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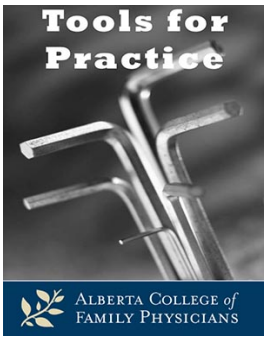

DPP-4 Inhibitors: Protecting your sweet heart?

Clinical Question: In Type 2 Diabetes, do dipeptidyl peptidase-4 (DPP-4) inhibitors affect outcomes [like cardiovascular disease (CVD)] other than glucose?

Bottom-line: While DPP-4 inhibitors lower A1c by 0.3-0.8%, they do not modify CVD or mortality. Adverse events were generally uncommon, but a tiny risk of pancreatitis remains possible, and saxagliptin increased hypoglycemia (~1 in 50) and heart failure (~1 in 150).

Evidence:

- Three non-inferiority Randomized Controlled Trials (RCTs) of DPP-4 inhibitors versus placebo in Type 2 Diabetes. Patients were mean age 61-66, 67-71% male, A1c 7.2-8.0%, and ≥74% past CVD.[1-3]
  - Saxagliptin 5 mg daily (SAVOR-TIMI 53):[1] 16,492 patients followed 2.1 years.
    - A1c ~0.3% better.
    - No difference in pooled CVD events (7.3% versus 7.2%) or specific CVD outcomes or death.
    - Adverse events: Statistically increased.
      - Heart failure (HF) hospitalization: Number Needed to Harm (NNH)=143.
      - Any hypoglycemia: NNH=53.
  - Alogliptin 25 mg daily (EXAMINE):[2] 5,380 patients followed 1.5 years.
    - A1c 0.36% better.
    - No difference in pooled CVD events (11.3% versus 11.8%) or specific CVD outcomes or death.
    - Adverse events: No statistical differences.[2,4]
  - Sitagliptin 100 mg daily (TECOS):[3] 14,671 patients followed 3.0 years.
    - A1c 0.29% better.
    - No difference in pooled CVD events (11.4% versus 11.6%) or specific CVD outcomes or death.
    - Adverse events: No statistical differences.
  - Microvascular: Minimal reporting.[1-2]
    - Sitagliptin:[3] No meaningful differences in diabetic eye disease (0.6% worse), neuropathy (0.3% worse), microalbuminuria (0.1% better).
    - Saxagliptin:[1] Statistically less worsening of microalbuminuria (13.3% versus 15.9%).

Context:

- These trials[1-3] were designed as non-inferiority studies (a design traditionally done versus active comparators).
  - Compared to placebo, they showed they are not worse than nothing.
- Pancreatitis: DPP-4 inhibitors had slightly, but non-statistically, more pancreatitis in each study.[1-3] Our pooled analysis (chi-square) of the three RCTs[1-3] showed statistical higher rate of pancreatitis: 0.29% versus 0.16% (p=0.015), NNH=798.
  - This should be confirmed in formal meta-analysis.
- Meta-analysis of glycemic control: 62 RCTs, 30,563 patients.[5]
  - DPP-4 inhibitors change in A1c (vs placebo): 0.76%.
- Canadian and Joint US & European Guidelines recommends DPP-4 inhibitors as one of the second-line options.[6,7]

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Disclosure:
Authors do not have any conflicts to disclose.

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