Thiazolidinedionlar

(Glitazonlar)

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Endokrinoloji ve Metabolizma Hastalıkları BD

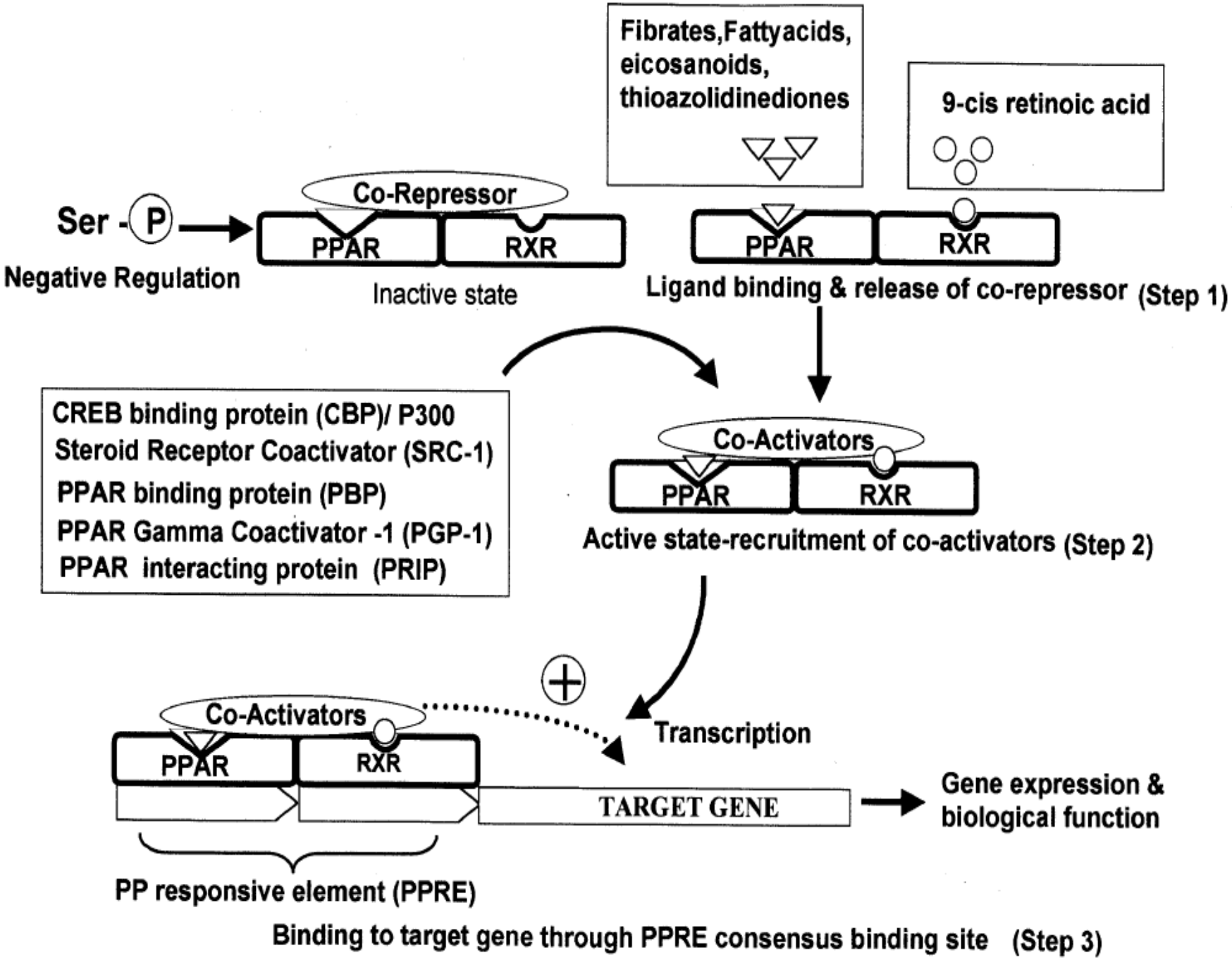
17 Mayıs 2008-Antalya

Thiazolidinedionlar (TZD)

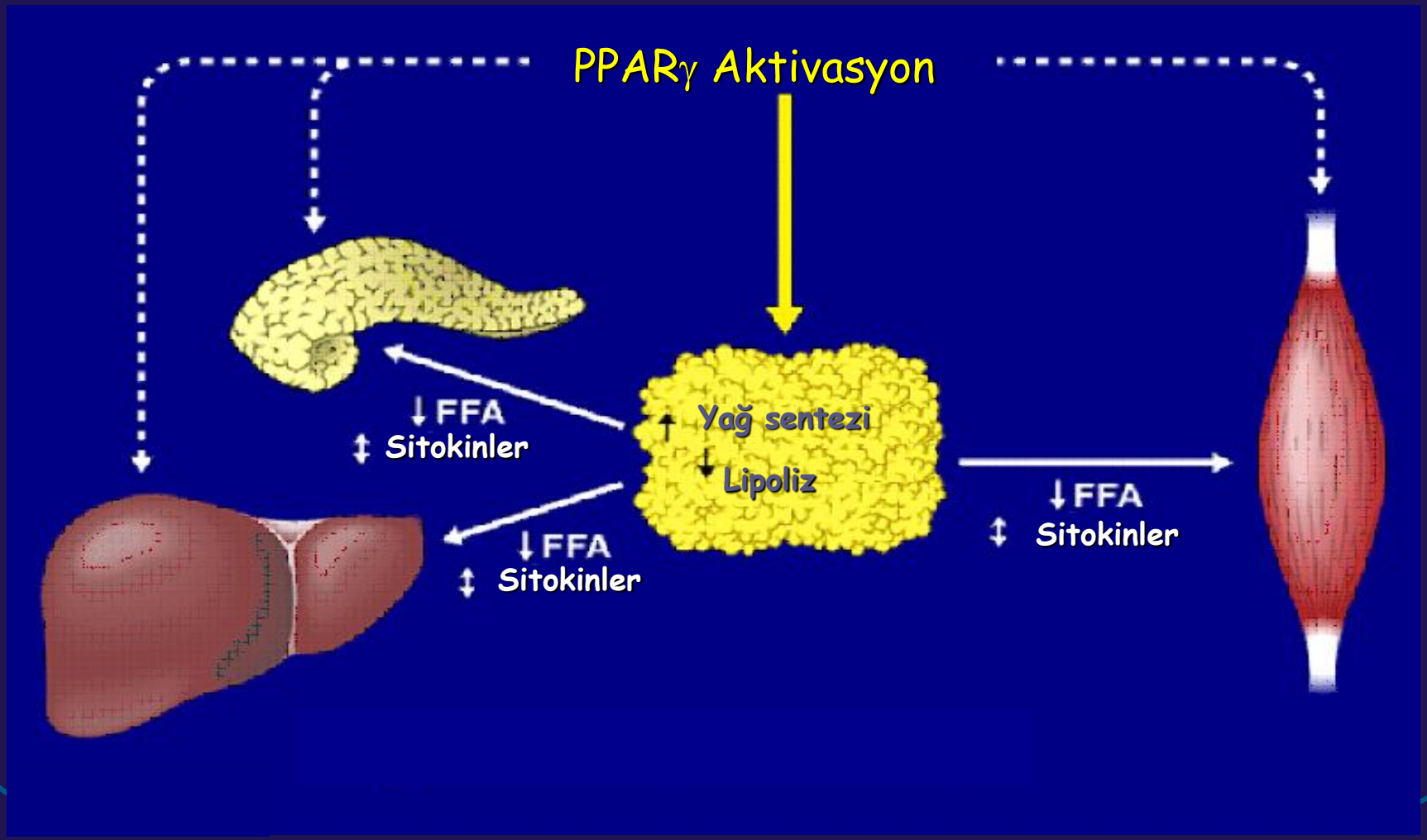
1. Etki mekanizması nasıldır ?

TZD etki mekanizması

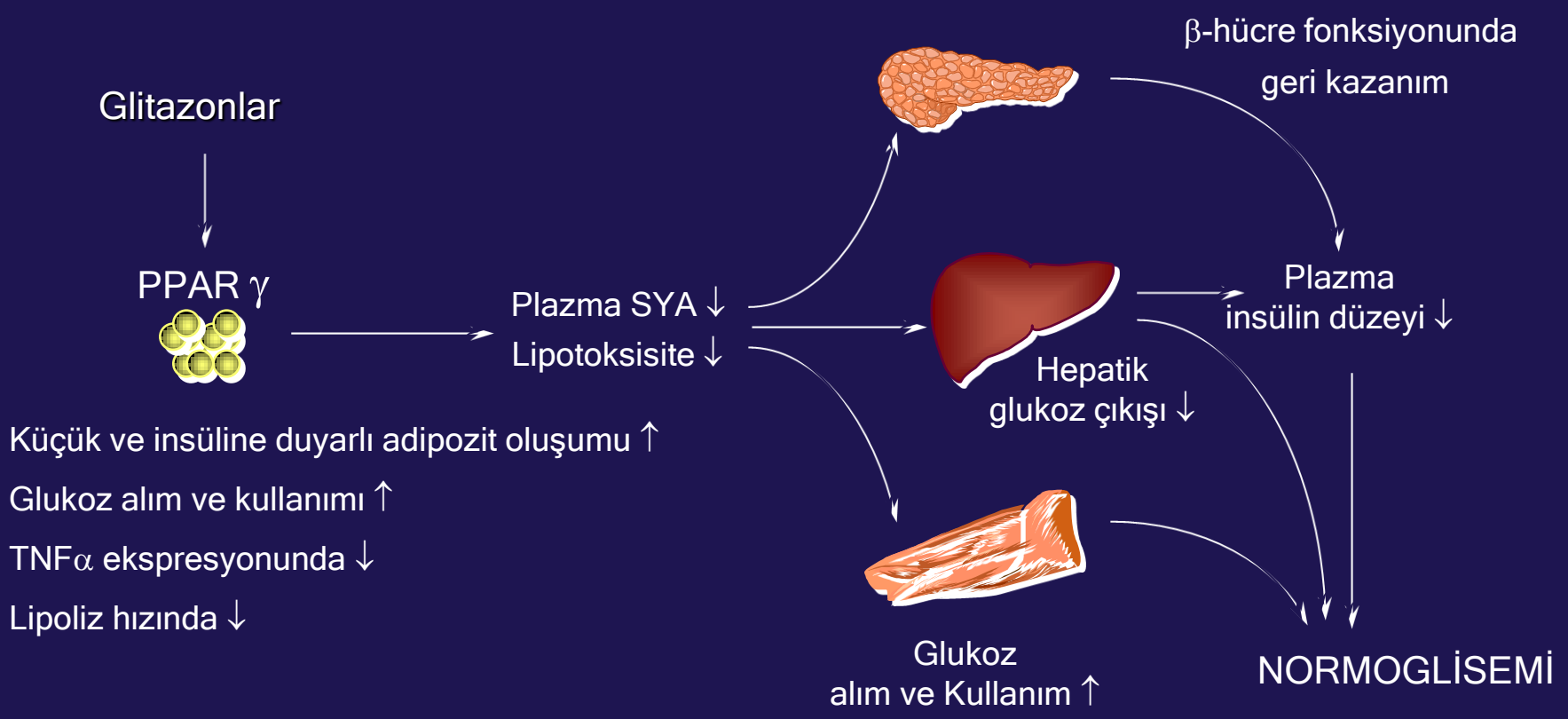
- PPARγ (peroxisome proliferator-activated receptor-PPAR) reseptör agonistidir
- Nükleer reseptör ailesinin bir üyesidir
- Gen ekspresyonuna neden olan transkripsiyon faktörüdürler
- Preadipositlerin adipositlere dönüşümünü sağlarlar
- Yağ, kas ve karaciğerde insülin direncini azaltırlar


Fibrates,Fattyacids,
eicosanoids,
thioazolidinediones
9-cis retinoic acid
Ser - P
Negative Regulation
Co-Repressor
PPAR
RXR
Inactive state
PPAR
RXR
Ligand binding & release of co-repressor (Step 1)
CREB binding protein (CBP)/ P300
Steroid Receptor Coactivator (SRC-1)
PPAR binding protein (PBP)
PPAR Gamma Coactivator -1 (PGP-1)
PPAR interacting protein (PRIP)
Co-Activators
PPAR
RXR
Active state-recruitment of co-activators (Step 2)
Co-Activators
PPAR
RXR
Transcription
TARGET GENE
Gene expression &
biological function
PP responsive element (PPRE)
Binding to target gene through PPRE consensus binding site (Step 3)

PPARγ:Metabolik Etki Yerleri



Glitazonlar PPAR$_\gamma$ aktivasyonu yoluyla hedef dokularda insülin direncini azaltıcı etki gösterirler



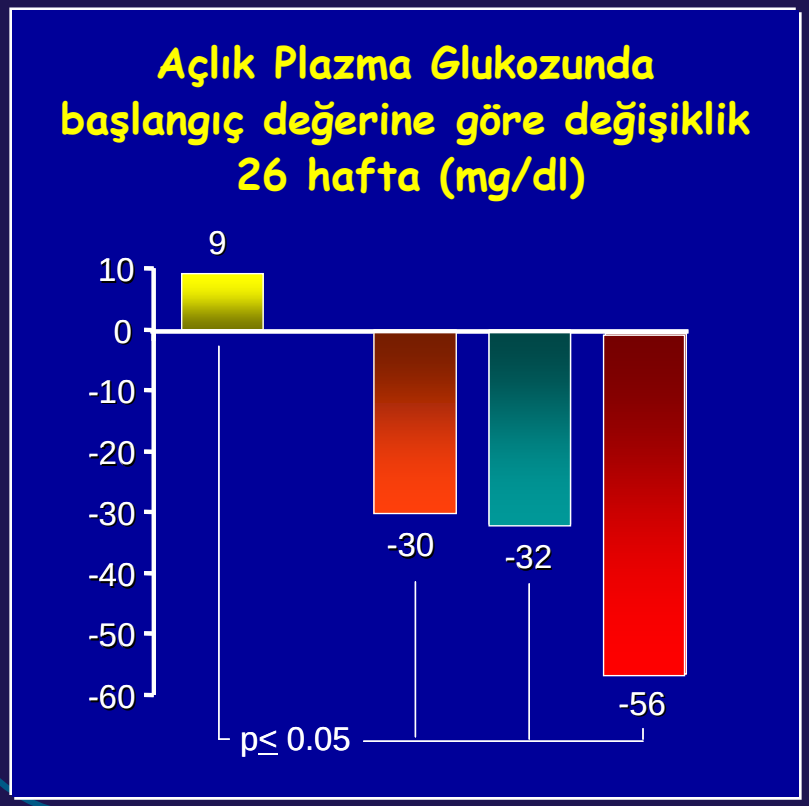
Glitazonlar PPARα üzerine de etki gösterirler.

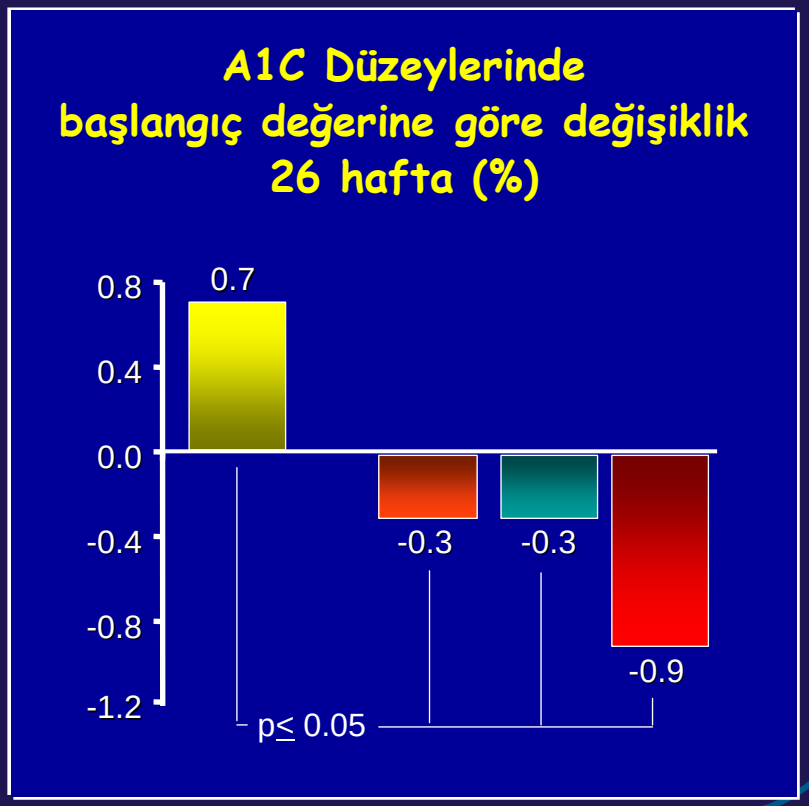
1. Doğru
2. Yanlış

Thiazolidinedionlar (TZD)

1. Etki mekanizması nasıldır ?
2. Kan şekerini düşürmede etkin midir?

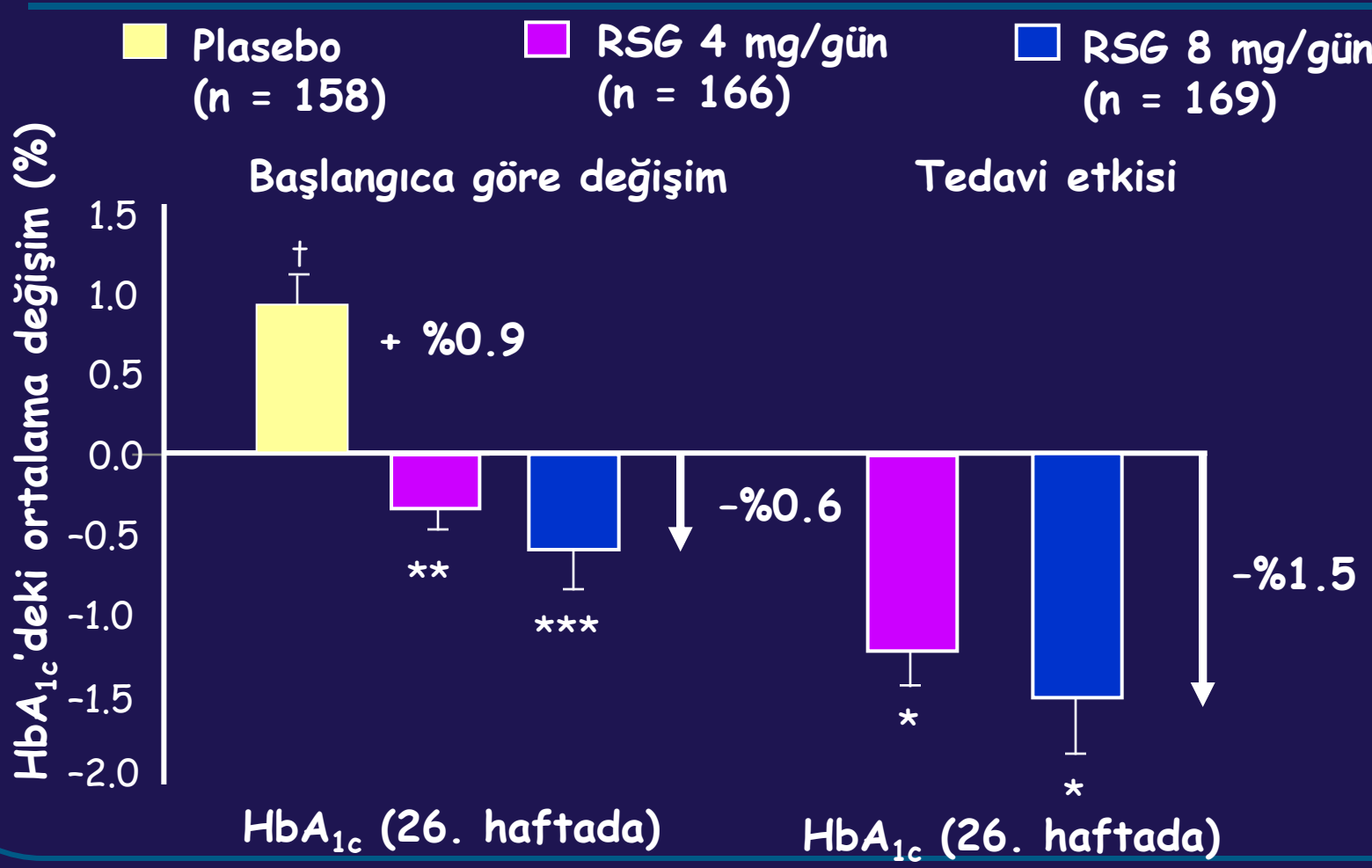
Pioglitazon Monoterapisinin Açlık Plazma Glukozu ve A1C Düzeylerine Etkisi (n=408)





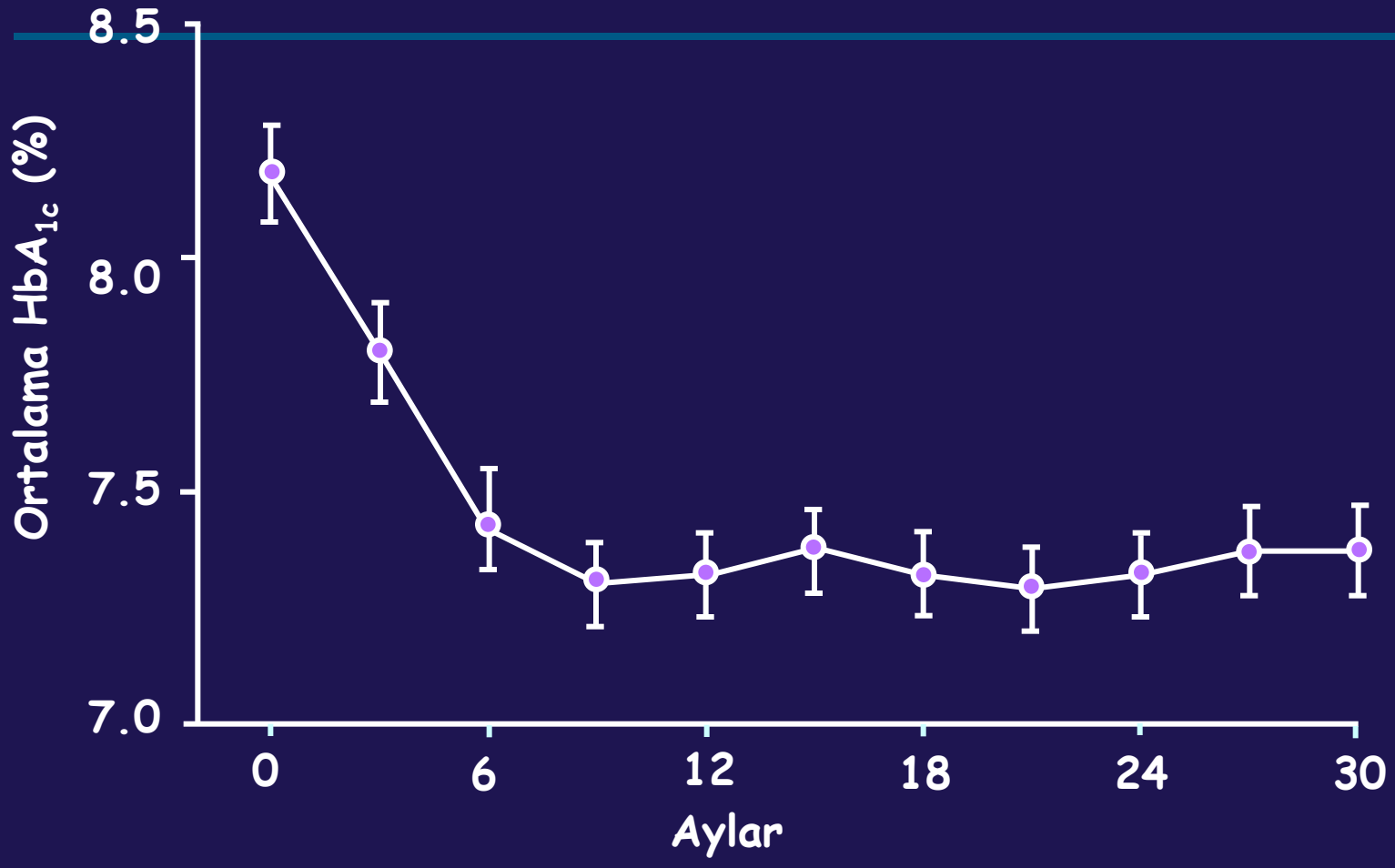
Diab Care 23: 1605,2000

Rosiglitazone etkinliği



J Clin Endocrinol Metab 2001; 86:280

Kalıcı glisemik kontrol (n = 171)

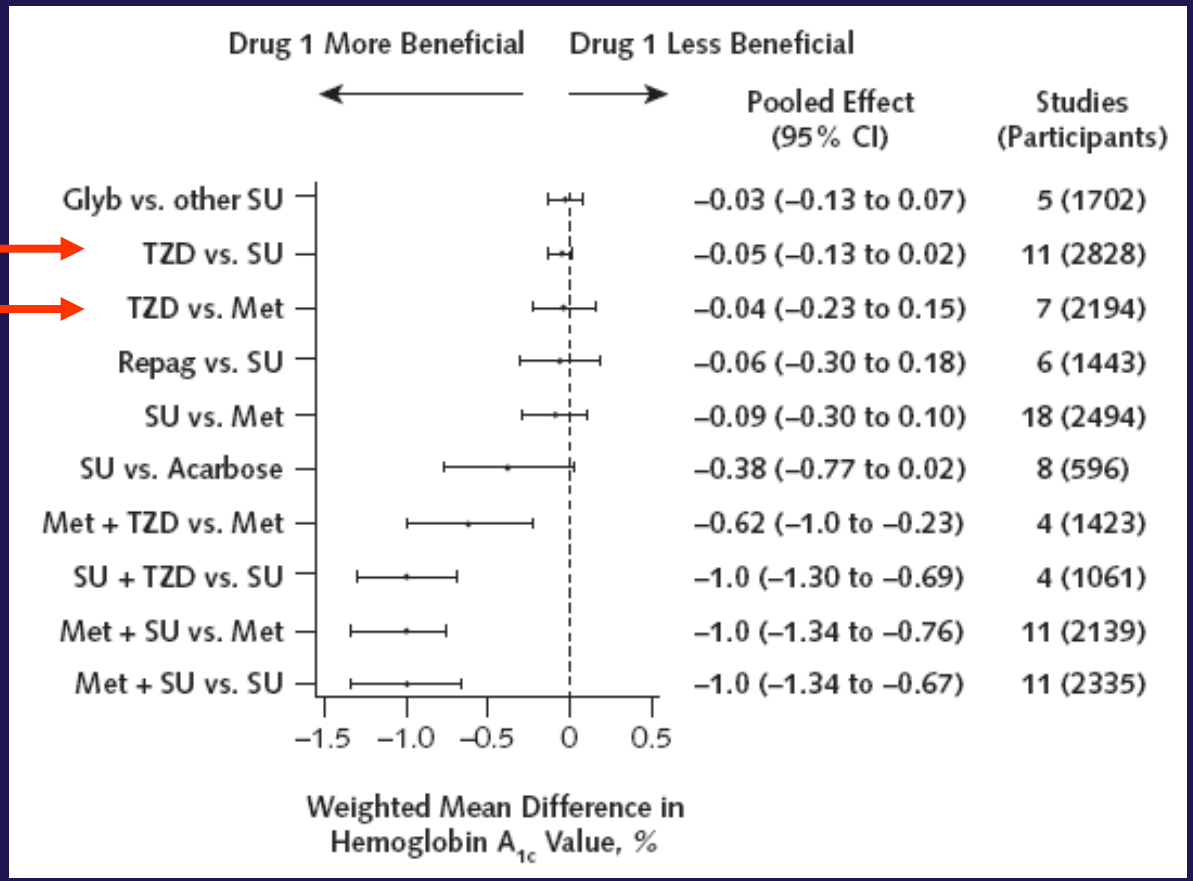


Diabetologia 2000: 43 (Suppl 1): A192.

Glitazonlar monoterapide HbA1c üzerine metformin kadar etkindirler.

1. Doğru
2. Yanlış

Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus



Ann Intern Med. 2007;147:386-399.

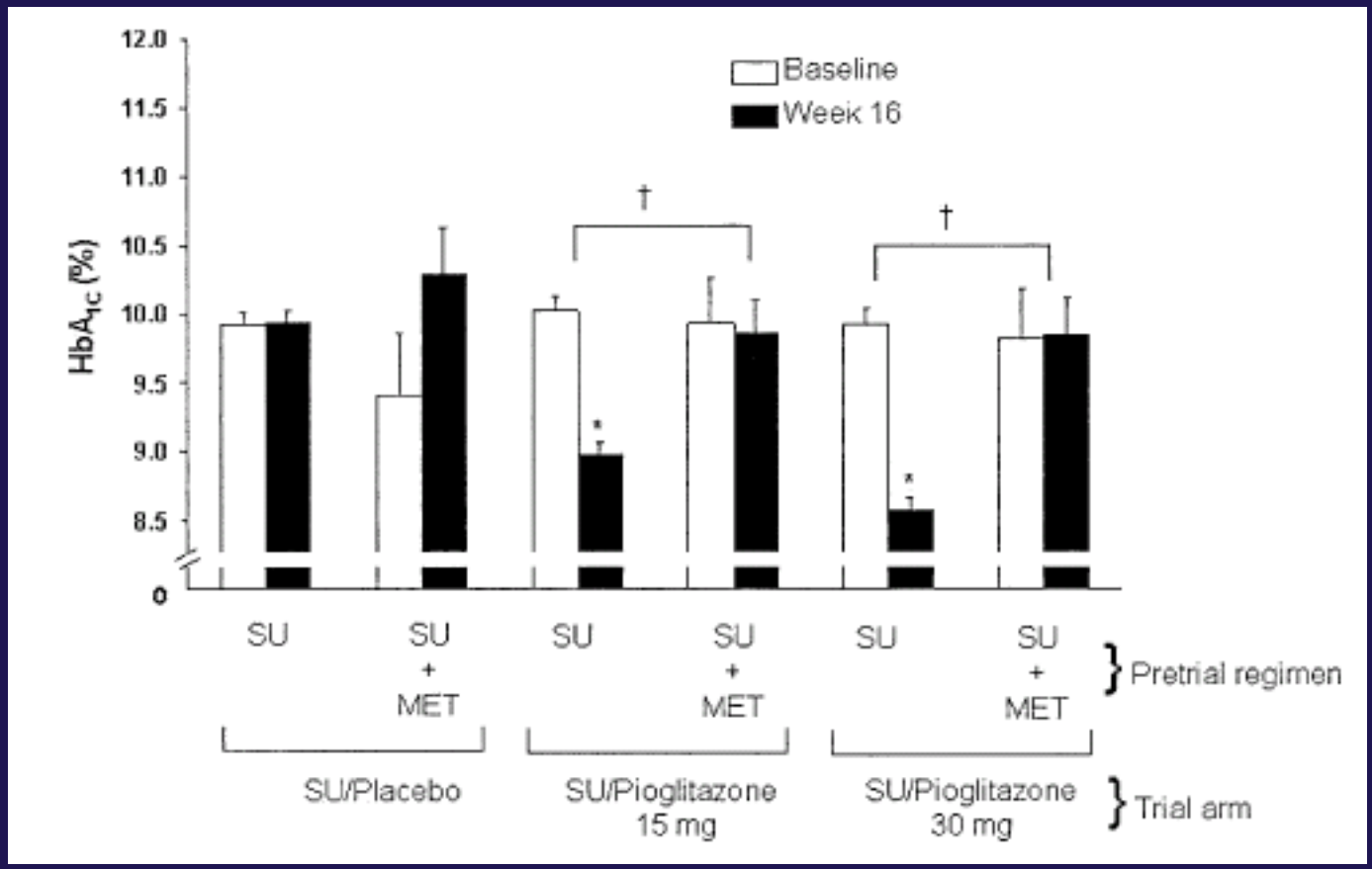
Thiazolidinedionlar (TZD)

1. Etki mekanizması nasıldır ?
2. Kan şekerini düşürmede etkin midir?
3. Diğer OAD ler ile kombine edilebilir mi?

Glitazonlar için hangisi doğrudur?

1. Metformin ile kombine edilmemelidir
2. Sulfonilüre ile kombine edilmemelidir
3. Akarboz ile kombine edilmemelidir
4. Repaglinid ile kombine edilmemelidir
5. İnsülin ile kombine edilmemelidir

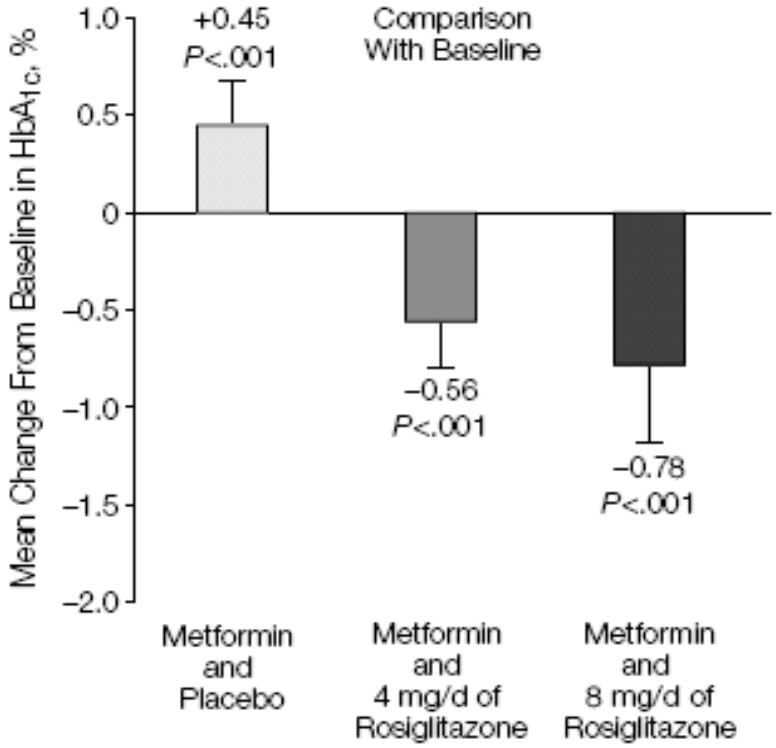
Combination therapy with pioglitazone plus metformin or sulfonylurea in patients with Type 2 diabetes Influence of prior antidiabetic drug regimen

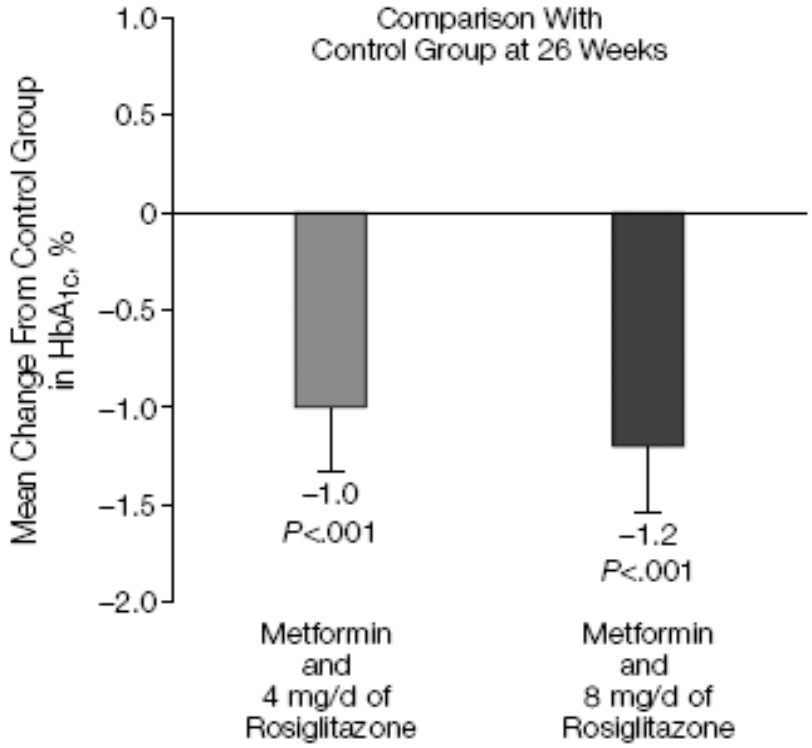


J Diab Comp. 2003; 17: 211

Effect of Metformin and Rosiglitazone Combination Therapy in Patients With Type 2 Diabetes Mellitus

A Randomized Controlled Trial





JAMA. 2000;283:1695-1702

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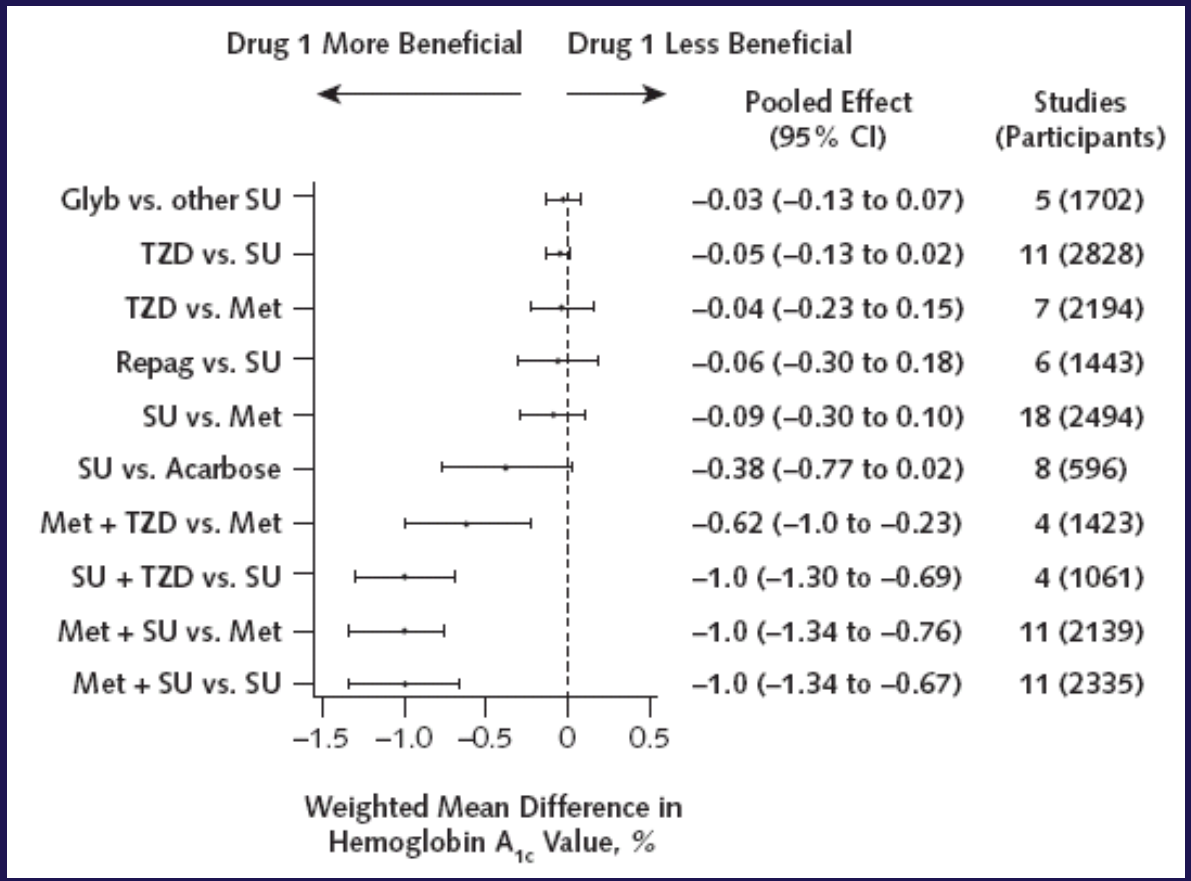


Ann Intern Med. 2007;147:386-399.

Thiazolidinedionlar (TZD)

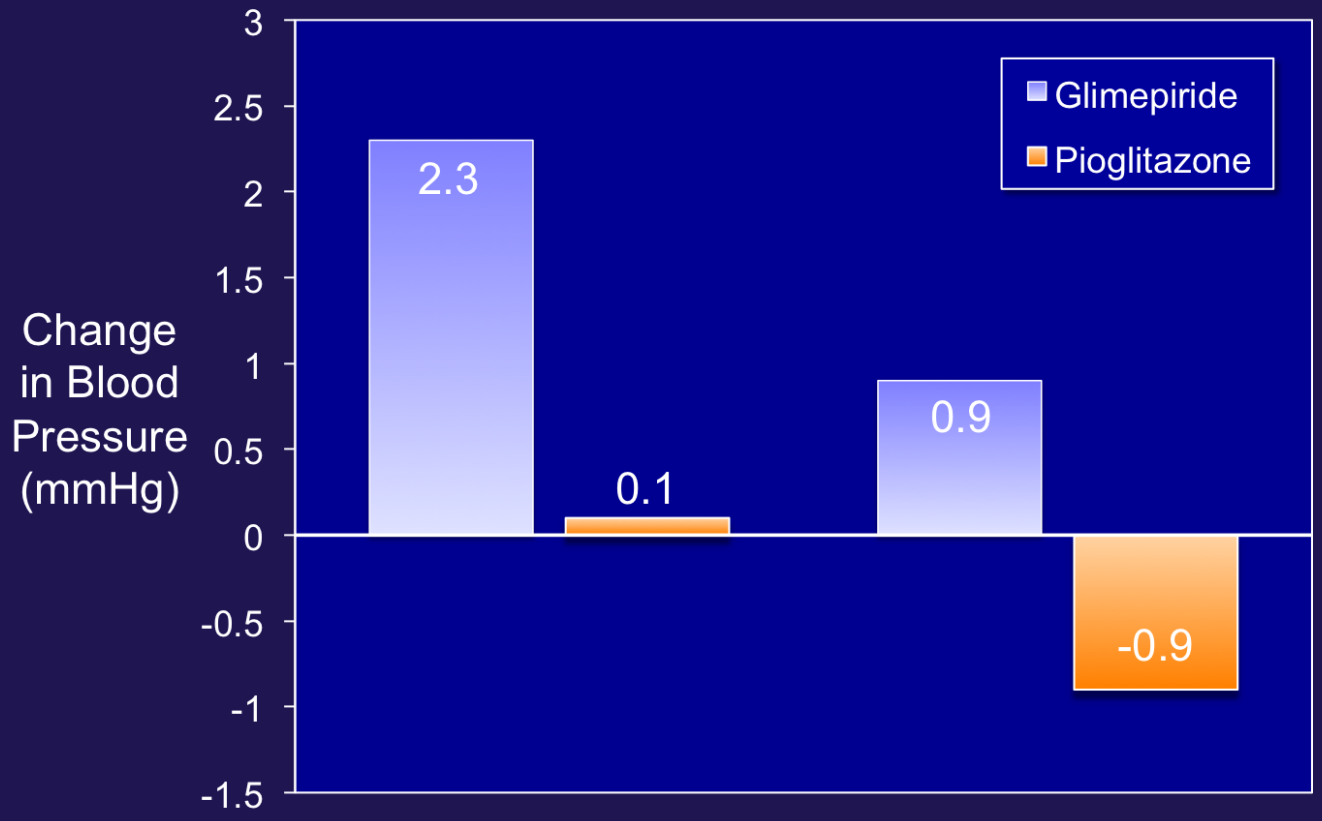
1. Etki mekanizması nasıldır ?
2. Kan şekerini düşürmede etkin midir?
3. Diğer OAD ler ile kombine edilebilir mi?
4. Kardiyovasüler etkileri nasıldır?

TZD-Kardiyovasküler etkileri

- Kan basıncı
- Lipidler
- Kardiyovasküler olaylar

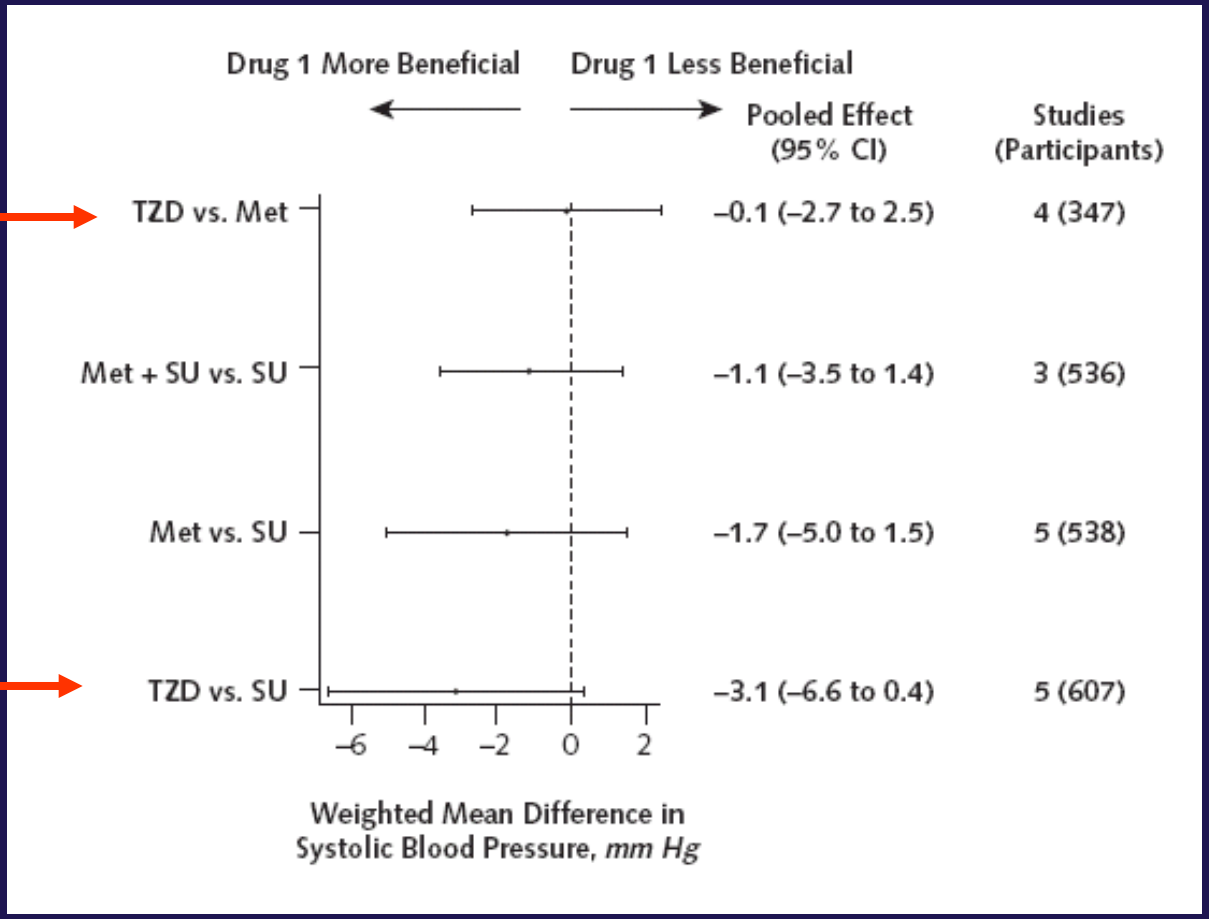
Comparison of Pioglitazone vs Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes

The PERISCOPE Randomized Controlled Trial



JAMA. 2008;299(13):1561-1573

Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus



Ann Intern Med. 2007;147:386-399.

TZD-Kardiyovasküler etkileri

- Kan basıncı
- Lipidler
- Kardiyovasküler olaylar

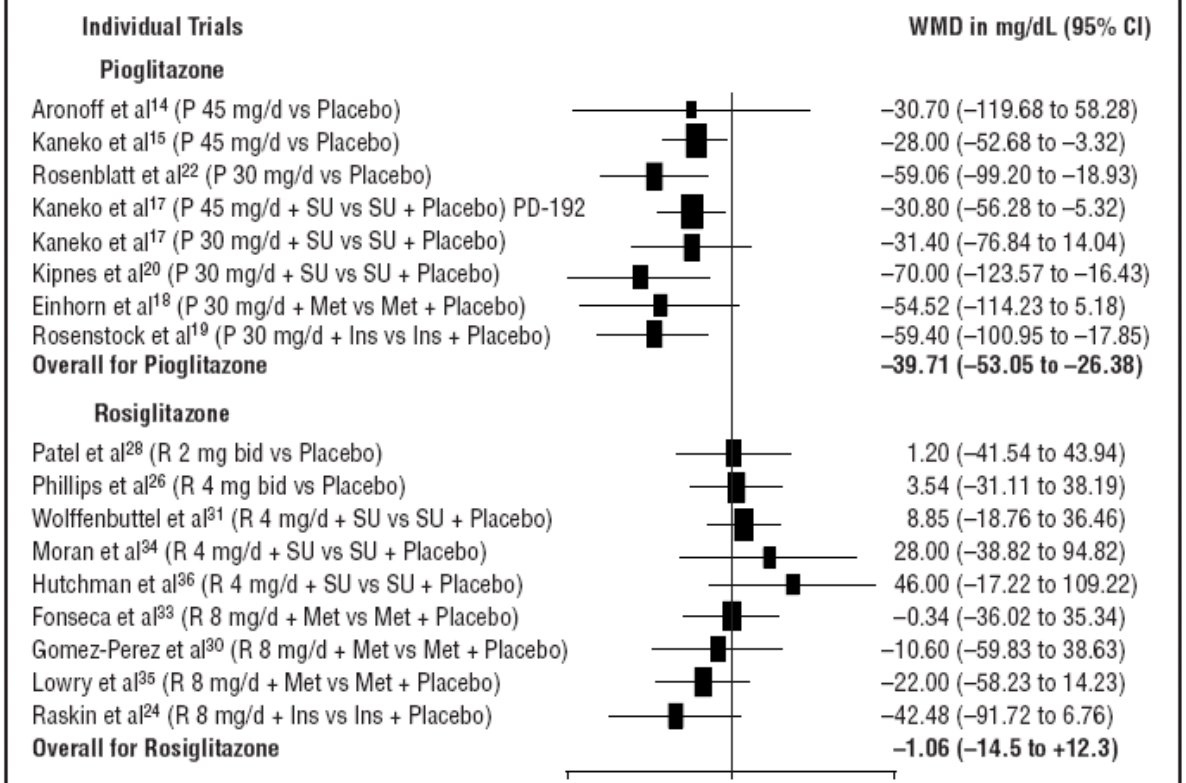
Glitazonların lipidler üzerine etkileri benzerdir.

1. Doğru
2. Yanlış

REVIEW ARTICLE

A Meta-analysis Comparing the Effect of Thiazolidinediones on Cardiovascular Risk Factors

Elaine Chiquette, PharmD; Gilbert Ramirez, PhD; Ralph DeFronzo, MD



Arch Intern Med. 2004;164:2097-210

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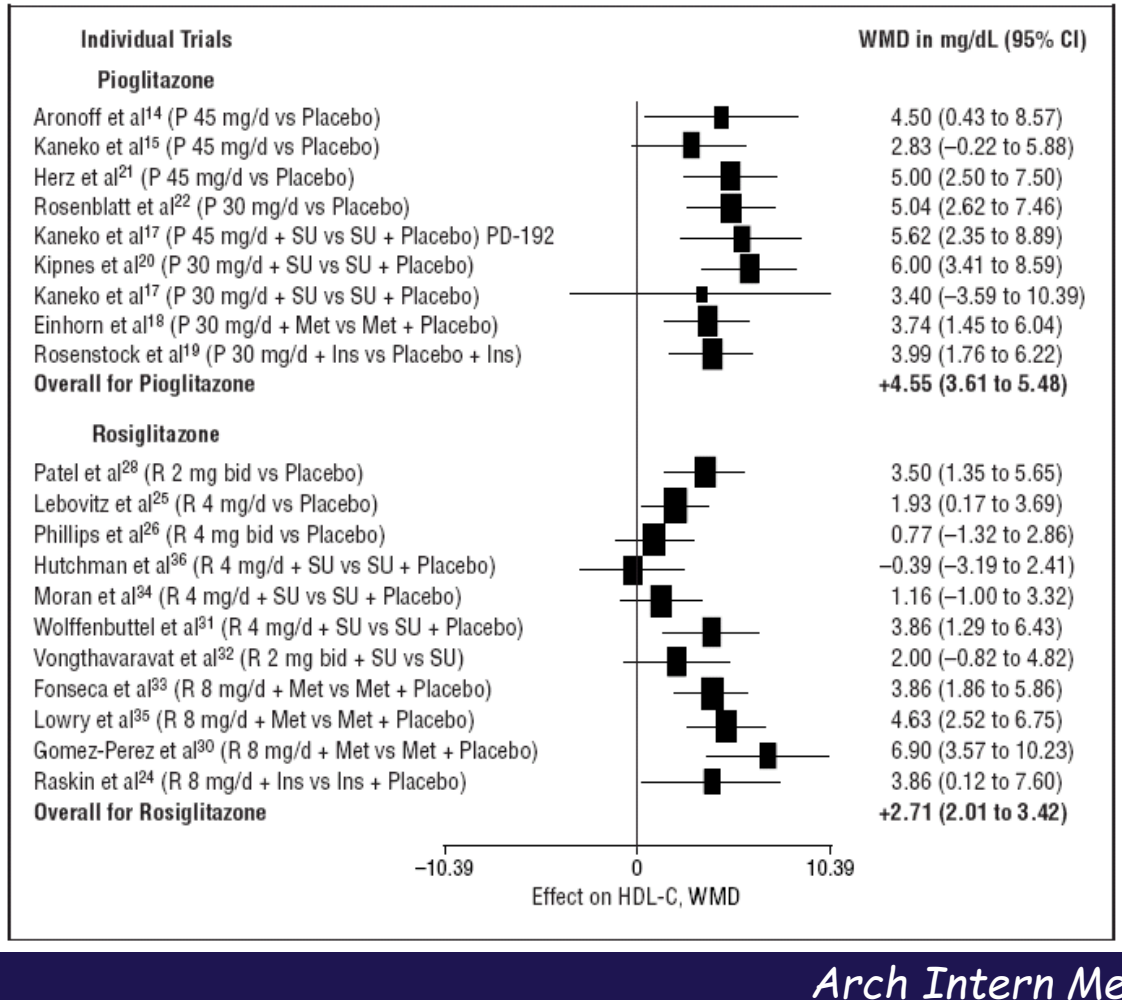

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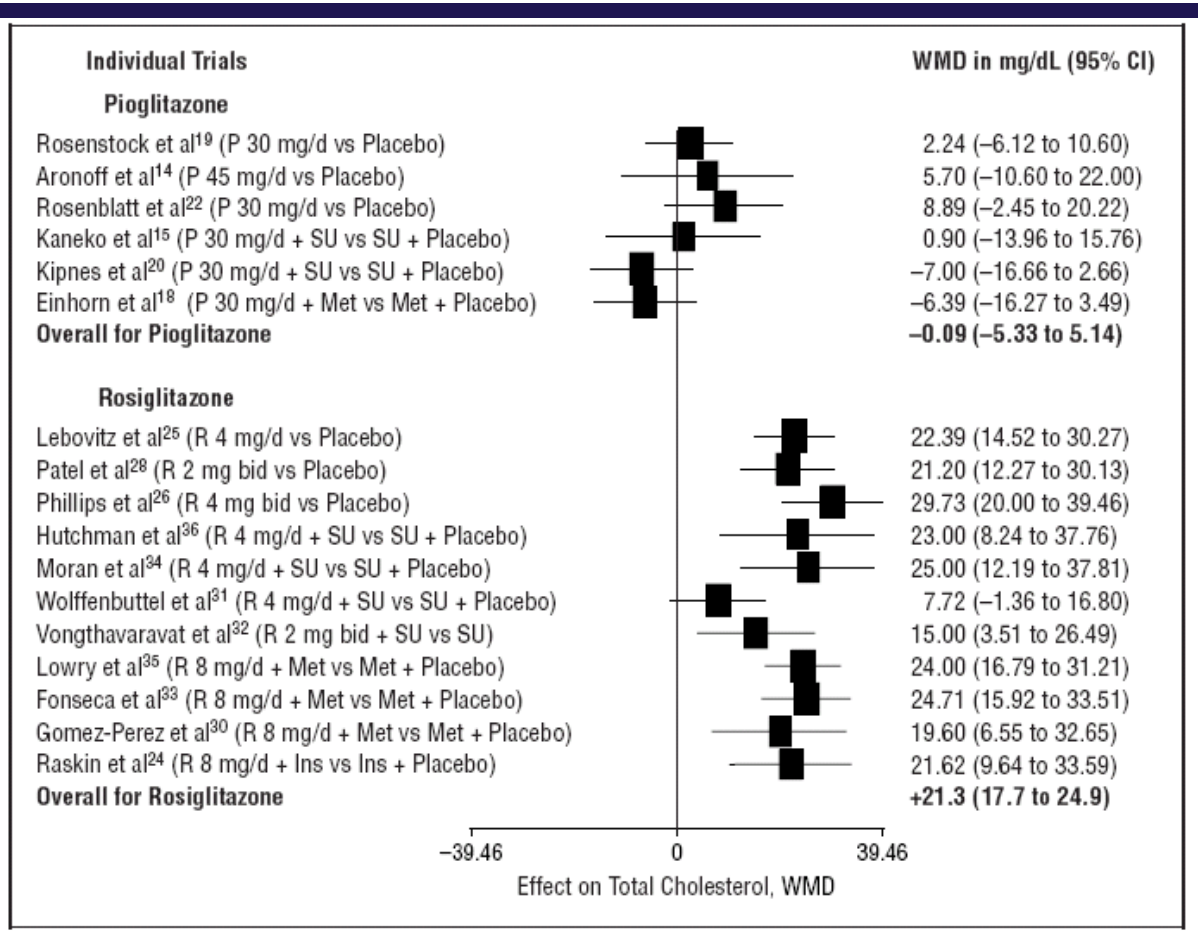

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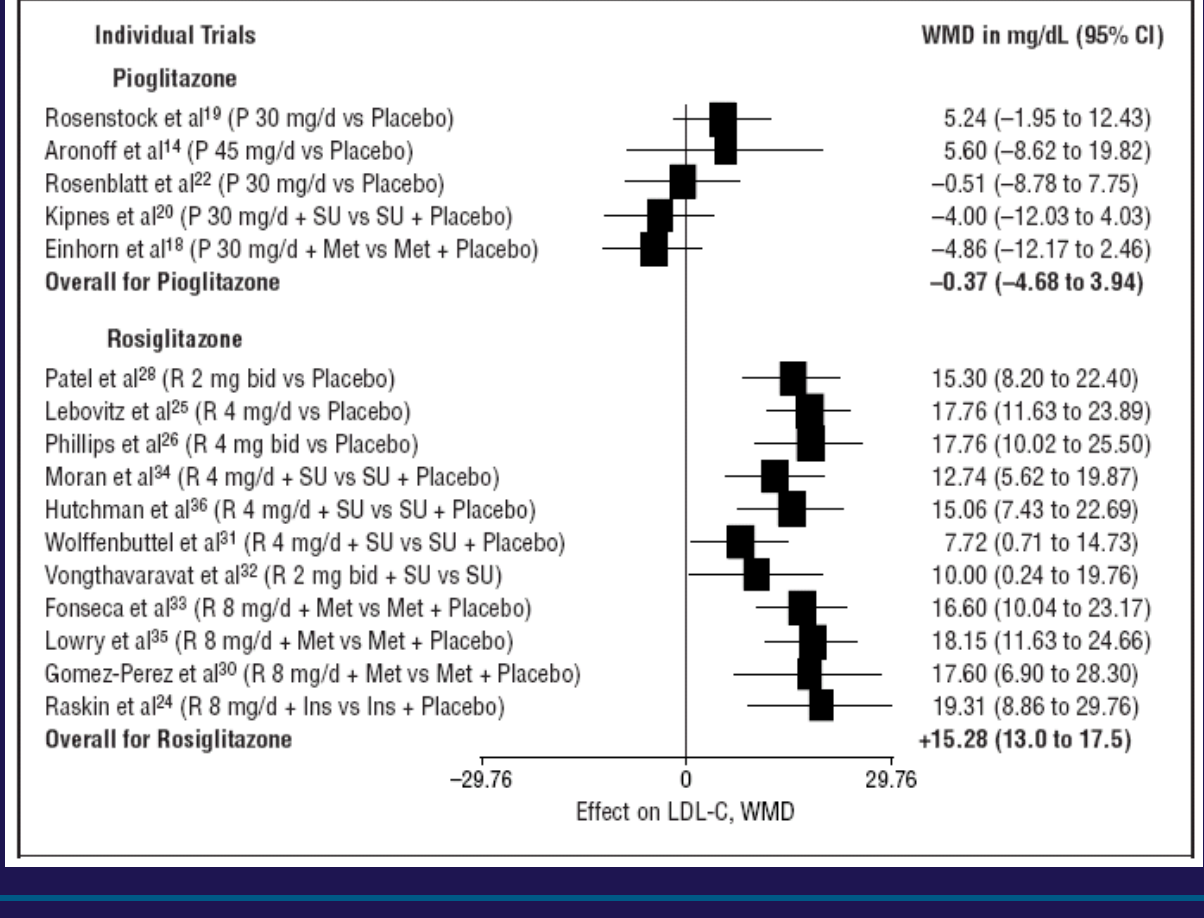

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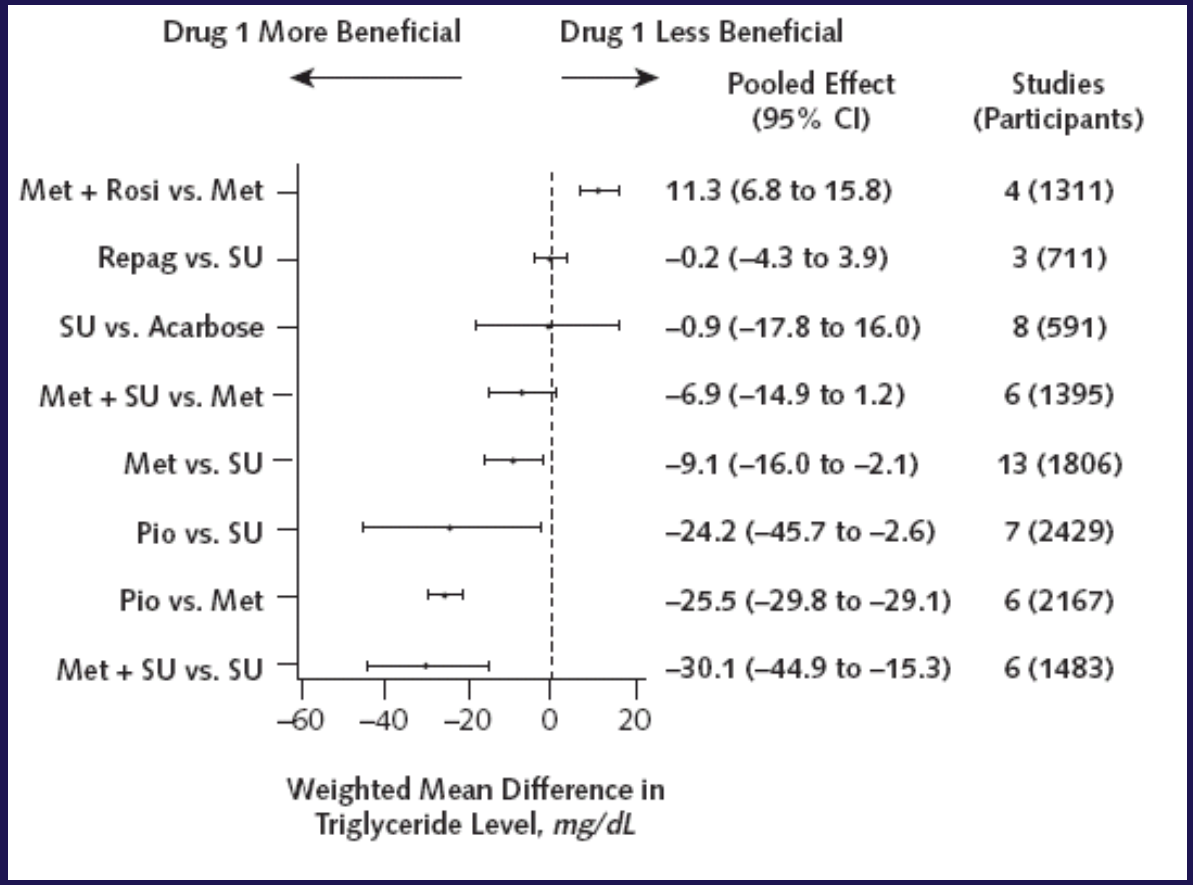
Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus



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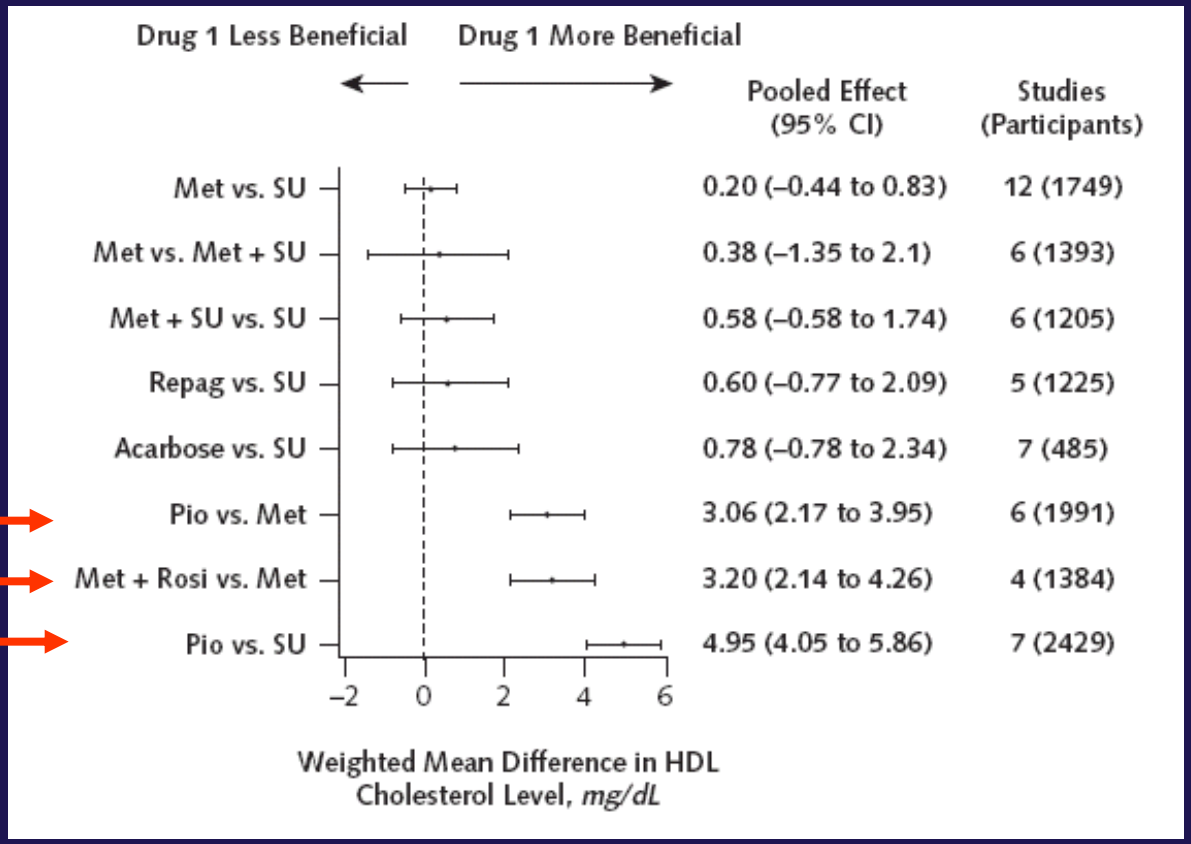

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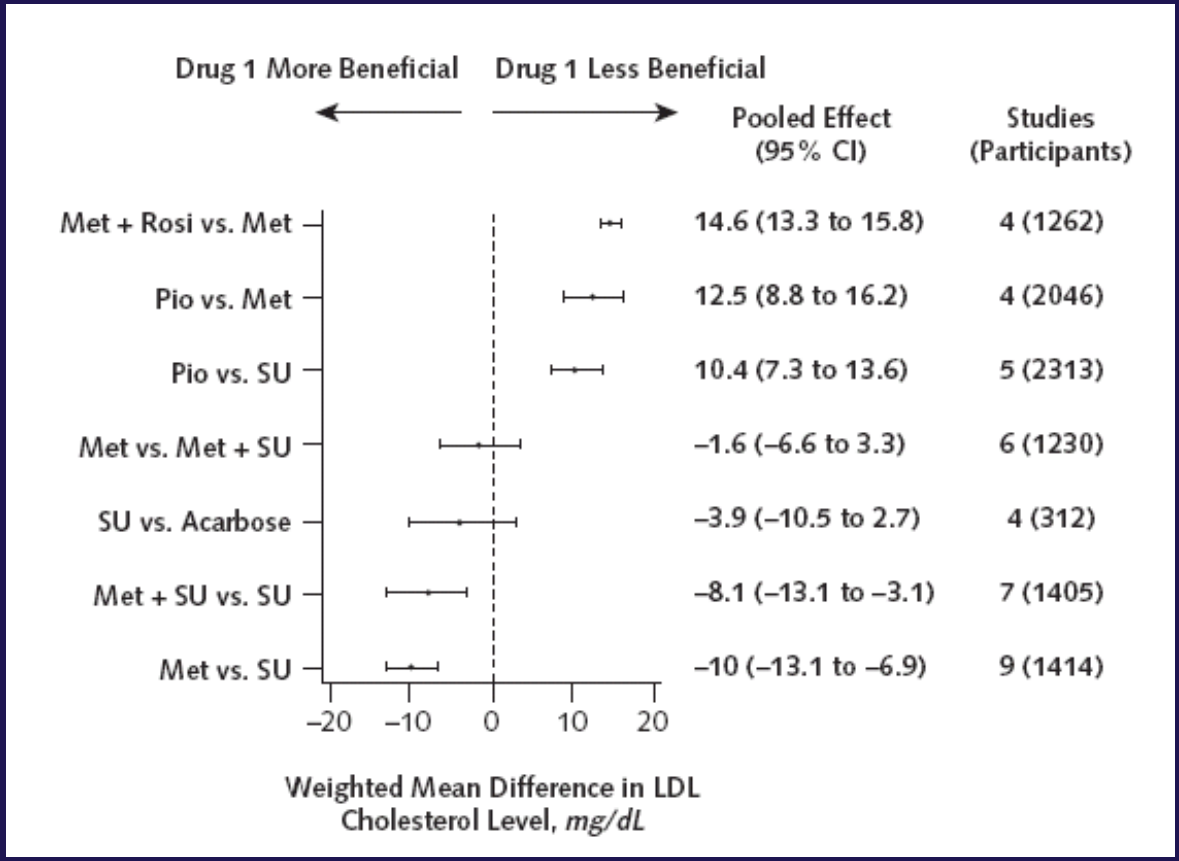
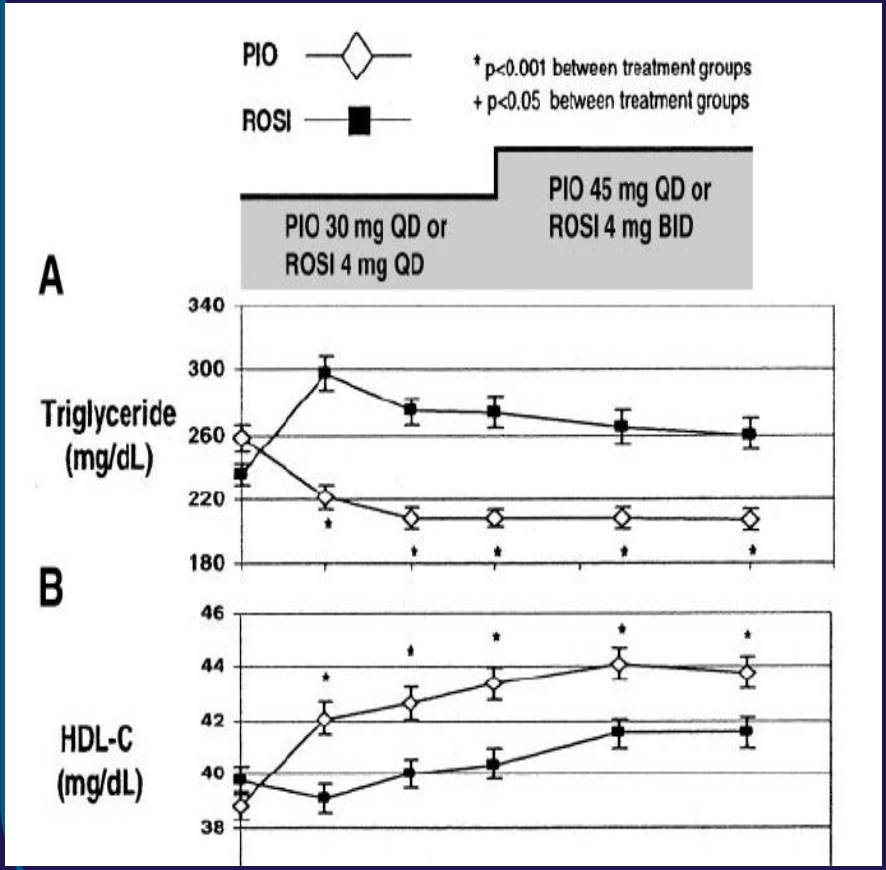
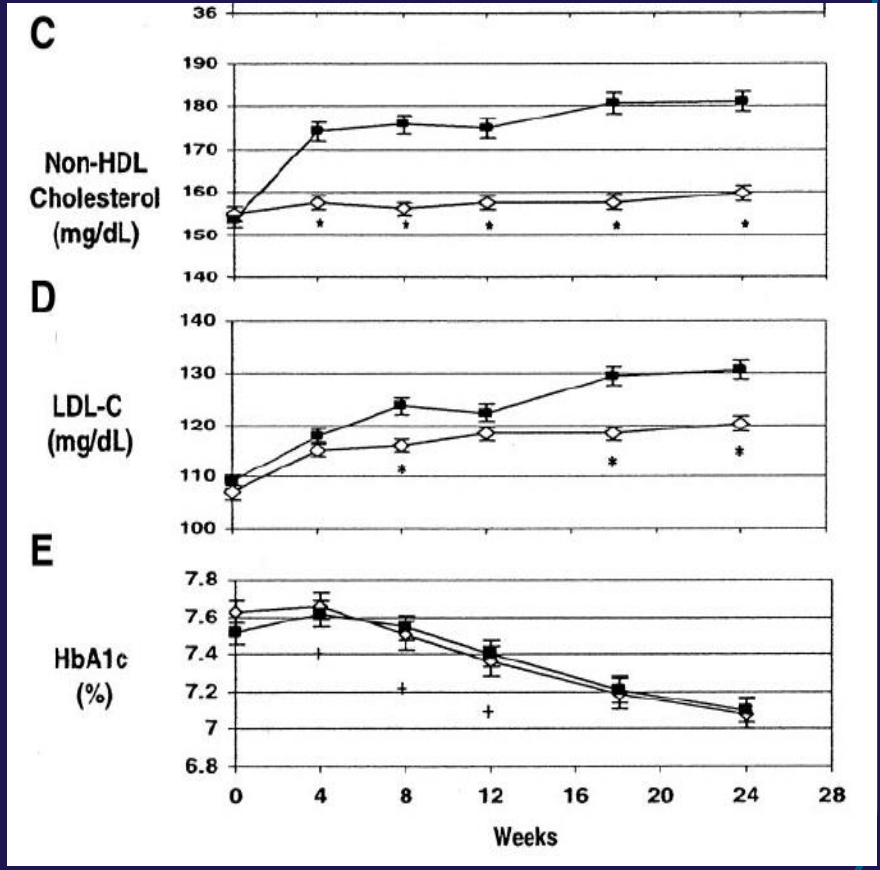


Ann Intern Med. 2007;147:386-399.

A Comparison of Lipid and Glycemic Effects of Pioglitazone and Rosiglitazone in Patients With Type 2 Diabetes and Dyslipidemia





Diabetes Care 28:1547–1554, 2005

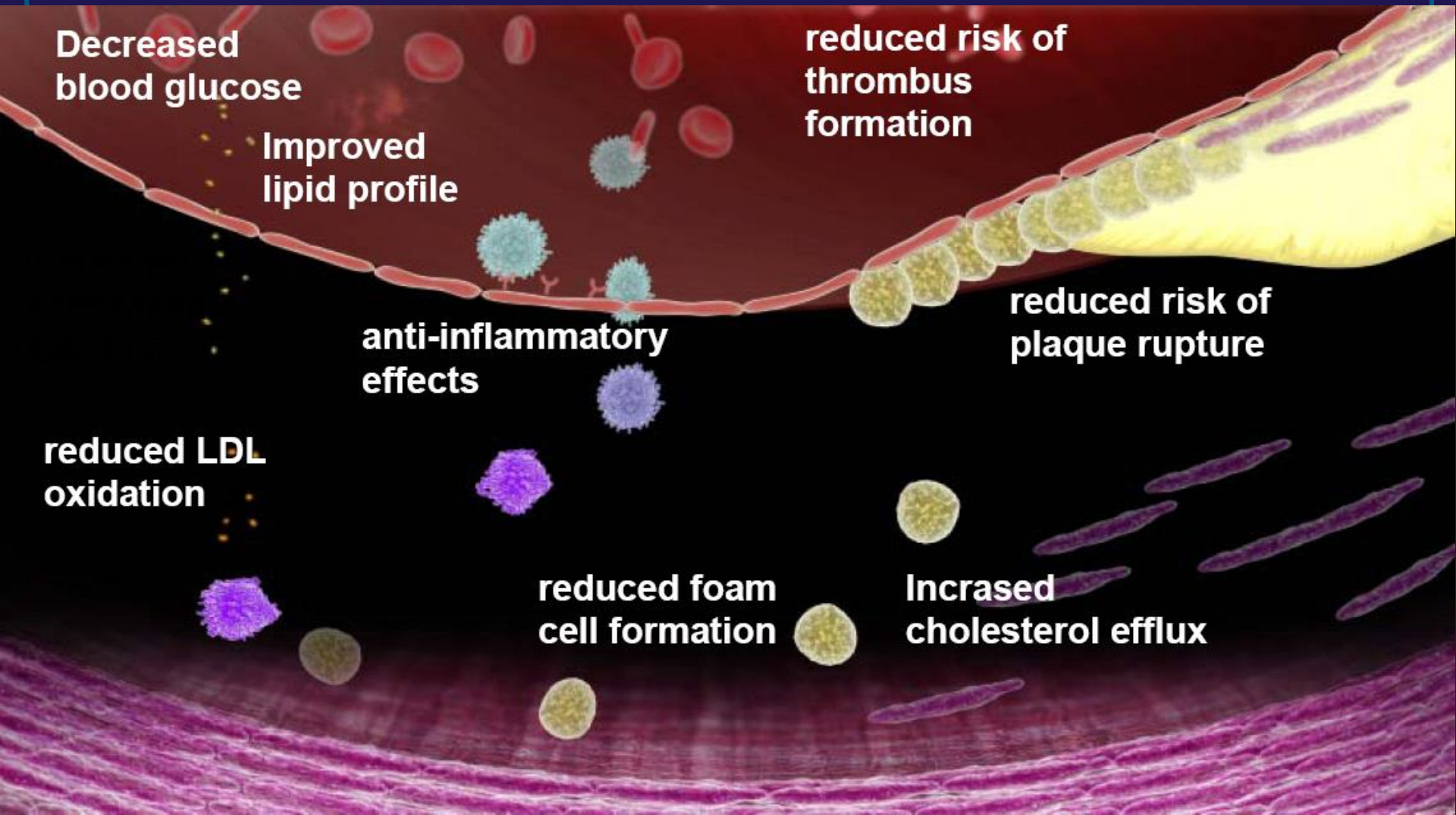
TZD-Kardiyovasküler etkileri

- Kan basıncı
- Lipidler
- Kardiyovasküler olaylar

Glitazonlar kardiyovasküler mortaliteyi azaltırlar.

1. Doğru
2. Yanlış

Koroner olayları önlemede OAD den beklentiler



Kardiyovasküler değerlendirme

- Dislipidemi
- İmflamasyon belirteçleri
- Vasküler düz kas proliferasyonu
- Vasküler reaktivite
- Karotid intima media kalınlığı

Kardiyovasküler sonlanımlar

- Mortalite
  - Kardiyovasküler mortalite
- İskemik kalp hastalığı
- Serebrovasküler hastalık
- Kalp yetmezliği
- Periferik damar hastalığı
- Hospitalizasyon

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.

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.

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

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

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

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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

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

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

Rosiglitazone Evaluated for Cardiovascular Outcomes — An Interim Analysis

Table 2. Hospitalization or Death from Cardiovascular Causes.*

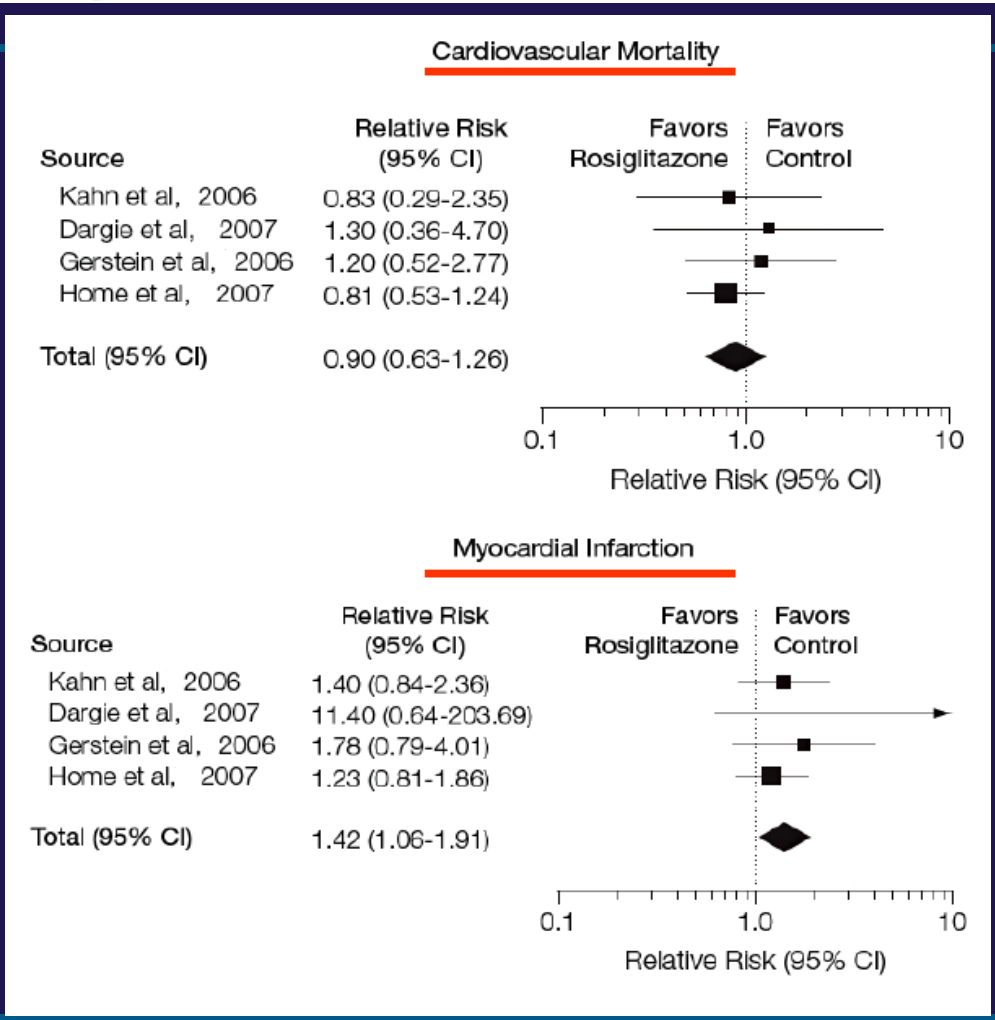
Variable	Rosiglitazone Group (N=2220)	Control Group (N=2227)	Hazard Ratio (95% CI)	P Value
	no. of patients			
Adjudicated events				
Primary end point	217	202	1.08 (0.89–1.31)	0.43
Death				
From cardiovascular causes†	29	35	0.83 (0.51–1.36)	0.46
From any cause	74	80	0.93 (0.67–1.27)	0.63
Acute myocardial infarction‡	43	37	1.16 (0.75–1.81)	0.50
Congestive heart failure‡	38	17	2.24 (1.27–3.97)	0.006
Death from cardiovascular causes, myocardial infarction, and stroke	93	96	0.97 (0.73–1.29)	0.83
Events adjudicated and pending adjudication				
Primary end point	267	243	1.11 (0.93–1.32)	0.26
Death				
From cardiovascular causes†	37	46	0.80 (0.52–1.24)	0.32
Acute myocardial infarction‡	49	40	1.23 (0.81–1.86)	0.34
Congestive heart failure‡	47	22	2.15 (1.30–3.57)	0.003
Death from cardiovascular causes, myocardial infarction, and stroke	109	114	0.96 (0.74–1.24)	0.74

N Engl J Med 2007;357:28-38.

Long-term Risk of Cardiovascular Events With Rosiglitazone

A Meta-analysis

14291 patients in 4 major but not cardio-vascular trials



JAMA 2007, 298: 1189

Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

A Meta-analysis of Randomized Trials

Table 3. Cardiovascular Event Rates for Combined Trials Stratified by Study Type[a]

	No. (%)			
	Pioglitazone (n = 8554)	Control (n = 7836)	Hazard Ratio (95% Confidence Interval)	*P* Value
Death/myocardial infarction/stroke	375 (4.38)	450 (5.74)	0.82 (0.72-0.94)	.005
Death	209 (2.44)	224 (2.86)	0.92 (0.76-1.11)	.38
Myocardial infarction	131 (1.53)	159 (2.03)	0.81 (0.64-1.02)	.08
Death/myocardial infarction	309 (3.61)	357 (4.56)	0.85 (0.73-0.99)	.04
Stroke	104 (1.22)	131 (1.67)	0.80 (0.62-1.04)	.09
Serious heart failure	200 (2.34)	139 (1.77)	1.41 (1.14-1.76)	.002
Death/serious heart failure	361 (4.22)	321 (4.10)	1.11 (0.96-1.29)	.17
Death/myocardial infarction/stroke/ serious heart failure	508 (5.94)	523 (6.67)	0.96 (0.85-1.09)	.54

[a]Very short-term, short-term, midterm, long-term, and PROactive studies were used as stratification variables.

JAMA. 2007;298(10):1180-1188

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

	First events			Total events	
	Pioglitazone (n=2605)	Placebo (n=2633)	HR (95% CI)	Pioglitazone	Placebo
Death	177	186	0·96 (0·78–1·18)	177	186
Non-fatal MI (including silent MI)	119	144	0·83 (0·65–1·06)	131	157
Stroke	86	107	0·81 (0·61–1·07)	92	119
Major leg amputation	26	26	1·01 (0·58–1·73)	28	28
Acute coronary syndrome	56	72	0·78 (0·55–1·11)	65	78
Coronary revascularisation	169	193	0·88 (0·72–1·08)	195	240
Leg revascularisation	80	65	1·25 (0·90–1·73)	115	92
Total	..	..	..	803	900

Data refer to first event of that particular type. MI=myocardial infarction.

Table 4: Effect of pioglitazone and placebo on each component of the primary endpoint

Lancet 2005; 366: 1279–89

Thiazolidinedionlar (TZD)

1. Etki mekanizması nasıldır ?
2. Kan şekerini düşürmede etkin midir?
3. Diğer OAD ler ile kombine edilebilir mi?
4. Kardiyovasüler etkileri nasıldır?
5. Avantajları-dezavantajları nelerdir?

Glitazonlar için hangisi doğrudur?

1. Mikroalbumiüri saptanan hastalarda kullanılmamalıdır
2. Serum kreatinin seviyesi normal seviyenin üzerinde olanlarda kullanılmamalıdır
3. Renal transplant hastalarda kullanılmamalıdır
4. Renal yetmezlikli hastalarda doz ayarlaması yapılmalıdır
5. Hiçbiri

TZD - Avantajları

- Etkin ilaçlardır
- Tüm OAD lerle kombine edilebilirler
- Renal yetmezlikte doz ayarlaması gerekmez
- İleri yaşlarda kullanılabilir
- Kontrendikasyonları azdır
- Toleransı yüksektir
- Plazma insülin seviyesini artırmazlar
- Hipoglisemi riski yoktur
- Beta hücre fonksiyonunu koruyucu etkisi olabilir
- Diyabetten koruyucu etki mümkün
- Mikroalbuminüriyi azaltıcı etkisi

TZD - dezavantajları

- Etkinliği uzun sürede ortaya çıkar
- Etkinliği doz bağımlı ve değişken
- Kilo artışına neden olur
- Su retansiyonu- ödem yapabilir
- Konjestif kalp yetmezliğinde kontrendike
- Lipid profiline etki
- Uzun süreli klinik deneyim yeterli değil
- Kırık riski
- Karaciğer toksisitesi
- Pahalı

Thiazolidinedionlar (TZD)

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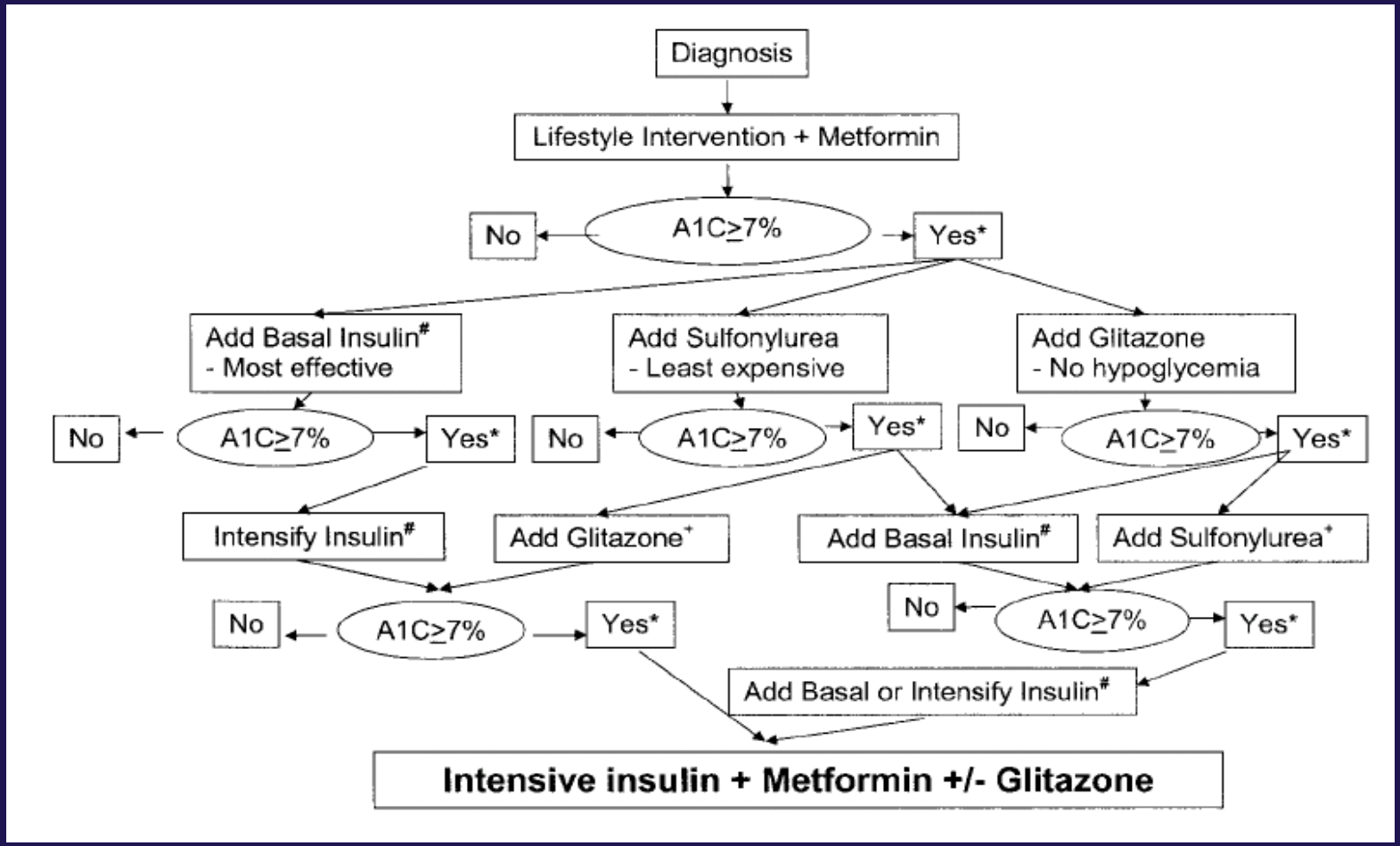
5. Avantajları-dezavantajları nelerdir?
6. Hangi hastalarda kullanılmalı-kullanılmamalıdır?

Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes



Diab Care,2006 29: 1963

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Update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

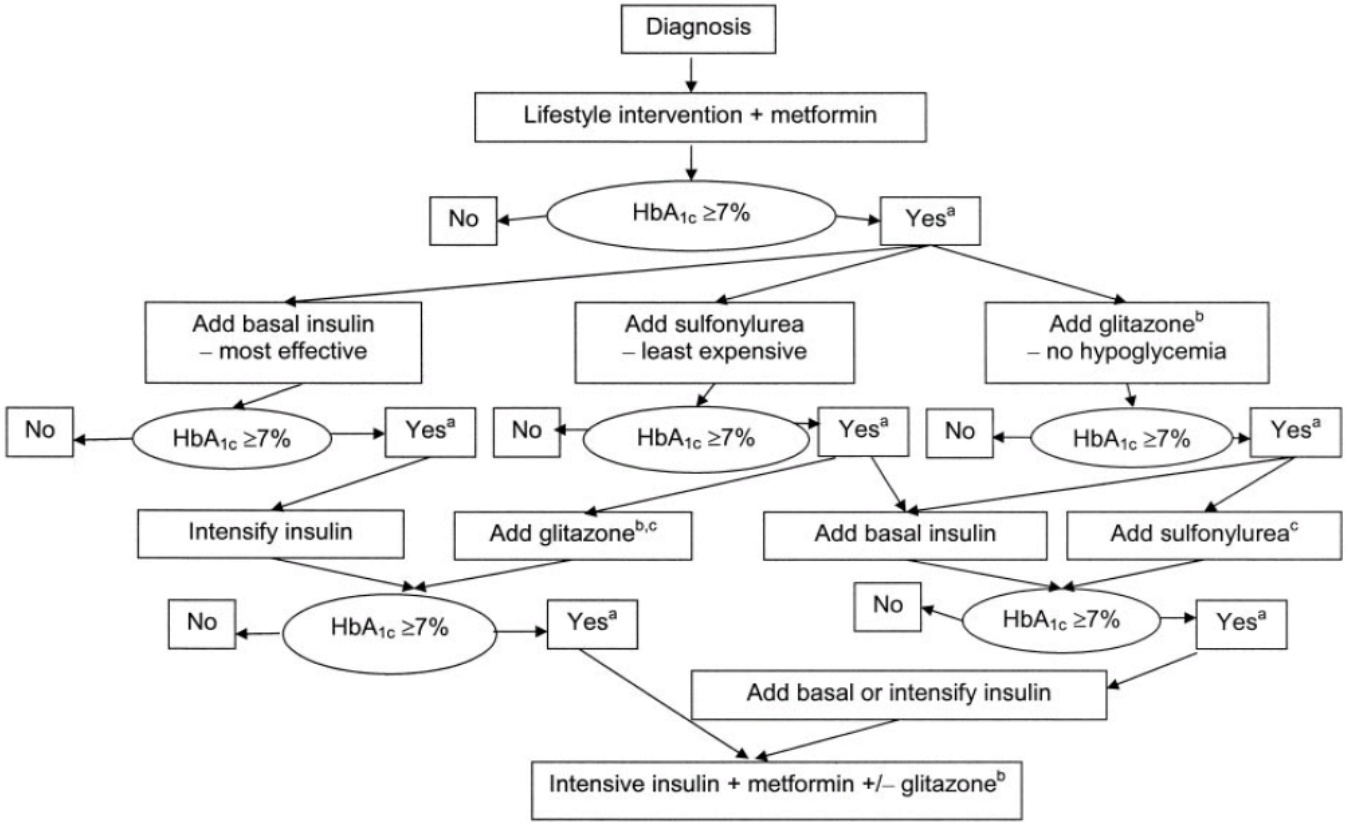

Figure 1—*Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle intervention at every visit. [a]Check A1C every 3 months until <7% and then at least every 6 months. [b]Associated with increased risk of fluid retention, CHF, and fractures. Rosiglitazone, but probably not pioglitazone, may be associated with an increased risk of myocardial infarction. [c]Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and lower expense.*

Diab Care,2008 31:173

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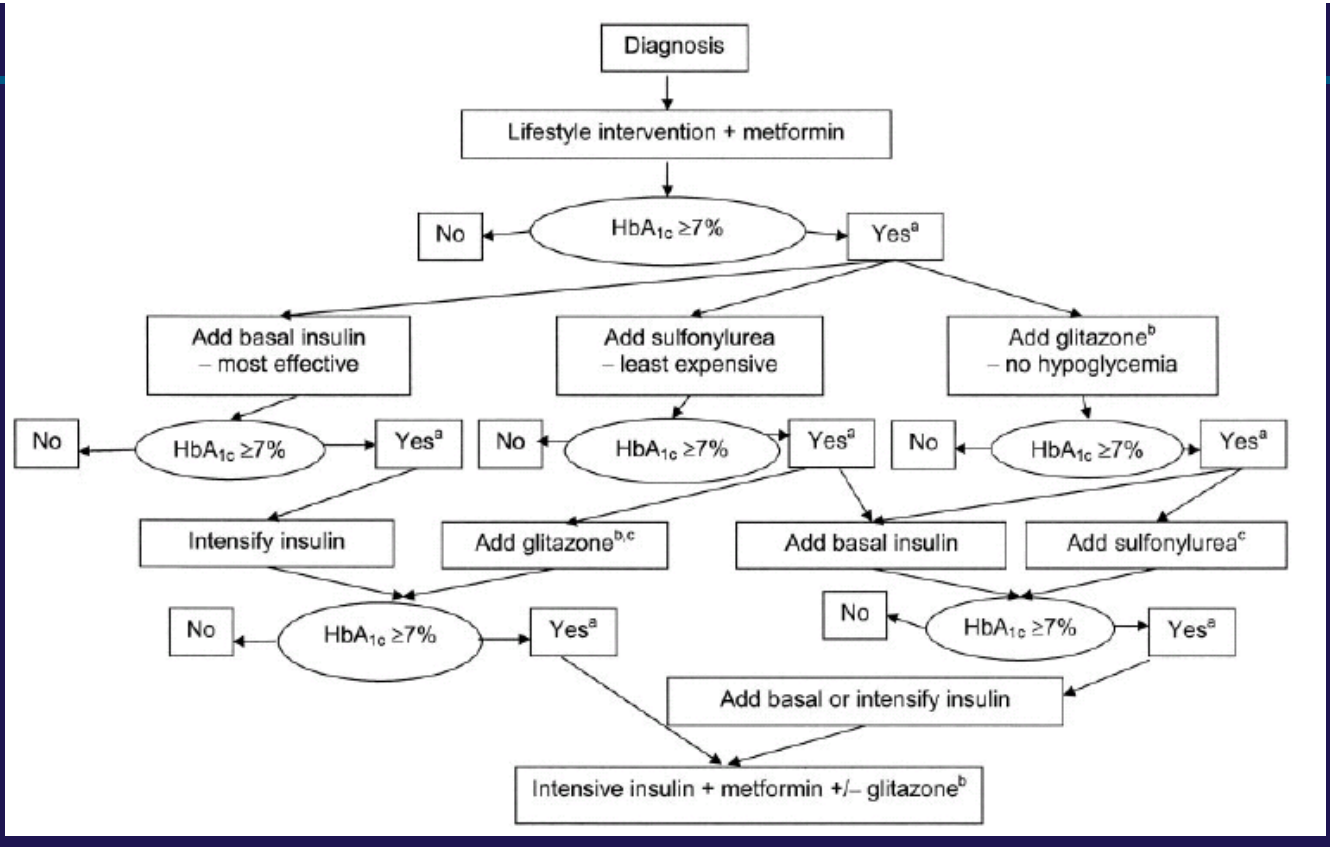

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Diab Care 2008, 31: 173

TZD - kontrendikasyonları

- Konjestif kalp yetmezliği
- Karaciğer yetmezliği
- Hipersensitivite

Thiazolidinedionlar (TZD)

1. Etki mekanizması nasıldır ?
2. Kan şekerini düşürmede etkin midir?
3. Diğer OAD ler ile kombine edilebilir mi?
4. Kardiyovasüler etkileri nasıldır?
5. Avantajları-dezavantajları nelerdir?
6. Hangi hastalarda kullanılmalı-kullanılmamalıdır?
7. İzlemde nelere dikkat edilmelidir?

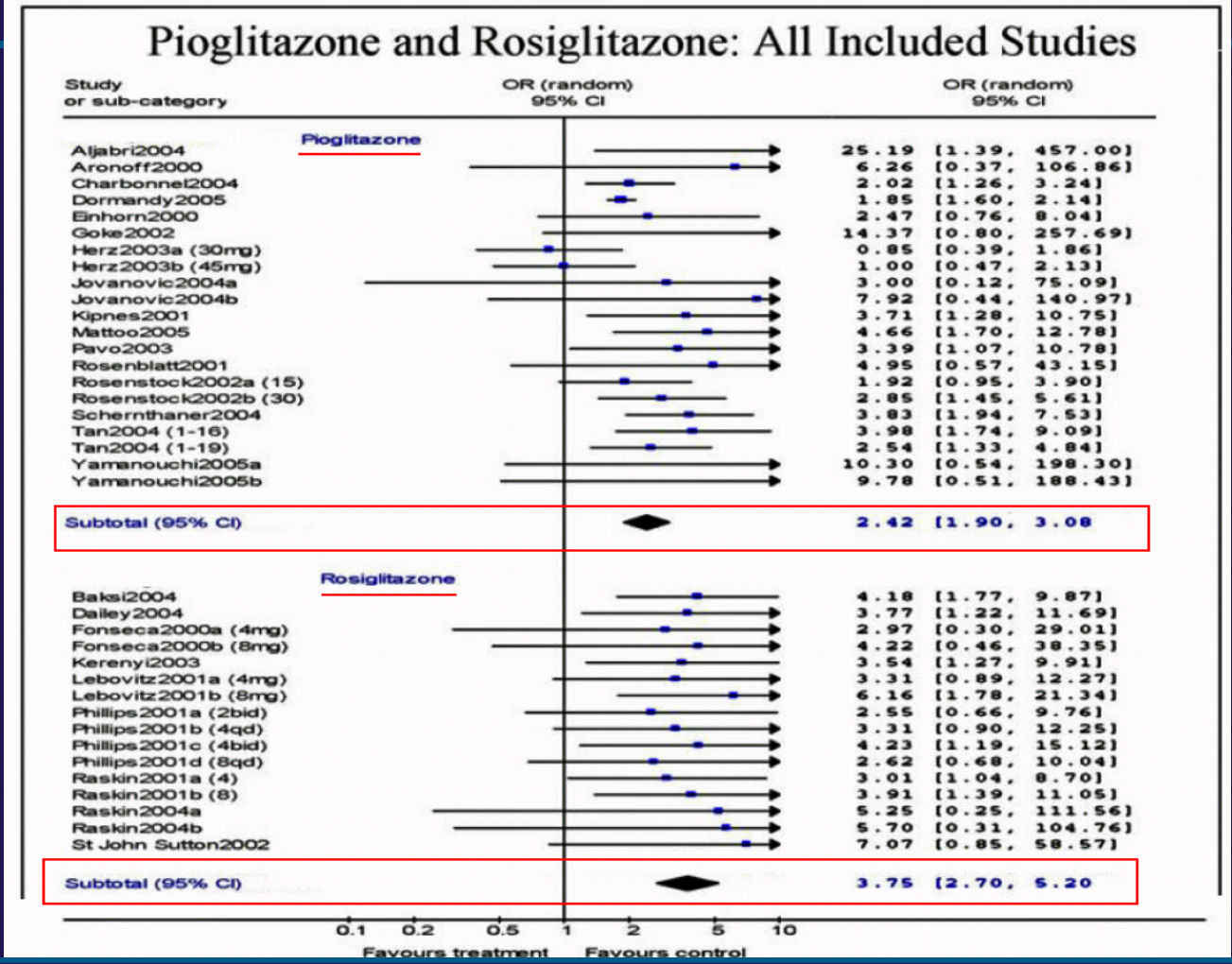
TZD- Yan etkiler

- Ödem
- Konjestif kalp yetmezliği
- Kilo artışı
- Hepatotoksisite ?

Thiazolidinediones and the risk of edema: A meta-analysis

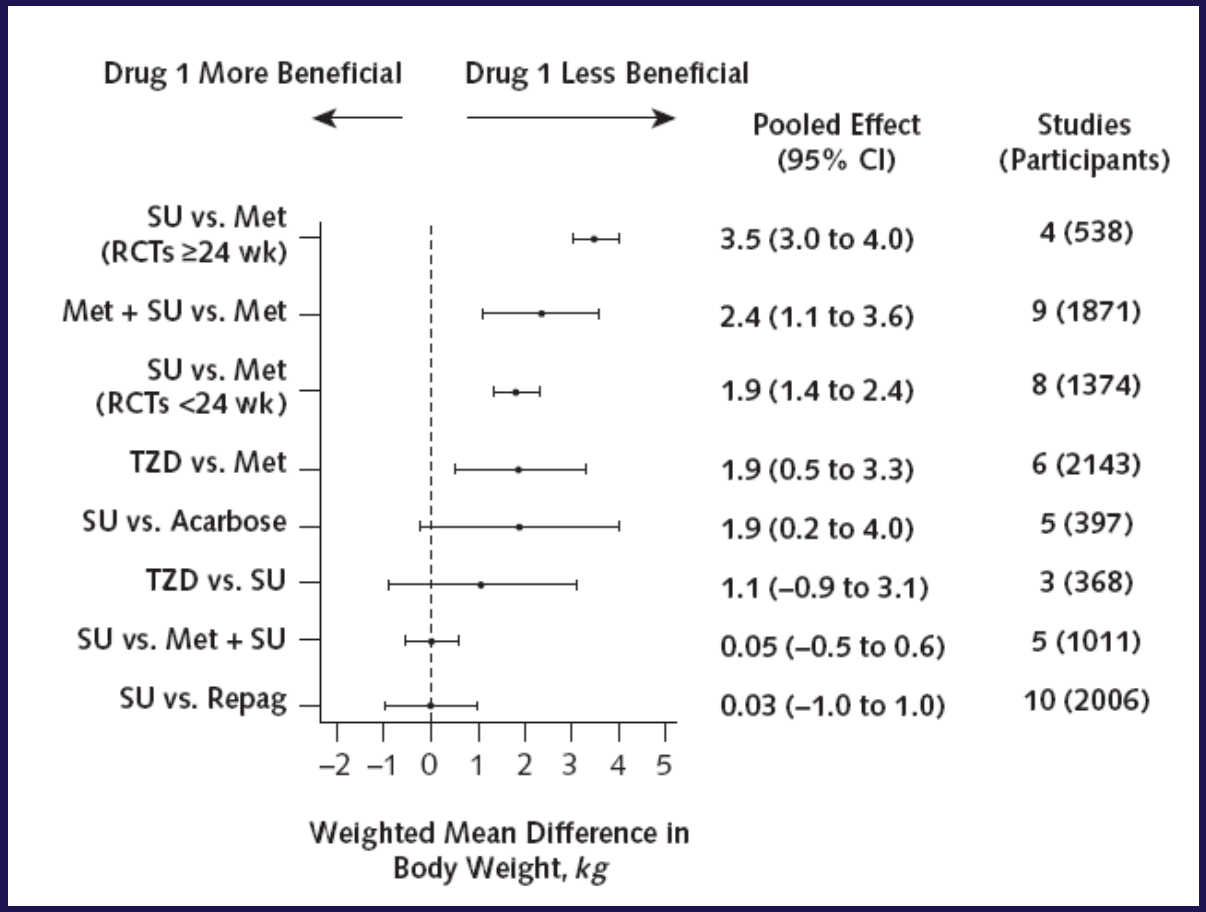
Helen D. Berlie, James S. Kalus , Linda A. Jaber

Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, United States



Diab Res Clin Prac, 2007, 76:279

Systematic Review: Comparative Effectiveness and Safety of Oral Medications for Type 2 Diabetes Mellitus



Ann Intern Med. 2007;147:386-399.

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