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Network meta-analysis of cardiovascular outcomes in randomised controlled trials of new classes of antidiabetic drugs

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Introduction: The prevalence of cardiovascular disease is high in patients with type 2 diabetes mellitus (T2DM). New antidiabetic drugs are required to demonstrate cardiovascular safety in outcome trials. However, they are rarely compared with each other in such trials. Therefore, we performed a network meta-analysis to compare the cardiovascular outcomes of the new classes of antidiabetic drugs.

Method: We searched for randomised controlled trials involving glucagon-like peptide-1 receptor agonists (GLP-1 RAs), sodium-glucose co-transporter 2 (SGLT-2) inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors in T2DM patients with cardiovascular outcomes, namely, major adverse cardiovascular events (MACE) and mortality, as endpoints. Both frequentist approach and Bayesian framework were used for analysis in R.

Results: Nine randomised controlled trials with altogether 72262 T2DM patients were included in our network meta-analysis [1-9]. SGLT-2 inhibitors and GLP-1 RAs reduced MACE (OR 0.86, 95%CI 0.77-0.95 and 0.89, 0.82-0.97, respectively), all-cause mortality (0.78, 0.69-0.88 and 0.89, 0.80-0.99, respectively), and cardiovascular mortality (0.76, 0.65-0.88 and 0.85, 0.73-0.99, respectively) when compared to placebo. Moreover, SGLT-2 inhibitors reduced MACE (0.87, 0.77-0.98), and cardiovascular mortality (0.75, 0.62-0.90) when compared to DPP-4 inhibitors. In contrast, DPP-4 inhibitors were not significantly different from placebo in cardiovascular outcomes but were associated with higher all-cause mortality when compared to SGLT-2 inhibitors (1.31, 1.13-1.53) and GLP-1 RAs (1.16,1.01-1.33).

Conclusions: SGLT-2 inhibitors and GLP-1 RAs reduce MACE and mortality compared to placebo. DPP-4 inhibitors are safe in that they do not worsen cardiovascular outcome, but are inferior to SGLT-2 in terms of MACE and cardiovascular mortality. This network meta-analysis shows clearly that SGLT-2 inhibitors and GLP-1 RAs should be the preferred treatment.

References:

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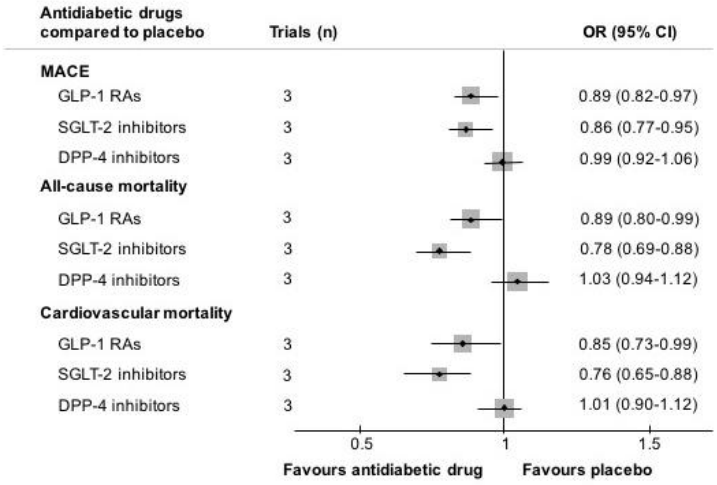

Trials included in the network meta-analysis

Study	**Drug**	**Drug class**	**Reference**
LEADER	Liraglutide	GLP-1 RA	Marso SP *et al.* (1)
SUSTAIN-6	Semaglutide	GLP-1 RA	Marso SP *et al.* (2)
ELIXA	Lixisenatide	GLP-1 RA	Pfeffer MA *et al.* (3)
EMPA-REG OUTCOME	Empagliflozin	SGLT-2 inhibitor	Zinman B *et al.* (4)
CANVAS	Canagliflozin	SGLT-2 inhibitor	Neal B *et al.* (5)
CANVAS-R	Canagliflozin	SGLT-2 inhibitor	Neal B *et al.* (5)
SAVOR-TIMI 53	Saxagliptin	DPP-4 inhibitor	Scirica BM *et al.* (6)
TECOS	Sitagliptin	DPP-4 inhibitor	Green JB *et al.* (7)
EXAMINE	Alogliptin	DPP-4 inhibitor	White WB *et al.* (8)