What is the Role for TZDs in Diabetes Management: Starting Lineup or Riding the Bench?

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Disclosures

The speakers have no conflicts of interest to disclose in relation to this presentation.

Learning Objectives

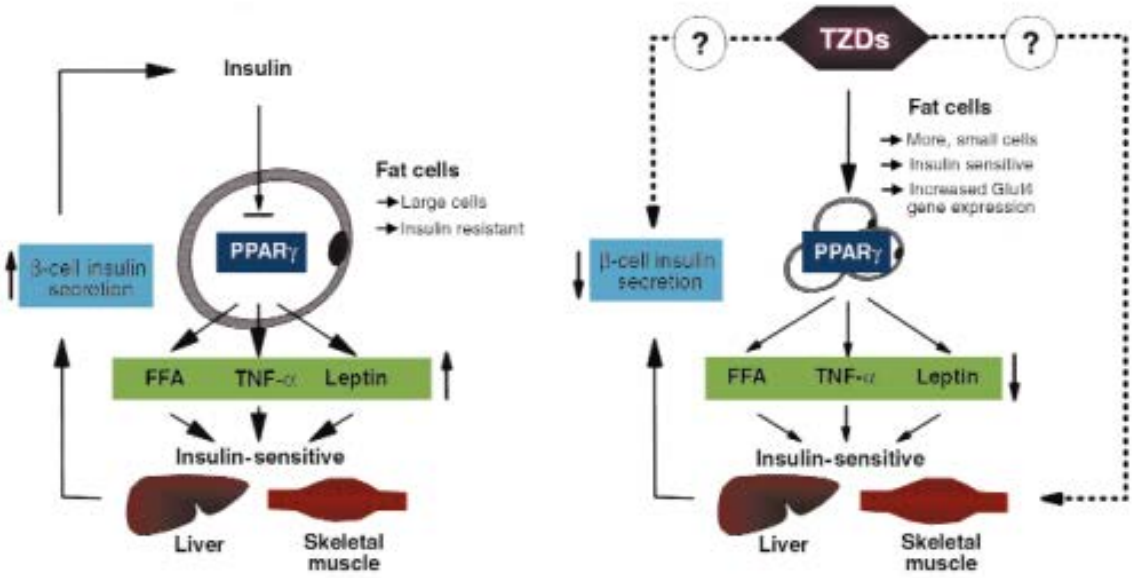
- Using the American Diabetes Association clinical practice guidelines, define how thiazolidinedione (TZD) medications fit within the standards of care
- Describe clinical situations where TZD medications offer a clinical advantage over other pharmacotherapeutic options.
- Identify current medical literature that describes the clinical benefits or harms produced by TZDs.

Poll #1

How often do you see pioglitazone or rosiglitazone used in your current clinical practice?

A. Frequently – almost every day
B. Sometimes – every 1-2 weeks
C. Rarely – once a month or less
D. Never – cannot remember the last time it was used
E. Not applicable – I do not work directly with patients

TZDs: Overview



Kahn CR, Chen L, Cohen SE. Unraveling the mechanism of action of thiazolidinediones. J Clin Invest 2000; 106 (11): 1305-1307.
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- 2 available medications
  - Pioglitazone (Actos®)*
  - Rosiglitazone (Avandia®)
- Main effects
  - Lowers plasma glucose
  - Lowers plasma insulin
  - Increase peripheral glucose uptake
  - Decrease triglyceride levels
- A1c decrease ~ 0.5-0.8%

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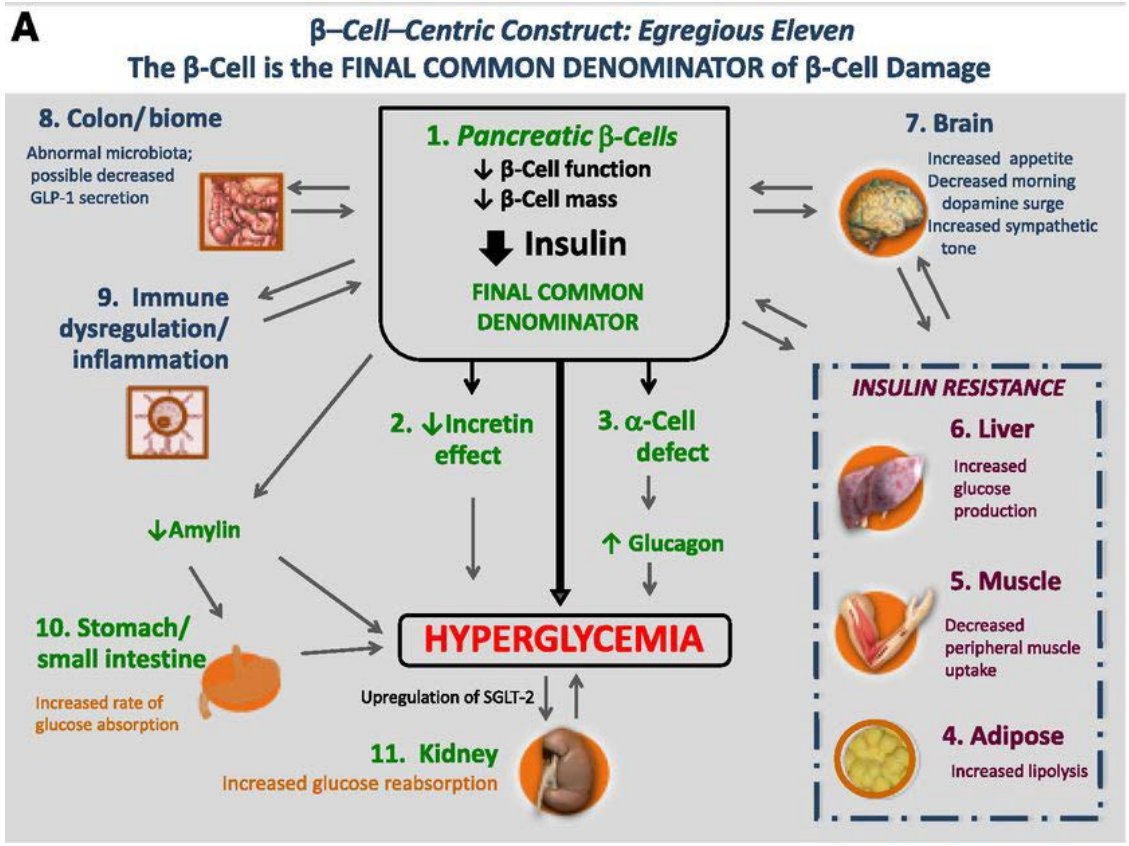
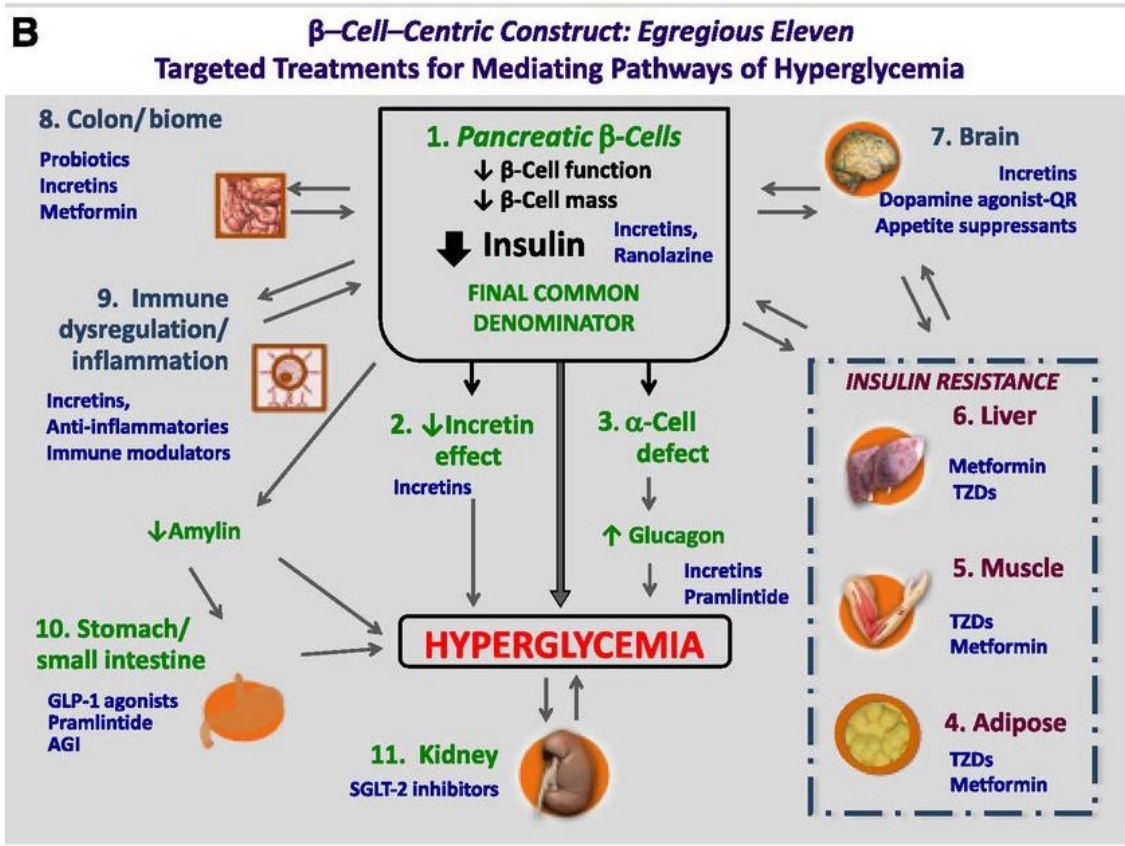
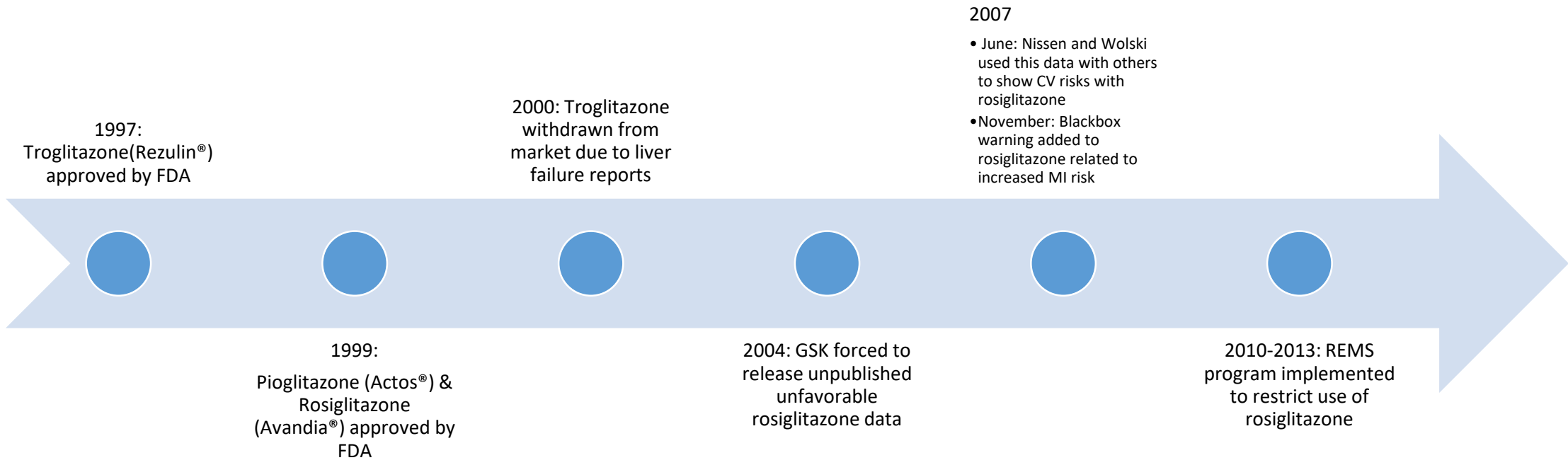




Stanley S. Schwartz et al. Dia Care 2016;39:179-186

Rise and Fall of TZDs



Current Utilization of TZDs

- Registry of Data from 2013-2016
  - 424,061 patients in analysis
  - TZDs = 5th most used drug class for type 2 diabetes
    - Typically, 2nd or 3rd medication added
    - <10% monotherapy
  - 40.3% of patients taking TZD had:
    - Clinical diagnosis of HF OR
    - EF <40% OR
    - Current use of loop diuretic
  - Pioglitazone - most clinically relevant TZD

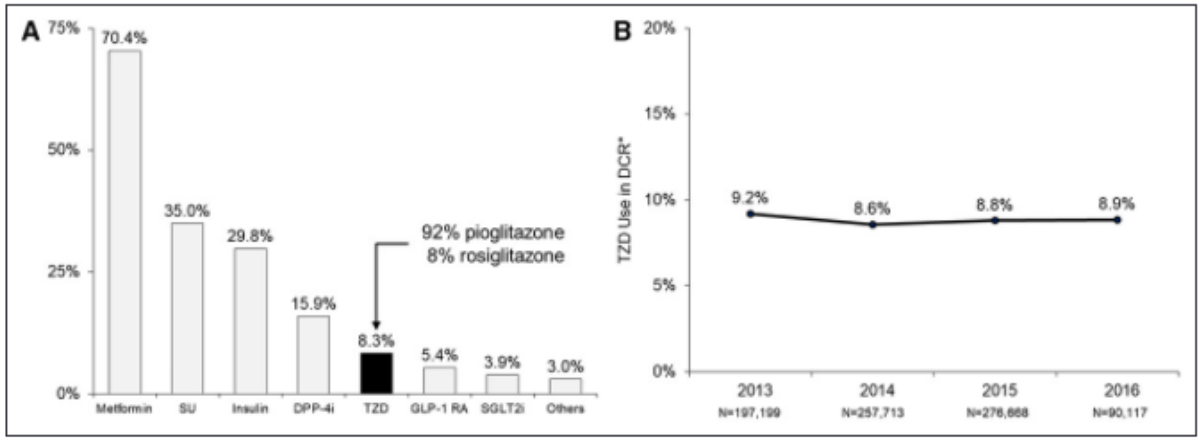


Figure. Use of thiazolidinediones in the Diabetes Collaborative Registry. **A**, Use of thiazolidinediones compared with other classes of glucose-lowering medications. **B**, Use of thiazolidinediones over time. *Patients could contribute data to multiple years, with the latest visit in each year used for each patient. DCR indicates Diabetes Collaborative Registry; DPP-4i, dipeptidyl peptidase-4 inhibitors; GLP-1 RA, glucagon-like peptide-1 receptor agonists; SGLT2i, sodium-glucose cotransporter 2 inhibitors; SU, sulfonylurea; and TZD, thiazolidinediones.

Arnold SV, Inzucchi SE, Echouffo JB, et al. Understanding contemporary use of thiazolidinediones: an analysis from the diabetes collaborative registry. Circulation: Heart Failure 2019; 12:e005855. doi: 10.1161/circheartfailure.118.005855

Poll #2

What clinical benefits come to mind when you think of thiazolidinediones?

“Put me in Coach”: Benefits of TZDs

- Glucose durability and efficacy
- Nonalcoholic steatohepatitis (NASH)
- Atherosclerotic benefits
- Hypoglycemic potential, cost, & route of administration

Glucose Durability and Efficacy

- Time to A1c neutrality of oral diabetes medications
  - TZDs with longest duration of 6-8 years
  - Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) with second longest duration at 5-7 years
- Combination therapy evaluated by Abdul-Ghani et al. in 2 studies
  - TZD/exenatide/metformin & TZD/exenatide vs basal-bolus insulin with durability up to 3 years

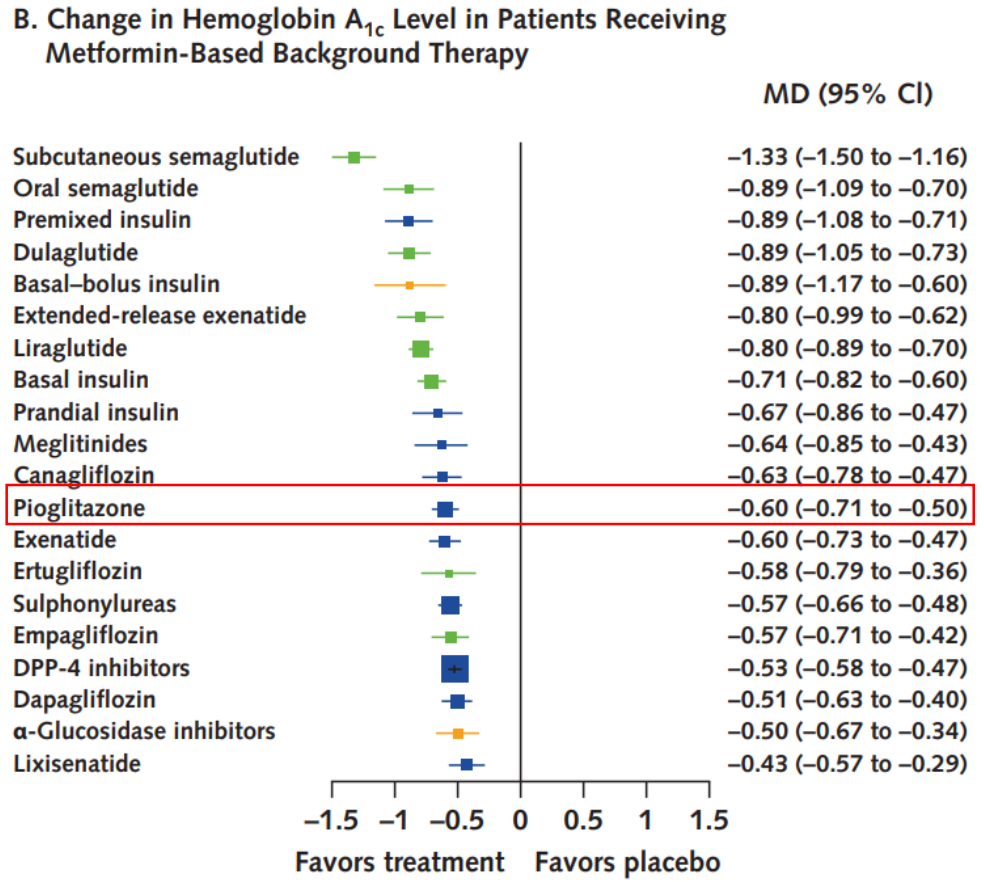
Medication or Class	Durability
Metformin	5 years
Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors)	3-4 years
Sulfonylureas (SU)	3-4 years
SGLT-2 inhibitors	5-7 years*
TZD	6-8 years*

* Predicted via linear extension of A1c trend

- The durability of oral diabetic medications: Time to A1c baseline and a review of common oral medications used by the primary care provider. Endocrinol Diabetes Metab J. 2018;2(3).
- Durability of Triple Combination Therapy Versus Stepwise Addition Therapy in Patients With New-Onset T2DM: 3-Year Follow-up of EDICT. Diabetes Care. 2021;44(2):433-439.
- Efficacy of Exenatide Plus Pioglitazone Vs Basal/Bolus Insulin in T2DM Patients With Very High HbA1c. J Clin Endocrinol Metab. 2017 Jul 1;102(7):2162-2170.

Glucose Durability and Efficacy

- Systematic Review and Meta-analysis by Tsapas, et al.
  - RCTs with duration ≥24 weeks
  - A1c change from baseline
  - Pioglitazone with a median decrease in A1c of 0.6% (95% CI 0.5% to 0.71%)
- Abdul-Ghani, et al. compared TZD combinations vs basal-bolus insulin
  - TZD/exenatide in patients with A1c > 10% and T2D of long duration (10.9 years)
    - A1c reduction of 1.1% (P<0.0001) at 3 years
  - TZD/exenatide/metformin in new-onset T2D
    - A1c reduction of 0.5% (95% CI 0.39-0.61%) at 3 years



- Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes: A Systematic Review and Network Meta-analysis. Ann Intern Med. 2020;173(4):278-286.
- Combination therapy with pioglitazone/exenatide improves beta-cell function and produces superior glycaemic control compared with basal/bolus insulin in poorly controlled type 2 diabetes: A 3-year follow-up of the Qatar study.
- Efficacy of Exenatide Plus Pioglitazone Vs Basal/Bolus Insulin in T2DM Patients With Very High HbA1c. J Clin Endocrinol Metab. 2017 Jul 1;102(7):2162-2170.

NASH

- Single-center, parallel-group, randomized, placebo-controlled study
  - Participants: T2D or prediabetes with biopsy-proven NASH
    - T2D: 48% pioglitazone vs 55% placebo
  - Intervention: hypocaloric diet and pioglitazone 45 mg daily or placebo for 18 months
  - Conclusion: Pioglitazone is effective at improving liver histologic scores in patients with T2D or prediabetes and NASH.

Table 2. Effect of 18 mo of Pioglitazone Treatment on Primary and Secondary Liver Histologic Outcomes*

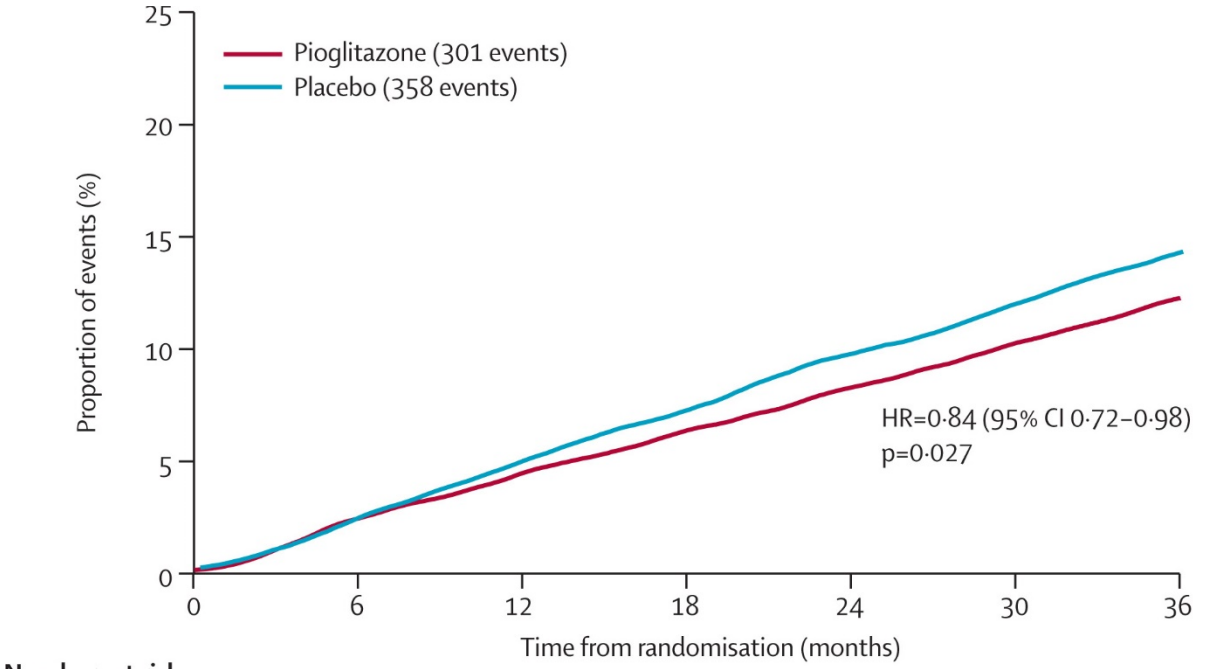
Outcome	Placebo (n = 51)	Pioglitazone (n = 50)	Treatment Difference (95% CI)	P Value
Primary outcome				
≥2-point reduction in NAS (in 2 categories) without worsening of fibrosis, *n (%)*	9 (17)	29 (58)	41 (23 to 59)	<0.001
Secondary outcomes				
Resolution of NASH, *n (%)*†	10 (19)	26 (51)	32 (13 to 51)	<0.001
Steatosis				
≥1-point improvement, *n (%)*	13 (26)	35 (71)	44 (25 to 63)	<0.001
Mean change in score (SD)	−0.2 (0.8)	−1.1 (1.0)	−0.9 (−1.3 to −0.5)	<0.001
Inflammation				
≥1-point improvement, *n (%)*	11 (22)	25 (49)	27 (8 to 46)	0.004
Mean change in score (SD)	−0.1 (0.8)	−0.6 (0.9)	−0.6 (−0.9 to −0.2)	<0.001
Ballooning				
≥1-point improvement, *n (%)*	12 (24)	25 (51)	27 (7 to 47)	0.004
Mean change in score (SD)	−0.2 (0.7)	−0.6 (0.6)	−0.4 (−0.7 to −0.2)	0.001
Fibrosis				
≥1-point improvement, *n (%)*	13 (25)	20 (39)	14 (−6 to 34)	0.130
Mean change in score (SD)	0 (1.2)	−0.5 (1.0)	−0.5 (−0.9 to 0)	0.039

NAS = nonalcoholic fatty liver disease activity score; NASH = nonalcoholic steatohepatitis.
* Multiple imputation was used to impute missing histologic data for patients who did not complete 18 mo of therapy (**Appendix**). Numbers of patients may not always seem to match the proportion because they were estimated from the combination of 40 imputed data sets.
† Defined as absence of NASH after 18 mo of therapy in patients with definite NASH at baseline.

Long-Term Pioglitazone Treatment for Patients With Nonalcoholic Steatohepatitis and Prediabetes or Type 2 Diabetes Mellitus: A Randomized Trial. Ann Intern Med. 2016;165(5):305-315.

Atherosclerotic Benefits

- PROactive Study
- Participants: Patients with T2D & ASCVD
- Intervention: pioglitazone with a target of 45 mg daily or placebo
- Median A1c: 7.8%
- Conclusion
  - Primary outcome not significant
    - Death from any cause, non-fatal MI, stroke, acute coronary syndrome, leg amputation, coronary revascularization, revascularization of leg
    - HR 0.9 (95% CI 0.8-1.02); p=0.095
  - Main secondary endpoint (prespecified, significant)
    - Death from any cause, non-fatal MI, stroke
    - HR 0.84 (95% CI 0.72-0.98); p=0.027



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(9493):1279-1289

Atherosclerotic Benefits

- PROactive Study
  - Death from any cause, non-fatal MI, stroke
  - HR 0.84 (95% CI 0.72-0.98); p=0.027
- Newer trials = CV death
- Leg revascularization refractory to
  - Antihypertensives
  - Lipid-lowering therapy
  - Glucose-lowering therapy

Trial	EMPA-REG OUTCOME	CANVAS	LEADER	SUSTAIN-6	REWIND
Drug	Empagliflozin	Canagliflozin	Liraglutide	Semaglutide	Dulaglutide
3-point MACE HR (95% CI)	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.87 (0.78-0.97)	0.75 (0.58-0.95)	0.88 (0.79-0.99)

- 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(9493):1279-1289.
- The forgotten, cost-effective cardioprotective drug for type 2 diabetes. *Diab Vasc Dis Res*. 2019;16(2):133-143.
- Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med 2015; 373:2117-2128.
- Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377:644-657.
- Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2016; 375:311-322.
- Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2016; 375:1834-1844.
- Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121-130.

Hypoglycemic Potential, Cost, & Route of Administration

- Hypoglycemia as an adverse event is absent unless combined with insulin or insulin secretagogue
- Covered by most insurers and on cash discount programs
  - Medicare beneficiaries and coverage gap
  - Patients on multiple high-cost medications
- Oral agent without special administration considerations

Class/Medication	Median NADAC* (monthly) in USD
Metformin (IR) Metformin (ER)	$2-3 $188-572
Sulfonylureas (IR & ER)	$4-11
Pioglitazone	$5
Meglitinides	$31-38
DPP-4 inhibitors	$175-456
GLP-1 RA (injectable) GLP-1 RA (oral)	$706-930 $738
SGLT-2 inhibitor	$284-501

* NADAC = National Average Drug Acquisition Cost

Professional practice committee: standards of medical care in diabetes—2021. Diabetes Care. 2021;44(Supplement 1):S3-S3.

Rebuttal

Poll #3

What clinical harms come to mind when you think of thiazolidinediones?

“Ride the Pine”: Risks of TZDs

- Cardiovascular
- Weight /Peripheral Edema
- Bone fracture
- Ophthalmic
- Cancer

https://www.publicdomainpictures.net/pictures/40000/velka/dugout.jpgtext

Cardiovascular Risks

- Meta-analysis by Nissen & Wolski
  - Included 42 trials
  - Data
    - Study level, not patient level data
    - Mix of published and unpublished
  - Average patient age: 56
  - Average A1c: 8.2%
  - Conclusion:
    - Suggests CV risk with rosiglitazone use
    - Called for manufacturer to release all data for more complete analysis

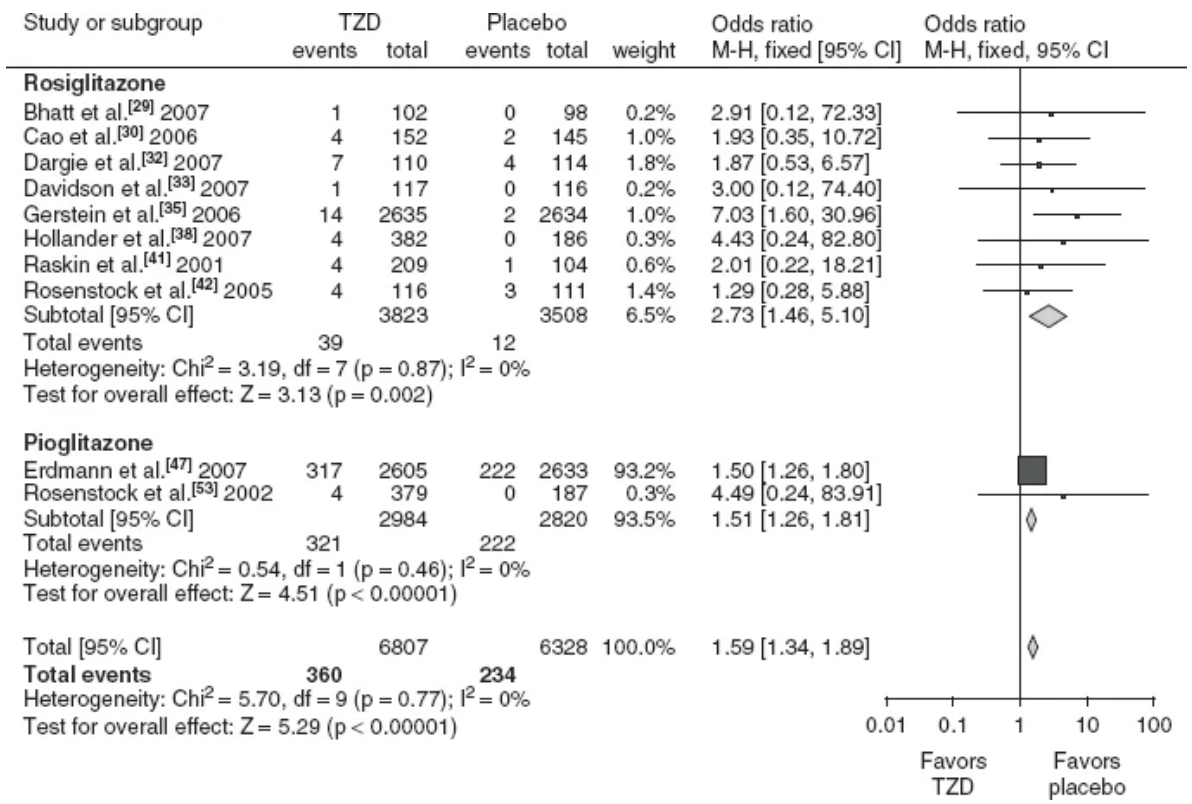
Table 5. Risk of Myocardial Infarction and Death from Cardiovascular Causes for Patients Receiving Rosiglitazone versus Several Comparator Drugs.

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

Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med 2007; 356: 2457-2471.

Cardiovascular Risks

- Meta-analysis by Hernandez, et al.
  - 29 placebo controlled trials
  - Included pre-diabetes and diabetes
  - Average patient age: 58
  - Average A1c: 8.5%
  - Number needed to harm (ranges)
    - Any HF: 35-220 (Rosi), 27-95 (Pio)
    - Severe HF: 80-134 (Rosi), 62-95 (Pio)
  - Conclusion:
    - TZD have ↑ HF risk
    - Difference seen most in studies > 12 months duration



Hernandez AV, Usmani A, Rajamanickam A, Moheet A. Thiazolidinediones and risk of heart failure in patients with or at high risk of type 2 diabetes mellitus. Am J Cardiovasc Drugs 2011; 11: 115-128.

Weight Gain/Peripheral Edema

- Influencing Factors
  - Improvements in glycemic control
    - ↓ glucosuria
  - ↑ adipocyte differentiation
    - More insulin sensitive molecules created in subcutaneous compartment
    - Redistributes from hepatic to subcutaneous
  - Expansion of plasma volume
    - Likely source of HF risk
  - Increased appetite?

- Average gain: ~7 lb
- Paradoxically increased weight tends to correlate with improved insulin resistance
- Peripheral Edema
  - TZD alone ~ 3.0-7.5% incidence
  - TZD + insulin ~15% incidence
  - Minimal responsiveness to diuretics
  - Dose dependent effect

Fonseca V. Effect of thiazolidinediones on body weight in patients with diabetes mellitus. Am J Med 2003; 115 (8A): 42S-48S.
Wilding J. Thiazolidinediones, insulin resistance and obesity: finding a balance. Int J Clin Pract 2006; 60 (10): 1272-1280.

Fracture Risk

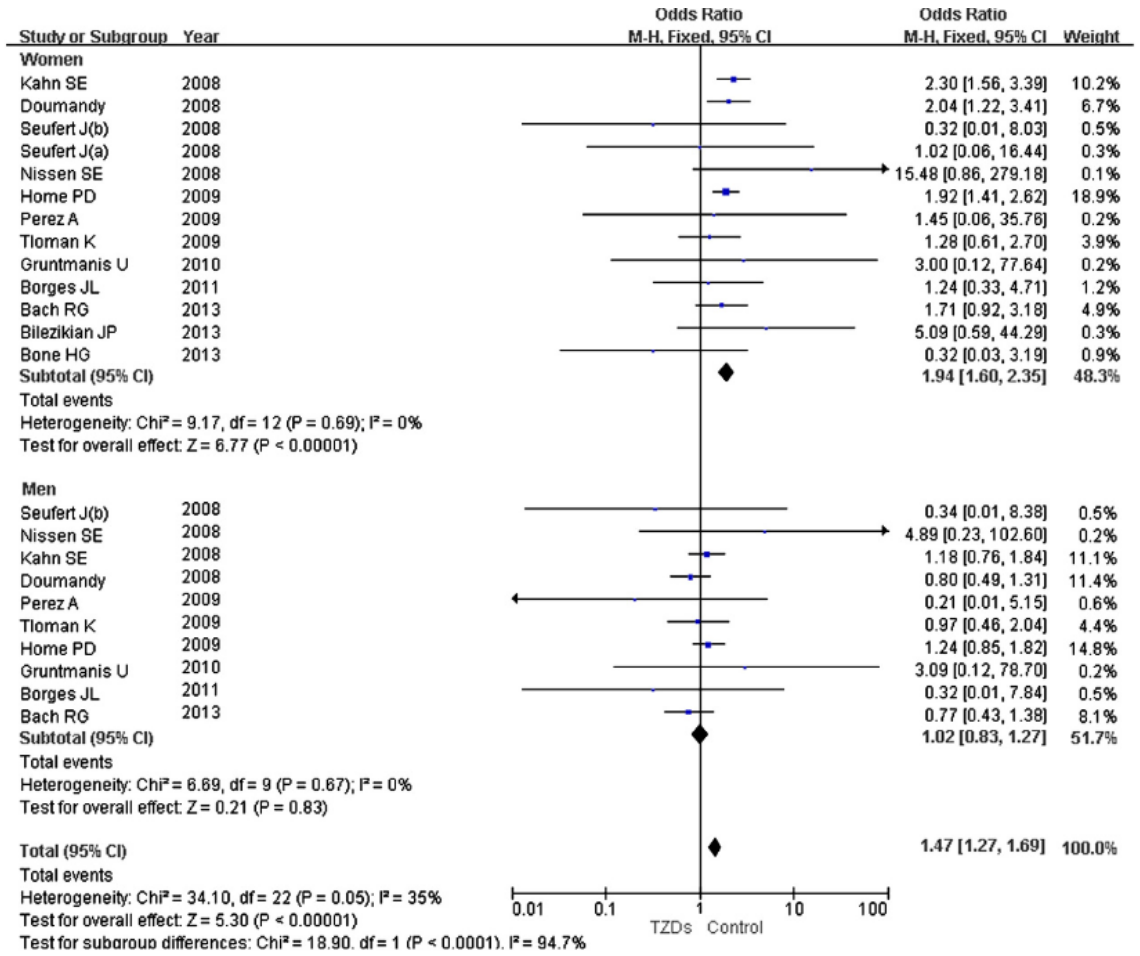


Fig. 2. Forest plot of odds ratio for TZDs and fracture risk.

- Meta-analysis by Zhu, et al.
  - 27 studies included
  - Increased risk of fractures in women, but not men
  - Risk is similar between pioglitazone and rosiglitazone
  - Risk is independent of age
  - No clear association with treatment duration

Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone 2014; 68: 115-123.

Ophthalmic Risks: Diabetic Macular Edema

- Idris, et al.
  - Retrospective, cohort study over ~ 10 year period
  - 103,368 patients evaluated
  - TZD use increased DME at all evaluated time points
    - 1 year risk: OR = 5.7 (4.1-7.9)
    - 1 year adjusted risk: OR= 2.3 (1.5-3.6)
    - 10 year risk: HR = 5.2 (4.3-6.3)
    - 10 year adjusted risk: HR =2.3 (1.7-3.0)
  - Insulin use increased risk
  - Similar results between 2 meds

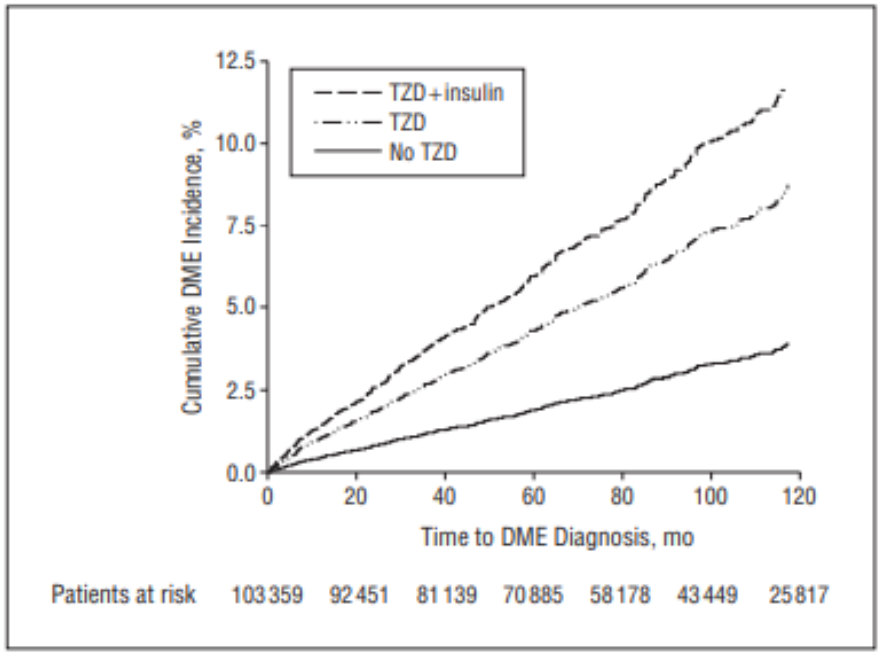


Figure. Kaplan-Meier time to diabetic macular edema (DME) curves according to thiazolidinedione use with or without insulin. The log-rank test gives an χ^2 statistic of 373 ($P < .001$), which shows a clear difference in DME incidence according to thiazolidinedione use. In a comparison of thiazolidinedione use with nonuse, the hazard ratio was 5.19 (95% CI, 4.31-6.25).

Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. Arch Intern Med 2012; 172 (13): 1005-1011. doi: 10.1001/archinternmed.2012.1938

Cancer Risk

- Meta-analysis by Bosetti, et al.
  - Overall: no increase in total cancer risk with TZD use
  - Exception = pioglitazone used > 2 years
    - Higher bladder cancer - 20% excess risk
    - Greater risk with higher cumulative dose and longer duration

Bosetti C, Rosato V, Buniato D, Zambon A, LaVecchia C, Corrao G. Cancer risk for patients using thiazolidinediones for type 2 diabetes: a meta-analysis. The Oncologist 2013; 18: 148-156.

Cancer Risk

Table 3| **Thiazolidinediones and risk of bladder cancer among cases of bladder cancer and matched controls***

Use of thiazolidinediones	No (%) of cases (n=376)	No (%) of controls (n=6699)	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)†
Never use of any thiazolidinedione	319 (84.8)	5856 (87.4)	1.00 (reference)	1.00 (Reference)
Exclusive ever use of pioglitazone	19 (5.1)	191 (2.9)	1.87 (1.13 to 3.09)	1.83 (1.10 to 3.05)
Exclusive ever use of rosiglitazone	36 (9.6)	596 (8.9)	1.16 (0.79 to 1.69)	1.14 (0.78 to 1.68)
Ever use of both pioglitazone and rosiglitazone	2 (0.5)	56 (0.8)	0.74 (0.18 to 3.08)	0.78 (0.18 to 3.29)

*Matched on year of birth, year of cohort entry, sex, and duration of follow-up.

†Adjusted for excessive alcohol use, obesity, smoking status, HbA_{1c}, previous bladder conditions, previous cancer (other than non-melanoma skin cancer), Charlson comorbidity score, and ever use of other antidiabetic agents (metformin, sulfonylureas, insulin, and other oral hypoglycaemic agents).

- Azoulay L, Yin H, Filion K, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. BMJ 2012; 344: e3645. doi: 10.1136/bmj.e3645.

Table 4| **Pioglitazone cumulative duration of use and cumulative dosage and risk of bladder cancer among cases of bladder cancer and matched controls***

Variables	No (%) of cases (n=376)	No (%) of controls (n=6699)	Crude rate ratio (95% CI)	Adjusted rate ratio (95% CI)†
Never use of any thiazolidinediones	319 (84.8)	5856 (87.4)	1.00 (reference)	1.00 (reference)
Cumulative duration of pioglitazone:				
≤12 months	1 (0.3)	27 (0.4)	0.69 (0.09 to 5.11)	0.56 (0.07 to 4.42)
13-24 months	2 (0.5)	11 (0.2)	2.99 (0.61 to 14.59)	3.03 (0.63 to 14.52)
>24 months	16 (4.3)	153 (2.3)	2.00 (1.16 to 3.45)	1.99 (1.14 to 3.45)
				P=0.050 for trend
Cumulative dosage of pioglitazone:				
≤10 500 mg	7 (1.9)	70 (1.0)	1.63 (0.72 to 3.69)	1.58 (0.69 to 3.62)
10 501-28 000 mg	6 (1.6)	68 (1.0)	1.75 (0.75 to 4.07)	1.66 (0.70 to 3.94)
>28 000 mg	6 (1.6)	53 (0.8)	2.44 (1.02 to 5.84)	2.54 (1.05 to 6.14)
				P=0.030 for trend

*Matched on year of birth, year of cohort entry, sex, and duration of follow-up.

†Adjusted for excessive alcohol use, obesity, smoking status, HbA_{1c}, previous bladder conditions, previous cancer (other than non-melanoma skin cancer), Charlson comorbidity score, and ever use of other antidiabetic agents (metformin, sulfonylureas, insulin, and other oral hypoglycaemic agents).

- Azoulay L, Yin H, Filion K, et al. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. BMJ 2012; 344: e3645. doi: 10.1136/bmj.e3645.

Alternatives to TZD in NASH

- GLP-1 agonists
  - Liraglutide (1.8mg daily)
    - Non-DM patients (n=52)
    - ↑ resolution of NASH vs placebo (RR 4.3, 1.0-17.7)
    - No difference in ALT/AST, fibrosis or NAFLD activity score
  - Exenatide (10mcg BID)
    - Type 2 DM patients (n=132)
    - ↑ reversal of liver fat vs insulin
    - All 6 severe cases improved to “non-severe” levels (only 3 of 5 in insulin)
- SGLT-2 inhibitors
  - Empagliflozin (25mg daily)
    - Single arm, open label pilot (n= 9)
    - Improved steatosis, fibrosis and hepatocyte ballooning
    - No difference in ALT/AST

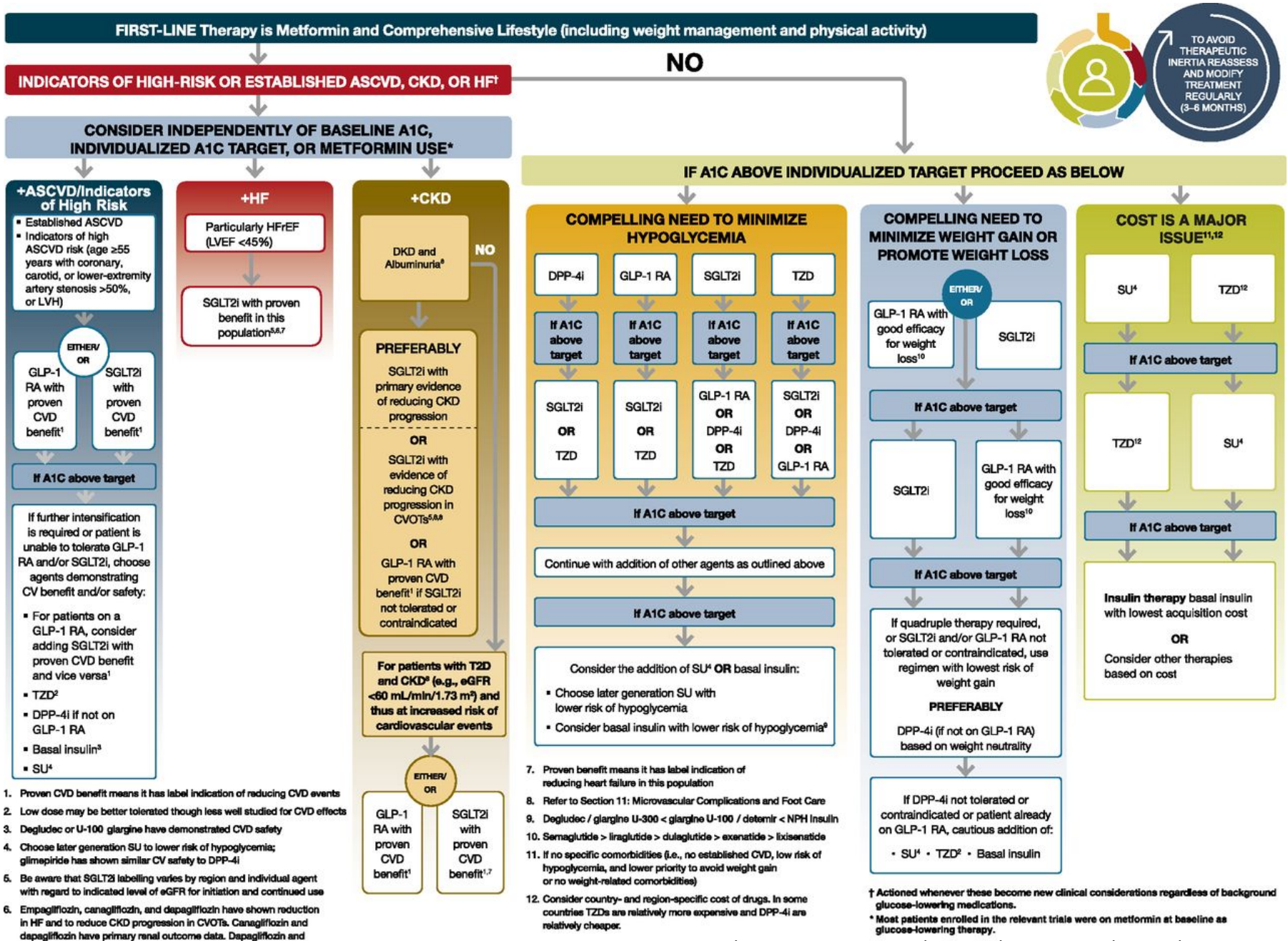
- Blazina I, Selph S. Diabetes drugs for nonalcoholic fatty liver disease: a systematic review. Systematic Reviews 2019; 8: 295. doi: 10.1186/s13643-019-1200-8
- Lai LL, Vethakkan SR, Nik Mustapha NR, Mahadeva S, Chan WK. Empagliflozin for the Treatment of Nonalcoholic Steatohepatitis in Patients with Type 2 Diabetes Mellitus. Dig Dis Sci. 2020 Feb;65(2):623-631. doi: 10.1007/s10620-019-5477-1.

Rebuttal

Assessment Question

Which adverse effect is associated with pioglitazone?

A. Atrial fibrillation
B. Bone fracture
C. Myocardial infarction
D. Weight loss



American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: Standards of Medical Care in Diabetes—2021. Diabetes Care 2021;44(Suppl. 1):S111–S124; https://doi.org/10.2337/dc21-S009. Reprinted with permission

Patient Case Example #1

38-year-old patient unable to tolerate blood draws, SMBG, or injectable medications without anesthesia. Checking glucose control via urinary glucose strips and mother reports they are still positive for glucosuria. Insurance formulary covers GLP-1 RA as injectable only.

PMH: developmental delay, T2D, HTN

Medications: metformin 1 g orally twice daily

Labs: HgbA1c 11% (1 month prior); all others within normal limits

Appropriate for pioglitazone?

Patient Case Example #2

52-year-old patient who is currently undomiciled and living in a shelter. Limited access to injectable supplies. Has had intermittent adherence to medications due to cost and housing insecurities. Last seen PCP 2 weeks ago and was diagnosed with acute balanitis (second instance this year). Reports significant polyuria, polydipsia, and unintended weight loss of 2.5 kg. Improving adherence to medications, but still intermittent. Recently reports improved adherence to metformin and glipizide. SMBG reported as 300-400 mg/dl for fasting and postprandial levels.

PMH: T2D, HTN, opioid abuse, tobacco abuse

Labs/Vitals: HgbA1c 13% (2 weeks prior), Ht: 190 cm, Wt: 68kg, BMI 18.8 kg/m^2, others within normal limits

Medications: metformin 1 g orally twice daily, glipizide 10 mg orally twice daily, insulin glargine 40 units daily, and insulin aspart 8 units three times daily before meals.

Would you consider pioglitazone for this patient?

“Late Inning Substitution”: Specific Situations to Consider TZDs

- Male or premenopausal female patients with food and/or housing insecurities
- Male patients with hypertension and elevated cardiovascular risk
- Individuals at high risk of hypoglycemic complications or frequent severe hypoglycemic events
- Patients unable to communicate symptoms of hypoglycemia
- Patients with incomplete improvement in NASH on GLP-1 RA or unable to afford or tolerate GLP-1 RA

Future Considerations

- Combination therapy and cardiovascular outcomes
  - Pioglitazone plus
    - GLP-1 RA
    - SGLT-2 inhibitor
    - GLP-1 RA and SGLT-2 inhibitor
- Secondary stroke prevention in a T2D population
- Combination therapy for NASH
- Prospective trial in patients with chronic kidney disease
- Compared against newer agents in combination with insulin or insulin secretagogues

Conclusion

- Clinical benefits of TZD are antihyperglycemic efficacy and durability, improvement in NASH, improvement in 3-point MACE in high-risk individuals, low cost, oral route, and low hypoglycemic risk
- Clinical risks of TZD therapy are increased heart failure risks, weight gain, risk of fracture, risk of macular edema, and risk of bladder cancer
- Clinically advantageous situations for TZDs include patients:
  - At high risk of hypoglycemic complications
  - Unable to afford newer therapies
  - With comorbidities that benefit from TZD therapy
  - Refusing injectable therapy in need of additional antihyperglycemic treatment

Post Debate Questions

Post-Test #1

The American Diabetes Association recommends TZDs to be used in type 2 diabetes patients who have:

A. Chronic kidney disease
B. a compelling need to minimize weight gain
C. a compelling need to minimize hypoglycemia
D. contraindications to insulin therapy

Post-Test #2

Which of the following is NOT a literature supported adverse effect of TZDs?

A. Bladder cancer
B. Diabetic macular edema
C. Heart failure
D. Fracture risk in men

Post-Test #3

Which of the following describes clinical benefits or risks identified in placebo-controlled studies with pioglitazone?

A. Improvement in rates of hospitalization related to heart failure and leg revascularization

B. Better long-term A1c control as monotherapy when compared with basal-bolus insulin therapy combined with metformin

C. Improvement in liver histologic markers in patients with concomitant NASH

D. Increased risk of heart failure exacerbations, hypoglycemia, and non-fatal myocardial infarction

Post-Test #4

In which patient scenario would adding a thiazolidinedione offer a unique advantage over all other antihyperglycemic therapy according to the most recent standard of care guidelines?

A. Recent myocardial infarction currently taking metformin and refusing injectable therapy due to a fear of needles
B. Has chronic kidney disease and is on dialysis with severe vitamin D deficiency and refuses injectable therapy
C. Has difficulty affording medications and is currently taking glipizide as monotherapy
D. History of stroke resulting in aphasia who is maximized on empagliflozin, metformin, and semaglutide

Post-Test #5

The PROactive trial demonstrated that pioglitazone had a statistically significant effect on which composite endpoint?

A. Improvement in all-cause mortality, leg amputation, and stroke
B. Improvement in stroke, non-fatal myocardial infarction, and death from any cause
C. Improvement in non-fatal myocardial infarction, stroke, and ankle edema
D. Improvement in non-fatal myocardial infarction, stroke, and osteoporosis

What is the Role for TZDs in Diabetes Management: Starting Lineup or Riding the Bench?

Assessment Questions

1. The American Diabetes Association recommends TZDs to be used in type 2 diabetes patients who have:
    a. Chronic kidney disease
    b. a compelling need to minimize weight gain
    c. a compelling need to minimize hypoglycemia
    d. contraindications to insulin therapy
2. Which of the following is NOT a literature supported adverse effect of TZDs
    a. Bladder cancer
    b. Diabetic macular edema
    c. Heart failure
    d. Fracture risk in men
3. Which of the following describes clinical benefits or risks identified in placebo-controlled studies with pioglitazone?
    a. Improvement in rates of hospitalization related to heart failure and leg revascularization
    b. Better long-term A1c control as monotherapy when compared with basal-bolus insulin therapy combined with metformin
    c. Improvement in liver histologic markers in patients with concomitant NASH
    d. Increased risk of heart failure exacerbations, hypoglycemia, and non-fatal myocardial infarction.
4. In which patient scenario would adding a thiazolidinedione offer a unique advantage over all other antihyperglycemic therapy according to the most recent standard of care guidelines?
    a. Recent myocardial infarction currently taking metformin and refusing injectable therapy due to a fear of needles
    b. Has chronic kidney disease and is on dialysis with severe vitamin D deficiency and refuses injectable therapy
    c. Has difficulty affording medications and is currently taking glipizide as monotherapy
    d. History of stroke resulting in aphasia who is maximized on empagliflozin, metformin, and semaglutide
5. The PROactive trial demonstrated that pioglitazone had a statistically significant effect on which composite endpoint?
    a. Improvement in all-cause mortality, leg amputation, and stroke
    b. Improvement in stroke, non-fatal myocardial infarction, and death from any cause
    c. Improvement in non-fatal myocardial infarction, stroke, and ankle edema
    d. Improvement in non-fatal myocardial infarction, stroke, and osteoporosis

Answer key: 1. C, 2. D, 3. C, 4. D, 5. B