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Type 2 Diabetes: Cardiovascular Outcomes with Metformin and Incretin Combination Therapy Compared to Metformin and Sulfonylureas

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Type 2 diabetes is a disease plaguing the American population, bringing along with it a number of complications. With millions of dollars spent annually to care for diabetic patients and the complications of diabetes, much remains to be known regarding newer medications and the effects of those complications. Two sodium glucose co-transporter 2 inhibitors, canagliflozin and empagliflozin, and one glucagon-like peptide-1 receptor agonist, liraglutide, have proven cardiovascular benefit; however, their use in combination with metformin has not been well studied when compared to metformin and sulfonylurea therapy. While there are studies underway evaluating such outcomes, a critical review of current literature has revealed a lack of research to aid in the decision-making process of type 2 diabetes treatment.

PREVALENCE

Type 2 diabetes mellitus is a disease affecting more than 23.1 million Americans, accounting for approximately 7.2% of the population.[1] It is estimated that only approximately 5% of this population has Type 1 diabetes mellitus, leaving about 21.9 million Americans who are living with Type 2 diabetes and the complications thereof. It is estimated that 33.9% of all US adults are living with prediabetes, based on fasting blood glucose levels and/or A1c levels.[1]

While it affects men and women equally, diabetes is a discriminatory disease that favors African Americans and Hispanics more than the non-Hispanic white population. It has a higher incidence in counties in the southern and Appalachian regions of the country, and its incidence is twice as high in those with education levels less than high school.[1] In the United States alone, diabetes accounted for $245 billion in medical expenditures in diagnosed patients.[1] This amount does not account for diagnosis, treatment, and complications of patients living with undiagnosed diabetes.

PATHOPHYSIOLOGY

Type 2 diabetes mellitus is characterized by two main pathophysiologic processes that jointly contribute to the progression of the disease. Over time, it is known that β cell function decreases in the pancreas leading to impaired insulin secretion and a decrease in overall response to glucose concentrations.[2] In addition, major organs within the body develop a resistance to insulin secreted by the pancreas. The human body then lacks response to what would typically be a normal concentration of insulin secreted to control rising glucose concentrations.[2] Researchers, scientists, and medical experts know that there is a genetic component that contributes to the predisposition for diabetes mellitus. It is also known that environmental factors and lifestyle choices contribute to declining β cell function. Increased caloric intake, poor dietary choices, and decreased activity levels contribute to the development of excess adipose tissue, and thus, the development of insulin resistance and decreased β cell function.[2] These facts guide clinician counseling of diet and exercise as an essential adjunct to the mainstay of therapy for diabetic patients.

STANDARDS OF CARE & TREATMENT

The current standard of care in the initial management of type 2 diabetes is lifestyle interventions and Metformin. Metformin is titrated up to a maximum daily dose of 2000mg, as the patient can tolerate.[3] Metformin as monotherapy has been shown to reduce A1c levels by approximately 1%.[3-4] According to current literature, an important consideration in the next step in glycemic control in patients with atherosclerotic cardiovascular disease is the initiation of a drug with known cardiovascular benefit in addition to Metformin.

Currently, three pharmaceutical agents have proven cardiovascular benefit (canagliflozin, empagliflozin, liraglutide), two of which have been FDA approved for such benefit (empagliflozin and liraglutide).[3-4] These drugs, however, have an associated financial barrier as they are significantly more expensive than other oral agents commonly used (i.e., sulfonylureas and thiazolidinediones).[4] It is known there is an association of increased mortality with decreased education status and financial wealth.[5] Providers don't know, however, whether or not the use of more affordable options (simply due to financial and socioeconomic factors) in combination with metformin is placing patients at higher risk of significant cardiovascular events than using newer agents, while more expensive, with proven cardiovascular benefits.

INCRETIN THERAPIES

In the management of type 2 diabetes, Incretin therapy encompasses two types of agents, GLP-1 agonists and DPP-4 Inhibitors. Glucagon-like peptide-1 receptor agonists (GLP-1 agonists) mimic the action of the glucagon-like peptide through binding to a surface hormone on β cells in the pancreas.[6] This increases β cell sensitivity to glucose, protects these cells from apoptosis, and triggers proliferation that increases β cell mass. These agents also suppress α cell secretion of glucagon, reducing glucose production within the liver and delaying gastric emptying. GLP-1 agonists also act on the hypothalamus to stimulate early satiety.[6]

Dipeptidyl peptidase 4 inhibitors (DPP-4 Inhibitors) act through preventing the enzymatic breakdown of GLP-1 and GIP (glucose-dependent insulinotropic polypeptide). These agents also stabilize levels of GIP, allowing its continued incretin effects to take place on β cells.[6-7]

DPP-4 INHIBITORS

Having only been approved for use for a little more than a decade, there is much to be discovered regarding this new class of antihyperglycemic agents and its effects on different organ systems. The TECOS trial sought to assess the long-term cardiovascular safety of adding Sitagliptin, the longest approved DPP-4 inhibitor, to usual care in patients with type 2 diabetes and cardiovascular disease. In this randomized, double-blind study, patients were assigned to add either sitagliptin or a placebo to their existing treatment plan. These patients were followed and cardiovascular outcomes were monitored, to include cardiovascular death, nonfatal MI or stroke, or hospitalization for unstable angina. Patients' A1c was measured periodically throughout the study and researchers found that at 4 months, the average A1c was lower in the sitagliptin group than the placebo group. In addition, sitagliptin group participants received fewer antihyperglycemic agents than placebo and those in the sitagliptin group were less likely to start insulin therapy.[7]

Researchers found there was no significant difference in the primary cardiovascular outcome and in the secondary cardiovascular outcome between the sitagliptin group and placebo. In addition, there was no significant difference in rate of hospitalization for heart failure, as is a concern for DPP-4 inhibitors.[7] This trial found that adding sitagliptin to a patient's medical regimen did not affect the rates of cardiovascular events. While this is true, the results cannot be extrapolated to include patients taking DPP-4 inhibitors for a longer period of time or to patients with more complicated medical presentations.[7] The TECOS trial, while critical in the evaluation of cardiovascular safety, failed to clarify the question of cardiovascular outcomes associated with DPP-4 inhibitors.

A meta-analysis of clinical trials performed by Wu et al. aimed to evaluate the cardiovascular safety and efficacy of DPP-4 inhibitors. In this study, prospective randomized controlled trials were obtained and evaluated for all-cause mortality, cardiovascular mortality, acute coronary syndrome, stroke, and heart failure outcomes. Some of the trials were placebo-controlled, while others used an active comparator. Multiple DPP-4 inhibitors were compared against metformin, sulfonylureas, and thiazolidinediones.

When compared to placebo and active comparators, there was no significant difference in all-cause mortality or in cardiovascular mortality. In comparison to active comparators, DPP-4 inhibitors showed a statistically significant reduction in acute coronary syndrome. There was a significant reduction in stroke when DPP-4 inhibitors were compared to active comparators. However, there was a significant increase in heart failure hospitalizations with DPP-4 inhibitors. This increase was significant only when compared to placebo groups but was not significant when compared to active comparators.[8]

In the same study, researchers discussed the effects of DPP-4 inhibitors that would suggest cardiovascular benefit. In addition to being weight neutral, or potentially contributing to weight loss, DPP-4 inhibitors decrease blood pressure, improve postprandial lipemia, reduce inflammatory markers, diminish oxidative stress, and improve endothelial function.[8] In addition, DPP-4 inhibitors improve cardiac contractility in diabetic patients. There have been no direct explanations provided for the increase in heart failure hospitalizations. While there has been a neutral effect found on all-cause and cardiovascular mortality, the implications of an increase in heart failure hospitalizations requires further evaluation.

Few studies have directly discussed cardiovascular outcomes of DPP-4 inhibitors. Jose and Inzuchhi review multiple DPP-4 inhibitors and discuss the cardiovascular effects of each. Sitagliptin does not appear to pose additional cardiovascular risk to patients.[9] In a study evaluating saxagliptin, researchers found no cardiovascular harm and a potential for a decrease in cardiovascular events (measured as death, myocardial infarction, stroke, revascularization procedures, and ischemia).[9] Studies evaluating alogliptin found a numerically lower risk of cardiovascular outcomes, although not statistically significant. One study that evaluated DPP-4 inhibitors showed a 31% reduction in cardiovascular events, a rate that hasn't been shown by many other studies prompting concern and the need for additional research.

GLP-1 AGONISTS

The LEADER trial was an integral trial in the treatment of type 2 diabetes and associated cardiovascular outcomes. In this multinational study, patients without a history of cardiovascular disease (CVD), but high risk, were evaluated alongside patients with known CVD to determine the effect of treatment with liraglutide compared to placebo on cardiovascular outcomes.[10] Researchers defined cardiovascular events as cardiovascular death, nonfatal MI, or nonfatal stroke in patients with type 2 diabetes. LEADER was unique in that it targeted high risk patients, either with or without a history of cardiovascular disease and comorbid cardiac related conditions.

Liraglutide is known to decrease A1c 1.0-1.5%. While its mechanism on cardiovascular risk requires further research, multiple mechanisms have been identified that could contribute to lowering the risk for type 2 diabetic patients. GLP-1 agonists account for significant weight loss and a decrease in systolic blood pressure. It is also hypothesized that there may be a direct effect

on cardiac myocytes and the endothelium. Studies have shown there is no negative impact on lipid profiles and cardiovascular risk and some results even favor an improvement in triglycerides and free fatty acids. Other studies have shown a decrease in BNP and PAI-1, two very important cardiac health markers.[10]

The LEADER trial found that fewer patients in the liraglutide group died from cardiovascular events, experienced nonfatal MIs or nonfatal strokes than those in the placebo group. In addition, the all-cause mortality was lower in the liraglutide group than the placebo group. The rates of nonfatal MI or stroke were lower in the liraglutide group when compared to placebo. This trial also showed a greater increase in weight loss and a greater decrease in systolic and diastolic blood pressure in the liraglutide recipients when compared to placebo, while experiencing a mild increase in heart rate.[11] The incidence of renal or retinal microvascular events was lower in the liraglutide group when compared to placebo, although the incidence of retinopathy was not significantly higher in the liraglutide group. It is important to outline the potential risks associated with the use of liraglutide, including pancreatitis, pancreatic cancer, and thyroid T-cell tumors. More research is needed to evaluate these potential complications of treatment.

Pfeffer et al. evaluated the effects of adding lixisenatide to a medication regimen for patients who recently experienced an acute coronary event. This study included patients who had experienced a myocardial infarction or had been hospitalized for unstable angina within the preceding 180 days. Researchers evaluated patients for cardiovascular death, MI, stroke, or hospitalization for unstable angina as primary outcomes. After randomization and addition of lixisenatide, researchers found that this drug was noninferior to placebo, but also did not find

superiority. There were no significant differences in heart failure hospitalizations or death rates, and there was no difference in serious adverse events, including pancreatitis, pancreatic cancer, or allergic reactions. Pfeffer et al. concluded there was no significant change in cardiovascular events with the addition of lixisenatide.[12]

A study by Nauck outlines a few disadvantages and advantages of incretin therapies, to include GLP-1 agonists and DPP-4 inhibitors. Important components that warrant further investigation include a potential for an increased risk of pancreatitis and neoplastic lesions that could promote the development of pancreatic cancer.[13] Previous studies have also raised concern of thyroid C-cell proliferation that could lead to thyroid cancers. Simply put, these findings certainly warrant further investigation and research. Despite the potential negative implications of using incretin therapies, there have been studies showing an association between use and a reduction in body weight.[13] GLP-1 agonists have also been shown to improve endothelial function, dilate blood vessels, and improve natriuresis and fluid excretion, thus reducing blood pressure. Due to a stimulation of glucose and oxygen intake into the myocardium, researchers have found a potential increase in cardiac output.[13]

TRADITIONAL THERAPY

Many healthcare providers prefer to use older and more traditional methods of oral combination therapies in the treatment of type 2 diabetes. These methods include metformin and sulfonylurea combination therapy. While certainly more affordable, these medications carry risks that should be carefully evaluated by prescribers.

A study by Roumie et al. evaluated the time to acute MI, stroke, or death in Metformin patients adding either insulin or a sulfonylurea. At the time of addition of the second medication,

patients had been stabilized on metformin for several months. Compared against patients who added sulfonylureas, the addition of insulin was associated with an increased risk of a composite of nonfatal cardiovascular outcomes and all-cause mortality.[14] These findings require further studies to comprehensively evaluate the effects of adding insulin versus oral medications and the efficacy of each.

A second study by Roumie et al. evaluated the effectiveness of sulfonylurea and metformin monotherapy on cardiovascular outcomes in the veteran population. Patients were evaluated for a composite outcome of hospitalization for acute MI, stroke, or death. This study showed that there was a higher rate of cardiovascular events in sulfonylurea monotherapy patients when compared to metformin monotherapy. This included glyburide and glipizide in the sulfonylurea group. It is important to note that this population included mostly white men. Data on women and minority groups was limited, although the study was representative of the veteran's health population. This study concluded the use of sulfonylureas is associated with an increased hazard of cardiovascular events or death when compared to metformin monotherapy.[14] It is also important to note that this study only compared the monotherapy use of metformin and sulfonylureas and did not evaluate combination therapy.

DISCUSSION

Providers should consider the practical aspects of these drugs prior to initiating therapy in diabetes patients. In an effort to target patient specific concerns, factors such as cost, hypoglycemia risk, weight change, efficacy and range of A1c reduction, and administration

method should be addressed. Of the drugs compared in this paper, metformin, GLP-1 agonists, and sulfonylureas are all highly effective drugs in the treatment of type 2 diabetes, while DPP-4 inhibitors are classified as intermediate.[16] It is known that excessive weight and adipose tissue has an impact on diabetes and the progression of the disease. Metformin has been shown to be weight neutral, with a slight possibility of weight loss. DPP-4 inhibitors are weight neutral while sulfonylureas cause weight gain. GLP-1 agonists have been proven to assist in weight reduction among type 2 diabetes patients.

In regard to cardiovascular disease and outcomes, DPP-4 inhibitors and sulfonylureas are neutral in mitigating risk. Metformin has a potential benefit for cardiovascular disease. Currently, one GLP-1 agonist has been FDA approved and shown to benefit cardiovascular outcomes – liraglutide.[16] Only one class of medications discussed in this paper, DPP-4 inhibitors, pose a potential risk for patients with comorbid heart failure.[16]

Renal effects of diabetic drugs should be carefully evaluated due to end organ damage caused by the pathophysiologic process of diabetes. While metformin should not be used in patients with eGFR <30, it does not lead to the progression of kidney disease. This is a common theme among diabetic medications. Liraglutide, a GLP-1 agonist, has been shown to benefit kidney disease in diabetic patients. Other GLP-1 agonists do require dosing adjustments for use in patients with kidney disease.[16]

Perhaps one of the most widely used aspects in the decision-making process of add on therapy for diabetics is the cost of the medication. Newer drugs come at higher costs that are typically not initially covered by insurance providers. Both GLP-1 agonists and DPP-4 inhibitors are high cost medications, while metformin and sulfonylureas are much cheaper, increasing

compliance with patients. It is also important to discuss with patients their desire to avoid or to use injectable therapies. Of the drugs discussed in this paper, GLP-1 agonists are injectable drugs. It is important to discern the level of compliance with injectable therapies a patient is likely to have. The proven benefits of a drug will not affect a patient if he/she is not using the drug at all or even using the drug correctly.[16]

Other important considerations include FDA issued warnings, black box warnings, and common side effects which could reduce use of certain medications. Metformin has well known gastrointestinal side effects that some patients are often unable to tolerate. These include diarrhea, nausea, abdominal pain, etc. The FDA has issued a black box warning for GLP-1 agonists due to some studies showing an increased risk of thyroid C-cell tumors with the use of liraglutide, albiglutide, dulaglutide, and extended release exenatide. These drugs, along with another member of the incretin family, DPP-4 inhibitors, also show a potential for a higher risk of pancreatitis, which needs further investigation. A special warning was issued for sulfonylureas following studies showing an increased risk of cardiovascular mortality. It is important to note this was a first-generation sulfonylurea called tolbutamide, which is no longer recommended for use.

CONCLUSION

The question posed regarding cardiovascular outcomes of metformin and sulfonylureas versus metformin and incretin therapies still remains. Simply put, there have been a lack of studies directly comparing combination therapy for type 2 diabetes. With the prevalence of diabetes in the United States alone, it is certainly an area that warrants further investigation to guide the standard of care in years to come.

Current studies are underway directly comparing combination therapies. The results of the CARMELINA trial by Boehringer Ingelheim and Eli Lilly & Co. are expected soon. This trial evaluates the cardiovascular outcomes of linagliptin. A second trial by the same researchers is nearing completion and results should be released soon. The CAROLINA trial directly compares linagliptin with a second-generation sulfonylurea, glimepiride. These trials should assist in determining directions for future research.

REFERENCES

1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Diabetesorg. 2017. http://www.diabetes.org/assets/pdfs/basics/cdc-statistics-report-2017.pdf. Accessed December 12, 2018.

2. Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present, and future. The Lancet. 2014;383(9922):1068-1083. doi:https://doi.org/10.1016/S0140-6736(13)62154-6.

3. Wexler DJ. Initial management of blood glucose in adults with type 2 diabetes mellitus. UpToDate. https://www.uptodate.com/contents/initial-management-of-blood-glucose-in-adults-with-type-2-diabetes-mellitus?search=type 2 diabetes treatment&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H26275125. Published November 19, 2018. Accessed December 12, 2018.

4. American Diabetes Association. Standards of Medical Care in Diabetes - 2018. Diabetes Care. 2018;41(Supplement 1). doi:https://doi.org/10.2337/dc18-SINT01.

5. Saydah SH, Imperatore G, Beckles GL. Socioeconomic Status and Mortality. Diabetes Care. 2013;36(1):49-55. doi:https://doi.org/10.2337/dc11-1864.

6. Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. Nature Reviews Endocrinology. 2009;5:262-269. https://www.nature.com/articles/nrendo.2009.48. Accessed December 12, 2018.

7. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *New England Journal of Medicine*. 2015;373(3):232-242. doi:10.1056/NEJMoa1501352.

8. Hopper I, Wu S, Skiba M, Krum H. Dipeptidyl Peptidase-4 Inhibitors and Cardiovascular Outcomes: Meta-analysis of randomized clinical trials. *Cardiovascular Therapeutics*. 2014;9(1):147-158. doi:10.1111/1755-5922.12075.

9. Jose T, Inzucchi SE. Cardiovascular effects of the DPP-4 inhibitors. *Diabetes and Vascular Disease Research*. 2012;9(2):109-116. doi:10.1177/1479164111436236.

10. Marso SP, Poulter NR, Nissen SE, et al. Design of the liraglutide effect and action in diabetes: Evaluation of cardiovascular outcome results (LEADER) trial. *American Heart Journal*. 2013;166(5):823-830. doi:10.1016/j.ahj.2013.07.012.

11. Marso SP, Daniels GH, Brown-Fransden K, Kristensen P, Mann JFE. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827.

12. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Type 2 Diabetes and Acute Coronary Syndrome. *New England Journal of Medicine*. 2015;374(11):2247-2257. doi:10.1056/NEJMoa1509225.

13. Nauck MA. A Critical Analysis of the Clinical Use of Incretin-Based Therapies: The benefits by far outweigh the potential risks. *Diabetes Care*. 2013;36(7):2126-2132. doi:10.2337/dc12-2504.

14. Roumie CL, Greevy RA, Grijalva CG, et al. Association Between Intensification of Metformin Treatment With Insulin vs Sulfonylureas and Cardiovascular Events and All-Cause Mortality Among Patients With Diabetes. *JAMA*. 2014;311(22):2288-2296. doi:10.1001/jama.2014.4312.

15. Roumie CL, Hung AM, Greevy RA, et al. Comparative Effectiveness of Sulfonylurea and Metformin Monotherapy on Cardiovascular Events in Type 2 Diabetes Mellitus. *Annals of Internal Medicine*. 2012;157(9):601-610. doi:10.7326/0003-4819-157-9-201211060-00003.

16. Chamberlain JJ, Johnson EL, Leal S, Rhinehart AS, Shubrook JH, Peterson L. Cardiovascular Disease and Risk Management: Review of the American Diabetes Association Standards of Medical Care in Diabetes 2018. *Annals of Internal Medicine*. 2018;168(9):640-650. doi:10.7326/m18-0222.