CONTROLLING DIABETES WITH CONTINUOUS GLUCOSE MONITORING

USING FINERENONE TO DECREASE CARDIOVASCULAR EVENTS IN DIABETIC PATIENTS WITH CKD

POTENTIAL OVERUSE OF SEMAGLUTIDE AND ITS SPECULATED IMPACT ON DIABETES TREATMENT

TIZEPATIDE (MOUNJARO®) - NEWLY APPROVED, FIRST IN CLASS FOR TYPE 2 DIABETES TREATMENT

THE USE OF GLP-1 AGONIST FOR NAFLD

2023 ADA STANDARDS OF CARE – WHAT’S BEEN UPDATED?
The 2023 American Diabetes Association’s Standards of Care has many updates compared to the 2022 standards which focus heavily on comorbidities and monitoring. Highlighted in the following paragraphs are a few of the updates related to pharmacotherapy.

Section 3, “Prevention or Delay of Type 2 Diabetes and Associated Comorbidities,” describes those at risk for developing type two diabetes mellitus (T2DM). Four new recommendations were added starting with the assessment of high-risk individuals who are receiving a statin. Because statin therapy can induce hyperglycemia, patients with prediabetes are at an higher risk for developing diabetes and should be monitored closer, especially if they are new to statin therapy. Similarly, people with prediabetes experiencing insulin resistance (but preserved beta cell function) and a history of stroke are recommended to consider pioglitazone due to the potential ASCVD benefits. Lastly, the American Diabetes Association focused heavily on the importance of considering pharmacotherapy to reduce the risk of obesity, hyperglycemia, and cardiovascular events in high-risk individuals.

Section 4, “Comprehensive Medical Evaluation and Assessment of Comorbidities,” has been updated to include a more thorough recommendation concerning COVID-19 and pneumococcal vaccines. The original Pfizer and Moderna boosters have been replaced by the omicron bivalent boosters. Other changes include the vaccine coverage, which allow a primary series of Pfizer or Moderna to be given to patients six months and older. The Janssen vaccine use has been restricted, therefore the Pfizer or Moderna bivalent vaccine may be given to any individuals who have been vaccinated with the Janssen vaccine. Additionally, recommendations have been put into action to address individuals with diabetes that have COVID-19. The guidelines emphasize individualized care, attentive care, and monitoring for post-COVID complications and ketoacidosis.

Sections 9 and 10 discuss approaches for weight management, cardiovascular, and kidney comorbidities in T2DM. Section 9, “Pharmacologic Approaches to Glycemic Treatment,” added recommendations that a patient may need combination therapy to have adequate glucose control, weight control, and cardiorenal protection, where it applies. Stronger emphasis was placed on the importance of weight management and how to create a patient-centered plan to achieve weight targets. The updated treatment algorithm is more streamlined, breaking each treatment option down from most to least efficacious, and includes the recently approved tirzepatide.

Section 10, “Cardiovascular Disease and Risk Management,” has updated the blood pressure recommendations to coincide with the 2017 ACC/AHA Hypertension guidelines. A blood pressure ≥ 120/80 mmHg is now considered elevated (rather than the previous ≥140/90) and ≥130/80 is stage 1 hypertension. Additionally, the blood pressure goals for hypertension are ≤130/80, which is in line with the ADA and ACC/AHA guidelines.

As for statin therapy, the LDL goals for both high-risk primary prevention and secondary prevention have been updated to <70 mg/dL and <55 mg/dL, respectively.

The American Diabetes Association 2023 update addressed other factors affecting people with diabetes and those at high risk for diabetes that were not discussed in this review. Please see the 2023 Guideline Update for a comprehensive list of all updates.

References:

The Use of GLP-1 Agonist for NAFLD

By: Emily Strickland, Pharm.D. Candidate, Class of 2024

Non-alcoholic fatty liver disease (NAFLD) is becoming increasingly common, especially in western countries due largely to the rise of obesity. Currently in the United States, NAFLD is the most common form of chronic liver disease, affecting around 25% of the population. In addition, NAFLD is becoming more prevalent in children due to the rise of childhood obesity. Most individuals present with no signs or symptoms, but fatigue, pain or discomfort in the upper right abdomen may be present. NAFLD is often found in patients due to abnormal liver enzymes. Common causes and/or risk factors include overweight or obesity, insulin resistance, type 2 diabetes, and high levels of triglycerides. Specifically type 2 diabetes has been found to be one of the most important risk factors for the progression of NAFLD to nonalcoholic steatohepatitis (NASH) or cirrhosis. First line treatment is weight loss in combination with a healthy diet and exercise. Currently, no pharmacologic treatments have been FDA approved for NAFLD. While no treatments have been FDA approved, there are recent studies which suggest that GLP-1 agonists may be promising treatment options.

Some previous studies looking at treatment for NAFLD have shown some effectiveness for the use of pioglitazone and/or bariatric surgery. Pioglitazone, an agent used to treat type 2 diabetes, is less commonly used today due to more efficacious agents being available.

Bariatric surgery has fallen out of favor due to the risks associated with the procedure. While neither of these options are ideal treatments for NAFLD, they both support the hypothesis that weight loss and improvement in hepatic insulin resistance are key to treating NAFLD. The idea of weight loss and improvement in insulin resistance have led to consideration of using GLP-1 agonists as a treatment option.

GLP-1 agonists help improve glycemic control while leading to a reduction in body weight and insulin resistance. Multiple trials have looked at the various GLP-1 agonists currently on the market with promising results.

While no treatments have been FDA approved, there are recent studies which suggest that GLP-1 agonists may be promising treatment options.
In a meta-analysis of the use of GLP-1 agonists for the treatment of NAFLD, the results showed that when compared to placebo, GLP-1 agonists improved the absolute percentage of liver fat content. Overall, liraglutide and semaglutide were found to be associated with a greater histologic resolution of NASH with no worsening of liver fibrosis.

Most of the current trials have been conducted on individuals with concurrent type 2 diabetes, however, 30% of the patients in the meta-analysis did not have a diagnosis of type 2 diabetes. These patients also showed improvement. Regarding the safety of GLP-1 agonists for NAFLD, the main adverse effect reported in the trials was mild to moderate gastrointestinal disorders. This closely resembles the adverse effects reported when GLP-1 agonists are used for the treatment of type 2 diabetes.

While more evidence is needed to determine the overall efficacy for the use of GLP-1 agonists in treating NAFLD, a key factor to consider are the other benefits a patient receives when using a GLP-1 agonist. Treatment benefits include treatment of type 2 diabetes, ASCVD benefit and reduction in chronic kidney disease. Even though no current treatments have yet to be FDA approved for the treatment of NAFLD, major progress has been made in finding more effective treatment for our patients.

References:

Tizepatide (Mounjaro®) – Newly Approved, First in Class for Type 2 Diabetes Treatment

By Monica Acharya, Pharm.D. Candidate, Class of 2023

In May 2022, the Food and Drug Administration (FDA) approved tizepatide for adults with type 2 diabetes mellitus (T2DM) to improve blood glucose levels in combination with diet and exercise. During clinical trials, tizepatide was found to be more effective compared to placebo and diabetes medications such as semaglutide, insulin degludec, or insulin glargine.

Tizepatide is the first medication in its class with a dual mechanism of action: GLP-1 agonist & GIP

Three different doses of tizepatide (5 mg, 10 mg, and 15 mg) were evaluated in clinical trials, and patients who received tizepatide 15 mg had a reduction in their A1C levels by more than 1.6 percentage points compared to placebo.
Diabetes in Focus

Tizepatide (Mounjaro®) – Newly Approved, First in Class for Type 2 Diabetes – cont.

In addition, patients who received tizepatide 15 mg had a reduction in their A1C levels by more than 0.5%, 0.9%, and 1% points compared to semaglutide, insulin degludec, and insulin glargine, respectively. Similarly, patients on tizepatide 15 mg also had a mean weight loss of more than 12 pounds, 29 pounds, and 27 pounds compared to semaglutide, insulin degludec, and insulin glargine, respectively.

Some common side effects of tizepatide include nausea, vomiting, diarrhea, constipation, decreased appetite, and abdominal pain. Serious adverse effects include risk of hypersensitivity reactions, thyroid c-cell tumors, pancreatitis, severe hypoglycemia, acute kidney injury, acute gallbladder disease, and diabetic retinopathy complications. Tizepatide is not indicated for patients with type 1 diabetes, children under 18 years of age, or those with a diagnosis of pancreatitis. Tizepatide is contraindicated in patients with a personal or a family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN 2).

Patients should be counseled on signs and symptoms of thyroid tumors such as a mass in the neck, dysphagia, dyspnea, and hoarseness. Additionally, tizepatide should not be used by pregnant women or those who are breastfeeding as it is unknown if the medication causes harm to the baby. Although tizepatide has no specific drug–drug interaction, it can affect the absorption of oral medications due to its ability to delay gastric emptying. Similarly, women of reproductive age who are on oral contraceptives should switch to a non-oral contraceptive method, or should add a barrier method for 4 weeks after initiation or dose increase of tizepatide. Hence, caution should be exercised with orally administered medications, especially those with a narrow therapeutic index like warfarin. No adjustments for renal or hepatic impairment are required for tizepatide.

In summary, tizepatide is a newly approved medication for patients with T2DM. It has a unique mechanism of action in that it targets both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoitropic polypeptide (GIP) receptors, which are involved in regulating blood glucose levels. GLP-1 and GIP are hormones that are secreted by the gut after a meal, and they enhance insulin secretion. They work by lowering fasting and postprandial glucose levels, increasing insulin sensitivity, removing excess glucose from the blood, preventing the liver from making and releasing excess glucose, decreasing food intake, and delaying gastric emptying.

Tizepatide comes in doses of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg per 0.5 mL as a pre-filled single-dose pen. The recommended starting dose of tizepatide is 2.5 mg subcutaneous once a week. After 4 weeks, the dose should be increased to 5 mg subcutaneously once a week, with a max dose of 15 mg subcutaneously once a week. Tizepatide can be injected at any time of the day, irrespective of mealtimes.

Tizepatide is the first medication in its class with a dual mechanism of action in which it activates both glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoitropic polypeptide (GIP) receptors, which are involved in regulating blood glucose levels. GLP-1 and GIP are hormones that are secreted by the gut after a meal, and they enhance insulin secretion. They work by lowering fasting and postprandial glucose levels, increasing insulin sensitivity, removing excess glucose from the blood, preventing the liver from making and releasing excess glucose, decreasing food intake, and delaying gastric emptying.

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In summary, tizepatide is a newly approved medication for patients with T2DM. It has a unique mechanism of action in that it targets both GLP-1 and GIP receptors, which regulate glucose levels in the blood. Tizepatide has a starting dose of 2.5 mg, and the dose can be titrated up in increments to best optimize the A1C level, with a maximum dose of 15 mg. Common side effects include gastrointestinal side effects, whereas serious side effects are related to the pancreas, kidneys, and thyroid.
Controlling Diabetes with Continuous Glucose Monitoring  
By Allison Dean, Pharm.D. Candidate, Class of 2024

Traditionally, fingerstick glucose monitoring has been used for patients with diabetes. For patients that are starting out in their diabetic journey or need to monitor their blood glucose frequently, this method can be confusing and inconvenient. Not only can there be inaccuracies with the patient’s obtaining blood glucose samples, but there are also variabilities in the meters’ blood glucose readings. However, in the last two decades, continuous glucose monitors (CGMs) have made big strides to become a popular alternative for patients.

CGMs can offer patients the ability to quickly and discreetly check their glucose levels. CGMs measure glucose levels 24 hours a day while wearing the device. Continuous glucose monitoring devices work by placing a sensor under the skin (usually on the stomach or arm) and measuring glucose levels in fluid under the skin. The measured levels are wirelessly sent to a receiver or an app on a smartphone.

There are three different types of CGMs: real-time, intermittently-scanned, and professional. Real-time continuous glucose monitors (rtCGM) continuously measure and display glucose levels. Intermittently-scanned continuous glucose monitors (isCGM) require scanning to display and record glucose levels. Some isCGM have alarms for hypo- and/or hyperglycemic events. Professional CGMs are placed on the patient in a healthcare office, worn for a specified time, and then used to assess glucose values and trends.

Some clear advantages of CGMs include their ability to alert patients of hypo- and hyperglycemic events and quickly see how their dietary decisions affect their blood glucose throughout the day. Additionally, in a study done by Martens et al, patients using CGMs reported high “benefits” scores and low “hassle” scores. While traditional blood glucose monitors give specific levels at a specific time, CGMs allow patients to track trends and see their levels increase and/or decrease over time. CGMs have also been shown to reduce the risk of hospitalization, improve diabetes control, and reduce hypoglycemia in patients.

References:
Controlling Diabetes with Continuous Glucose Monitoring – Cont

However, there are some challenges with CGMs. For example, they represent new technology and can be expensive. Additionally, since continuous glucose monitors measure glucose levels in the interstitial fluid (ISF), it can take time for ISF glucose levels to be equivalent to blood glucose levels. CGMs also may require calibration and/or frequent replacement of sensors. Additionally, the American Diabetes Association’s 2023 Standards of Care recommend that patients with CGMs also have access to blood glucose monitoring at all times, which could lead to additional costs for patients.

Patients and providers should also be aware of medications that may interfere with CGM readings. Medications that interfere with Dexcom G6® include acetaminophen doses >4g/day and hydroxyurea which can both cause higher than actual glucose readings. Vitamin C (ascorbic acid) in doses of >500mg/day can interfere with FreeStyle Libre® systems by causing higher readings than actual levels. Acetaminophen, alcohol, and hydroxyurea can interfere with Medtronic Guardian® devices. Mannitol and tetracycline can interfere with Senseonics Eversense® devices.

The American Diabetes Association recommends early initiation of CGMs in insulin-dependent patients, including those with type 1 diabetes, in their 2023 Standards of Care guidelines. The early initiation was shown to have benefits in patients of all ages in lowering both A1c and hypoglycemic events. The importance of continued access to the patient’s CGM device was also stated in order for patients to have consistent outcomes.

At this time, most of the studies and benefits of CGMs are seen in patients with type 1 diabetes or those with type 2 diabetes on insulin regimens. However, more studies are being performed for patients with type 2 diabetes on non-insulin regimens, and it is assumed that CGMs will also provide benefit for these patients.

The technology that is used for continuous glucose monitoring will continue to evolve. There is technology developing using contact lenses that monitor blood glucose. As devices continue to improve, patients’ glucose levels will be measured more accurately. This will allow healthcare providers to treat patients with diabetes more effectively.

References:
Potential Overuse of Semaglutide and its Speculated Impact on Diabetes Treatment

By Eboni Thomas, Pharm.D. Candidate, Class of 2025

Diabetes is one of the most prevalent disease states throughout North America. New treatments for diabetes are constantly being developed, but use of some medications originally intended for diabetes has recently changed. Semaglutide is a part of a group of antidiabetic drugs known as GLP-1 agonists. Their mechanism of action involves lowering glucose through the stimulation of GLP-1 receptors. The spike in usage of semaglutide can be accredited to several factors such as new indications and increased adherence due to effectiveness of the medication.

Semaglutide has seen an increase in usage in both the United States and Canada in recent years. Money spent on semaglutide went from 13.5 million in 2019 to 227 million in 2021. According to Canada’s National Diabetes Surveillance system, the age-standardized prevalence rate of diabetes increased by 3.3% per year. From this information, we can assume that patients with diabetes account for some of the increased uptake, but are not solely responsible. The overuse of semaglutide might be accredited to patients without diabetes using the medication for weight loss and weight management.

As a GLP-1 analogue, semaglutide promotes weight loss by slowing gastric emptying and decreasing hunger. As a result, it was FDA approved for the treatment of adult obesity in June 2021. The medication’s indication for weight management is new and could explain why the drug supply has been dwindling recently. Essentially, the recent shortage of semaglutide and other GLP-1 agonists are due to the demand of two prevalent disease populations: diabetes and obesity.

A potential consequence to a supply shortage of any GLP-1 agonist would be that patients with diabetes are not able to receive one of the most effective treatments. Studies show that lack of convenience and cost of treatment are some of the most common reasons for nonadherence to medications for diabetes. A supply shortage of semaglutide and other GLP-1 agonists may contribute to nonadherence and thus uncontrolled diabetes as result of lack of access.
Overall, there is a steady increase in drug expenditures of semaglutide and other GLP-1 agonists. These medications have newly approved indications that cause it to be in high demand, leaving both patients with diabetes and obesity without proper supply.

This class of diabetic medication is not being replenished quickly enough and within the next few years there may be an observable impact on diabetes management and treatment.

References:

Using Finerenone to Decrease Cardiovascular Events in Diabetic Patients with CKD

By Caitlin Quibeuf, Pharm.D. Candidate, Class of 2024

Kidney disease is an important sequelae for healthcare professionals to be aware of in patients with type 2 diabetes. One in 3 adults with diabetes, both type 1 and type 2, may already have chronic kidney disease. To put it into perspective, 37 million Americans currently are diagnosed with type 2 diabetes. Therefore, about 12 million of these patients may already have chronic kidney disease.

This important disease state associated with diabetes is caused by high blood sugar levels which leads to damage of the vessels in the kidneys. This causes damage to the nephrons which do the work of filtering out the blood, removing waste, and creating urine. Kidney damage can lead to other complications including gout, anemia, secondary hyperparathyroidism, bone disease, fluid buildup, and heart disease.
Kidney disease in patients with diabetes, specifically type 2 diabetes, can exacerbate the cardiovascular risk associated with diabetes. In a trial called FIGARO-DKD, they dove further into this issue, studying the effect of finerenone, a selective nonsteroidal mineralocorticoid receptor antagonist, on cardiovascular events in patients with chronic kidney disease (CKD) and type 2 diabetes. This study was a phase 3, multicenter double-blind trial that included patients with type 2 diabetes with stage 2–4 CKD, moderately elevated albuminuria defined as urinary albumin-to-creatinine ratio of 30 – <300, and an eGFR of 24–90 mL/min/1.73 m. Type 2 diabetic patients with stage 1–2 CKD, severely elevated albuminuria defined as urinary albumin-to-creatinine ratio of 300–5000, and an eGFR of at least 60 mL/min/1.73 m were also included. These patients were also required to be 18 years or older and have a serum potassium level of 4.8 mmol/L or less at the beginning of the trial. Excluded from this trial were patients with symptomatic chronic heart failure with reduced ejection fraction.

They randomized 7437 patients into finerenone or placebo group. The primary outcome studied was a time-to-event analysis of a composite of death from cardiovascular causes, nonfatal myocardial infarctions, nonfatal strokes, or hospitalizations for heart failure. There were many secondary outcomes, all assessed in a time-to-event analysis. The first set of secondary outcomes was first occurrences of kidney failure (considered as a sustained eGFR of less than 15 mL/min/1.73 m), sustained decrease from baseline eGFR of at least 40% for at least 4 weeks, and end-stage kidney disease (defined as initiation of chronic dialysis or kidney transplantation). The second set of secondary outcomes was hospitalization for any cause, death from any cause, change in the urinary albumin-to-creatinine ratio from baseline to month 4, and kidney outcomes (kidney failure, sustained decrease of eGFR from baseline for at least 4 weeks, and death from renal causes).

The median follow up time was 3.4 years. Figure A, taken from the study, shows both the primary and secondary outcomes. The researchers found that the primary outcomes (incidence of death from cardiovascular causes, nonfatal myocardial infarction or nonfatal stroke) were significantly lower in the finerenone group than the placebo group (hazard ratio, 0.87; 95% CI, 0.76 to 0.98; P=0.03). The primary composite outcome of incidence of hospitalization for heart failure was also lower in the finerenone group than in the placebo group (hazard ratio, 0.71; 95% CI, 0.56 to 0.90). They found that the number of patients needed to be treated with finerenone to prevent one primary outcome event was 47. These results were found to be consistent across the patient groups. A secondary outcome that was found to be better in the finerenone group was a reduction of urinary albumin-to-creatinine ratio from baseline. The reduction with finerenone was 32% greater than placebo. Secondary outcomes found no difference between the finerenone group and placebo group were incidence of kidney failure, death from renal causes, and death from any cause. Hyperkalemia was the only adverse effect documented more frequently in the finerenone group. However, no cases resulted in death and few with permanent discontinuation of the regimen. Finerenone was also found to have a modest effect on blood pressure.
In conclusion, the results from the FIGARO-DKD trial showed that finerenone was helpful in reducing cardiovascular events, particularly hospitalizations due to heart failure, in patients with type 2 diabetes and stage 2–4 CKD with moderately elevated albuminuria or stage 1–2 CKD with severely elevated albuminuria. The researchers did disclose that while they had a large population of patients with CKD, the majority of the patients were Caucasian. Therefore, the results of this study may not be able to be generalized to all populations. Future studies testing the efficacy of finerenone in patients of more diverse backgrounds would be necessary due to the prevalence of diabetes and CKD in minority populations.

### Table: Finerenone versus Placebo Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>FInerenone (N=3666)</th>
<th>Placebo (N=3666)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome</td>
<td>458 (12.4)</td>
<td>519 (14.2)</td>
<td>0.87 (0.76–0.98)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>194 (5.3)</td>
<td>214 (5.8)</td>
<td>0.90 (0.74–1.09)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>103 (2.8)</td>
<td>102 (2.8)</td>
<td>0.99 (0.76–1.31)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>108 (2.9)</td>
<td>111 (3.0)</td>
<td>0.97 (0.74–1.26)</td>
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<tr>
<td>Hospitalization for heart failure</td>
<td>117 (3.2)</td>
<td>163 (4.4)</td>
<td>0.71 (0.56–0.90)</td>
</tr>
<tr>
<td>Kidney composite outcome with ≥40% decrease in eGFR from baseline</td>
<td>350 (9.5)</td>
<td>395 (10.8)</td>
<td>0.87 (0.76–1.01)</td>
</tr>
<tr>
<td>Kidney failure</td>
<td>46 (1.2)</td>
<td>62 (1.7)</td>
<td>0.72 (0.49–1.05)</td>
</tr>
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<td>End-stage kidney disease</td>
<td>32 (0.9)</td>
<td>49 (1.3)</td>
<td>0.64 (0.41–0.995)</td>
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<td>Sustained decrease in eGFR of &lt;15 ml/min/1.73 m² from baseline</td>
<td>28 (0.8)</td>
<td>38 (1.0)</td>
<td>0.71 (0.43–1.16)</td>
</tr>
<tr>
<td>Sustained ≥40% decrease in eGFR from baseline</td>
<td>338 (9.2)</td>
<td>385 (10.5)</td>
<td>0.87 (0.75–1.00)</td>
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<tr>
<td>Death from renal causes</td>
<td>0 (0.0)</td>
<td>2 (0.0)</td>
<td></td>
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<tr>
<td>Hospitalization for any cause</td>
<td>1573 (42.7)</td>
<td>1605 (43.8)</td>
<td>0.97 (0.90–1.04)</td>
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<tr>
<td>Death from any cause</td>
<td>333 (9.0)</td>
<td>370 (10.1)</td>
<td>0.89 (0.77–1.04)</td>
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<tr>
<td>Kidney composite outcome with ≥57% decrease in eGFR from baseline</td>
<td>108 (2.9)</td>
<td>139 (3.8)</td>
<td>0.77 (0.60–0.99)</td>
</tr>
<tr>
<td>Sustained ≥57% decrease in eGFR from baseline</td>
<td>90 (2.4)</td>
<td>116 (3.2)</td>
<td>0.76 (0.58–1.00)</td>
</tr>
</tbody>
</table>

Figure A: Finerenone versus Placebo Outcomes

References: