Thank you for joining us for this activity entitled, “Cardiovascular Risk Reduction in Type 2 Diabetes: Applying Trial Data into Cardiology Practice.” This activity is jointly provided by USF Health and Rockpointe and is supported by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Lilly USA, and Novo Nordisk. We now turn the program over to the presenting faculty.

**Michael E. Nassif, MD:** My name is Michael Nassif. I'm an Assistant Professor of Medicine at Saint Luke’s Mid America Heart Institute in the inner city of Missouri, Kansas City. I am joined by Dr. Prakash Deedwania, who is a Professor of Medicine at UCSF School of Medicine in San Francisco. As members of the steering committee, Dr. Deedwania and myself developed the content for this program.

We have pertinent disclosures for the faculty as well as the non-faculty contributors.

Our educational objectives today are to recognize the burden and intersection of cardiovascular disease in Type 2 diabetes, as well as to assess the benefits observed in recent cardiovascular outcome trials and as they specifically address the reductions in cardiovascular disease amongst patients with Type 2 diabetes.

**Take Home Points**
We are going to point out that really since 2015, there’s been a fundamental paradigm shift in Type 2 diabetes management. We now have two classes of medications, specifically SGLT-2 inhibitors, as well as long-acting, GLP-1 receptor agonist, which improve cardiovascular outcomes, which has now been seen both in multiple randomized, controlled trials as well as real-world data. This has led us to shift our focus from a former hemoglobin A1C and glucose lowering centric point of view to where we are actually able to and we should focus on comprehensive cardiovascular risk reduction. Cardiologists should be at the forefront of this movement. After all, why would cardiologists not be interested in prescribing medications which reduce cardiovascular death?

Slide 6 - OASIS Study: Total Mortality
Some background really for almost 20 years, we have realized that diabetes is a cardiovascular disease risk equivalent. This came from the OASIS study, which demonstrated that patients with diabetes and no cardiovascular disease essentially have the same risk as patients with no diabetes and cardiovascular disease.

Slide 7 – Causes of Death in T2DM
And it’s long been known that patients with Type 2 diabetes predominantly suffer from and die from ischemic heart disease.

Slide 8 - How to Reduce the Burden of CVD in T2DM
Thus, it made some sense that if we were going to attempt to reduce the burden of atherosclerotic cardiovascular disease in Type 2 diabetes that we would start with a strategy of glucose lowering.

Slide 9 - Effects of More vs Less Intensive Glycemic Control
However, even though this seemed like the most logical first step, this has now been attempted at least four separate large, randomized, controlled clinical trials. As you can see in this meta-analysis, the mortality is on the wrong side of neutral as well as the cardiovascular mortality is on the wrong side of neutral.

**Slide 10 – Four Major Trials of Intensive Glucose Control**

In spite of randomizing many thousands of patients with many years of follow-up, all we were able to say with intensive glucose lowering is that patients died, but they died with a lovely surrogate biomarker endpoints.

**Slide 11 - How to Reduce the Burden of CVD in T2DM**

The next large-scale effort was aggressive blood pressure control in an attempt to reduce cardiovascular death and outcomes amongst the patients with Type 2 diabetes.

**Slide 12 - ACCORD Randomized ~5,000 Patient**

The largest study was ACCORD, which did have an arm which was aggressive intensive blood pressure lowering. As you can see here, the primary outcome was completely neutral. The only benefit was a mild benefit in stroke prevention with intensive blood pressure lowering.

**Slide 13 – ADA Treatment Recommendations for T2DM and Confirmed Hypertension**

The American Diabetes Association has recommended a target blood pressure of less than 140/90 in most patients with Type 2 diabetes with certain caveats as to which agents to start with as shown here.

**Slide 14 - How to Reduce the Burden of CVD in T2DM**

Thus far, focusing on glucose lowering, as well as aggressive blood pressure control has not been successful for primary prevention.
Slide 15 - Diabetes – Aspirin Guidelines
There’s also been significant effort in antiplatelet therapy in Type 2 diabetes both as a primary and a secondary prevention. Aspirin as primary prevention has been a very hot topic of late. The most recent guidelines, the AHA/ADA, do recommend the primary prevention strategy in patients with established diabetes, but it has a level of evidence Grade C and the Europeans do not recommend aspirin for primary prevention in patients with Type 2 diabetes.

Slide 16 – Aspirin for Primary Prevention of Cardiovascular Events in People with Diabetes
There are numerous well done meta-analysis, which do show some benefit in men, but there does appear to be an important effect of sex with women having less of a benefit if then there is a significant bleeding risk to aspirin for primary prevention, which likely balances out the benefit.

Slide 17 - CAPRIE
Looking at stronger antiplatelets, such as clopidogrel, the CAPRIE study included patients that were post MI or stroke that had diabetes and it showed that there was an increased effect of clopidogrel over aspirin in patients that were higher risk, such that the benefit was amplified in patients with diabetes. It was even further amplified in patients with diabetes treated with insulin.

Slide 18 – CURE: Clopidogrel in Addition to Aspirin in Patients with ACS and Diabetes
Similarly, the CURE study had a similar population to CAPRIE, but they were post acute coronary syndrome. Again, the benefits associated with clopidogrel were, consistent and again were amplified in those patients with Type 2 diabetes.
Slide 19 - ASCEND
Perhaps the best data we now have on primary prevention with antiplatelets was from the ASCEND trial. ASCEND essentially showed that while there was a reduction in cardiovascular events, this was counterbalanced by an increase in major bleeding with aspirin and the results were that aspirin, primary prevention was largely neutral in patients with Type 2 diabetes.

Slide 20 - THEMIS Study Design
The trial we are waiting for – and we have seen topline results – is the THEMIS study. THEMIS will add a lot as the largest ever randomized trial conducted in primary prevention. This trial included over 19,000 patients with Type 2 diabetes, who have coronary disease, but have not had a history of MI or stroke. This is a primary prevention population. The topline results have said that the trial was positive for its primary endpoint, but we have not seen all the details in the publication, which we’ll anticipate later in 2019.

Slide 21 - How to Reduce the Burden of CVD in T2DM
There’s been a success of antiplatelets for secondary prevention. The one place we have had some success in reducing cardiovascular risk in patients with Type 2 diabetes is in lipid lowering therapy.

Slide 22 – Efficacy of Lipid-lowering Drugs for Diabetics
This is an analysis of multiple randomized controlled trials, which essentially shows that lipid lowering therapies lowered coronary events. Of note, the patients did remain with a very high event rate even though they are on lipids. Also of note that the benefit is
greater LDL lowering in Type 2 diabetics than with the general population, but there is a much larger effect in secondary prevention than there is in primary prevention.

Slide 23 - Statin Guidelines for T2DM
The most recent statin guidelines have advocated for high potency statin in patients over the age of 40 with type 2 diabetes. An important subject but for another talk is also, use of PCSK9 inhibitors on top of statins as lipid lowering therapies.

Slide 24 - How to Reduce the Burden of CVD in T2DM
Thus far, four separate strategies to reduce the burden of cardiovascular disease in patients with Type 2 diabetes have been largely unsuccessful in primary prevention with some mild successes in lipid lowering therapy. What we have seen a paradigm shift over the past three to four years is in looking at comprehensive cardiovascular risk. For the first time ever, we’ve seen the benefit of glucose lowering therapies on this comprehensive cardiovascular risk.

Slide 25 - Progress Made Treating Ischemic Heart Disease
Thus far, we’ve focused on ischemic heart disease, but it is important to note that even independent of ischemic heart disease, cardiovascular disease, such as heart failure still makes up significant morbidity and mortality of patients with Type 2 diabetes.

Slide 26 – Impact of Heart Failure in the US
Heart failure in particular is a significant economic burden, which is increasing at a near exponential rate as our population ages.

Slide 27 – ALTITUDE
In a secondary analysis of altitude, heart failure is actually the number one cause of hospitalization in patients with Type 2 diabetes and renal insufficiency.
Likewise, heart failure was the most common cause of death. Heart failure is contributing the most to both morbidity and mortality in modern cardiovascular outcome studies.

It's been known for a long time that diabetes and congestive heart failure have complex intersection with the rates and prevalence of heart failure increasing dramatically as hemoglobin A1C increases.

In an analysis of the PARADIGM-HF trial, which is the largest ever randomized trial of heart failure patients to date, it was noted that in total 74% of patients had either undiagnosed diabetes, diagnosed Type 2 diabetes, or prediabetes. Nearly, 3/4 of patients in contemporary heart failure trials have some degree of dysglycemia.

While it’s known that diabetes is a risk factor for heart failure, there’s also evidence that the relationship is more complex, and that heart failure is also a risk factor for Type 2 diabetes. Looking at cohort studies of congestive heart failure patients, you can predict their future incident of diabetes based on the amount of loop diuretics they take with patients on the highest dose loop diuretics having the highest likelihood of developing diabetes.
This is Medicare data, but particularly in patients with elderly over the age of 65 or on Medicare, patients who have diabetes and then develop incident heart failure have very poor outcomes with near 75% mortality over the next five years.

**Slide 33 - HFrEF or HFpEF**

Heart failure has two flavors. There is what we now call heart failure with preserved ejection fraction, which is most notable by a small left ventricle that is concentrically hypertrophied, which looks very different than our typical heart failure with reduced ejection fraction, which has a dilated left ventricle can have some eccentric LV remodeling.

**Slide 34 – HFpEF: Prevalence Is Increasing**

Heart failure with preserved ejection fraction is increasing in incidence dramatically where it's now the most common form of congestive heart failure, and this increase is likely to continue, again, as our population ages.

**Slide 35 - Metabolic Traits Are Strong Predictors of HFpEF**

Meanwhile, Type 2 diabetes and dysglycemia is associated with both forms of heart failure. It is a much stronger relationship with heart failure with preserved ejection fraction than it does with heart failure with reduced ejection fraction. The predominate evidence of this is from Sanjiv Shah and is looking at insulin resistance. While insulin resistance predicted the incident HFpEF strongly, it had no association with predicting future heart failure with reduced ejection fraction. Likewise, fasting glucose was highly statistically significantly associated with incident HFpEF, but not HFrEF. Waist to hip ratio predicted both forms of heart failure, and BMI also predicted both forms of heart
failure, but had a much stronger and statistically significantly associated relationship with HFpEF than with HFrEF.

**Slide 36 - Evidence-based Approach to Diagnosing HFpEF**

Recently, there has been an evidence-based approach to predicting who has HFpEF when seen in clinic. This HFpEF 2 score from Dr. Reddy and Dr. Borlaug at the Mayo clinic is very helpful and it also gives numerous weight to patients that are overweight, which is very common with our Type 2 diabetes population, also those with hypertension, AFib pulmonary hypertension, elderly, and those with elevated filling pressures on echo. But you can see here in this scoring system how obese patients with Type 2 diabetes are very likely to have HFpEF when they have certain clinical features.

**Slide 37 - HFpEF in 2018**

There is strong evidence, predominantly from Dalane Kitzman’s group, that obesity and visceral adiposity not only is associated with, but is a predominant driver of HFpEF in the heart’s responses to metabolic syndrome.

**Slide 38 - HFpEF: No Treatments?**

Thus far for HFpEF, we’ve had no successful treatments whom we have tried classical drugs for heart failure with reduced ejection fraction. This is surmising angiotensin receptor blockers in CHARM were very effective in HFrEF, but had no benefit in HFpEF. Likewise, ACE inhibitors had a strong benefit in HFrEF but none in HFpEF. Betablockers, which have a strong mortality and morbidity benefit in HFrEF also have no benefit in HFpEF.

**Slide 39 - Caloric Restriction and 7-kg Weight Loss Improve HFpEF**
There has been one non-pharmalogical intervention that's been shown to improve outcomes in patients with heart failure with preserved ejection fraction and that is caloric restriction. This is again, data by Dalane Kitzman. He showed that caloric restriction associated with a seven kilogram weight loss improved both MRI and echo measures of diastolic function. It improved patients cardiopulmonary exercise testing and VO2 max, and also improved heart failure specific quality of life by KCCQ.

**Slide 40 - HFP EF and DM**

There is an increasing body of literature that HFP EF is not only associated with, but there’s likely some causation with obesity, central adiposity, and a metabolic syndrome. Caloric restriction thus far has been the only convincing therapy for HFP EF. All traditional heart failure with reduced ejection fraction therapies have thus far failed in patients with HFP EF, but targeting obesity, insulin resistant in metabolic syndrome makes lots of sense. There’s some data we’ll go over later, which has shown significant promise. Hence, there are currently multiple randomized, controlled trials of SGLT-2 inhibitors in patients with HFP EF.

**Slide 41 - Summary**

Summarizing, cardiovascular disease and Type 2 diabetes are intricately linked. Heart failure is a leading cause of morbidity and mortality in patients with Type 2 diabetes. There is increasing evidence that HFP EF is actually a metabolic syndrome and it’s a systemic disorder, which manifests in diastolic function of the heart. Thus far, many diabetes therapies prior to 2015 had either neutral or worsened cardiovascular outcomes, as well as obesity. However, some newer therapies, which we’ll go over have shown significant promise, not only in weight loss metabolic syndrome, but
possibly improving heart failure outcomes. One of the large questions we hope to address is, “Where do cardiologists fit into this paradigm shift?”

Slide 42 - Cardiovascular Outcomes Trials

Prakash Deedwania, MD: This is Prakash Deedwania and thank you, Michael, for that nice discussion about the background for diabetes and cardiovascular disease. It is my task now to continue the discussion talking about the cardiovascular outcome trial.

Slide 43 - Large CV Outcomes Trials in Diabetes

Ever since the concern about rosiglitazone in patients with cardiovascular disease, the FDA has mandated that any new antidiabetic drug to be introduced in the market will require cardiovascular safety as demonstrated by a non-inferiority with the standard treatment in terms of cardiovascular outcome. That has led to a large number of cardiovascular outcome trials. Clearly, we can see that there are nearly a hundred thousand patients that have been studied in these various trials, particularly with these three classes of new agents: DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists, and I shall discuss with each of these categories in detail with you.

Slide 44 - Dipeptidyl Peptidase (DPP)-4 Inhibitors

First, the DPP-4 inhibitors, which are our oldest kid on the block, if you will, amongst these newer antidiabetic drugs. These are the drugs that are commonly used because they enhance glucose dependent insulin secretion and decrease glucose dependent excessive glucagon secretion. Amongst the DPP-4 inhibitors that are currently available, we have alogliptin, linagliptin, saxagliptin, and sitagliptin. In general, these drugs do reduce hemoglobin A1C, but not dramatically. The range is somewhere
between half to 0.8%. They are generally weight neutral. The big advantage is that in general, they have low hypoglycemia risk. However, this hypoglycemia risk can increase if these agents are used in conjunction with insulin or insulin secretagogues and depending on the A1C, consider reducing insulin or secretagogue dose when adding a DPP-4 inhibitors.

Slide 45 - DPP-4 Inhibitors: General Safety and Tolerability

All drugs have side-effects and DPP-4 inhibitors do as well, but these are mostly nonspecific. Some of the side-effects that have been observed are Upper Respiratory Infection with some of the agents, nasopharyngitis with some others, headache, and urinary tract infection, which has been demonstrated only with saxagliptin. There have been some label updates with FDA, particularly for risk of heart failure based on the data from the SAVOR trial with saxagliptin and alogliptin with EXAMINE trial. These agents can also precipitate or produce arthritis, which has been seen not frequently, but with all of the four DPP-4 inhibitors. If the patient has significant chronic kidney disease, then one must consider reducing the dose of these agents, except for linagliptin.

There are drug interactions that we should be aware of and this is particularly, as I mentioned, the risk of hypoglycemia can be increased when these agents are used in conjunction with insulin or sulfonylurea and other insulin secretagogues. Certainly, one should monitor patients who are receiving digoxin and sitagliptin, and there is no dose adjustment that’s needed where there could be interactions. Use of linagliptin with a strong CYP3A4 inducer, such as carbamazepine, rifampin, phenytoin, and St. John’s
Wort is not recommended due to decreased exposure with linagliptin. Also, reduce the dose of saxagliptin for patients that are taking a strong CYP3A4 or 5 inhibitors, such as ketoconazole.

**Slide 46 - The DPP-4 Inhibitor Studies**

This summarizes three of the major trials that have been published with DPP-4 inhibitors. One of the first one was the SAVOR-TIMI 53 trial for saxagliptin, then we have TECOS with sitagliptin on the bottom, and then we have the EXAMINE trial in the middle with alogliptin. You can see all of these because of excitement, these papers have been published in the New England Journal of Medicine.

**Slide 47 - Comparison of Primary Endpoint Rates**

This summarizes the actuarial curve for these three studies. You can see clearly on SAVOR-TIMI 53 with saxagliptin, with TECOS with sitagliptin, and EXAMINE with alogliptin, the curve of the control patients labelled as placebo, and the study in DPP-4 inhibitor in all three of these studies, they are almost superimposable suggesting that there is absolutely no effect of these agents in terms of cardiovascular outcome. These studies do suggest and they did meet the criteria by FDA of non-inferiority, but no particular advantage of these agents except, as I mentioned, in SAVOR-TIMI 56 and TIMI 53, slight increased risk of heart failure with saxagliptin.

**Slide 48 - SGLT-2 Inhibitors for Treatment of T2DM**

Let’s move on to the next two classes of newer antidiabetic drugs, which are very exciting. Perhaps the most exciting class of agents are the SGLT-2 inhibitors because they have shown great promise. SGLT-2 inhibitors’ benefits are shown in this slide. You can see that they have an insulin independent action. And that is because they
primarily work by blocking the reabsorption of filtered glucose in the proximal tubule, thereby leading to glycosuria, improved glycemic control, and with the glycosuria, there would also be diuresis. In addition to that, recent data show that they also lead to natriuresis. With the glycosuria, there is caloric loss that is then subsequently responsible for possible weight loss. There is lower risk of hypoglycemia because the reabsorption will not take place. SGLT-2 inhibitor will not work if the glucose in the tubule is at low levels. Compliment the action of antidiabetic agents with this class of drugs because they are insulin independent and as I said, they can be used even in patients who have extreme degree of insulin resistance. Thereby, they can also be considered regardless of the diabetes duration whereby the insulin resistance progressively increases. 

Because of the glucose spilling in the urine, there are significant side-effects that are related to the genitourinary system. They could be responsible for recurrent UTI and unless proper hygienic measures are used, there could be increased risk of genital microbial or fungal infection, both in men as well as in women, and because, as I’ve mentioned, there is also a lot of sodium, as well as diuresis with glycosuria, they usually decrease blood pressure and one needs to be cognizant of this fact because if your patient is on antihypertensive drugs, one needs to adjust the doses of these drugs accordingly. Initially, these drugs showed some worsening of renal function, particularly in the first three months or so, but as you will see later on, these drugs have been found to be nephroprotective. Because of diuresis, there is some increased hematocrit initially and a minor increase in LDL cholesterol has been also noted.

Slide 49 - SGLT-2 Inhibitors: Safety and Tolerability
This summarizes the safety and tolerability of SGLT-2 inhibitor. As we already discussed, the most commonly reported adverse events that are noticed in 5% or more of the people are female genital microbial infection with all of them, urinary tract infection that has been noticed with these three agents listed: cana, dapa, and empagliflozin, increased urination, which we should not be surprised because of the glycosuria, is listed on canagliflozin, but can be seen in any of them, and nasopharyngitis has been reported with dapagliflozin.

Obviously, if the patient has significant renal impairment, these drugs might not work as well and this list below shows you that canagliflozin should be not used if GFR is between 45, but less than 60. And certainly, if GFR is less than 45, do not use canagliflozin. Similarly, for dapagliflozin: do not use if GFR is less than 60, Empa: do not use if GFR is less than 45, and ertugliflozin: do not use if GFR less than 30. You can see in general, the theme is if there is significant CKD Stage 4 to 5, then these drugs might not work and there will be a significant increased risk of side-effects, so these drugs should not be considered.

There are some drug interactions that we should be aware of. Canagliflozin when used, one should be monitoring digoxin level, consider increasing to 300 mg dose if concomitant UGT inducers because as we talked earlier, rifampin, phenytoin, phenobarbital, and ritonavir in patients with a GFR greater than 60 may require additional glycemic control, and consider another agent if GFR is between 45, but less than 60. Empagliflozin, as we talked about, these diuretics may enhance potential for
volume depletion. Actually, this can be seen with any of the three, but it was noticed in the trial with the EMPA-REG OUTCOME, and that’s why it’s listed, particularly in the warning. Of course, all of us are aware about the risk of lower leg amputation, particularly the large toe amputation, and FDA has put it as a warning of increased leg/foot amputation. However, subsequent, the real-life data will not support it, but in the present time, it is still listed as a warning.

Slide 50 - The SGLT-2 Inhibitor Studies

This shows the two large studies that came out, the first one, the EMPA-REG OUTCOME trial, which was published in 2015, and of course, the CANVAS trial, which was published in 2017. Certainly, we have seen significant benefit of these drugs in patients with diabetes.

Slide 51 - EMPA-REG Trial: CV Death, MI and Stroke

This summarizes the EMPA-REG OUTCOME trial, which was the first one, as I said, and created a lot of excitement. It certainly surprised everybody with these results. You can see here that for the three-point MACE, there are substantial benefits. You can see here there was 14% reduction for a relative risk of 0.86. Cardiovascular death was reduced even more remarkably, primarily due to heart failure related death reduction, as we’ll discuss in a moment, and also, nonfatal MI was reduced, but the confluence interval overlap is the line of unity and nonfatal stroke was not reduced. There was slight increase, but that was also nonsignificant.

Slide 52 - EMPA-REG OUTCOMES

This shows the cardiovascular outcome. On the left panel, we have death from any cause and you can see that those will diverge from somewhere between trial to 18
months and then continue to diverge throughout the study period for a net reduction of 32%. On the right-hand side, we have the most remarkable results, which surprised all of us, and that’s the reduction in hospitalization for heart failure, and very interestingly is the curves separate right from the get-go, almost within one to three months and then continue to diverge. This suggests to us, like many other effects of these and other antidiabetic agents, this is most likely hemodynamic effect, which is responsible for such a dramatic early separation of this curve for hospitalization for heart failure.

**Slide 53 - CANVAS: MACE with Canagliflozin**

This summarizes the primary endpoints for CANVAS trial which was in three-point MACE: cardiovascular death, nonfatal myocardial infarction or nonfatal stroke. Again, you can see a significant reduction. It was P less than 0.0001 for non-inferiority, and P equal to 0.0158 for superiority. It met most of the criteria.

**Slide 54 - CANVAS and EMPA-REG Outcomes**

We have superimposed the results of CANVAS and EMPA-REG OUTCOME trial. You can see basically that these effects are nearly superimposable except some minor differences, but particularly pleased, not the effect on heart failure, hospitalization for heart failure. They are consistently very similar and this is very, very important point to note because we have previously noticed this kind of effect only in another class of agent, such as beta blocker, a consistent effect across the board. Also, you can see that in front of CV death and hospitalization for heart failure, very similar results, and although I have not yet discussed, but we can see here the beneficial effects of these agent on renal endpoint as well, progression to macroalbuminuria, as well as renal
composite outcome, which consisted of renal replacement therapy, doubling of serum
creatinine or transplantation.

Slide 55 - Renal Benefits of SGLT-2 Inhibitors

This shows the major effects of these agents, both the EMPA-REG OUTCOME trial, as
well as the CANVAS canagliflozin. On the left-hand side, you can see the GFR over
time and this is adjusted mean GFR. And as one would expect, in the placebo are
there, shown in white, you see a progressive decline over time in the GFR as we
expect it in elderly people and particularly in the presence of diabetes, whereas in
patients who are on empagliflozin in both doses, 10 or 25 milligrams, you can see there
are actually a slight drop initially, which is stabilized so that over this long period of 192
weeks, there is no further decline, which is a dramatic effect. Also, as I mentioned, the
doubling of serum creatinine, renal replacement therapy or renal death, you can see
here both empagliflozin on the top and canagliflozin on the bottom show substantial
benefit in favor of SGLT-2 inhibitor.

Slide 56 - DECLARE-TIMI 58 Study Design

The newest study in this class of agent is shown here. This is the DECLARE-TIMI 58
study, the largest study in this category of almost 17,160 patients. In this particular
study, dapagliflozin, another SGLT-2 inhibitor was used in 10 milligram/once a day,
plus the standard of care or matching placebo plus the standard of care. This primary
endpoint was again three-point MACE timed to occurrence of cardiovascular death,
nonfatal MI, or nonfatal stroke. Goal primary efficacy endpoint was three-point MACE
and composite of CV death or heart failure, key secondary endpoint, very similar to
other studies, the renal composite endpoint and all-cause mortality.
The inclusion criteria for this study was somewhat different, which is important to note, and that this study like the other two had most of the patients who are predominantly with multiple risk factor for cardiovascular disease, but a few of them really had established cardiovascular disease. Although they could be included if they have Type 2 diabetes older than 40 years of age with established CVD or 55 years of age in man and 60 or older in female with one of the following risk factors: risk of lipedema, hypertension, or currently smoking, multiple risk factor group. And they were excluded obviously if their hemoglobin levels seem like already controlled or very high, if they have creatinine clearance less than 60mL per minute, or they have had a recent, acute cardiovascular or cerebrovascular event within eight weeks from the randomization. If they have any lifetime history of bladder cancer or recurrent UTI, or history of any malignancy within five years, they were excluded as well.

Here, you can see the composite. This study was presented at the American Heart Association and the paper was published subsequently in the New England Journal of Medicine, and you can see the results of this trial is 17% reduction in the composite endpoint of CV death or heart failure hospitalization. As you can see, this was predominantly attributed by a 27% reduction in heart failure hospitalization and hardly any effect on cardiovascular death in and of itself.

If we summarize these three studies, it’s very important because they have some divergent effect. One has to carefully look at what kind of patient was enrolled. As I
mentioned, already in the DECLARE-TIMI 58 study, most of the patients were primary prevention (60%), only 40% of them had established disease. In the CANVAS program, it was the other way around. About 2/3 of them were secondary prevention candidate and 1/3 primary prevention. In contrast, the EMPA-REG OUTCOME, most of the patients were already with established cardiovascular disease and as said, they were secondary prevention cases. You can see that shown further expanded in this.

**Slide 60 - Meta-analysis of SGLT-2 Inhibitor Trials**

There has been a meta-analysis published in Lancet and here, you can see when you look at the CV death or hospitalization for heart failure. Clearly, you can see that patients with established atherosclerotic disease show significant effect whereas patients with multiple risk factor, you can see that both in CANVAS and DECLARE studies, which are the two that had the patients for primary prevention are only with risk factor with no preexisting disease, there is a benefit in favor of these agents, but this does not read as statistically significant. As you can see, there was overall 16% reduction, but the PE is 0.06.

**Slide 61 - Meta-analysis of SGLT-2 Inhibitor Trials**

When we look at heart failure, either with patients with prior history of heart failure or with no history of heart failure, you can see the benefit across the board.

Very clearly, you can notice that the benefit was greatest in the CANVAS trial, but your confluence intervals are overlapping. And even in DECLARE-TIMI 58, which as you recall only 1/3 of the patients about 40% had secondary prevention category of patient, there was also a significant reduction there, a 21% reduction.
And in patients who had no history of heart failure, again, you can see dramatic reductions across the board for an aggregate reduction of 21%. And these are very impressive results suggesting that perhaps in the future, if the ongoing studies, that there are many right now, that show that it can prevent heart failure, this will become a standard therapy for both patients with established heart failure, as well as those who are at risk of developing heart failure, but obviously, we have to wait and see the results of these ongoing trials.

**Slide 62 - Meta-analysis of SGLT-2 Inhibitor Trials**

This particular slide shows a meta-analysis of all SGLT-2 inhibitor trials that have been published to date for the renal composite endpoint. Again, you can see across the board, the patients with atherosclerotic cardiac disease or only with risk factors because for kidney, it really doesn’t matter if they have hypertension, which is the most common risk-factor in these patients or established cardiovascular disease. There is substantial reduction in the renal endpoint in both category of patients.

**Slide 63 - GLP-1 RAs**

Let’s move on to the last category of the newer antidiabetic drugs that I wanted to discuss with you, and these are the GLP-1 receptor agonist. The GLP-1 receptor agonists that have been studied are dulaglutide, exenatide, and extended-release, and liraglutide, and lixisenatide, and semaglutide. These agents are somewhat similar, but they have direct effect on enhancing glucose dependent insulin secretion, glucose dependently decreased, excessive glucagon secretion, in addition, they slow the gastric emptying and enhance satiety.
These agents initially were found to be very effective for weight reduction in these patients. It could range anywhere from half to almost full kilogram in patients. The placebo extracted hemoglobin A1C reduction could be somewhere between half to 1.5% at this point and they also additionally systolic repressive reduction and improvement in dyslipidemia in many of these studies noted. These studies show greater A1C reduction and great reduction for GLP-1 receptor agonist versus DPP-4 inhibitors. There is also low hypoglycemic risk and are clearly, as with any other agents, the risk of hypoglycemia can increase when these agents are used with insulin or insulin secretagogue. Depending on A1C, one should consider reducing the dose of insulin or insulin secretagogue when adding GLP-1 receptor agonist.

**Slide 64 - LEADER Trial: Primary Outcomes**

The first study in this class of agents we come across was LEADER trial with liraglutide - and this data published in 2016 show that the composite endpoint of CV death, nonfatal MI, or nonfatal stroke was significantly reduced. First of all, it is highly significant for non-inferiority, but it’s also significant in favor of liraglutide for superiority as we see earlier of 0.01. This established also the efficacy of these agents for cardiovascular protection. Notice if you will, particularly on the right-hand diagram and also in the left-hand, that these drugs take some time unlike SGLT-2 inhibitors, particularly for heart failure, where the curve separated early on. Here, we can see that it takes about 18 to 24 months to curve to start really separating. This to me suggests that these drugs are more structurally altering drugs, sort of having anti-arteriosclerotic mechanism, amongst other things, and this can be certainly conceptualized based on their effects on lipid, blood pressure, rate reduction, etcetera.
Slide 65 - SUSTAIN 6: CV Outcomes

In addition to that, we have very exciting results of SUSTAIN 6 from semaglutide. Even though a smaller study, we sure to follow up, you can see here again, a highly significant noninferiority boundary in favor of semaglutide and also 0.02 superiority in favor of primary outcome. In addition to that very dramatic result, if you will, for nonfatal stroke that was seen. And again, the curve here separate quite early, which again, is somewhat unexplainable if it’s the only structural changes. But as we can see, there are fewer strokes and overall, the PE is only of borderline significance 0.04. nonfatal infarction took a little longer. That does not by itself reach statistical significance and death from any cause was not significantly altered.

Slide 66 - Multifactorial Intervention

I want to emphasize that when we talk about control of diabetes, we really need to look at multifactorial intervention, and this study, the STENO-2 trial, a smaller study of 160 patients by Gaede and coworker clearly emphasizing that when you control all of the risk factors. The hemoglobin A1c are less than 6.5, the cholesterol reduction with the statin, the triglyceride reduction with whatever drug maybe be needed, and control of blood pressure, particularly when RAS blockers has been used and a smoking cessation, as well as in this case, aspirin use, there was a substantial reduction which initially was shown up to eight years, but now that we have 13-year follow-up data showing clearly a beneficial effect of this multifactorial intervention trial.

Slide 67 - Poor CV Risk Factor Control in Diabetes

However, despite all these benefit that have been noted, we can see here that we are not doing that well in terms of controlling the various risk factor. In this particular
observation from the enhanced database by Ford and coworker, we can see that
during the last 10 years or so, there are some improvements, but not nearly as much
as we’d like to see in terms of control of hemoglobin A1c, also in terms of blood
pressure control, and LDL goals are to be less than a hundred, but now recommended
to be less than 70. 40% to 50% of adults with diabetes have not achieved CVD risk
factor control.

I’ll hand it over now to Dr. Nassif to talk about how we are doing in terms of applying
these study outcome data to clinical practice. Michael?

**Slide 68 - Applying the Data to Clinical Practice**

**Michael E. Nassif, MD:** Thank you, Dr. Deedwania. Yes, I wanted to finish by
pointing out one, how important it is for cardiologists to understand this data, and two,
and more importantly, how important it is for cardiologists to actually apply and
implement this data and this paradigm shift in Type 2 diabetes management.

**Slide 69 – Circulation**

Myself and numerous others have made a call for cardiologists to embrace these
glucose lowering therapies that do improve cardiovascular outcomes, as Dr.
Deedwania just showed us, the SGLT-2 inhibitors as well as the GLP-1 receptor
agonists.

**Slide 70 - SGLT-2 Inhibitors Continue To Be Underused**

Unfortunately, thus far, our calls have not been embraced. This is data from Boston,
showing SGLT-2 inhibitor prescriptions. Although overall, the trend has increased with
the EMPA-REG OUTCOME trial CANVAS and the FDA labelling, however, if you look
at the very bottom in the purple color is the amount of cardiologists prescribing these drugs and it has remained woefully low, as far as cardiologists getting involved.

Slide 71 – Common Excuses

When we ask what are the reasons for this, often, cardiologists say that it's not their role or their job to control glucose. As I think Dr. Deedwania emphasized, it’s not about glucose control. This is strictly about decreasing cardiovascular risk. It has been shown in trials of both the GLP-1s and the SGLT-2s is that this lowering of cardiovascular risk is completely independent of hemoglobin A1c.

It's also frequently mentioned that cardiologists don’t want to step on the toes of referring internists, family practitioners, or endocrinologists. But as I pointed out in the beginning, if cardiologists aren’t interested in decreasing cardiovascular mortality, then I’m not sure why we became cardiologists in the first place. Given that it’s our disease and our endpoint, we must own it.

Some people also mentioned side effects, which is true. As Dr. Deedwania mentioned, there is some side effects of these medications and there are some drug interactions. Relatively speaking, they are few and far between. I think one of the strongest data points is that both the EMPA-REG OUTCOMES trial patients were statistically, significantly more likely to have an adverse event on placebo than they were on SGLT-2 inhibitors, and cardiologists as a specialty, we routinely prescribe amiodarone, digoxin, dofetilide. We can certainly learn to monitor and to manage side effects.
Slide 72 - Missed Opportunities

The biggest reason cardiologists need to get involved in this is for patients. This is administrative data from YALE, New Haven, which was presented at the Endocrine Society meeting. It showed that out of nearly 80,000 patients with both Type 2 diabetes in established cardiovascular care, nearly half of them had been seen in a cardiology clinic by a cardiologist whereas only about 10% of them have the luxury of seeing an endocrinologist. Patients were over five times more likely to be seen by a cardiologist if they had established cardiovascular disease and Type 2 diabetes.

Slide 73 - Number Needed to Treat (NNT) to Prevent One Death Across Landmark Trials in Patients with High CV Risk

Why this is important is as Dr. Deedwania showed us, the number needed to treat empagliflozin in the EMPA-REG OUTCOME trials was not all that high. Just for some comparisons, simvastatin – and this is in the early 90s when we had very little therapy – the pre-statin era needed 30 patients to prevent one death. In 2000, the pre-ACE inhibitor era, the ramipril study showed that the number needed to treat was 56 to prevent one death. Then now, 2015, with EMPA-REG, we had patients on both statins and ACE inhibitors already at baseline, the great majority, and in spite of this, the number needed to treat was 39 to prevent one death in the EMPA-REG OUTCOMES trials.

Slide 74 - It is estimated that a 60-year-old patient with T2DM and established CVD could, on average, live 2.5 years longer when treated with empagliflozin

Looking at this slightly differently, if you look by age in the median difference in survival between empagliflozin and placebo in EMPA-REG, the average patient lived 2.5 years
longer if they were in the empagliflozin arm. When we talk about the cardiologists not treating this, it’s an incredibly missed opportunity for tens of thousands of patients that one health care system alone to prolong their life and their quality of life.

Slide 76 – Case 1

A clinical vignette, which highlights a lot of which we have discussed is a 52-year-old male. He has hypertension, peripheral arterial disease, and has a history of amputations and Type 2 diabetes, a nonsmoker. He is currently on dual antiplatelet therapy lisinopril, metformin, and rosuvastatin.

Slide 76 – Case 1 (cont)

The patient’s blood pressure is 142/96, heart rate is 68. He is obese. BMI is nearly 33, his hemoglobin A1c is 7.3%. Likewise, his LDL cholesterol is 70, HGL was 42. The patient already is adherent to dietary restrictions. During discussion, you tell the patient your concern that he is at high risk for future atherosclerotic events. The patient says he is willing to take an additional oral medication. The question is, “Which of the following, would lower his risk?”

In this instance, there are two classes of medications, which we know it decrease risk of future cardiovascular adverse events, and those would be the GLP-1 receptor agonists or the SGLT-2 inhibitors. Given the patient’s preference for an oral medication, the SGLT-2 inhibitors would be ideal. There would be some hesitancy to put the patient on canagliflozin, given his history of peripheral arterial disease and amputations. As we mentioned, it does carry a black box warning for lower extremity
amputations. Thus, the most appropriate answer would be to start the patient on empagliflozin.

Slide 77 – Thank you

Thank you very much for joining us today. I’d like to remind you that to receive credit for this program, you must take the post-test and fill out the evaluation. Your participation is very important as it will help us assess the educational relevance and impact of this CME activity and provide valuable insights for future CME.