THE OREGON STATE DRUG REVIEW©
AN EVIDENCE BASED DRUG THERAPY RESOURCE
http://pharmacy.oregonstate.edu/drug-policy/newsletter
September 2020 Volume 10 Issue 7

Cardiovascular Outcomes Associated with Newer Therapy Classes for Type 2 Diabetes Mellitus

Kathy Sentena, Pharm.D. Drug Use Research and Management, Oregon State University College of Pharmacy

There is a well-established correlation between type 2 diabetes mellitus (T2DM) and an increased risk of adverse cardiovascular (CV) outcomes. Cardiovascular disease affects approximately 32.2% of patients with T2DM on a global scale, responsible for around 50% of the mortality in patients with T2DM.[1] In 2008, the Food and Drug Administration (FDA) started to require drug manufacturers to conduct cardiovascular outcome trials to verify that the newer diabetes therapies for T2DM were void of increased risk (≤ 30%) of adverse CV effects.[2] The majority of newer diabetes therapies have completed CV outcome trials, assessing CV safety by analyzing major adverse CV events (MACE): CV death, nonfatal myocardial infarction (MI), and stroke. The focus of this newsletter will summarize the findings of the Drug Effectiveness Review Project (DERP) report on CV outcomes with the newer therapy classes for T2DM as well as review the evidence behind the new heart failure (HF) indication for dapagliflozin.

Drug Effectiveness Review Project Report on Newer Diabetes Therapies and CV Outcomes

The DERP looked specifically at the CV outcomes with the newer diabetes therapies (**Table 1**).[2] Eligible studies included randomized clinical trials and prospective or retrospective cohort studies (≥10,000 patients) published from January 1, 2017 to October 2, 2019.[2] Sixteen randomized controlled trials (RCTs) were identified including 15 placebo-controlled trials and one active control trial.[2] Ten of the RCTs were new to this review and six RCTs were from the original systematic review done by DERP in 2017.[2] Trials included adult patients with T2DM which were managed with standard of care therapy for glucose control and CV risk management. Important efficacy outcomes were mortality (all-cause and CV), and CV events (fatal or non-fatal MI, fatal or nonfatal stroke, and hospitalization for heart failure).

Table 1. Drugs Included in the DERP Report on Newer Diabetes Therapies and Cardiovascular Outcomes†[2]

Class	Generic Names	Brand Names
SGLT-2 inhibitors	Ertugliflozin Empagliflozin Dapagliflozin Canagliflozin	Steglatro* Jardiance Farxiga Invokana
DPP-4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin	Nesina Tradjenta Onglyza Januvia
GLP-1 receptor agonists	Oral semaglutide Subcutaneous semaglutide Lixisenatide Dulaglutide Albiglutide Exenatide ER Liraglutide Exenatide	Rybelsus Ozempic Adlyxin Trulicity Tanzeum‡ Bydureon Victoza Byetta

Abbreviations: DPP-4 = dipeptidyl peptidase-4; ER = extended release; GLP-1 = glucagon-like peptide 1; SGLT-2 = sodium-glucose cotransporter-2
Key: † Combination products were included for all classes; * No studies met inclusion criteria; ‡ No longer on the market

The CV outcome evidence compiled by DERP for the newer diabetes therapy classes are presented in **Table 2**. The glucagon-like peptide 1 receptor agonists (GLP-1 RAs) were the only drug class that demonstrated a small risk reduction in all-cause mortality, with approximately a 1% absolute difference between active therapy and placebo (number needed to treat [NNT] of 71-100 over 2.1 to 3.8 years).[2] As a class, the dipeptidyl peptidase-4 (DPP-4) inhibitors had a neutral effect on CV outcomes; however, there was a higher risk of heart failure (HF) for saxagliptin compared to placebo (3.5% vs. 2.8%; number needed to harm [NNH] 143 with a median follow up of 2.1 years).[2] There was moderate quality of evidence that sodium-glucose cotransporter-2 (SGLT-2) inhibitors reduced the risk for hospitalizations due to heart failure with a NNT of 42 to 80 (mean follow up of 2.6 to 4.2 years).[2]

Table 2. Cardiovascular Outcomes for Classes of Newer Diabetes Therapies versus Placebo[2]

Outcome	All-Cause Mortality	Stroke	Myocardial Infarction	Hospitalization for HF
GLP-1 RAs *Pooled results from 7 trials*	***Small risk reduction*** *(moderate QoE)†*	***No effect*** *(low QoE)†*	***No conclusion**** *(very low QoE)†*	***No effect*** *(moderate QoE)†*
DPP- 4 Inhibitors *Pooled results from 5 trials*	***No effect*** *(moderate QoE)†*	***No effect*** *(moderate QoE)†*	***No effect*** *(low QoE)†*	***No effect*** *(low QoE)†*
SGLT-2 Inhibitors *Pooled results from 4 trials*	***No effect*** *(moderate QoE)†*	***No effect*** *(low QoE)†*	***No effect*** *(moderate QoE)†*	***Significant risk reduction*** *(moderate QoE)†*

Abbreviations: DPP-4 = dipeptidyl peptidase 4; ER = extended release; GLP-1 RA= glucagon-like peptide 1 receptor agonist; HF = Heart Failure; QoE = quality of evidence; SGLT-2 = sodium-glucose cotransporter-2; XR = extended release
Key: * Evidence was insufficient so no conclusion could be made †Cochrane GRADE methodology[5] was used to determine quality of evidence designation; High – randomized trials or double-upgraded observational studies, Moderate – downgraded randomized trials and upgraded observation studies, Low – double-downgraded randomized trials or observation studies or Very Low – triple-downgraded randomized trials

Severe Adverse Events

Rates of severe adverse events were low for the classes of newer diabetes therapies; however adverse events in general are common with GLP-1 RAs and SGLT-2 inhibitors. Saxagliptin was associated with a greater risk of severe adverse events compared to placebo by 1.8% (number needed to harm [NNH] 56 with a median follow up of 2.1 years).[2] SGLT-2 inhibitors had a significant reduction in risk of severe adverse reactions with canagliflozin, dapagliflozin and empagliflozin compared to placebo, ranging from 2.1% to 4.1%.[2]

There was low quality evidence to suggest GLP-1 RAs had fewer severe adverse reactions compared to placebo.

Limitations

The studies included in the DERP report had limitations that should be considered when applying results to patients with T2DM. The median length of included trials was 2.9 years, which may not have been long enough to sufficiently capture CV outcomes. Multi-site international design of included studies may reduce the generalizability of findings to patients receiving health care in the United States (US). Differences in standards of care may have also influenced the results. External validity is reduced by the inclusion of patients with a 10 year or greater history of diabetes with established CV disease or at high risk of CV disease. There is insufficient evidence on the CV implications of these therapies in patients who are not at high CV risk. Additionally, there were no CV outcome studies that directly compared one newer diabetes therapy to another, so no comparative assessment between drugs or classes could be made.

Dapagliflozin and Heart Failure

Dapagliflozin is the first diabetes therapy to be approved for use in patients without diabetes, as well as those with T2DM, to reduce the risk of CV death and hospitalization for HF in adults with HF with reduced ejection fraction (NYHA class II-IV).[3] Evidence from a phase 3, placebo-controlled, randomized clinical trial demonstrated that dapagliflozin statistically significantly reduced the composite primary outcome of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death compared to placebo (**Table 3**).[4] Comparions among other pre-specified subgroups favored dapagliflozin compared to placebo for the outcomes of hospitalization or an urgent visit for HF (10% vsersus 13.7%) and for CV death (9.6% verus. 11.5%) (p-values not reported).[4] Primary outcome results were similar for patients with and without T2DM. Patients with NYHA class III or IV HF were not found to have a statistically significant benefit from dapagliflozin compared to placebo for the primary endpoint (hazard ratio [HR] 0.90 (95% CI, 0.74 to 1.09; p>0.05).[4] Results are most applicable to the study patient population, which included patients who were at higher risk of hospitalization for HF and CV death compared to other trials and were also on optimized therapy for HF.

Table 3. Dapagliflozin vs. Placebo in Patients with Heart Failure[4]

Comparison	Population	Primary Outcome	Results
Dapagliflozin 10 mg daily **Vs.** **Placebo** **(n=2373)**	Patients with or without diabetes with NYHA class II, III, or IV HF and an ejection fraction of 40% or less	Composite outcome of worsening HF (hospitalization or an urgent visit resulting in intravenous therapy for HF) or CV death	Dapagliflozin: 386 (16.3%) Placebo: 502 (21.2%) HR 0.74 (95% CI, 0.65 to 0.85) P<0.001 ARR 4.9% /NNT 21 over a median of 18.2 months

Abbreviations: ARR – absolute risk reduction; CV – cardiovascular; HF – heart failure; HR – hazard ratio; NNT – number needed to treat; NYHA – New York Heart Association

Conclusion

Based on current evidence, patients with T2DM, who are at high risk for CV disease or have established CV disease, may receive some CV benefit from the use of GLP-1 RAs or SGLT-2 inhibitors. Pooled analyses of the class effect of the newer diabetes therapies on the outcomes of stroke or MI risk is of low-to-moderate quality, without definitive evidence of benefit. Lastly, limited evidence suggests that dapagliflozin may have a role in reducing the risk of worsening HF or CV death in patients, with and without T2DM, who have HF with reduced ejection fraction.

For a more comprehensive review of the DERP summary please visit: https://www.orpdl.org/durm/meetings/meetingdocs/2020_08_06/archives/2020_08_06_DM_DERPSummary.pdf

The newer diabetes therapies are recommended second-line after metformin for Oregon Health Plan (OHP) patients. The following medications are preferred for OHP patients:

DPP-4 Inhibitors*
- Saxagliptin
- Sitagliptin
- Sitagliptin/metformin

GLP- Receptor Agonist†
- Exenatide
- Exenatide ER
- Liraglutide
- Dulaglutide

SGLT-2 Inhibitors*
- Dapagliflozin
- Empagliflozin
- Canagliflozin

* Subject to clinical PA criteria
† PA required if not prescribed in conjunction with metformin

Peer Reviewed By:
Nanette Bultemeier, PharmD, BCPS, BC-ADM, CDCES, Clinical Pharmacy Specialist, Providence Medical Group and Tracy Klein, PhD, ARNP, Washington State University Vancouver, Washington

References

1. Einarson T, Acs A, Ludwig C, Panton U. Prevalence of Cardiovascular Disease in Type 2 Diabetes: A Systematic Literature Review of Scientific Evidence From Across the World in 2007-2017. Cardiovascular Diabetol. 2018;17(1):83.
2. Drug Effectiveness Review Project. Newer Diabetes Drugs and Cardiovascular Diseae Outcomes: Update. February 2020.
3. Farxiga (dapagliflozin) [product information]. Willington, DE. AstraZeneca Pharmaceuticals LP. 2020.
4. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *Journal of Medicine*. 2019;381(21):1995-2008. doi:10.1056/NEJMoa1911303
5. Cochrane Handbook for Systematic Reviews of Interventions, v. 5.1.0 (2011). The Cochrane Collaboration. (http://handbook.cochrane.org)