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Cardiovascular outcome trials (CVOT) using newer anti-diabetic agents in chronic kidney disease: A systematic review and meta-analysis

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Background and Aims:
The latest consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommends metformin and lifestyle intervention as first-line therapy for type 2 diabetes. Second-line therapy recommendation is the use sodium-glucose cotransporter 2 (SGLT 2) inhibitors (if estimated glomerular filtration rate [eGFR] is adequate) or GLP-1 receptor agonists if eGFR is inadequate (or SGLT-2 inhibitors not tolerated). No recommendation is made for dipeptidyl peptidase-4 (DPP-4) inhibitors. Therapy choices are limited for patients with both type 2 diabetes and moderate-to-severe chronic kidney disease (CKD) and it is unclear from published data if observed cardiovascular benefits of newer anti-diabetic agents extend to the CKD cohort. The aim of this study was to undertake a systematic review of all published CVOT trials using newer anti-diabetic agents (GLP-1 receptor agonists, DPP-4 inhibitors and SGLT 2 inhibitors).

Method:
We searched MEDLINE (via PubMed and the Cochrane Central Register of Controlled Trials) up to 1st December 2019. Data was stratified by trial entry eGFR into normal (eGFR ≥60 ml/min) and CKD (eGFR <60 ml/min), with data extracted for primary major cardiovascular event (MACE) rates such as cardiovascular death, stroke and/or myocardial infarct. A meta-analysis with random effects model was performed to estimate overall hazard ratios (HRs) for MACE with newer anti-diabetic agents stratified by eGFR. Inter-study heterogeneity was assessed with the I2 index and Cochran's Q test.

Results:
We analysed 13 studies from 16 that were eligible after our search strategy, with 2 excluded due lack of data stratified by eGFR and 1 excluded due to combined MACE/renal outcomes. The studies (GLP-1 agonists; n=6, DPP-4 inhibitors; n=4, SGLT 2 inhibitors; n=3) had a combined total of 128,266 participants (22.1% with eGFR <60 ml/min). HR for MACE with GLP-1 agonists for participants with eGFR ≥60 ml/min was 0.87 (95% CI 0.77-0.98; p=0.02) and for participants with eGFR <60 ml/min was 0.90 (95% CI 0.78-1.04; p=0.14). HR for MACE with DPP-4 inhibitors for participants with eGFR ≥60 ml/min was 0.99 (95% CI 0.92-1.07; p=0.86) and for participants with eGFR <60 ml/min was 0.99 (95% CI 0.91-1.08; p=0.86). HR for MACE with SGLT 2 inhibitors for participants with eGFR ≥60 ml/min was 0.98 (95% CI 0.88-1.10; p=0.78) and for participants with eGFR <60 ml/min was 0.82 (95% CI 0.70-0.96; p=0.01). Significant heterogeneity was observed in the meta-analyses for each newer anti-diabetic therapy drug class stratified by eGFR.

Conclusion:
Among the newer anti-diabetic agents, our study suggests efficacy for prevention of MACE in the setting of CKD exists only for SGLT 2 inhibitors and not with GLP-1 receptor agonists or DPP-4 inhibitors. Targeted CVOT studies incorporating participants with diabetes and CKD are critical to guide glycaemic management in these high-risk patients. Until then, we suggest recommendations for second-line therapy in patients with

type 2 diabetes and renal impairment should be amended to reflect the current evidence base supporting prevention of MACE with SGLT 2 inhibitors versus other anti-diabetic agents.