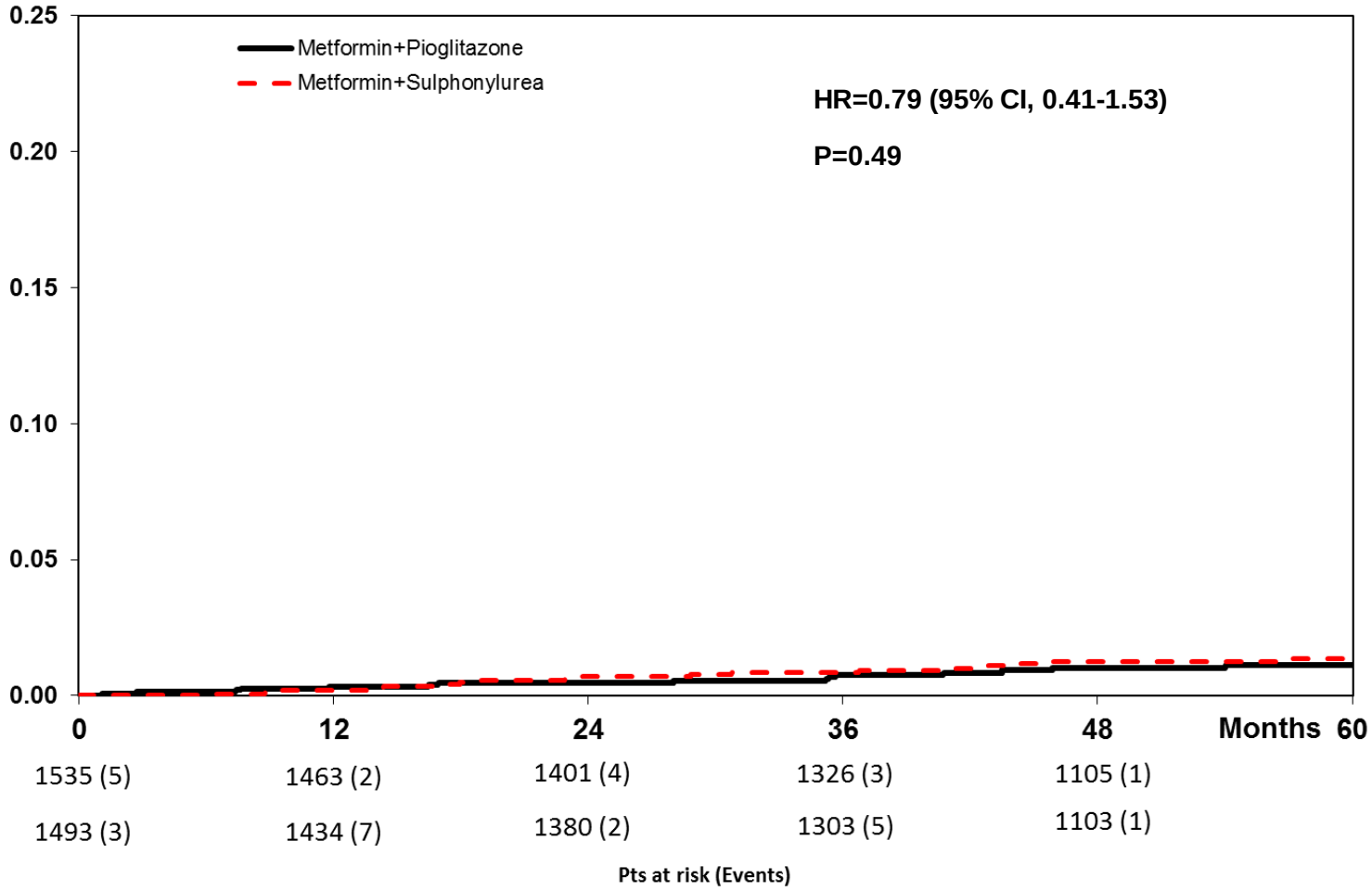
All-cause death



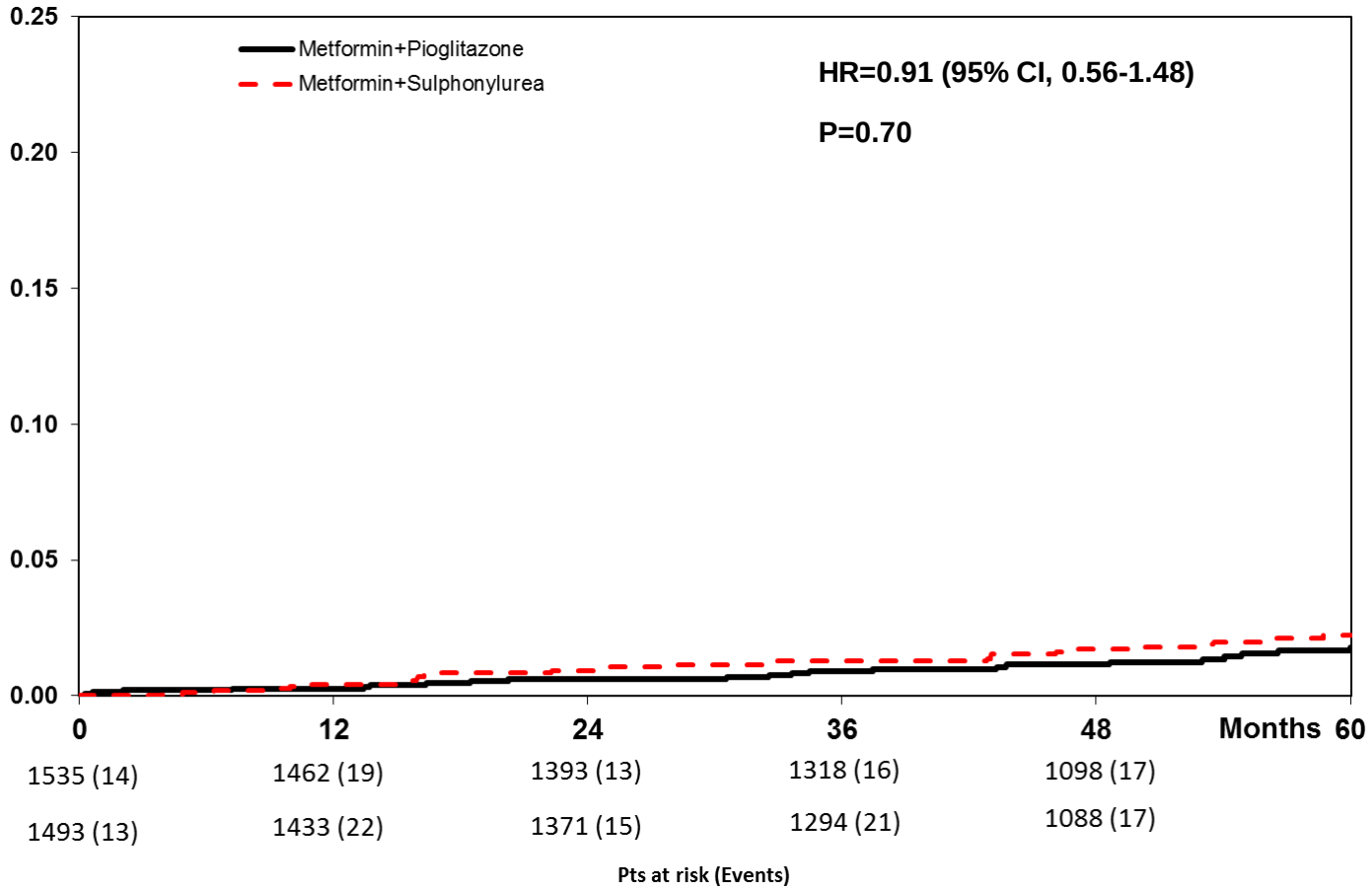
Time to non-fatal MI



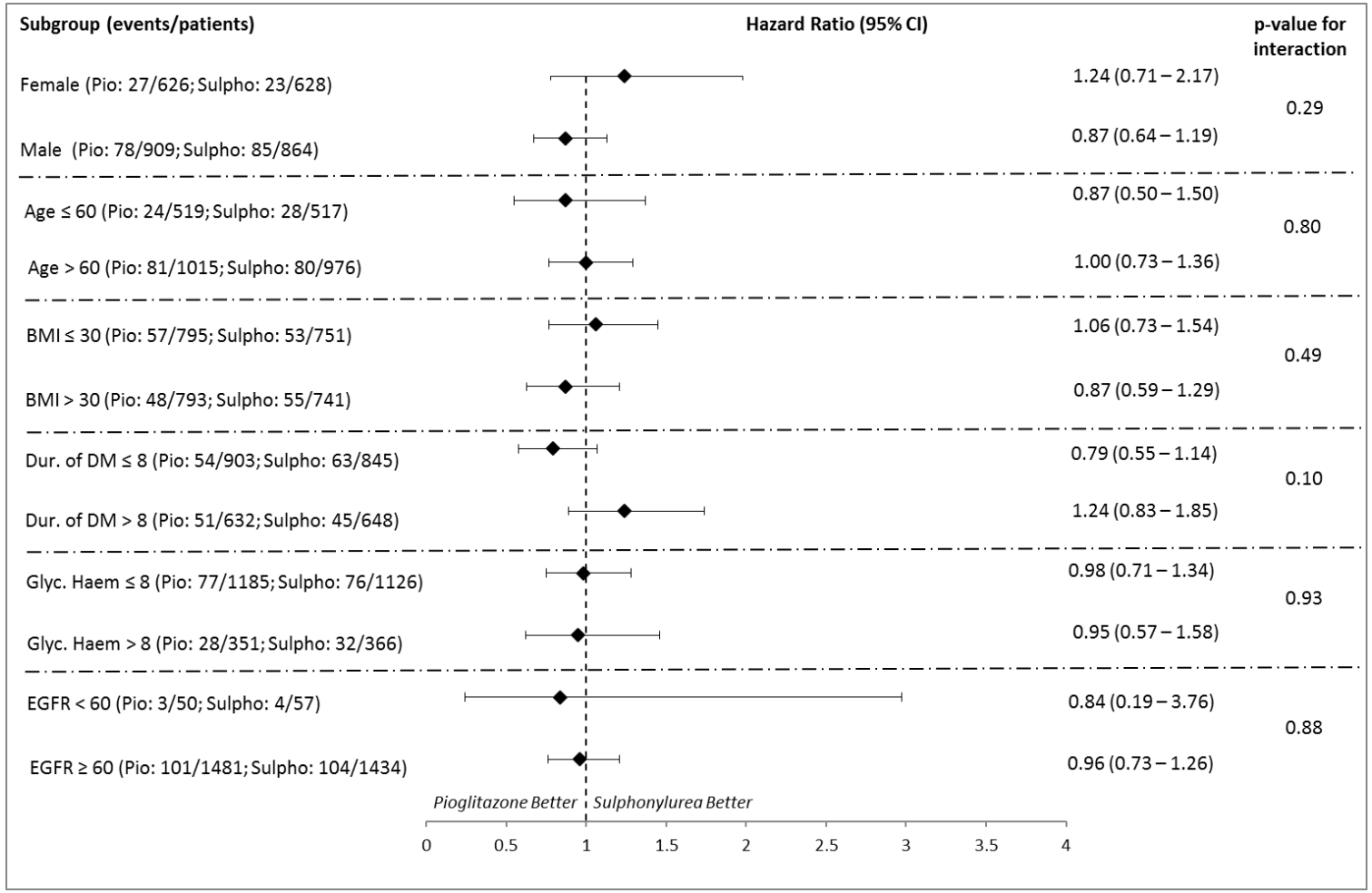
Time to non-fatal stroke



Time to urgent coronary revascularization

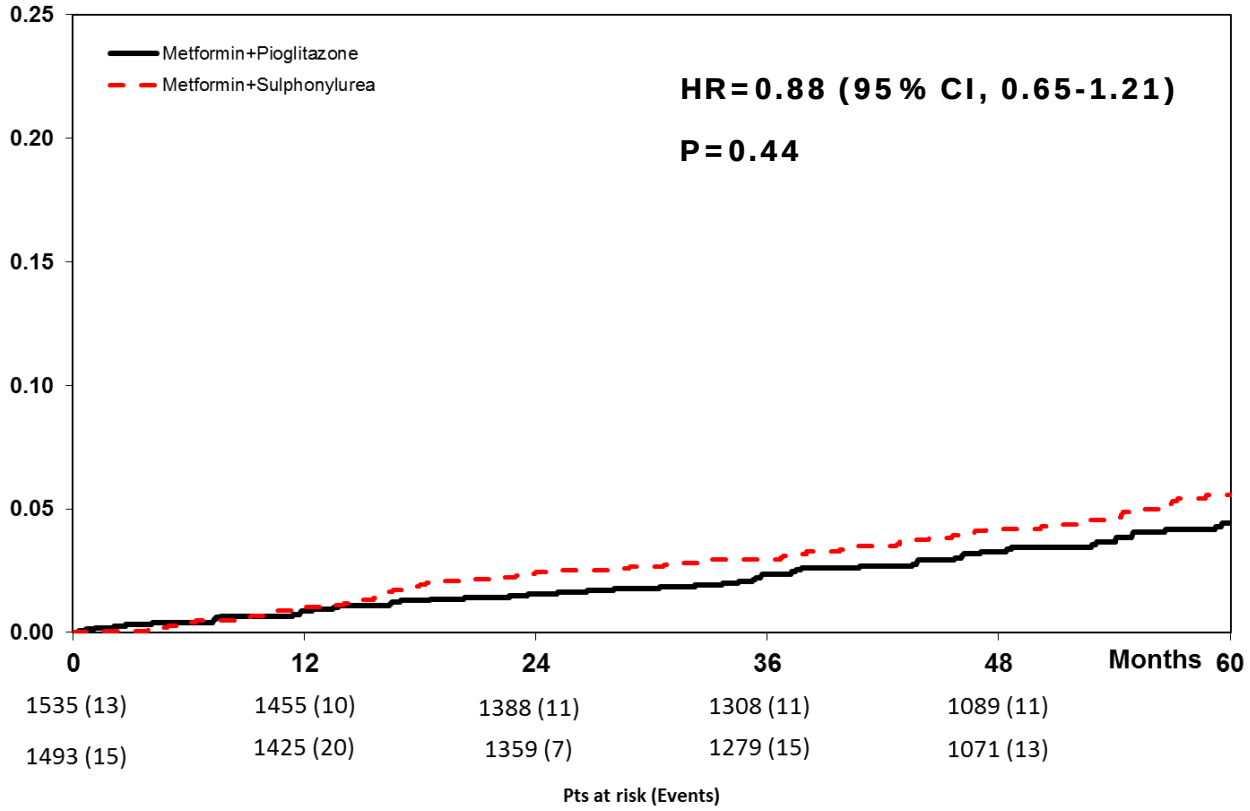


Primary outcome: subgroup analyses



Key secondary outcome

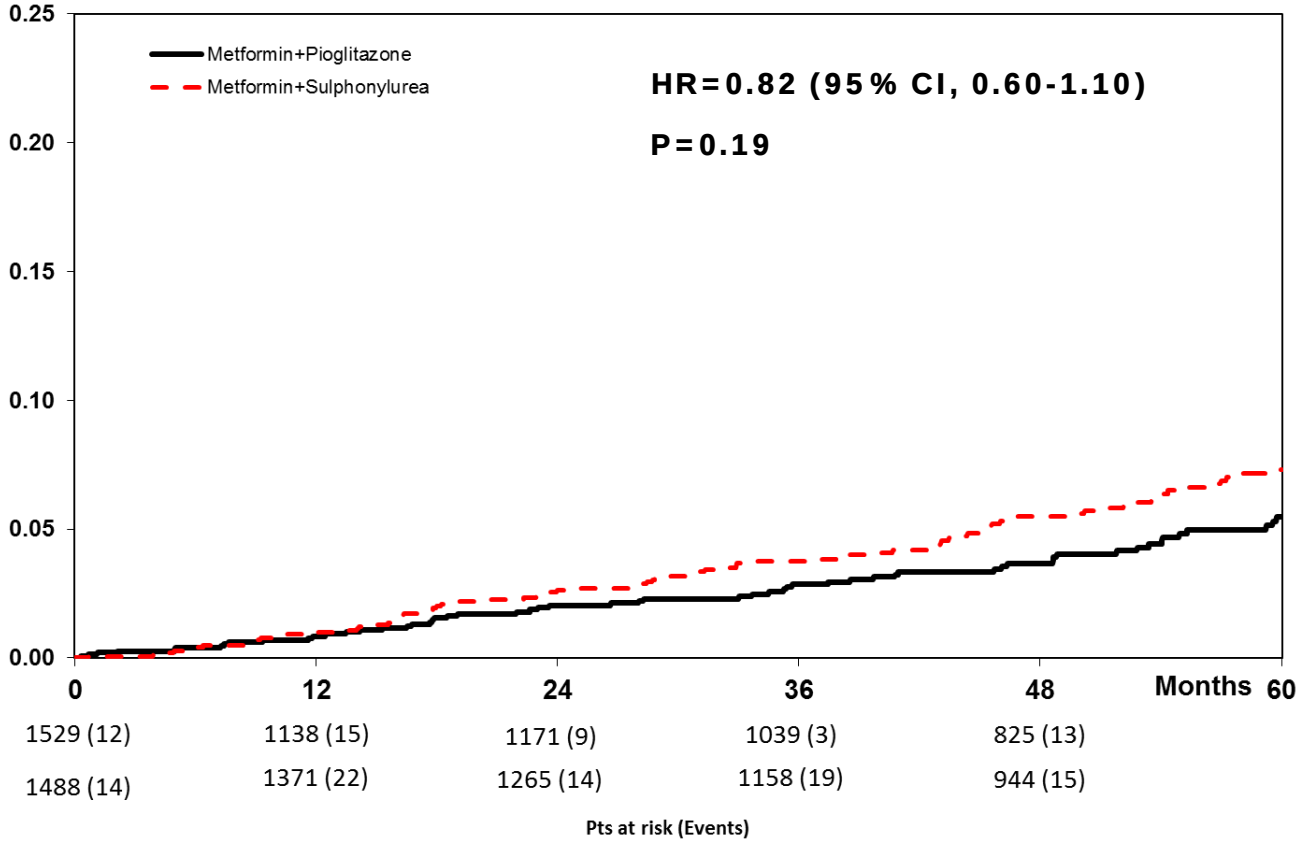
Sudden death, fatal and non-fatal MI (including silent MI), fatal and non-fatal stroke, major leg amputation (above the ankle), coronary, leg or carotid arteries revascularization



The cumulative incidences were estimated with the use of the Kaplan –Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. MI myocardial infarction; CI: confidence interval; HR: hazard ratio.

Primary outcome, on treatment population

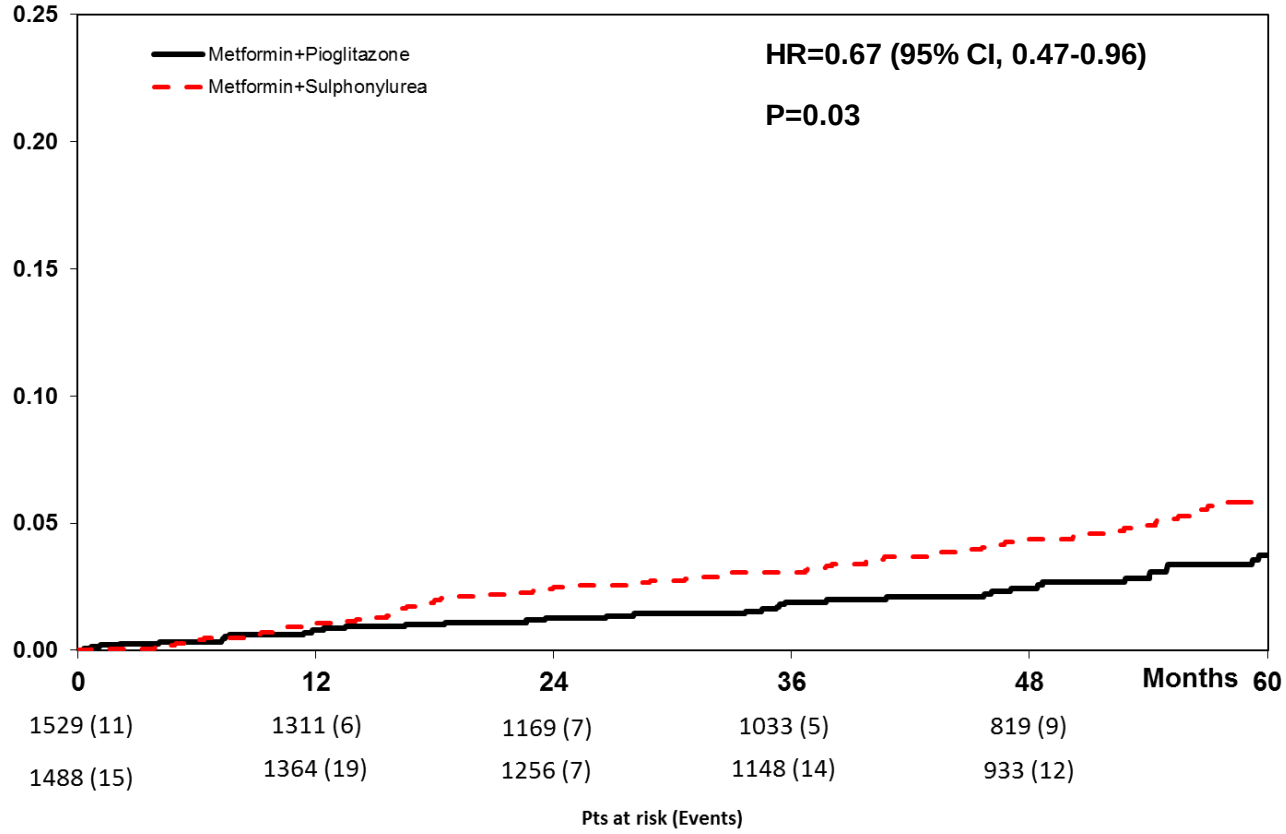
All-cause death, non-fatal MI - including silent MI, non-fatal stroke, urgent coronary revascularization



Data from follow-up trial periods when subjects were exposed to the assigned study drug. Subjects were censored at the time of permanent study drug discontinuation. For this set of analysis, the treatment period included additional 30 days after study drug discontinuation.

Key secondary outcome, on treatment population

Sudden death, fatal and non-fatal MI (including silent MI), fatal and non-fatal stroke, major leg amputation (above the ankle), coronary, leg or carotid arteries revascularization



Data from follow-up trial periods when subjects were exposed to the assigned study drug. Subjects were censored at the time of permanent study drug discontinuation. For this set of analysis, the treatment period included additional 30 days after study drug discontinuation.

Summary

Outcome	HR (95%CI) Pio vs. SU	P value
Intention to treat analysis		
Primary composite outcome	0.96 (0.74-1.26)	0.79
All-cause death	1.10 (0.75-1.61)	0.63
Non fatal MI -including silent MI	0.87 (0.48-1.55)	0.63
Non fatal stroke	0.79 (0.41-1.53)	0.49
Urgent coronary revascularization	0.91 (0.56-1.48)	0.70
Key secondary outcome	0.88 (0.65-1.21)	0.44
On treatment analysis		
Primary composite outcome	0.82 (0.60-1.10)	0.19
Key secondary outcome	0.67 (0.47-0.96)	0.03



Safety profile of the study drugs

Aldo P Maggioni
ANMCO Research Center - Firenze, Italy

Diabete Ricerca

SID Società Italiana di Diabetologia
fondata nel 1964

Disclosures

- Director of the **ANMCO Research Center** that receives **public grants** of research from Oxford University, NIH, Canadian Government, PHRI, SID and **private grants** of research from Bayer, Sanofi-Aventis, Amgen, AstraZeneca, Menarini, Boehringer Ingelheim, DalCor.
- Scientific Coordinator of **ESC EurObservational Research** supported by unrestricted grants from Abbott Vascular, Bayer AG, Bristol Myers Squibb, Pfizer, Boehringer Ingelheim , Daiichi Sankyo, Menarini, Novartis, Sanofi-Aventis, Servier, Amgen, Boston Scientific, MSD.
- **Member of Trial Committees** (SC, EC, CEC, DSMB) sponsored by Novartis, Cardiorentis, AstraZeneca, Bayer, Sanofi, Fresenius.

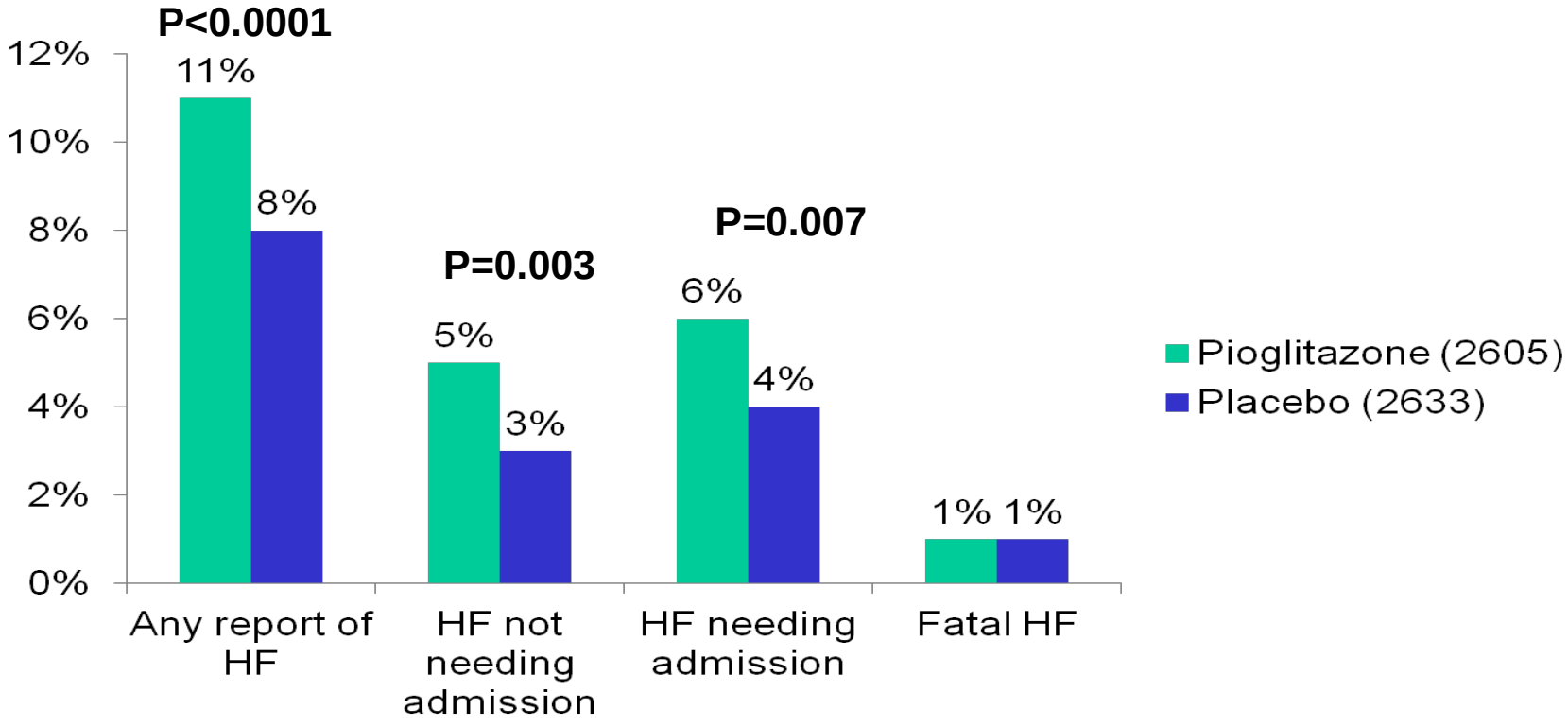
Agenda

- Pioglitazone safety concerns
- Sulfonylurea safety concerns
- Evidence from TOSCA
- Conclusions

Agenda

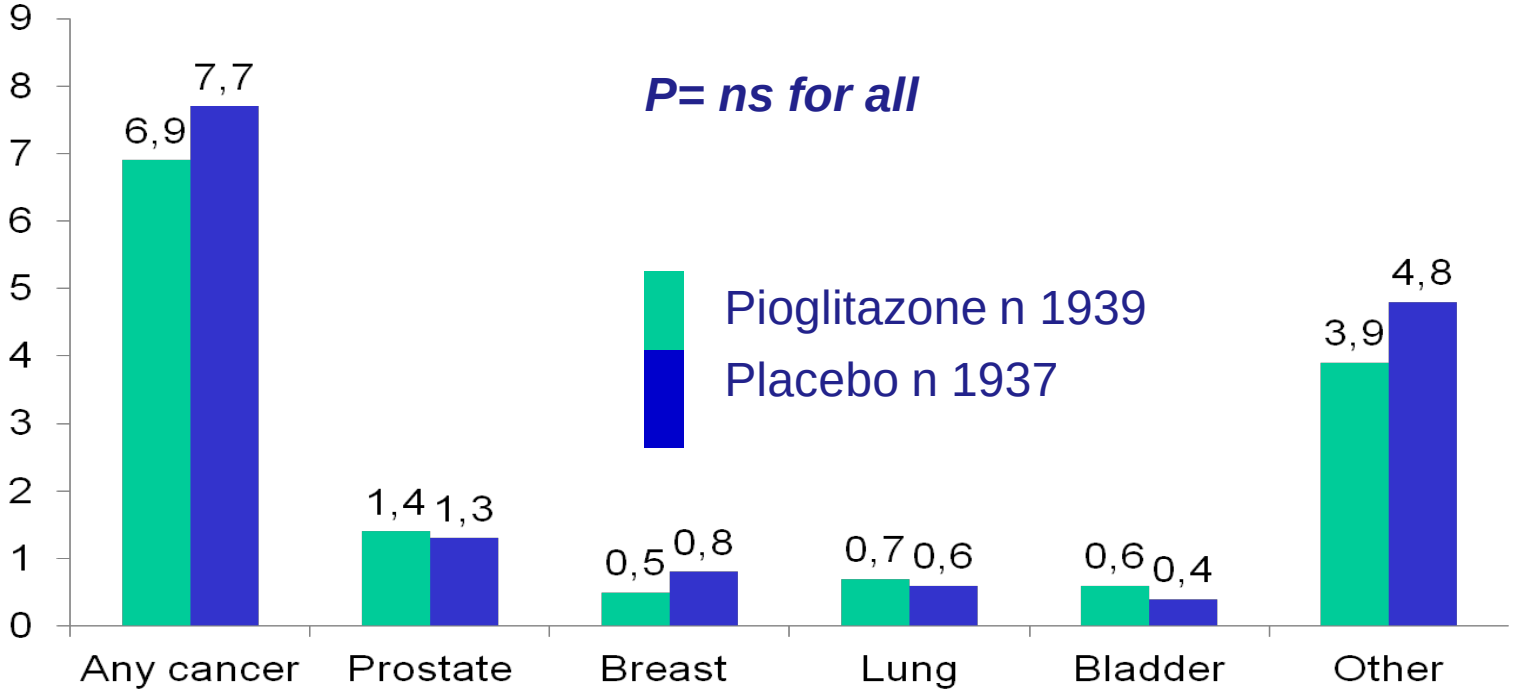
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Pioglitazone and Heart Failure



PROACTIVE Trial. Lancet 2005;366:1279

Pioglitazone and cancer



IRIS Trial. N Eng J Med 2016; 374:1321

IRIS Trial: other adverse events

Adverse events			
Event	*Pioglitazone n. 1939 n.pts (%)*	*Placebo n.1937 n.pts (%)*	*P value*
Heart Failure*	51 (2.6)	42 (2.2)	0.35
Bone fracture**	99 (5.1)	62 (3.2)	0.003
Bone fracture	133 (6.9)	94 (4.9)	0.008
Weight gain >4.5 Kg >13.6 Kg	 1013 (52.2) 221 (11.4)	 653 (33.7) 88 (4.5)	 <0.001 <0.001
Macular edema	3 (0.2)	2 (0.1)	0.66
Edema	691 (35.6)	483 (24.9)	<0.001

**resulting in hospitalization or death*
*** requiring hospitalization, surgery or procedure*

IRIS Trial. N Engl J Med 2016; 374:1321

Agenda

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Sulfonylurea safety concerns

Sulfonylurea+metformin and risk of mortality

All-cause mortality		CVD mortality		CVD hospitalization or mortality	
n.of studies	RR (95% CI)	n.of studies	RR (95% CI)	n.of studies	RR (95% CI)
All (10)	1.19 (0.88-1.62)	6	1.29 (0.73-2.27)	7	1.43 (1.10-1.85)
6*	1.36 (0.93-2.04)	5	1.63 (1.11-2.39)	6	1.55 (1.28-1.87)
4**	1.34 (0.73-2.47)	3	1.72 (0.93-3.20)	4	1.50 (12.5-1.78)

*Studies that did not control for duration of diabetes excluded

** Studies that did not control for duration of diabetes or previous CVD excluded

Rao AD et al. Diabetes Care 2008; 31:1672

Sulfonylurea safety concerns
(Cancer mortality)

	N. Patients	Cancer deaths N (%)	Adjusted HR (95% CI)
Oral antidiabetics			
Metformin	6969	245 (3.5)	1.0*
Sulfonylurea	3340	162 (4.9)	1.3 (1.1-1.6)
Insulin use			
No insulin	8866	323 (3.6)	1.0*
Insulin use	1443	84 (5.8)	1.9 (1.5-2.4)

*Reference category for HR

Mean follow-up 5.4±1.9 years

Bowker SL et al. Diabetes Care 2006;29: 254

Agenda

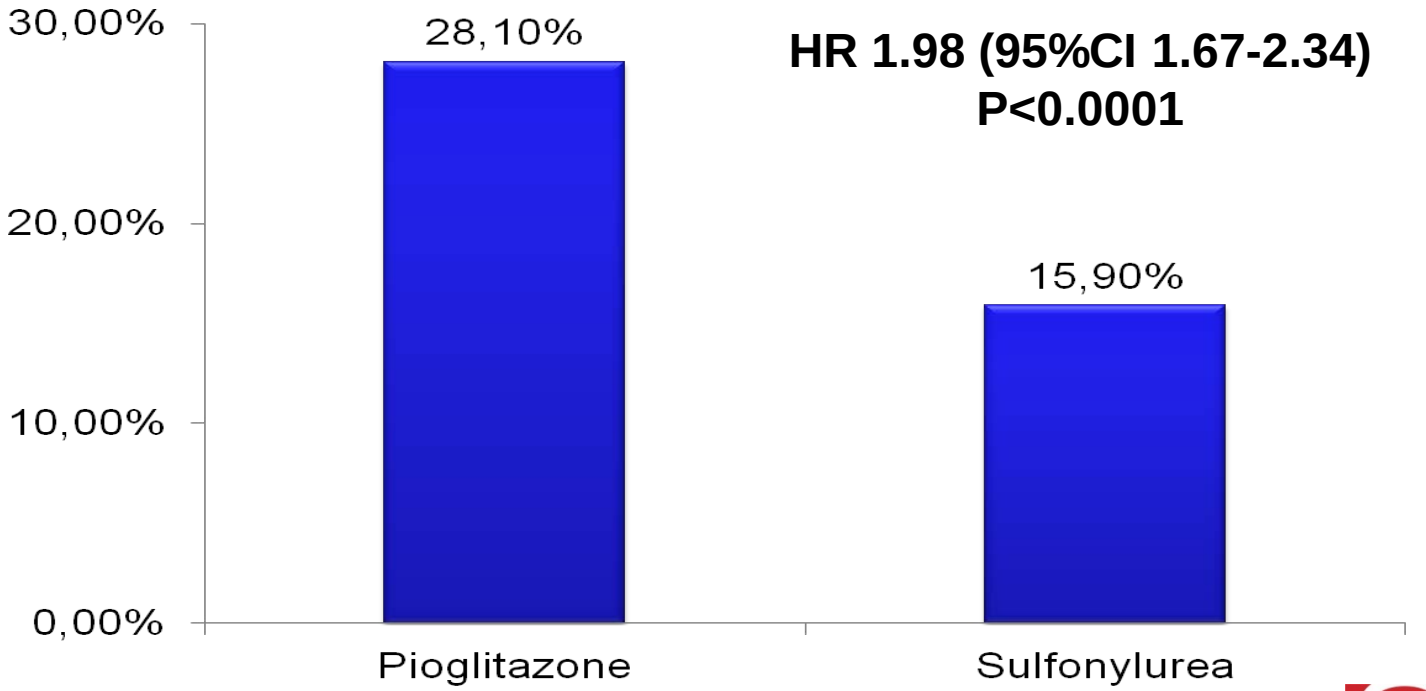
- Pioglitazone safety concerns
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The clinical context of TOSCA

Patients at low cardiovascular risk:

- mean age 62 years
- 11% with a prior CV disease
- relatively well controlled CV risk factors
  - smokers: 18%
  - SBP: 134 mmHg
  - LDL: 100 mg/dl
  - HbA1c: 7.7%

Permanent drug discontinuation



HR 1.98 (95%CI 1.67-2.34)
P<0.0001

Reasons for premature drug discontinuation

	Pioglitazone (N= 432/1535)	*Sulfonylurea (N= 238/1493)*
	N (%)	N (%)
Adverse event	62 (14.3)	16 (6.7)
Patient decision	170 (39.3)	44 (18.5)
Elevated ALT	5 (1.2)	-
Suspected heart failure	11 (2.5)	-
Treatment failure	30 (6.9)	39 (16.4)
Other	147 (34.0)	134 (57.3)

Safety assessment

Central adjudication of:

- New cancer *(occurrence and data of diagnosis, in particular pre/post randomization, confirmed by istology, biopsy)*
- Pathological bone fracture *(break in a diseased bone due to weakening of bone structure by pathologic processes with no or slight trauma)*
- Macular edema *(confirmed by OCT)*

Adjudicated Serious Events

	Pioglitazone (N=1535)	*Sulfonylurea (N=1493)*	*P value*
	N (%)	N (%)	
Any serious adverse events	208 (13.6)	195 (13.1)	0.69
Heart Failure	19 (1.2)	12 (0.8)	0.11
Any fracture Pathological fractures - Male (1774) - Female (1254)	*27 (1.8)* 6 (0.4) 3 (0.3) 3 (0.5)	*36 (2.4)* 4 (0.3) 1 (0.1) 3 (0.5)	*0.24* 0.75 0.61 1.00
Macular edema	7 (0.5)	3 (0.2)	0.34

New cancer diagnosis (adjudicated)

	Pioglitazone (N= 1535)	*Sulfonylurea (N=1493)*	*P value*
	N (%)	N (%)	
Any cancer	**78 (4.0)**	**71 (4.2)**	**0.68**
Lung	9 (0.59)	3 (0.20)	0.15
Colo-rectal	12 (0.78)	9 (0.60)	0.66
Breast	3 (0.20)	4 (0.27)	0.72
Bladder	8 (0.52)	8 (0.54)	1.00
Pancreatic	2 (0.13)	6 (0.40)	0.17
Other	44 (3.00)	41 (3.10)	0.91

Hypoglycemic events

	Pioglitazone (N=1535)		*Sulfonylurea (N=1493)*		*IRR ** (95%CI)*
Hypoglycemic events*	N (%)	N events	N (%)	N events	
Severe	1 (0.1)	2	24 (1.6)	33	0.06 (0.01-0.25)
Moderate	147 (9.6)	515	484 (32.4)	1868	0.27 (0.24-0.30)

*defined as a glucose value lower than 60 mg/dl graded as moderate (not requiring assistance) or severe (requiring assistance)
** Incidence rate ratio

Serious adverse events reported (not adjudicated)

	Pioglitazone (N=1535)	*Sulfonylurea (N=1493)*	*P value*
	N (%)	N (%)	
Infections and infestations	22 (1.4)	11 (0.7)	0.07
Muscoloskeletal and connettive tissue disorders	8 (0.5)	11 (0.7)	0.46
Nervous system disorders	18 (11.7)	16 (10.7)	0.79
Gastrointestinal disorders	20 (13.0)	18 (12.1)	0.81

Other safety outcomes (not adjudicated)

	Pioglitazone (N=1535)	*Sulfonylurea (N=1493)*	*P value*
	N (%)	N (%)	
New or worsening nephropathy	282 (23.0)	270 (22.7)	0.28
Respiratory, thoracic and mediastinal disorders	16 (1.04)	5 (0.3)	0.03

Agenda

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Safety summary

In a context of a population of patients with T2DM at relatively low risk, the adverse drug reactions occurred with an expected profile:

- Pioglitazone was associated with a higher number (but not statistically significant) of HF episodes.
- Sulfonylurea was associated with a significantly higher rate of symptomatic hypoglycemic events.
- No differences were observed in terms of any type of cancer (specifically bladder cancer), macular edema or pathological fractures.



Implications for clinical practice

Enzo Bonora

Endocrinology, Diabetes and Metabolism
University of Verona, Italy

Diabete Ricerca

SID Società Italiana di Diabetologia
fondata nel 1964

EB - Disclosures (last 5 years)

Research grants

Astrazeneca, Genzyme, Menarini Diagnostics, Novo Nordisk, Roche

Consulting activities

Abbott, Astrazeneca, Boehringer Ingelheim, Janssen, Johnson & Johnson, Eli Lilly, MSD, Novo Nordisk, Sanofi, Servier, Takeda

The scenario of T2DM treatment when TOSCA.IT was designed in 2007

First step: Metformin unless contraindicated or not tolerated.

Second step: Add a sulphonylurea or a thiazolidinedione.

Third step: Triple oral therapy or addition of basal insulin.

* Acarbose might be added at all steps.

The scenario of T2DM treatment when TOSCA.IT was completed in 2017

First step: Metformin unless contraindicated or not tolerated.

Second step: Add one drug out of 7 classes (including insulin), many with molecules sometimes different in efficacy and safety.

Third step: Triple therapy with multiple choices among several possible combinations.

Main goal in diabetes care

Changing the natural history of the disease

Preserving and ideally restoring beta-cell function

- good metabolic control for a longer time

Preventing target organ damage

- less myocardial infarction, stroke and all manifestations of CVD
- less retinopathy, nephropathy and all manifestations of microvascular disease

Key messages from the trial (1)

Cardiovascular perspective

In patients on metformin monotherapy with a low cardiovascular risk in whom an intensification of treatment is necessary due to poor glucose control and the choice is the addition or either sulphonylureas (gliclazide or glimepiride) or pioglitazone, because other therapeutic options are not tolerated, contraindicated, inappropriate, unavailable or unaffordable, **pioglitazone does not result in a lower all-cause or CVD death but might provide some CVD (atherosclerotic) benefits.**

All-cause death and cardiovascular outcomes in TOSCA.IT

	ITT analysis	P values	On treatment analysis	P values
All-cause death	1.10 [0.75-1.61]	0.63	1.08 [0.71-1.65]	0.70
CVD death	2.24 [0.69-7.28]	0.18	1.66 [0.47-5.88]	0.43
Nonfatal AMI	0.87 [0.48-1.55]	0.63	0.63 [0.32-1.24]	0.18
Nonfatal Stroke	0.79 [0.41-1.53]	0.49	0.67 [0.32-1.42]	0.30
Urgent PTCA	0.91 [0.56-1.48]	0.70	0.62 [0.35-1.11]	0.11
Key secondary Outcome	0.88 [0.65-1.21]	0.44	0.67 [0.47-0.96]	0.03

Key Secondary Outcome: sudden death, fatal and non fatal AMI, fatal and non fatal stroke, major leg amputation (above the ankle), any revascularization of coronary, carotid or leg arteries.

Key messages from the trial (2)

Blood glucose perspective

When metformin monotherapy fails and the choice is the addition of either pioglitazone or a sulphonylurea (gliclazide or glimepiride) because other therapeutic options are not tolerated, contraindicated, inappropriate, unavailable or unaffordable **pioglitazone is better.**

Greater durability with a longer period off insulin.

Lower risk of hypoglycemia (virtually no severe hypoglycemia).

Key messages from the trial (3)

Safety perspectives

***Heart failure*:** slightly but not significantly higher rate with pioglitazone. Few cases over 4,5 years (19 PIO vs. 12 SU, i.e. excess of ~1 case per 1000 patient-year, if any). No fatality. *Remark: NYHA 1-4 were excluded from trial.*

***Pathological bone fractures*:** no differences and very few cases over 4,5 years (6 PIO vs. 4 SU, i.e. excess of 0.3 case per 1000 patient-year, if any). *Remark: pathological fractures were focused on.*

***Cancer*:** no significant differences (78 PIO vs. 72 SU, i.e. excess of <1 case per 1000 patient-year, if any; bladder cancer 8 vs. 8 cases).

Head-to-head: a synopsis from TOSCA.IT

	Pioglitazone better	Sulphonylurea better	No difference
HbA1c	√		
Durability	√		
Hypoglycemia	√		
All-cause death (ITT)			√
CVD death (ITT)			√
Ischemic CVD	√ (on treatment)		√ (ITT)
Heart failure		√ (?)	
Pathologic bone fractures			√
Cancer (in particular bladder)			√

TOSCA.IT strengths and weaknesses

Strengths

- Large trial, long follow-up
- Subjects at low CVD risk
- Head-to-head of active drugs
- Comparison of low cost (generic) drugs
- Exclusion of subjects in the class NYHA 1-4 (appropriate use of pioglitazone)
- Adjudication of pathologic bone fractures (more specific assessment of this adverse event)
- Careful assessment of cancer, in particular bladder cancer
- Industry independence (under the mandate of the Italian Diabetes Society)

Weaknesses

- Stopped before the planned number of events occurred (a futility analysis suggested not to continue)
- Many cases of discontinuation of pioglitazone (mainly after the media storm on bladder cancer)
- No double blind design (but blinded adjudication of events)

T2DM treatment and CVOT when TOSCA.IT was designed in 2007 – just 1 study

PROActive: pioglitazone better than placebo on top of background treatment in subjects with prior CVD – only the secondary endpoint (MACE)

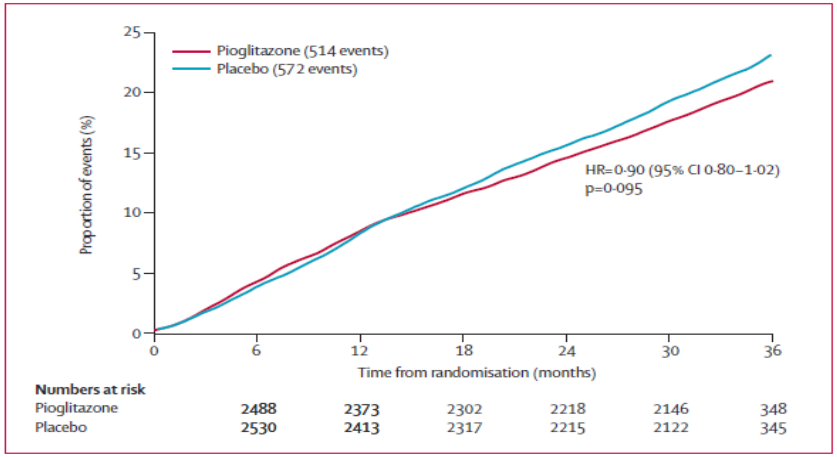


Figure 2: **Kaplan-Meier curve of time to primary endpoint***
*Death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg.

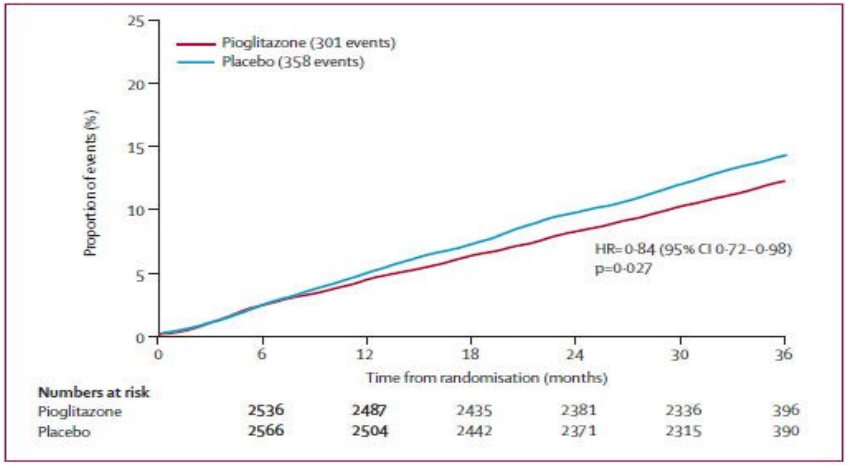


Figure 3: **Kaplan-Meier curve of time to main secondary endpoint***
*Death from any cause, non-fatal myocardial infarction (excluding silent myocardial infarction), or stroke.

Dormandy et al – Lancet 2005; 366: 1279

T2DM treatment and CVOT when TOSCA.IT was completed in 2017 – many studies

	Drug	Comparator	Prior CVD (%)	CVD benefit vs. comparator
PROActive (2005)	Pioglitazone	Placebo	100	Yes
RECORD (2009)	Rosiglitazone	SU/MET	18	No
HOME (2009)	Metformin	Placebo	20	Yes
ORIGIN (2012)	Glargine	Standard care	59	No
SAVOR –TIMI (2013)	Saxagliptin	Placebo	78	No
EXAMINE (2013)	Alogliptin	Placebo	100	No
ELIXA (2015)	Lixisenatide	Placebo	100	No
TECOS (2015)	Sitagliptin	Placebo	74	No
EMPA-REG (2015)	Empagliflozin	Placebo	100	Yes
LEADER (2016)	Liraglutide	Placebo	81	Yes
SUSTAIN (2016)	Semaglutide	Placebo	83	Yes
CANVAS (2017)	Canagliflozin	Placebo	72	Yes
TOSCA (2017)	Pioglitazone	Sulphonylureas	11	No (Yes?)

TOSCA.IT is the only large head-to-head study comparing available drugs

Lessons from CVOT in T2DM

Subjects with established CVD (~25%): treatment added to metformin should include drugs with a documented CVD benefit (pioglitazone, liraglutide, SGLT-2 inhibitors). **We know very well what to do with these subjects.**

Subjects apparently at low CVD risk (~75%): treatment added to metformin should primarily include drugs with the best benefits/risks ratio. Benefits include glucose lowering effects on brief, middle and long term, improvement of other CVD risk factors, prevention of chronic complications. Risks include hypoglycemia and adverse effects (e.g., heart failure, fractures, infections, etc.). **We have many options but we have few certainties with these subjects.** In particular, we have very few head-to-head comparisons.

CVOT with head-to-head comparisons

Study	Contrast	No.	Age (yr)	Duration (yr)	HbA1c (%)	FU (yr)	Prior CVD (%)	Composite Primary Outcome	Result
RECORD Lancet 2009	Rosiglitazone vs. SU/MET (dual)	4447	58	7	7.9	5.5	18	CVD death CVD hospitalization	No difference
ORIGIN NEJM 2012	Glargine vs. Standard care (combined)	12537 (DM 88%)	63	5.5	6.4	6.2	59	MACE Revascularization HF hospitalization	No difference
SPREAD-DIMCAD Diab Care 2013	Metformin vs. Glipizide (mono)	304	63	6	7.1	5.0	100	Death MACE Revascularization	Metformin better
TOSCA 2017	Pioglitazone vs. SU (dual)	3028	62	8	7.7	4.5	11	Death MACE Revascularization	No difference
CAROLINA Expected 2019	Linagliptin Glimepiride (mono, combo)	6041	65	6	7.2	~6.0	34	MACE	???

Diabete Ricerca

SID Società Italiana di Diabetologia

Conclusions

Type 2 diabetes is a heterogeneous and progressive disease and its care requires a patient-centered approach which generally includes changes of treatment and addition of drugs to drugs across the years.

Pioglitazone shows definite metabolic but uncertain CVD advantages when compared to sulphonylureas in the treatment of subjects with T2DM who fail to metformin monotherapy and have a low CVD risk.

Under certain clinical circumstances pioglitazone and sulphonylureas can still remain an option for the combined treatment of T2DM.

Important notice

This is a study of pioglitazone vs. sulphonylureas in low CVD risk patients.

Any extrapolation to patients with high CVD risk for prior events (e.g. myocardial infarction or stroke) should be avoided.

Any extrapolation of these results to a comparisons of either pioglitazone or sulphonylureas with other anti-hyperglycemic drugs would be definitely inappropriate.

Acknowledgments

Italian Medicine Agency (AIFA) for supporting the trial

TOSCA Investigators from 57 diabetes centers for their dedication

Patients who volunteered for their willingness to contribute

AMD – Associazione Medici Diabetologi
and
ANMCO – Associazione Nazionale Cardiologi Ospedalieri
for their collaboration

Information

Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial

Olga Vaccaro, Maria Masulli*, Antonio Nicolucci, Enzo Bonora, Stefano Del Prato, Aldo P Maggioni, Angela A Rivellese, Sebastiano Squatrito, Carlo B Giorda , Giorgio Sesti, Paolo Mocarelli, Giuseppe Lucisano, Michele Sacco, Stefano Signorini, Fabrizio Cappellini, Gabriele Perriello, Anna Carla Babini, Annunziata Lapolla, Giovanna Gregori, Carla Giordano, Laura Corsi, Raffaella Buzzetti, Gennaro Clemente, Graziano Di Cianni, Rossella Iannarelli, Renzo Cordera, Olga La Macchia, Chiara Zamboni, Cristiana Scaranna, Massimo Boemi, Ciro Iovine, Davide Lauro, Sergio Leotta, Elisabetta Dall'Aglio, Emanuela Cannarsa, Laura Tonutti, Giuseppe Pugliese, Antonio C Bossi, Roberto Anichini, Francesco Dotta, Antonino Di Benedetto, Giuseppe Citro, Daniela Antenucci, Lucia Ricci, Francesco Giorgino, Costanza Santini, Agostino Gnasso, Salvatore De Cosmo, Donatella Zavaroni, Monica Vedovato, Agostino Consoli, Maria Calabrese, Paolo di Bartolo, Paolo Fornengo, Gabriele Riccardi, for the Thiazolidinediones Or Sulphonylureas Cardiovascular Accidents Intervention Trial (TOSCA.IT) study group† under the mandate of the Italian Diabetes Society*

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