Efficacy and safety of thiazolidinediones in diabetes patients with renal impairment: a systematic review and meta-analysis

Short running title: Thiazolidinediones for diabetes patients with renal impairment

Authors

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Supplementary text1 Search strategy

PubMed

1	"Diabetic Nephropathies" [MH]
2	"Kidney Diseases, Cystic"[MH]
3	Nephritis[MH]
4	"Renal Insufficiency, Chronic"[MH]
5	"Renal Dialysis"[MH]
6	Uremia[MH]
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Embase and CENTRAL (via OVID)

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65 controlled clinical trials as topic/
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91 limit 90 to english language
92 limit 91 to human [Limit not valid in CANTRAL; records were retained]

Supplementary Table 1 Risk of bias of included studies

Risk of bias in randomized controlled trials

Of the 19 RCTs, nine (47.4%) reported adequate random sequence generation, seven (36.8%) blinded patients and six (31.6%) blinded care givers and patients. A total of 14 (73.7%) trials followed up more than 90% patients, but only three adequately compared prognostic factors. In conclusion, these 19 RCTs were at moderate to high risk of bias, of which ten (52.6%) trials were at high risk, the remaining 9 (47.4%) trials were at moderate risk (Table 1).

Table 1 *Risk of bias of randomized controlled trials*

Study	Adequate randomization sequence generation	Adequate allocation concealment	Adequate blinding of patients	Adequate blinding of care givers	Blinding of outcome assessor	Free from selective reporting	Adequate follow up	Adequate comparability of prognostic factors	Qualitative of risk of bias
Abe 2007 [19]	Definitely yes	Probably no	Definitely no	Definitely no	Definitely no	Definitely yes	Definitely yes	Probably no	High risk
Abe 2008 [20]	Probably yes	Probably no	Definitely no	Definitely no	Definitely no	Definitely yes	Definitely yes	Probably no	High risk
Abe 2010 [16]	Definitely yes	Probably no	Definitely no	Definitely no	Definitely no	Definitely yes	Definitely yes	Probably no	High risk
Agarwal 2005 [17]	Definitely yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely yes	Definitely yes	Definitely yes	Moderate risk
Agrawal 2003 [21]	Probably yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably no	Moderate risk
Arashnia 2015 [22]	Probably yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably no	Moderate risk
Banerji 2010 [23]	Definitely yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely yes	Definitely yes	Probably no	High risk
Chan 2011 [24]	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Definitely yes	Probably no	Moderate risk
Galle 2012 [25]	Probably yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Probably no	Definitely yes	Moderate risk
Jin 2007 [26]	Definitely yes	Probably yes	Probably no	Probably no	Probably no	Definitely yes	Definitely yes	Probably no	Moderate risk
Katavetin 2006 [27]	Definitely yes	Definitely yes	Definitely yes	Definitely no	Probably no	Definitely yes	Probably yes	Probably no	Moderate risk
Morikawa 2011 [28]	Probably yes	Probably yes	Definitely no	Definitely no	Definitely no	Definitely yes	Definitely yes	Definitely yes	Moderate risk
Nakamura 2000 [29]	Probably yes	Probably yes	Probably no	Probably no	Probably no	Definitely yes	Probably yes	Probably no	High risk
Nakamura 2001 [30]	Probably yes	Probably yes	Definitely yes	Definitely yes	Probably no	Definitely yes	Probably yes	Probably no	Moderate risk
Nakamura 2004 [31]	Definitely yes	Definitely yes	Probably no	Probably no	Probably no	Definitely yes	Definitely yes	Probably no	High risk

Nakamura 2006 [32]	Probably yes	Definitely yes	Probably no	Probably no	Probably no	Definitely yes	Definitely yes	Probably no	High risk
Pistrosch 2012 [33]	Probably yes	Probably yes	Definitely yes	Definitely yes	Probably yes	Definitely yes	Probably yes	Probably no	Moderate risk
Wong 2005 [34]	Definitely yes	Definitely yes	Definitely no	Definitely no	Definitely no	Definitely yes	Definitely yes	Probably no	High risk
Yanagawa 2004 [35]	Probably yes	Probably no	Probably no	Probably no	Probably no	Definitely yes	Definitely yes	Probably no	High risk

Risk of bias in cohort studies

Of the three observational studies, all studies selected exposure and control from same source, and all studies had confident in ascertaining exposure and control. Two studies conduct well adjustment for prognostic factors between exposure and control cohort. In conclusion, one study was at low risk of bias, one were at moderate risk and another one was at high risk (Table 2).

Table 2 *Risk of bias of cohort studies*

Author	**Selection from same population**	**Ascertainment of exposure**	**Ascertainment of control**	**Outcome of interest was not present at baseline**	**Adequate comparability of prognostic factors**	**Assessment of prognostic factors**	**Ascertainment of outcomes**	**Adequate follow up**	**Similar co-interventions**	**Qualitative of risk of bias**
Brunelli 2009 [14]	Definitely yes	Definitely yes Drug prescription in the routine clinical practice	Definitely yes Drug prescription in the routine clinical practice	Definitely yes	Definitely yes Cox proportional hazards models adjusted age, race, sex, body mass index, facility standardized mortality ratio	Definitely yes From electronic health record	Definitely yes From electronic health record	Probably no Retrospective cohort	Probably no	Moderate risk
Chen YH 2015 [36]	Definitely yes	Definitely yes Drug prescription in the routine clinical practice	Definitely yes Drug prescription in the routine clinical practice	Definitely yes	Definitely no	Definitely yes From electronic health record	Definitely yes From electronic health record	Probably no Retrospective cohort	Probably no	High risk
Ramirez2009 [15]	Definitely yes	Definitely yes From a prospective cohort	Definitely yes From a prospective cohort	Definitely yes	Definitely yes Adjustments included the two TZD types and insulin; age, gender, race BMI, years with ESRD, comorbid conditions, hemoglobin, serum glucose, total cholesterol concentration	Probably yes	Definitely yes From a prospective cohort	Probably yes	Probably yes	Low risk

Supplementary Table 3 Subgroup analyses of HbA1c, FPG, serum lipids and edema

Table 3 Subgroup analyses of HbA1c, FPG, serum lipids and edema

Outcomes	No. of Studies (patients)	Effect estimate (95% CI)	P value of test for overall effect	I^2	P value of interaction
HbA1c					
Different degree of RI					
Non-ESRD	10 (623)	-0.57 (-1.05, -0.08)	0.02	73%	0.68
ESRD	5 (222)	-0.69 (-1.04, -0.35)	<0.0001	55%	
Different TZDs					
Pioglitazone	12 (476)	-0.64 (-0.97, -0.31)	0.0001	62%	0.97
Rosiglitazone	3 (369)	-0.62 (-1.51, 0.27)	0.17	83%	
Different control					
Placebo/no additional drugs	9 (607)	-0.90 (-1.24, -0.56)	<0.00001	73%	0.003
Active drugs	6 (238)	-0.16 (-0.50, 0.18)	0.36	0%	
FPG					
Different degree of RI					
Non-ESRD	5 (467)	-25.17 (-54.66, 4.31)	0.09	95%	0.97
ESRD	5 (228)	-20.66 (-36.77, -4.56)	0.01	32%	
Different TZDs					
Pioglitazone	8 (336)	-27.17 (-50.18, -4.16)	0.02	84%	0.91
Rosiglitazone	2 (359)	-24.23 (-68.33, 19.87)	0.28	97%	
Different control					
Placebo/no additional drugs	8 (615)	-32.26 (-53.13, -11.39)	0.002	90%	0.008
Active drugs	2 (80)	3.94 (-12.96, 20.84)	0.65	0%	
TG					
Different degree of RI					
Non-ESRD	5 (213)	-21.41 (-55.71, 12.88)	0.13	29%	0.83
ESRD	6 (264)	-16.84 (-38.89, 5.21)	0.22	75%	
Different TZDs					
Pioglitazone	8 (327)	-26.38 (-40.56, -12.19)	0.0003	25%	0.05
Rosiglitazone	3 (150)	31.81 (-24.73, 88.35)	0.08	61%	
Different control					
Placebo/no additional drugs	9 (402)	-15.57 (-38.83, 7.70)	0.19	73%	0.84
Active drugs	2 (75)	0.35 (-152.80, 153.50)	1.00	0%	
TC					
Different degree of RI					
Non-ESRD	7 (311)	-3.07 (-12.89, 6.76)	0.54	29%	0.26
ESRD	5 (206)	8.09 (-8.61, 24.79)	0.34	44%	
Different TZDs					
Pioglitazone	9 (367)	-7.00 (-13.77, -0.23)	0.04	0%	0.006
Rosiglitazone	3 (150)	13.51 (0.48, 26.54)	0.04	0%	
Different control					
Placebo/no additional drugs	9 (402)	3.75 (-6.75, 14.26)	0.48	46%	0.17

Active drugs	3 (115)	-8.32 (-21.76, 5.11)	0.22	0%	
LDL					
Different degree of RI					
Non-ESRD	2 (110)	9.48 (-1.35, 20.31)	0.09	0%	0.48
ESRD	3 (130)	1.95 (-15.86, 19.76)	0.83	53%	
Different TZDs					
Pioglitazone	3 (118)	8.30 (-12.82, 29.41)	0.44	73%	0.77
Rosiglitazone	2 (122)	4.66 (-6.61, 15.94)	0.42	0%	
Different control					
Placebo/no additional drugs	4 (200)	2.76 (-9.96, 15.47)	0.67	55%	0.39
Active drugs	1 (40)	12.00 (-4.93, 28.93)	0.16	-	
HDL					
Different degree of RI					
Non-ESRD	4 (185)	3.12 (-0.52, 6.77)	0.09	6%	0.74
ESRD	6 (264)	4.02 (0.18, 7.87)	0.04	59%	
Different TZDs					
Pioglitazone	8 (327)	4.84 (2.50, 7.18)	<0.0001	22%	0.01
Rosiglitazone	2 (122)	-1.92 (-6.66, 2.82)	0.43	0%	
Different control					
Placebo/no additional drugs	8 (374)	3.54 (0.47, 6.60)	0.02	47%	0.83
Active drugs	2 (75)	4.34 (-2.51, 11.20)	0.21	56%	
Edema					
Different degree of RI					
Non-ESRD	5 (1169)	2.94 (1.11, 7.76)	0.03	0%	0.98
ESRD	2 (103)	3.05 (0.33, 28.32)	0.33	0%	
Different TZDs					
Pioglitazone	4 (208)	1.67 (0.36, 7.75)	0.51	0%	0.67
Rosiglitazone	2 (371)	3.83 (0.64, 23.08)	0.14	0%	
TZDs	1 (693)	4.03 (1.02, 15.95)	0.05	-	
Different control					
Placebo/no additional drugs	4 (474)	3.50 (0.86, 14.18)	0.08	0%	0.64
Active drugs	3 (798)	2.03 (0.34, 12.15)	0.44	43%	

Supplement Figure 1 Risk of hypoglycemia in diabetes patients with renal impairment for the TZDs versus control groups from RCTs

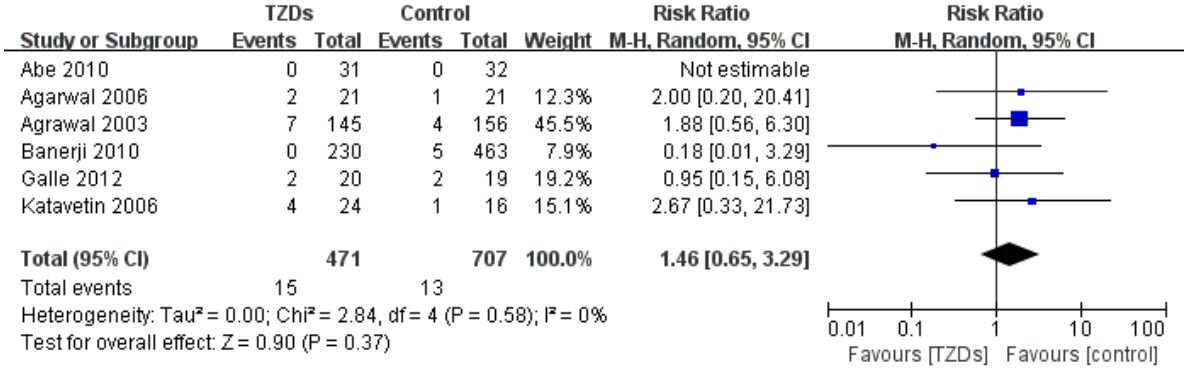

Fig 1 Risk of hypoglycemia in patients with diabetes mellitus and renal impairment for the TZDs versus control groups from RCTs