

- Shannon Dunlay: 00:04 Welcome and thank you for joining this podcast on cardiovascular disease and diabetes for healthcare professionals. The goal of this ongoing series is to reduce cardiovascular death and incidence of heart attacks and strokes in people with diabetes, and it's based on the new collaborative initiative between the American Heart Association and the American Diabetes Association, Know Diabetes by Heart. This series is brought to you by founding sponsors, Boehringer Ingelheim, and Eli Lilly and Company, Diabetes Alliance, and Novo Nordisk, and national sponsors, Sanofi and Astra Zeneca. I'm doctor Shannon Dunlay from the Mayo Clinic and I'll be discussing diabetes and heart failure.
- Shannon Dunlay: 00:51 Today we're going to be discussing several questions that are important to consider when managing patients with diabetes who are at risk for heart failure or those that have heart failure. The first question that a clinician may ask is how common is heart failure in patients with type 2 diabetes? Well, what we know is that both heart failure and type 2 diabetes are extremely common in the United States. More than 29 million Americans have type 2 diabetes. About six and a half million have heart failure and both of them have increased over time and are expected to continue to increase. Although diabetes is associated with an increased risk for myocardial infarction and stroke, heart failure is often underappreciated as a complication of diabetes. Patients with diabetes are at approximately double the risk of developing heart failure compared to those without diabetes. This has been confirmed in several different epidemiologic studies including the Framingham heart study, the cardiovascular health study, Mesa, and the National Health and Nutrition Examination survey.
- Shannon Dunlay: 01:44 Some of the studies have even suggested that patients who are women with diabetes are at even higher risk for developing heart failure. And overall if you look at all patients with diabetes, about 10 to 20% of them have heart failure. And what we know is that patients with diabetes can develop both types of heart failure, including heart failure with reduced ejection fraction and heart failure with preserved ejection fraction. So when we think about which patients with diabetes are at highest risk for developing heart failure, there are several risk factors to consider. First patients who have poor glycemic control are at increased risk for developing heart failure. We know that as hemoglobin A1C increases, so does the risk of developing incident heart failure. In addition, patients that are older and those who have complications of diabetes like nephropathy and retinopathy, also at higher risk for developing heart failure.

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- Shannon Dunlay: 02:30 Finally, patients who have risk factors for heart failure like coronary artery disease, peripheral arterial disease, obesity, and hypertension are also at higher risk for developing heart failure. What we do know is that if we look at patients with heart failure, those with diabetes have worse outcomes than those without. And we know that patients with diabetes who have heart failure are at higher risk for death and higher risk for hospitalization compared to patients with heart failure without diabetes. So once patients have developed both conditions then they're at increased risk for worse outcomes.
- Shannon Dunlay: 02:59 The next question a clinician may ask is how does diabetes contribute to the development of heart failure? Well, there are a couple of different ways. First diabetes often causes structural heart disease and heart failure through the development of myocardial ischemia and infarction. Patients with diabetes often have risk factors for coronary artery disease such as hypertension and hyperlipidemia, but also hyperglycemia accelerates atherosclerosis via inflammation and other mechanisms.
- Shannon Dunlay: 03:27 Diabetes can also cause cardiac dysfunction and heart failure without coronary artery disease and this is term to diabetic cardiomyopathy. There are many abnormalities in glucose regulation of metabolism and diabetes that can contribute to the development of diabetic cardiomyopathy. This is a complicated topic but a few things to consider is that hyperglycemia itself can cause alterations in metabolism and glucose regulation including formation of advanced glycation end products, activation of local Renin-angiotensin system, abnormal calcium handling that can result in increased fibrosis and impaired myocardial relaxation and diastolic dysfunction. In addition, the diabetic heart can have increased reliance on free fatty acids for energy, which can result in lipids accumulating in heart cells and eventually can cause cell death. All of these mechanisms together can contribute to the development of diabetic cardiomyopathy. Another question a clinician may ask is what impact, if any, do glycemic medications have on the risk of heart failure and heart failure outcomes?
- Shannon Dunlay: 04:26 Well, we're learning a lot more about this over the last several years, but yes, glycemic medication choice can impact risk of developing heart failure, can also impact heart failure outcomes. For older glycemic medications such as metformin, sulfonylureas, and insulin we have some information about risk of heart failure that's provided mostly by observational studies. We have a lot more information on newer medications, and this is in part because the FDA mandated that trials be conducted to

evaluate cardiovascular safety in some of these newer glyemic medications. And while most of them focused on looking at impact of glyemic medications on major adverse cardiovascular events, many included risk of heart failure as a secondary end point.

Shannon Dunlay: 05:05 So, let's talk a little bit about each of the common glyemic medication classes that we might use in patients with diabetes and what we know about how that may impact the risk of developing heart failure or heart failure outcomes.

Shannon Dunlay: 05:16 One of the medications that's commonly use in patients with diabetes is metformin and based on the available data, it is reasonable to use metformin in patients with diabetes at risk for heart failure or in those with established heart failure. Metformin was previously contraindicated in patients with heart failure due to a risk of lactic acidosis, but based on data from multiple observational studies which suggested survival benefit and some that suggested lower risk of heart failure hospitalization in patients treated with metformin compared with sulfonylurea is the FDA has since removed heart failure as a contraindication to metformin use in 2006. Certainly, in patients who are presenting with shock, including cardiogenic shock or are at risk for lactic acidosis, metformin should be held or discontinued.

Shannon Dunlay: 05:56 There is some limited data on sulfonylureas and how they may impact risk of development of heart failure in patients with diabetes. The available data has some conflicting findings, but several observational studies have suggested that sulfonylurea therapy may be associated with increased risk of heart failure compared with metformin and other agents. And because of this there are probably better choices if you're worried about heart failure risk including medications such as metformin and SGLT2 inhibitors compared with sulfonylureas. But there is an ongoing trial, the CAROLINA trial, that includes patients that have been randomized to either linagliptin, a DPP-4 inhibitor, or glimepiride, a sulfonylurea. And the results of that will be informative.

Shannon Dunlay: 06:40 Next, let's talk about thiazolidinediones. Thiazolidinediones are not recommended in patients with established heart failure and may also increase the risk of heart failure in patients with diabetes. This data is based on findings from randomized controlled trials including the PROactive trial and the RECORD trial, as well as meta-analyses of trials that have shown an increased risk of heart failure events with rosiglitazone and pioglitazone in patients with diabetes.

- Shannon Dunlay: 07:05 In addition, thiazolidinediones have been associated with fluid retention and heart failure in patients with heart failure with reduced ejection fraction. And for that reason, TZDs should really be avoided in patients who have diabetes who are at high risk for heart failure and certainly in those who have a history of heart failure.
- Shannon Dunlay: 07:23 Insulin as another medication that's often used in patients with diabetes and it's often required to achieve adequate glycemic control. The data on insulin and risk of heart failure are pretty limited. And the only randomized controlled trial assessing cardiovascular safety of insulin was the ORIGIN trial and this randomized patients with prediabetes or diabetes to insulin glargine or standard care and they found no difference in outcomes including risk of heart failure hospitalization and the two groups. Some observational studies have suggested that perhaps insulin is associated with increase in heart failure risk, but the problem is that patients who are requiring insulin are often sicker and have more comorbid conditions, and even though they adjust for these things, those data are at high risk for residual confounding. For this reason, insulin is a medicine that may be required to manage patients with diabetes to achieve adequate glycemic control and can be used in patients at high risk for heart failure or those with established heart failure but just requires close monitoring.
- Shannon Dunlay: 08:20 So now that we've talked about some of the older medications, let's focus more on the newer medications where we have more information available about risk of heart failure from the cardiovascular outcomes trials. So we're going to be talking about first GLP-1 receptor agonists and then the DPP-4 inhibitors. And finally the SGLT-2 inhibitors.
- Shannon Dunlay: 08:36 The GLP-1 receptor agonists that are available include albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide. In the cardiovascular outcome trials, the tested GLP-1 receptor agonists had mostly beneficial effects on cardiovascular outcomes, but no effect on risk of heart failure hospitalization. These included data from the ORIGIN trial, LEADER, SUSTAIN 6, and EXSCEL.
- Shannon Dunlay: 09:03 There was no difference in risk of heart failure hospitalization across all of the trials. Based on these data, we know that GLP-1 receptor agonists may reduce the risk of major adverse cardiovascular events and mortality in diabetes, but don't have impact on risk of heart failure hospitalization. There was hope based on some animal and human studies that GLP-1 receptor agonists may be beneficial in patients with established heart

failure, but smaller studies have found no benefit. The FIGHT trial in patients with heart failure with reduced ejection fraction randomized patients to liraglutide and unfortunately there was a tendency toward higher risk of heart failure readmission in those patients. And there was another trial of liraglutide from Denmark and there were no effects on ejection fraction after about six months and more serious adverse cardiac events in patients treated with liraglutide. So based on these data GLP-1 receptor agonists should be used cautiously in patients with heart failure with reduced ejection fraction and recent heart failure hospitalization.

Shannon Dunlay: 09:57 Next, we'll talk about DPP-4 inhibitors including alogliptin, linagliptin, saxagliptin, and sitagliptin. Overall in the cardiovascular outcome trials, there was no evidence that DPP-4 inhibitors provide cardiovascular benefit. In patients with diabetes at high cardiovascular risk some DPP-4 inhibitors may increase the risk of heart failure hospitalization, and because of this there are perhaps better choices for patients at high cardiovascular risk than DPP-4 inhibitors. The three trials that tested DPP-4 inhibitors included the SAVOR-TIMI 53 trial, the EXAMINE trial, and the TECOS trial. The only trial that had an increased risk of heart failure hospitalization was the SAVOR-TIMI 53.

Shannon Dunlay: 10:37 Finally, let's talk a little bit about SGLT-2 inhibitors. This includes canagliflozin, dapagliflozin, empagliflozin. SGLT-2 inhibitors are the first class of glucose lowering medications that have been demonstrated to reduce risk of heart failure hospitalization in patients with diabetes and so there's been a lot of excitement around their potential use in this space.

Shannon Dunlay: 10:58 All three cardiovascular outcome trials that have been published demonstrated lower risk of heart failure hospitalization with SGLT-2 inhibitors. There was a 35% decrease in the risk of heart failure hospitalization and the EMPA-REG trial. A 33% decrease in risk of heart failure hospitalization and the CANVAS Program. And most recently published a 27% decreased risk of heart failure hospitalization in the DECLARE-TIMI 58 trial. There's also international registry data that has shown consistent findings. All of these trials included patients who had or were at high risk for cardiovascular disease but only a small fraction, about 10 to 14% across the three trials had a history of heart failure at enrollment. There have been some secondary data analysis published that suggest that their beneficial effects are present in both patients with and without a history of heart failure. The mechanisms by which SGLT-2 inhibitors may reduce heart

failure risk are still under investigation and not entirely clear, but there are some hypothesized reasons.

Shannon Dunlay: 11:56 First, they are known to have a diuretic effect and possibly reduce plasma volume, and that could contribute to the benefits in reducing heart failure hospitalization. But animal studies have suggested that there may be more pleiotropic effects beyond just the diuretic effect as they have shown some reductions in oxidative stress, improvement in endothelial function and anti-inflammatory effects. Because of these interesting findings, there has been growing interest in using SGLT-2 inhibitors as a treatment for heart failure even in patients without diabetes and there are several ongoing trials including EMPEROR-PRESERVED and REDUCED, DAPA-HF trial and at one of the DELIVER trials that include patients with and without diabetes to specifically test whether SGLT-2 inhibitors may be used as a treatment for heart failure itself. Based on this current knowledge, SGLT-2 inhibitors are good choice for patients with diabetes at high risk for heart failure and those with diabetes and a history of heart failure. We do need to await trial data to determine if they are beneficial in patients with heart failure but not diabetes.

Shannon Dunlay: 12:56 A related question at clinicians who care for patients with heart failure may ask is do the medications we use for treating heart failure have an impact on development of diabetes and diabetes control? Well, yes they can. We've known him for quite some time that angiotensin converting enzyme inhibitors and angiotensin receptor blockers may reduce the risk of developing heart failure in patients with heart failure with reduced ejection fraction. This was based on data from the SOLVE trial and the CHARM trial. We also have newer data about ascubitril/valsartan and angiotensin receptor neprilysin inhibitor from the PARADIGM trial suggests that it may result in greater reductions in hemoglobin A1C compared with ACE inhibitors. And so, ACE inhibitors, ARBs, and ARNIs do appear to have some beneficial effects on glycemic control and development of diabetes.

Shannon Dunlay: 13:41 Mineralocorticoid receptor antagonists like spironolactone and eplerenone have been shown in patients without heart failure to negatively impact some glycemic measures. There are some limited data in patients with heart failure to suggest that spironolactone but not eplerenone may increase hemoglobin A1C in patients with heart failure with reduced ejection fraction. This should not lead clinicians to shy away from prescribing these medications, but it may be a good idea to keep an eye on

glycemic control after initiation in your patients with heart failure with reduced ejection fraction.

Shannon Dunlay: 14:11 And finally, beta blockers. We do have some information about how they impact glycemic control. There are some limited data to suggest that those with alpha blocking properties like carvedilol may have more favorable effects on glycemic parameters and patients with heart failure with reduced ejection fraction. Carvedilol has been shown to decrease insulin levels, reduce hemoglobin A1C, and reduce incidents of diabetes in patients with heart failure with reduced ejection fraction. Certainly, patients should be treated with a beta blocker where indicated and carvedilol may be a good choice if you're concerned about glycemic control.

Shannon Dunlay: 14:47 So in summary, the key take home point is that when you're managing patients with diabetes who are at risk for heart failure or have heart failure, it's important to remember that management of one condition can impact outcomes of the other. This is particularly true when you're thinking about which medications you're using to manage the patient's diabetes or the patient's heart failure. And it's important to consider what potential downstream effects this could have on the patient's health.

Shannon Dunlay: 15:18 Thank you very much for listening and stay tuned for upcoming podcasts.