Effects of Newer Antidiabetic Agents on Cardiovascular Outcomes in Older Adults: Systematic Review and Meta-analysis

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Purpose

- The burden of older adults with diabetes is expected to reach 276 million by 2045.
- Old age is an independent risk factor for cardiovascular (CV) disease and there is a two-to-four-fold increased risk of CV disease in patients with Type 2 diabetes (T2DM). Therefore, old age, diabetes, and CV disease is a challenging triad for clinicians.
- Robust cardiovascular outcome trials (CVOTs) were mandated by U.S Food and Drug Administration (FDA) in 2008 to prove CV safety for newer anti-diabetic agents.
- CVOTs measured three-point / four-point major adverse cardiovascular outcomes (MACE) including a composite of CV death, myocardial infarction (MI), stroke and/or unstable angina.
- All the newer anti-diabetic agents have demonstrated CV safety, and some even demonstrated a CV benefit, but data in older adults (≥ 65 years) is limited.
- We designed this meta-analysis (PROSPERO ID CRD42021260167) to study the CV outcomes of newer antidiabetic drugs in older adults at high risk of CV disease.

Methods and Data Analysis

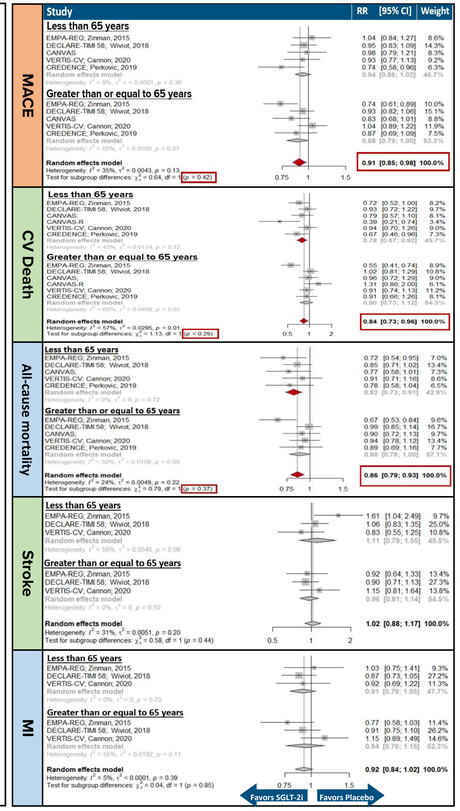
- PubMed and the Cochrane Central Register of Controlled Trials was searched from March 1, 2008, to June 30, 2021.
- **Inclusion criteria:** Randomized, controlled CV or renal outcome trials testing new anti-diabetic agents (dipeptidyl peptidase-4 inhibitors [DPP-4i], glucagon-like peptide-1 receptor agonists [GLP-1RA], and sodium/glucose cotransporter 2 inhibitors [SGLT-2i]) in patients with T2DM. Trials with at least 1000 adult participants, with ≥12 months follow-up, reporting MACE as an outcome and had available data for sub-groups by age.
- **Outcomes:** Primary outcome included 3P-MACE and secondary outcomes included CV death, all-cause mortality (ACM), MI, and stroke in age sub-groups.
- Two authors independently screened studies, extracted data, and evaluated risk of bias. Conflicts were resolved by consensus/third author. Missing/unpublished data was obtained from the corresponding authors for this analysis.
- Trials were grouped according to three classes of anti-hyperglycemic drugs, with age sub-groups <65 years and ≥ 65 years.
- Random-effects models were used to estimate relative risk (RR) with 95% confidence interval (CI) for MACE, its components and all-cause mortality (ACM). Inter-study heterogeneity was tested by the I^2 index. A chi-square test was done to assess differences between the age sub-groups (p-interaction). P-interaction was considered statistically significant at < 0.1.
- All analyses were applied using SAS (9.4) and R (4.10).

Results: SGLT-2 inhibitors

- Of 2,685 articles screened, **five** CVOTs were selected.
- **The trials included**
  - ⇒**EMPA-REG** (Empagliflozin)
  - ⇒**CANVAS** (Canagliflozin)
  - ⇒**CREDENCE** (Canagliflozin)
  - ⇒**DECLARE-TIMI 58** (Dapagliflozin)
  - ⇒**VERTIS-CV** (Ertugliflozin)
- **N= 46, 969**
- **Older adults:** 45—50%
- **Duration of trials** ranged from 2.4 to 4.2 years

Baseline characteristics:

- ⇒**Age:** 63 years
- ⇒**BMI:** 30 — 32 kg/m^2
- ⇒**HbA1c:** 8.1 – 8.3 %
- ⇒**Diabetes duration** >10 years
- ⇒**History of CV disease:** 41 – 100 %
- ⇒**History of heart failure:** 10 — 24 %
- ⇒**eGFR ≤ 60 ml/min:** 7 — 60%

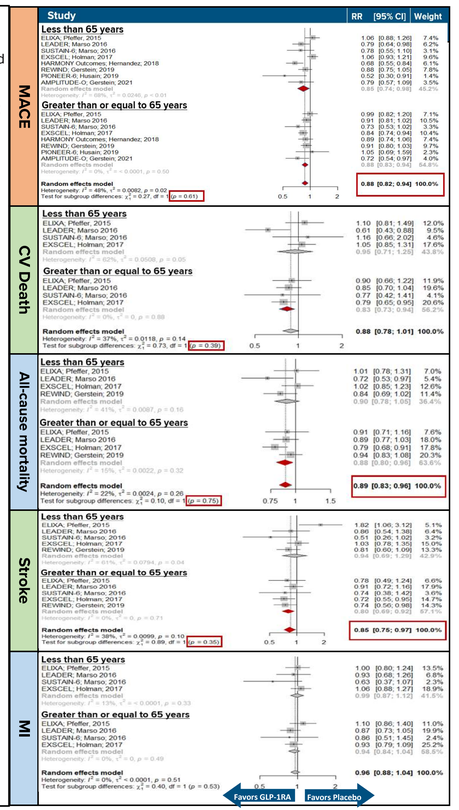


Results: GLP-1R agonists

- Of 2,607 articles screened, **eight** CVOTs were selected
  - ⇒**ELIXA** (Lixisenatide)
  - ⇒**LEADER** (Liraglutide)
  - ⇒**EXSCEL** (Exenatide)
  - ⇒**HARMONY** (Albiglutide)
  - ⇒**REWIND** (Dulaglutide)
  - ⇒**SUSTAIN-6** (injectable Semaglutide)
  - ⇒**PIONEER-6** (oral Semaglutide)
  - ⇒**AMPLITUDE-O** (Efpeglenatide)
- **N= 60,080**
- **Older adults:** 34 — 75%
- **Duration of trials** ranged from 1.3 to 5.4 years

Baseline features:

- ⇒**Age:** 64 years
- ⇒**BMI:** 30 — 33 kg/m^2
- ⇒**HbA1c:** 7.3 – 8.9%
- ⇒**Diabetes duration** >10 years
- ⇒**H/o CV disease:** 32 – 100%
- ⇒**H/o heart failure:** 9 — 22%
- ⇒**eGFR ≤ 60 ml/min:** 22 — 32%

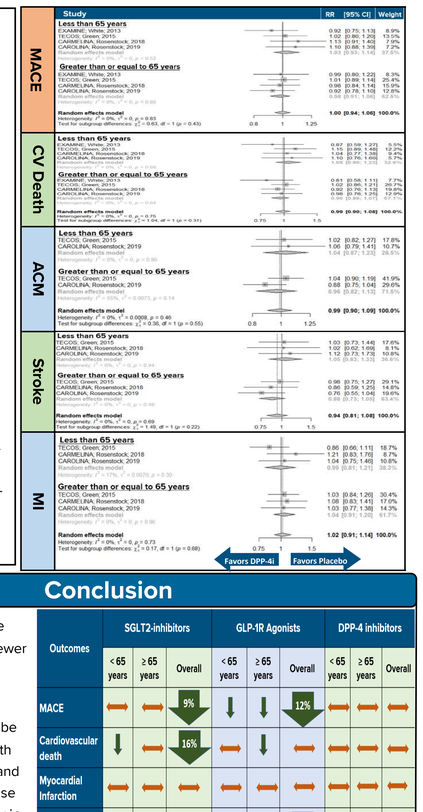


Results: DPP-4 inhibitors

- Of 1,866 articles screened, **four** CVOTs were selected.
- **The trials included**
  - ⇒**EXAMINE** (Alogliptin)
  - ⇒**TECOS** (Sitagliptin),
  - ⇒**CARMELINA** (Linagliptin)
  - ⇒**CAROLINA** (Linagliptin)
- **N = 33,063**
- **Older adults:** 35 —58%
- **Duration of trials** ranged from 1.5 to 6.3 years

Baseline characteristics:

- ⇒**Age:** 64 years
- ⇒**BMI**: 28 – 31 kg/m^2
- ⇒**HbA1c**: 7 – 8%,
- ⇒**Diabetes duration:** 6 – 15 years
- ⇒**History of CV disease:** 42—100%
- ⇒**History of heart failure:** 5 — 28%
- ⇒**eGFR ≤ 60 ml/min:** 19 — 62%



Conclusion

- These results confirm that the overall CV safety profile of newer anti-diabetic agents is unchanged in older individuals.
- Though all three classes can be used safely in older adults with high CV risk, use of SGLT-2i and GLP-1RA are preferred because of their demonstrated efficacy in reduction of adverse cardiovascular outcomes in all age sub-groups.

Outcomes	SGLT2-inhibitors			GLP-1R Agonists			DPP-4 inhibitors		
	< 65 years	≥ 65 years	Overall	< 65 years	≥ 65 years	Overall	< 65 years	≥ 65 years	Overall
MACE	⟷	⟷	↓ 9%	↓	↓	↓ 12%	⟷	⟷	⟷
Cardiovascular death	↓	⟷	↓ 16%	⟷	↓	⟷	⟷	⟷	⟷
Myocardial Infarction	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷	⟷
Stroke	⟷	⟷	⟷	⟷	↓	↓ 15%	⟷	⟷	⟷
All-cause mortality	↓	⟷	↓ 14%	⟷	↓	↓ 11%	⟷	⟷	⟷

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