52° Congresso Nazionale SIGG
Firenze, novembre 2007

Rosiglitazone ed outcome primari: luci ed ombre

Edoardo Mannucci

UNIVERSITA' DEGLI STUDI DI FIRENZE
Dipartimento di Area Critica Medico-Chirurgica
Cattedra di Geriatria e Gerontologia

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

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N Engl J Med 2007;356:2457-71.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Available online at www.sciencedirect.com
ScienceDirect
Metabolism Clinical and Experimental 56 (2007) 1396–1401
Metabolism
Clinical and Experimental
www.elsevier.com/locate/metabol

Peroxisome proliferator–activated receptor γ agonist improves arterial stiffness in patients with type 2 diabetes mellitus and coronary artery disease

Jie Yu[a,1], Nan Jin[b,1], Guang Wang[a,*], Fuchun Zhang[a], Jieming Mao[a], Xian Wang[a,b]

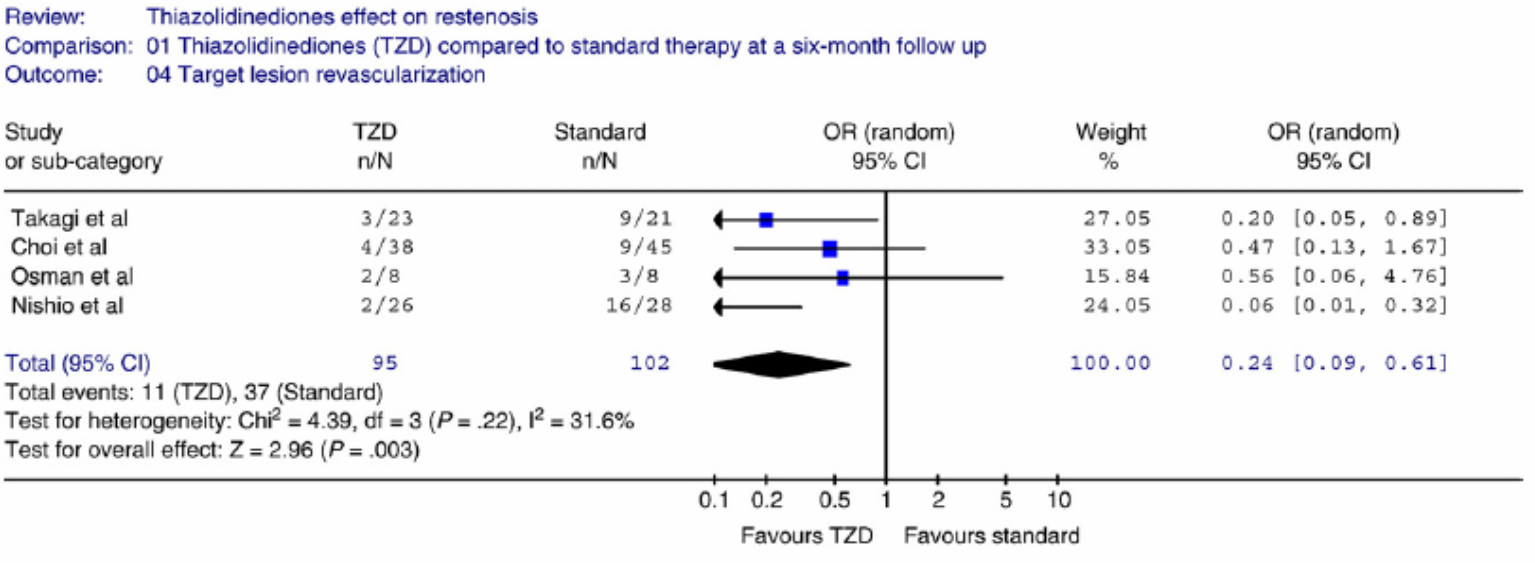
Table 2
Metabolic parameters and PWV before and after 12-week follow-up in diabetic patients with CAD

Parameters	Diabetes with CAD (n = 21)		Diabetes with CAD + RSG (n = 25)	
	Baseline	After 12 wk	Baseline	After 12 wk
Metabolic parameters				
Total cholesterol (mmol/L)	4.49 ± 0.15	4.03 ± 0.17 *	4.50 ± 0.14	3.75 ± 0.11 **
HDL (mmol/L)	1.10 ± 0.06	1.28 ± 0.06 *	1.13 ± 0.05	1.30 ± 0.06 *
LDL (mmol/L)	2.79 ± 0.14	2.33 ± 0.15 *	2.81 ± 0.14	2.0 ± 0.09 **
Triglycerides (mmol/L)	1.85 (1.40-2.33)	1.43 (1.03-1.81)	1.70 (1.48-2.48)	1.43 (1.08-2.08)
Fasting insulin (mIU/L)	10.4 ± 1.22	10.41 ± 1.24	12.4 ± 1.37	9.7 ± 1.11
Fasting plasma glucose (mmol/L)	6.40 ± 0.30	6.73 ± 0.33	6.0 ± 0.4	5.56 ± 0.17 †
HbA_{1c} (%)	6.83 ± 0.27	6.3 ± 0.17	6.45 ± 0.20	5.88 ± 0.10 *,†
HOMA-IR	3.03 ± 0.39	3.28 ± 0.2	3.45 ± 0.30	2.61 ± 0.21 *,†
PWV (cm/s)	1669 ± 53.8	1670 ± 41.3	1615 ± 44.4	1525 ± 43.1 *,†
MCP-1 (pg/mL)	304 ± 54.2	262 ± 50.1	392 ± 42.0	273 ± 40.0 *
CRP (mg/L)	2.04 ± 0.31	1.33 ± 0.29	1.71 ± 0.24	0.73 ± 0.09 **,†

Effect of thiazolidinedione therapy on restenosis after coronary stent implantation: A meta-analysis of randomized controlled trials

Evangelos S. Rosmarakis, MD,[a,b] and Matthew E. Falagas, MD, MSc, DSc[a,c] *Athens, Greece; and Boston, MA*

Figure 3



(Am Heart J 2007;154:144-50.)

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

Lancet 2005; 366: 1279–89

John A Dormandy, Bernard Charbonnel, David J A Eckland, Erland Erdmann, Massimo Massi-Benedetti, Ian K Moules, Allen M Skene, Meng H Tan, Pierre J Lefèbvre, Gordon D Murray, Eberhard Standl, Robert G Wilcox, Lars Wilhelmsen, John Betteridge, Kåre Birkeland, Alain Golay, Robert J Heine, László Kordonyi, Markku Laakso, Moisés Lopez Martínez, Antonis Noacks, Valdis Pirags, Toomas Podar, André Scheen, Werner Scherbaum, Guntram Schernthaner, Ole Schmitz, Jan Škrha, Ulf Smith, Jan Taton, on behalf of the PROactive investigators*

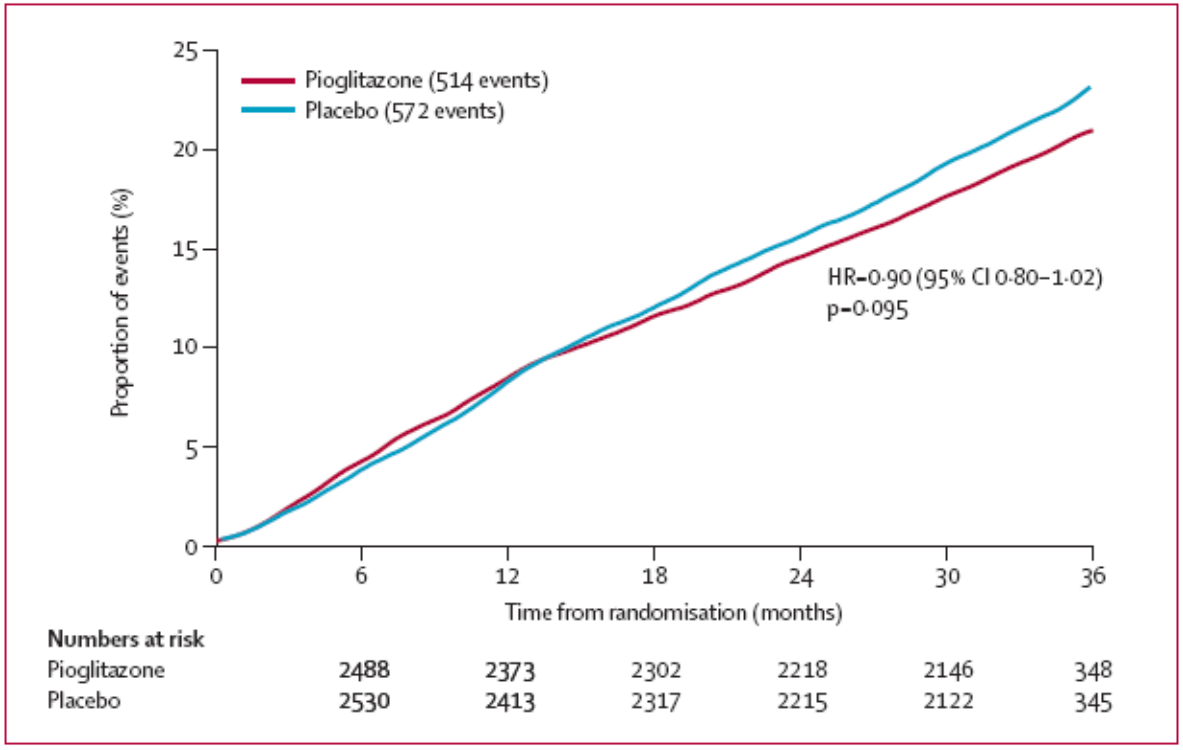
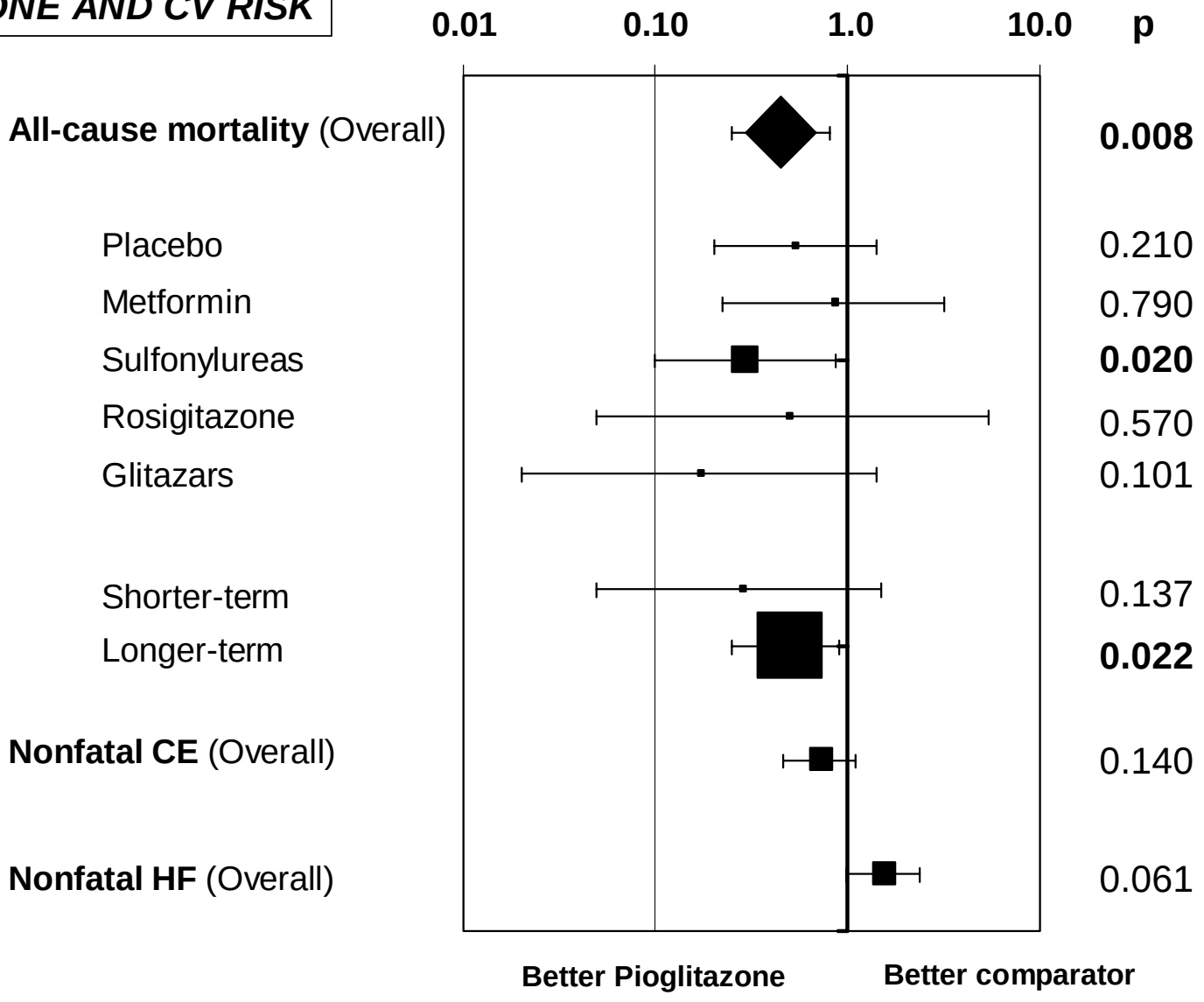


Figure 2: **Kaplan-Meier curve of time to primary endpoint***

*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.

PIOGLITAZONE AND CV RISK



Mannucci, Monami, Lamanna, Gensini, Marchionni - *submitted*

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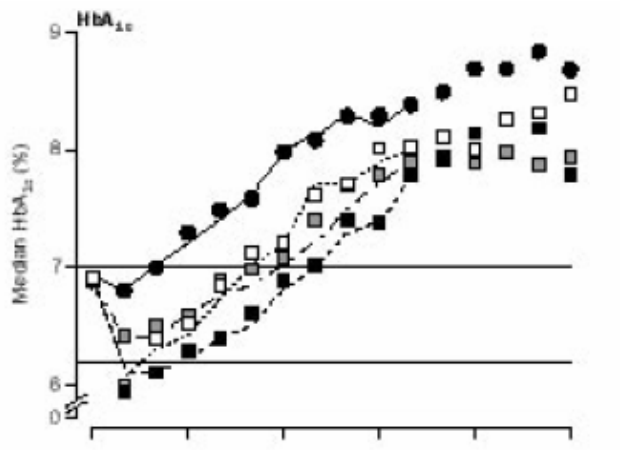
Table 5. Risk of Myocardial Infarction and Death from Cardiovascular Causes for Patients Receiving Rosiglitazone versus Several Comparator Drugs.

Comparator Drug	Odds Ratio (95% CI)	P Value
Myocardial infarction		
Metformin	1.14 (0.70–1.86)	0.59
Sulfonylurea	1.24 (0.78–1.98)	0.36
Insulin	2.78 (0.58–13.3)	0.20
Placebo	1.80 (0.95–3.39)	0.07
Combined comparator drugs	1.43 (1.03–1.98)	0.03
Death from cardiovascular causes		
Metformin	1.13 (0.34–3.71)	0.84
Sulfonylurea	1.42 (0.60–3.33)	0.43
Insulin	5.37 (0.51–56.52)	0.16
Placebo	1.22 (0.64–2.34)	0.55
Combined comparator drugs	1.64 (0.98–2.74)	0.06

Articles

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)

*UK Prospective Diabetes Study (UKPDS) Group**



All-cause mortality	p=0·62							
Chlorpropamide (n=619)		136	190	20·5	19·9	0·87	1·02 (0·82–1·27)	
Glibenclamide (n=615)		121	190	18·2	19·9	0·43	0·91 (0·73–1·15)	
Insulin (n=911)		184	190	18·6	19·9	0·48	0·93 (0·76–1·14)	
Myocardial infarction	p=0·66							
Chlorpropamide (n=619)		100	162	15·8	17·9	0·28	0·87 (0·68–1·12)	
Glibenclamide (n=615)		90	162	14·1	17·9	0·056	0·78 (0·60–1·01)	
Insulin (n=911)		149	162	15·8	17·9	0·24	0·87 (0·70–1·09)	
Stroke	p=0·072							
Chlorpropamide (n=619)		33	47	5·1	5·0	0·96	1·01 (0·65–1·56)	
Glibenclamide (n=615)		45	47	7·0	5·0	0·12	1·38 (0·92–2·06)	
Insulin (n=911)		42	47	4·4	5·0	0·48	0·86 (0·57–1·31)	
Amputation or death from PVD	p=0·10							
Chlorpropamide (n=619)		5	15	0·8	1·6	0·13	0·47 (0·17–1·28)	
Glibenclamide (n=615)		5	15	0·8	1·6	0·14	0·48 (0·17–1·31)	
Insulin (n=911)		17	15	1·8	1·6	0·82	1·08 (0·54–2·17)	
Microvascular	p=0·30							
Chlorpropamide (n=619)		68	104	10·0	11·6	0·33	0·86 (0·63–1·17)	
Glibenclamide (n=615)		49	104	7·7	11·6	0·017	0·66 (0·47–0·93)	
Insulin (n=911)		77	104	8·2	11·6	0·015	0·70 (0·52–0·93)	

Limitations of Nissen and Wolski's meta-analysis

- Inclusion of trials with non-cardiovascular endpoints
- Selection of trials (duration >24 wk, GSK-sponsored)
- Questionable statistical methods: Peto's analysis, fixed effect model
- Different duration of follow-up in rosiglitazone and comparator groups

Limitations of Nissen and Wolski's meta-analysis

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REVIEW

Long-term Risk of Cardiovascular Events With Rosiglitazone

A Meta-analysis

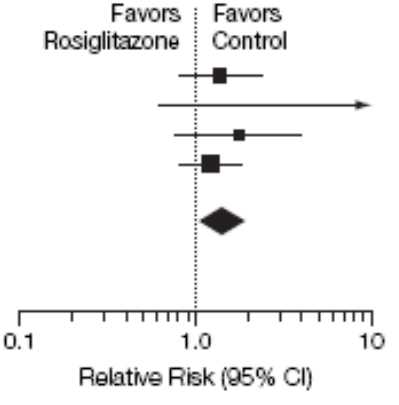
Sonal Singh, MD
Yoon K. Loke, MBBS, MD
Curt D. Furberg, MD, PhD

JAMA. 2007;298(10):1189-1195

Myocardial Infarction

Source	No. of Events/Total (%) Rosiglitazone	Control	Weight, %	Relative Risk (95% CI)
Kahn et al,[7] 2006	24/1456 (1.6)	34/2895 (1.2)	31.52	1.40 (0.84-2.36)
Dargie et al,[16] 2007	5/110 (4.5)	0/114 (0)	0.68	11.40 (0.64-203.69)
Gerstein et al,[5] 2006	16/2635 (0.6)	9/2634 (0.3)	12.47	1.78 (0.79-4.01)
Home et al,[12] 2007	49/2220 (2.2)	40/2227 (1.8)	55.33	1.23 (0.81-1.86)
Total (95% CI)	6421	7870	100.00	1.42 (1.06-1.91)

Total events: 94 (rosiglitazone), 83 (control)
Test for heterogeneity: $\chi^2_3 = 2.77$ ($P = .43$), $I^2 = 0\%$
Tests for overall effect: $Z = 2.33$ ($P = .02$)



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The NEW ENGLAND JOURNAL of MEDICINE

AUGUST 30, 2007

Rosiglitazone and Cardiovascular Risk

Michael B. Bracken, Ph.D., M.P.H.
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New Haven, CT 06510
michael.bracken@yale.edu

Table 1. Comparison of Statistical Analyses of 42 Trials Involving Rosiglitazone.*

Test Statistic	Value (95% CI)	
	Myocardial Infarction	Death from Cardiovascular Causes
Data from Nissen and Wolski[1]		
Relative risk	1.27 (0.95–1.71)	1.33 (0.84–2.12)
Odds ratio	1.28 (0.95–1.72)	1.33 (0.83–2.13)
Peto odds ratio	1.43 (1.03–1.98)	1.64 (0.98–2.74)
Risk difference	0.00 (0.00–0.00)	0.00 (0.00–0.00)
Data from Nissen and Wolski plus RECORD[2]		
Relative risk	1.24 (0.97–1.58)	1.07 (0.76–1.49)
Odds ratio	1.24 (0.97–1.59)	1.07 (0.76–1.50)
Peto odds ratio	1.33 (1.02–1.73)	1.15 (0.81–1.64)
Risk difference	0.00 (0.00–0.00)	0.00 (0.00–0.00)

PERSPECTIVE | Annals of Internal Medicine

Uncertain Effects of Rosiglitazone on the Risk for Myocardial Infarction and Cardiovascular Death

George A. Diamond, MD; Leon Bax, MSc; and Sanjay Kaul, MD

Ann Intern Med. 2007;147:578-581.

Table 1. Meta-analytic Odds Ratios for Myocardial Infarction and Cardiovascular Death*

Meta-analytic Method	Myocardial Infarction		Cardiovascular Death	
	k	Odds Ratio (95% CI)	*k*	Odds Ratio (95% CI)
Fixed, Peto	38	1.43 (1.03–1.98)	23	1.64 (0.98–2.74)
Fixed, IV (TAC)†	38	1.34 (0.97–1.84)	23	1.46 (0.88–2.42)
Fixed, IV (CC)†	38	1.29 (0.94–1.76)	23	1.31 (0.80–2.13)
Fixed, MH (TAC)	38	1.36 (1.00–1.84)	23	1.51 (0.94–2.44)
Fixed, MH (CC)	38	1.28 (0.95–1.72)	23	1.33 (0.83–2.13)
Fixed, MH (TAC+)	42	1.35 (1.00–1.82)	42	1.39 (0.91–2.13)
Fixed, MH (CC+)	42	1.26 (0.93–1.69)	42	1.17 (0.77–1.77)

* CC = constant correction for continuity; CC+ = constant correction for continuity that includes all zero-total-event studies; IV = inverse variance; *k* = number of studies; MH = Mantel–Haenszel; TAC = treatment arm correction for continuity; TAC+ = treatment arm correction for continuity that includes all zero-total-event studies.

† Results from analogous random-effects analyses are identical.

STATISTICS IN MEDICINE
Statist. Med. 2007; **26**:4375–4385
Published online 3 September 2007 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/sim.3060

Fixed *vs* random effects meta-analysis in rare event studies: The Rosiglitazone link with myocardial infarction and cardiac death‡

Jonathan J. Shuster[1,*,†], Lynn S. Jones[2] and Daniel A. Salmon[1,3]

[1]*Department of Epidemiology and Health Policy Research, College of Medicine, University of Florida, Gainesville, FL 32610, U.S.A.*
[2]*Midwest Clinical Research, Dayton, OH 45408, U.S.A.*
[3]*Department of International Health, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD 21205, U.S.A.*

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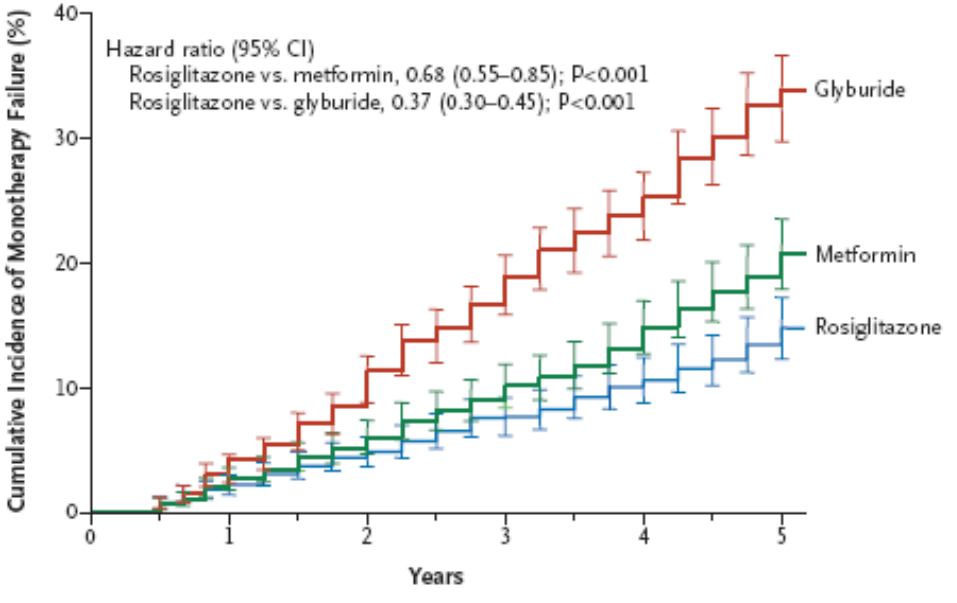
- **Different duration of follow-up in rosiglitazone and comparator groups**

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

Steven E. Kahn, M.B., Ch.B., Steven M. Haffner, M.D., Mark A. Heise, Ph.D., William H. Herman, M.D., M.P.H., Rury R. Holman, F.R.C.P., Nigel P. Jones, M.A., Barbara G. Kravitz, M.S., John M. Lachin, Sc.D., M. Colleen O'Neill, B.Sc., Bernard Zinman, M.D., F.R.C.P.C., and Giancarlo Viberti, M.D., F.R.C.P., for the ADOPT Study Group *

N Engl J Med 2006;355:2427-43.



No. at Risk

Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

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Rosiglitazone and Cardiovascular Risk

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Matteo Monami, M.D., Ph.D.
Niccolò Marchionni, M.D.

University of Florence
50141 Florence, Italy
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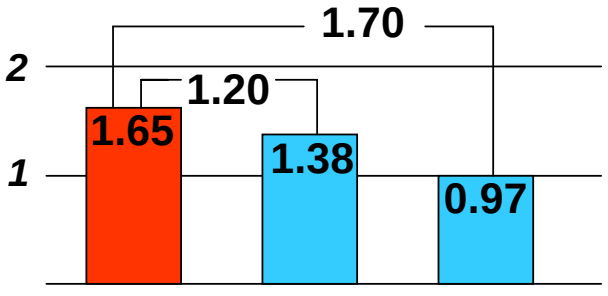
	Rosig.	Metf.	Glybur
# cases	24	20	14
Patients	1456	1454	1441
% pat.	1.65	1.38	0.97



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	Rosig.	Metf.	Glybur
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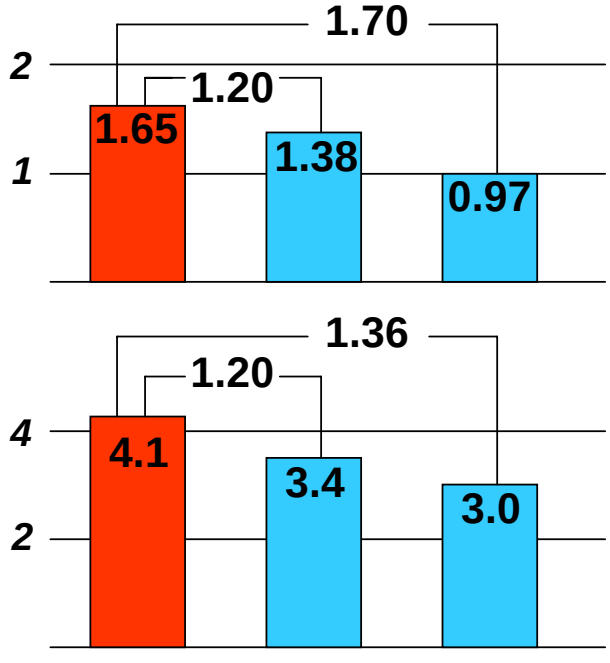
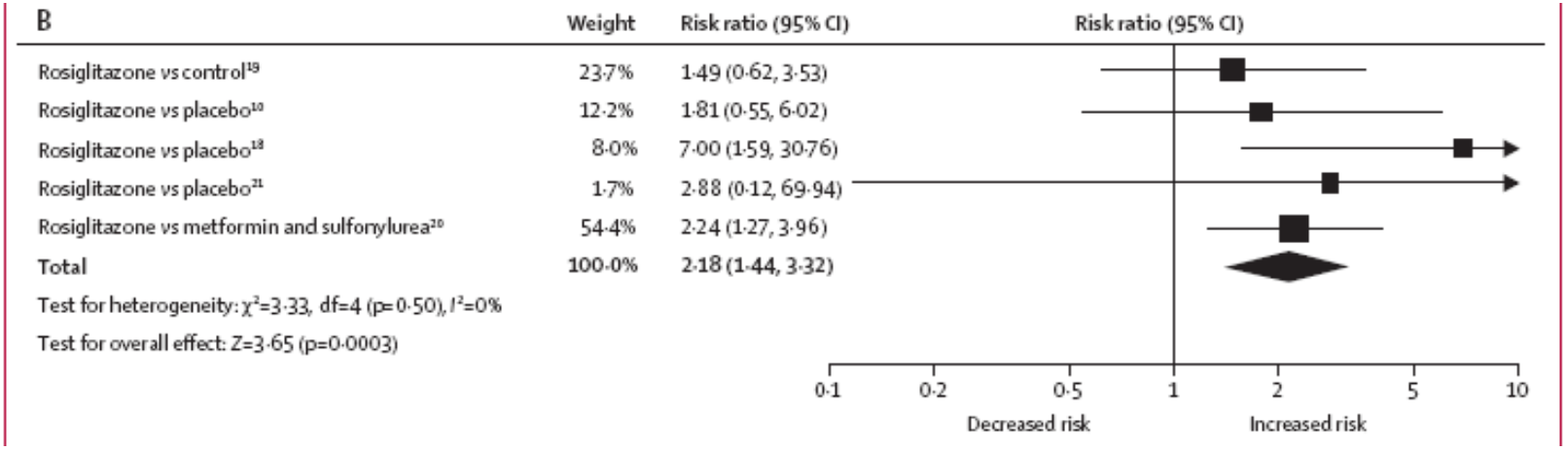
Follow-up (y)	4.0	4.0	3.2
Incidence(0/00)	4.1	3.4	3.0



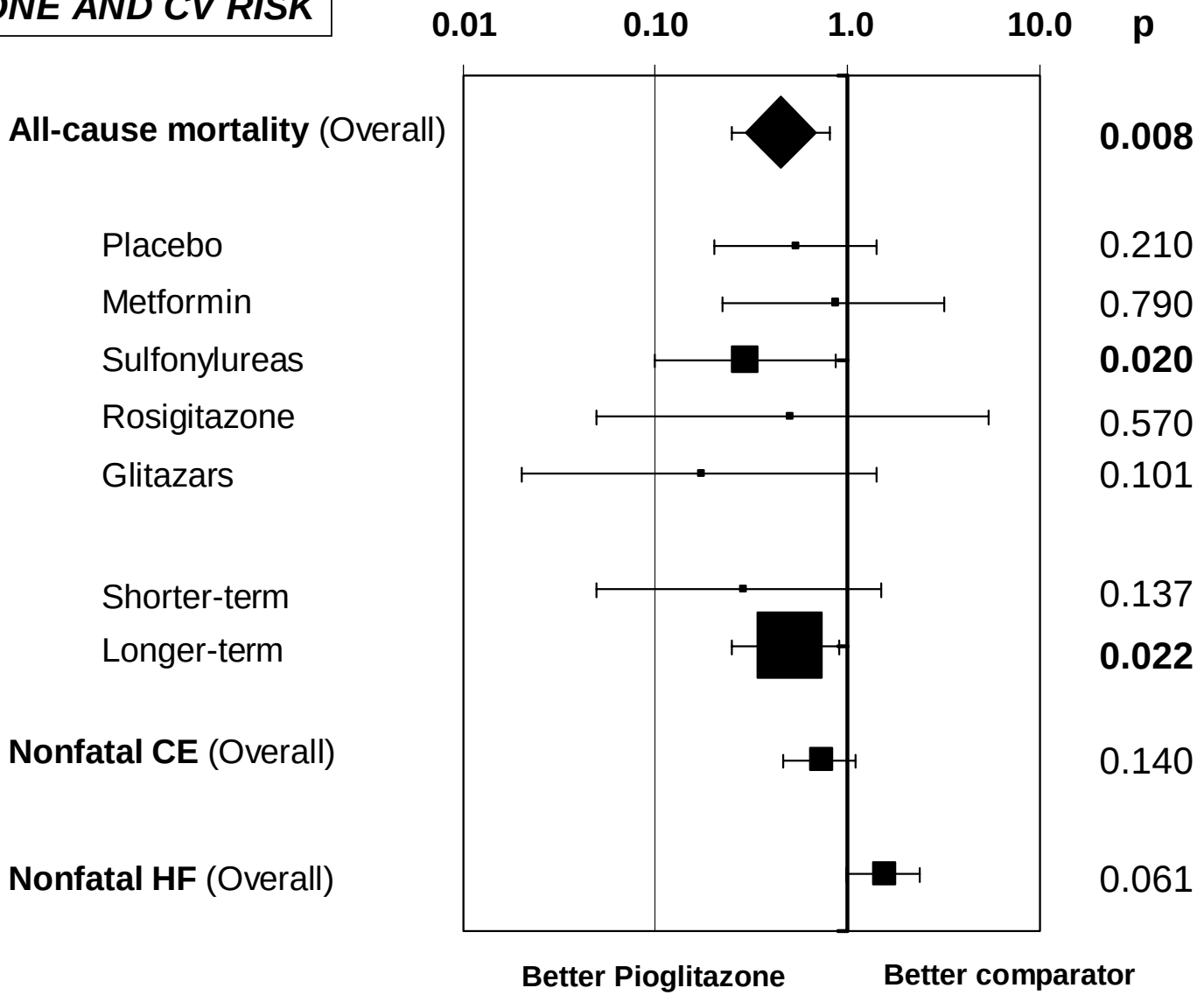
Congestive heart failure and cardiovascular death in patients with prediabetes and type 2 diabetes given thiazolidinediones: a meta-analysis of randomised clinical trials

Rodrigo M Lago, Premranjan P Singh, Richard W Nesto

Lancet **2007; 370: 1129–36**



PIOGLITAZONE AND CV RISK



Mannucci, Monami, Lamanna, Gensini, Marchionni - *submitted*

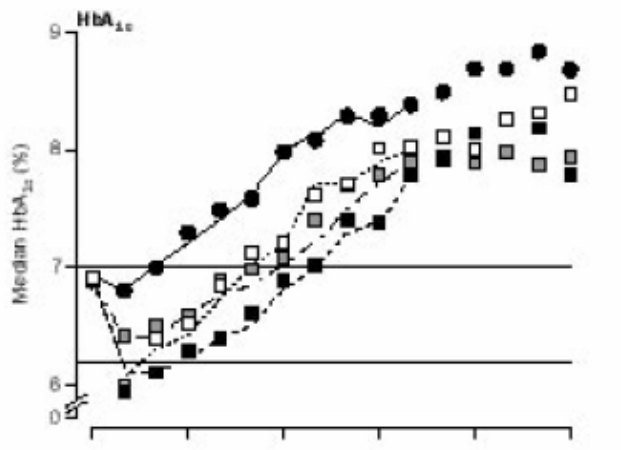
Rosiglitazone and cardiovascular risk

- Rosiglitazone (as well as pioglitazone) increases the risk of hospitalization for heart failure; for this reason, its use in patients with coronary artery disease (or any heart disease) should be very cautious.
- At present, there is no evidence that rosiglitazone increases the risk of myocardial infarction. The results of recent meta-analyses are unsubstantial.
- Although rosiglitazone reduces the risk of re-stenosis after coronary agioplasty, this drug does not appear to confer any protection from cardiovascular disease in primary prevention.

Articles

Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)

*UK Prospective Diabetes Study (UKPDS) Group**



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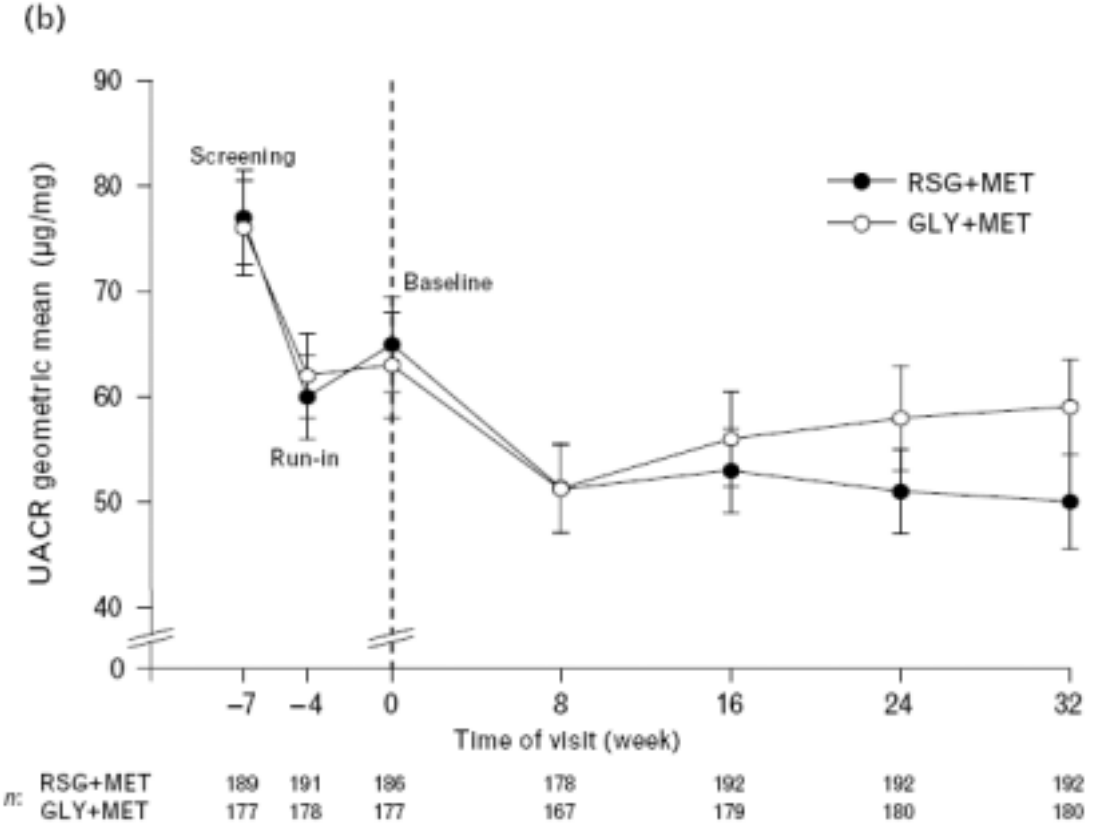
Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type 2 diabetes patients with microalbuminuria

George L. Bakris[a], Luis M. Ruilope[b], Stephen O. McMorn[c], Wayde M. Weston[c], Mark A. Heise[c], Martin I. Freed[d] and Lisa E. Porter[e]



Journal of Hypertension 2006, 24:2047–2055

Glycemic Durability of Rosiglitazone, Metformin, or Glyburide Monotherapy

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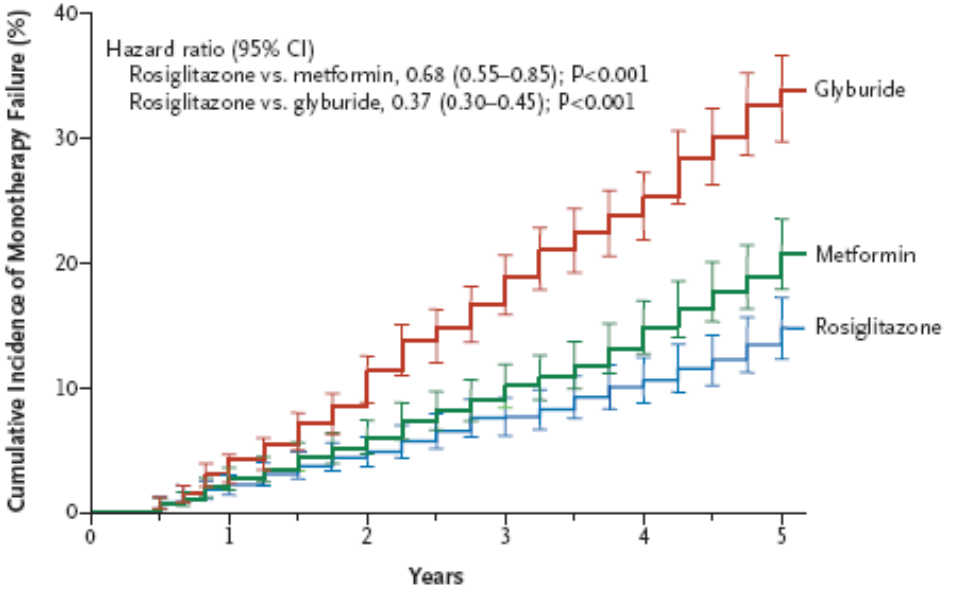
N Engl J Med 2006;355:2427-43.



No. at Risk

Rosiglitazone	1393	1207	1078	957	844	324
Metformin	1397	1205	1076	950	818	311
Glyburide	1337	1114	958	781	617	218

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	Rosiglitazone	Metformin	Glyburide
	number of patients (percent)		
Men	32 (3.95)	29 (3.36)	28 (3.35)
Women	60 (9.30)	30 (5.08)*	21 (3.47)*
Lower limb	36 (5.58)	18 (3.05)†	8 (1.32)*
Upper limb	22 (3.41)	10 (1.69)	9 (1.49)†
Spinal	1 (0.16)	1 (0.17)	1 (0.17)

Rosiglitazone stimulates adipogenesis and decreases osteoblastogenesis in human mesenchymal stem cells

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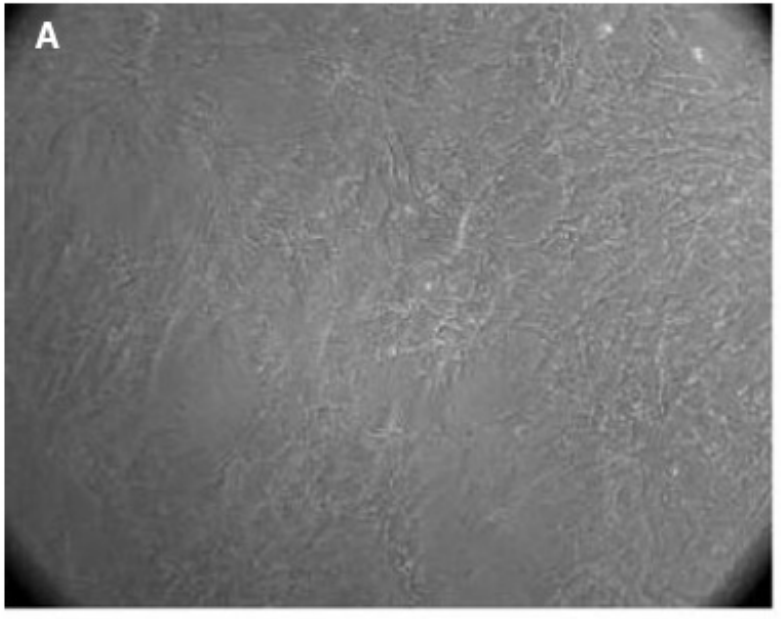

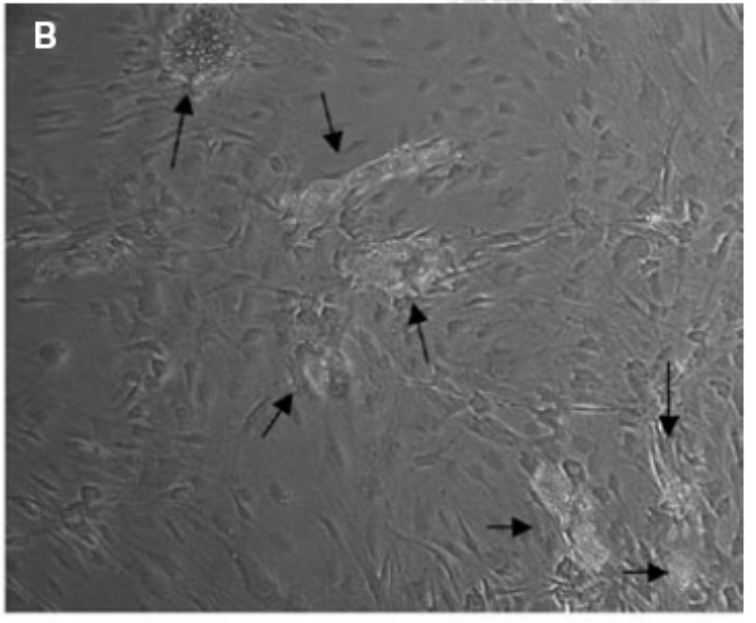

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BONE FRACTURES AND HYPOGLYCAEMIC TREATMENT IN TYPE 2 DIABETIC PATIENTS: A CASE-CONTROL STUDY.

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