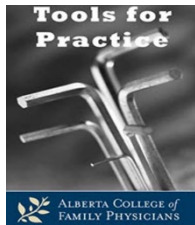


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DPP-4 inhibitor update: Thousands studied but still no evidence of clinical benefits

Clinical Question: In type 2 diabetes, do dipeptidyl peptidase-4 (DPP-4) inhibitors improve patient-oriented outcomes like cardiovascular disease (CVD)?

Bottom Line: DPP-4 inhibitors have no effect on patient-oriented outcomes like CVD (example myocardial infarction or stroke) or death. They increase the risk of hypoglycemia, pancreatitis and likely heart failure hospitalization. The choice for second line therapy after metformin should focus on drugs that reduce the risk of CVD (ie. SGLT-2 inhibitors or GLP-1 agonists).

Evidence:

- Four systematic reviews¹⁻⁴ of three randomized controlled trials (RCTs) designed to assess patient-oriented outcomes over 2.5 years (SAVOR-TIMI⁵, EXAMINE⁶, TECOS⁷) like CVD. Versus placebo, DPP-4 inhibitors:
 - Improved HbA1c: ³ 0.3-0.5%.
 - No effect on CVD outcomes (overall or CVD mortality, myocardial infarction, or stroke) in those with or without previous CVD.^{1,3,4} Example: CVD death, Risk Ratio 1.01 (95% CI 0.91-1.12).¹
- Three additional systematic reviews⁸⁻¹⁰ including smaller trials found similar.
- Microvascular:
 - Retinopathy: Meta-analysis (7 RCTs) found DPP-4 inhibitors increased risk (versus placebo): number needed to harm (NNH)=430 over 18 months.¹¹
 - Nephropathy: Two meta-analyses^{12,13} found DPP-4 inhibitors improve albuminuria but not clinical renal outcomes like end stage renal disease (ESRD), dialysis, or transplantation.
 - RCT of 6979 higher CVD/renal risk patients not included above but designed to evaluate renal outcomes:¹⁴
 - DPP-4 inhibitors did not improve renal composite outcome of ESRD, death, or sustained 40% decrease in eGFR versus placebo.
 - Albuminuria progression (a surrogate marker) reduced: 5.9% versus 7.5% placebo, number needed to treat (NNT)=30.
 - Limitations: short duration trial (~2 years)

- o No trials found evaluating the effect of DPP-4 inhibitors on diabetic neuropathy.
- Harms (over 2.5 years): acute pancreatitis (NNH 834);¹ heart failure hospitalization (286);^{1,15} hypoglycemia (NNH 70).¹

Context:

- Examples of DPP-4 inhibitors include sitagliptin, saxagliptin, or linagliptin.
- DPP-4 inhibitor RCTs⁵⁻⁷ designed as non-inferiority trials and were non-inferior to placebo:
 - o Meaning, DPP-4 inhibitors are not worse than nothing (for CVD).
- DPP-4 class is the #15 top spending for drug classes (~\$207 million/year).¹⁶
- Second-line therapy after metformin should focus on agents that improve CVD outcomes (e.g. SGLT-2 inhibitors or GLP-1 agonists).

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Disclosures:

Authors do not have any conflicts of interest to declare.

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