

TITLE PAGE

Assessing the need for pioglitazone in the treatment of patients with type 2 diabetes: A meta-analysis of its risks and benefits from prospective trials

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Supplementary Table 1: Assessment of quality of evidence for the outcomes analyzed using the GRADE system

Outcomes of interest	Trials, n	Effect size: MH-OR; (95% CI)	P-value	I ²	Grading of Recommendations, Assessment, Development, and Evaluation
MACE	5	0.86; (0.75–0.98)	0.03	0.000	⊕⊕⊕⊕
MI	5	0.85; (0.68–1.06)	0.14	0.000	⊕⊕⊕⊖
Stroke	5	0.77; (0.60–0.99)	0.04	0.000	⊕⊕⊕⊖
CV death	3	0.88; (0.35–2.24)	0.79	5.51	⊕⊕⊕⊖
ACM	6	0.94; (0.76–1.16)	0.58	0.000	⊕⊕⊕⊕
Nephropathy progression	3	0.95; (0.74–1.21)	0.68	75.65	⊕⊕⊕⊖
hHF	5	1.47; (1.26–1.71)	<0.001	<0.001	⊕⊕⊕⊖
HF	3	1.48; (1.21–1.81)	<0.001	<0.001	⊕⊕⊖
Cancer	3	1.02; (0.83-1.25)	0.86	0.000	⊕⊕⊖⊖
Fracture	4	1.31; (0.98-1.76)	0.06	22.77	⊕⊕⊖⊖
Macular edema	1	2.28; (0.59-8.82)	0.23	NA	⊕⊖⊖⊖
Anaemia	2	2.56; (1.56-4.20)	<0.001	24.83	⊕⊖⊖⊖
Drug discontinuation	3	1.09; (0.89-1.34)	0.38	10.59	⊕⊖⊖⊖

Supplementary figure 1: Web search strategy

Search Name: Pio: Cochrane Library (Access provided by Royal College of Physicians)

Date Run: 12/08/2018 17:43:52

Comment:

ID	Search	Hits
#1	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees	17440
#2	MeSH descriptor: [Thiazolidinediones] explode all trees	1811
#3	MeSH descriptor: [Pioglitazone] explode all trees	1053
#4	#2 OR #3	1811
#5	#1 OR #2 OR #3 in Trials	18087
#6	#1 AND #4	1083
#7	(major adverse cardiac events):ti,ab,kw (Word variations have been searched)	5899
#8	(MACE):ti,ab,kw (Word variations have been searched)	2957
#9	(myocardial infarction):ti,ab,kw (Word variations have been searched)	30757
#10	(stroke):ti,ab,kw (Word variations have been searched)	54538
#11	(cardiovascular death):ti,ab,kw (Word variations have been searched)	12329
#12	(all-cause mortality):ti,ab,kw (Word variations have been searched)	9388
#13	(heart failure):ti,ab,kw (Word variations have been searched)	35467
#14	(hospitalization for heart failure):ti,ab,kw (Word variations have been searched)	10194
#15	(microvascular outcomes):ti,ab,kw (Word variations have been searched)	1384
#16	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	113261
#17	#16 AND #5	1410
#18	#16 AND #6	127

Supplementary Figure 2: Quality of selected studies using the Cochrane risk of bias algorithm

PROactive ¹¹ 2005	+	+	+	+	+	+	+
TOSCA.IT ¹² 2017	+	+	+	+	+	+	+
PROFIT-J ¹³ 2014	?	?	-	-	+	+	+
Kaku et al ¹⁴ 2009	?	?	-	+	+	?	+
J-SPIRIT ¹⁵ 2017	?	?	-	?	+	?	?
Lee et al ¹⁶ 2013	?	?	?	?	+	?	?
PERISCOPE ⁷ 2008	+	+	+	+	+	+	+
Kaneda et al ¹⁷ 2009	?	?	+	-	+	?	+
Giles et al ²⁶ 2008	?	+	?	?	+	-	?
Giles et al ²⁷ 2010	?	?	+	?	+	?	?

Random sequence generation

Allocation concealment

Blinding of participants and personnel

Blinding of outcome assessment

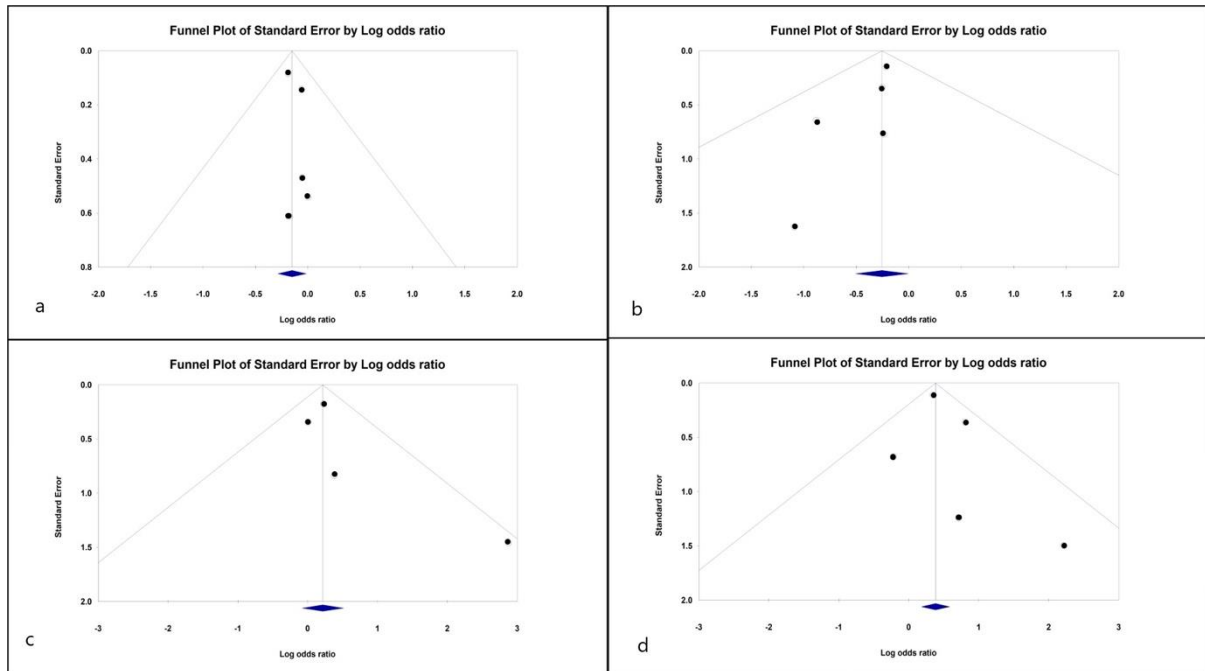
Incomplete outcome data

Selective reporting

Other bias

+ Low risk of bias
-High risk of bias
? Unclear risk of bias

Supplementary figure 3: Funnel plots assessing publication bias (a) MACE, (b) Stroke, (c) Fracture risk, and (d) hHF.



Supplementary Figure 4: Sensitivity analysis comparing Pioglitazone versus non-active control on (a). MACE, (b). Stroke, and (c). hHF.

