expert roundtable »

Discussion on Key Heart Failure Risk Factors in Patients With Type 2 Diabetes Mellitus

Moderated by: **Henry Punzi, MD[1,2]**
Discussants: **Peter A. McCullough, MD, MPH[3]; Subodh Verma, MD[4]**

DR PUNZI: Hello. My name is Dr Punzi. I'm an internist and hypertension specialist in the Dallas-Fort Worth area. With me are Dr McCullough and Dr Verma and we will be discussing the issue of heart failure (HF). The purpose for this discussion is to educate primary care physicians, cardiologists, and endocrinologists on the key HF risk factors in patients with type 2 diabetes mellitus (T2DM). The issue of HF is pretty significant. In the United States, there are 6.5 million adults with HF. The American Heart Association (AHA) statistics show that 1 of every 8 deaths in 2017 was related to HF.[1] Two percent of the population has HF and the cost of HF in 2012 was about $30.7 billion. We have numerous studies that show that, in the treatment of T2DM, there is a significant benefit in the reduction of HF hospitalizations.

With that, I'd like to have Dr McCullough introduce yourself and give a little bit of your background on HF and the clinical aspects. One of the important problems that we see is, as clinicians who have been educated over the past 2 to 3 decades, that diabetes has not been on the list of major risk factors for the incidence of HF. Even in the latest 2019 statistics from the AHA, in their summary, they have diabetes way down on the list when compared with other risk factors.[1] Dr McCullough, will you discuss that for us?

The following Expert Roundtable Discussion was held on January 16, 2020.

The discussion focused primarily on:
1. The link between type 2 diabetes mellitus and heart failure;
2. How heart failure affects patients with type 2 diabetes mellitus;
3. Available heart failure risk prediction tools;
4. How to identify patients with type 2 diabetes mellitus at risk for heart failure;
5. Screening for heart failure risks in patients with type 2 diabetes mellitus; and
6. The role of dapagliflozin in decreasing the risk for heart failure in patients with type 2 diabetes mellitus.

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STUDIES DISCUSSED:
CREDENCE, DAPA-HF, DECLARE-TIMI 58, FRAMINGHAM HEART STUDY, HOPE, REACH, SAN ANTONIO HEART STUDY, SAVOR-TIMI 53, SPRINT

COMPOUNDS DISCUSSED:
dapagliflozin, dipeptidyl peptidase-4 inhibitors, metformin, ramipril, sodium-glucose cotransporter-2 inhibitors, sulfonylureas

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DR MCCULLOUGH: Yes, well, thank you for that opening introduction and set of remarks. I'm Peter McCullough. I'm an internist and cardiologist and Vice Chair of Medicine at Baylor University Medical Center in Dallas, TX. As a medical cardiologist, I've been particularly interested in the interface between heart and kidney disease and diabetes, of which 90%

is T2DM and is the leading cause of chronic kidney disease. In my view, some of the early epidemiologic studies including the Framingham Heart Study[2] really miss the connection between HF and diabetes. I think largely because during that time HF was dominated by patients with coronary heart disease and valvular disease and there was a really heavy overlay of untreated hypertension. So, the modern epidemiologic observations are, just as you stated, that T2DM really is a major risk for HF.

DR PUNZI: Dr Verma, would you care to introduce yourself and give us your perspective on the association of T2DM and HF?

DR VERMA: Yes, I'm Subodh Verma. I'm a cardiac surgeon and a Professor at the University of Toronto with an interest in diabetes and cardiovascular disease, specifically diabetes and HF. I'm involved in all of the major large outcome trials with sodium-glucose cotransporter-2 (SGLT-2) inhibitors in the treatment of HF.

I completely agree with what Professor McCullough just said—it is not until recently that we've had an appreciation of a problem that is actually quite old and that is that HF is a common occurrence in people with diabetes and one of the most fatal, grievous complications of T2DM. I think the fact that we're now seeing that rates of ischemic heart disease are declining because of good antiatherosclerotic treatments, the importance of HF as an outcome in patients with diabetes is becoming apparent.

You don't value what you don't measure, and it wasn't until the cardiovascular outcome trials, even the initial ones with dipeptidyl peptidase-4 (DPP-4) inhibitors, which showed a neutral outcome on major adverse cardiovascular events, that we were reminded how important HF was as an outcome. Then, of course, from there came the SGLT-2 inhibitor trials that have shown us not only the importance of this outcome, but that this is something that can be prevented and potentially even treated in people with diabetes.

DR PUNZI: Thank you, Dr Verma. So, I think one of the issues at hand for some of our colleagues is HF—how does this disease affect our patients? Having trained many years ago, the treatment of HF was merely symptomatic, trying to make the patient feel better, but there was no improvement in the mortality. We know that the 30-day mortality for HF is about 10%, at 1 year is between 20% and 30%, and at 5 years is between 45% and 60%.[3] So, I think that as clinicians we should be more aware of what the morbidity and mortality implications are when the patient is diagnosed early on with HF. With that said, Dr McCullough, tell us can weidentify these patients earlier in the disease process and get a good handle on what to do or not to do with these patients?

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> *~ Subodh Verma, MD*

DR MCCULLOUGH: The largest study in HF, REACH,[3] demonstrated that roughly half of the patients with HF had HF with reduced ejection fraction (EF), which was the traditional view of HF, and half had HF with preserved EF. One of the important observations, supported by many other studies, is that HF has a very high cause-determined mortality, meaning that a patient with HF has roughly a 90% chance of dying of HF—HF would be the cause of death. The two major divisions in mortality are either pump failure death or sudden arrhythmic death.

There is an urgency to identify patients with HF because there really are disease-modifying mortality-reducing therapies in HF. One of the things we showed in REACH years ago was that about a third of patients were diagnosed in an ambulatory setting alone and about two thirds were diagnosed with an incident hospitalization. I think a real goal would be to identify more patients before they're ever hospitalized in the ambulatory setting. So, it really takes a clinical suspicion, the use of blood testing for natriuretic peptides—brain natriuretic peptide or N-terminal pro-brain natriuretic peptide—and the use of echocardiography for the detection of HF in the ambulatory setting.

DR PUNZI: Dr Verma, would you care to comment on that?

DR VERMA: Yes, so again, I would agree with my colleague and maybe add a couple of comments to say that we now have data that in people with diabetes of all of the known complications, having diabetes plus HF carries the worst mortality compared with any other complication in diabetes, whether it's peripheral arterial disease or chronic kidney disease, prior myocardial infarction, or history of retinopathy, etc. So, just recognizing the fact that this combination is one of the worst with respect to mortality is important, but it also begs the question on why we are waiting until people fall off the cliff and develop this bad diagnosis. We should be really investing in trying to understand how to identify these patients earlier.

There are various ways of doing that. Some have already been articu-

lated nicely by Professor McCullough. They can either be based on clinical suspicion, duration of diabetes, looking at biomarkers, looking at people who have multiple risk factors, and really having a heightened sense of suspicion of occult HF with preserved or reduced EF in these patients early, because when we say diabetes and HF to primary care physicians or to other clinicians, immediately they think about patients with established HF who have classic signs and symptoms of HF. You have therapies, you can modify their prognosis to some extent—but, really, by then, the horse has left the barn.

DR PUNZI: The damage is done.

DR VERMA: The damage has been done and the opportunity to prevent that has been lost. So, I think that is a key feature. I'll also add that this link between HF and renal disease is a very important one because both of these are complications that occur not only coincident with each other in people with diabetes but really serve to accelerate, in a bidirectional fashion, the outcome of each entity such that renal disease is a very strong determinant of HF and as the pump gets worse so does the kidney. So this bad relationship between the heart and the kidney is also something that inevitably happens in this population and requires us to think about the prevention not just of HF but the prevention of the cardiorenal or the HF renal continuum in this patient population.

DR PUNZI: Right. Thank you, Dr Verma. Looking at the context of risk factors such as diabetes, hypertension, and coronary heart disease, Dr Haffner of the San Antonio Heart Study[4] felt that in his patient population, a diagnosis of diabetes carried a similar cardiovascular risk to coronary heart disease. This coincides with what we're seeing today, where 50% of people with T2DM could end up developing HF.

There are some European studies that evaluated the prevalence of HF in diabetic patients. Dr Shah and colleagues[5] in the United Kingdom studied a large prospective cohort using linked electronic health records. Of the 1,921,260 patients, 34,198 had diabetes (1.8%). Of these diabetic patients, 6137 (17.9%) had a first cardiovascular presentation, the most common of which were peripheral vascular disease (992 [16.2%] of 6137 patients) and HF (866 [14.1%] of the 6137 patients).

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> *~ Peter A. McCullough, MD, MPH*

Dr Boonman-de Winter et al[6] evaluated 605 patients aged 60 and older with T2DM. The standardized diagnostic workup included medical history, physical examination, ECG, and echocardiography. Of the 581 patients studied, 161 (27.7%) were found to have previously unknown HF: 28 (4.8%) with reduced EF and 133 (22.9%) with preserved EF. Left ventricular dysfunction was also diagnosed in 150 patients (25.8%); 146 (25.1%) had diastolic dysfunction. This implies that in the diabetic population we're starting to see HF manifesting earlier in the disease process and without the physician's knowledge. How do we predict which diabetic patients are at greater risk? What tools can clinicians use at the bedside to evaluate these patients? There is also a paradigm shift on when we should start treatment of hypertension, and also in the hypertensive diabetics. I think that when you look at data from numerous studies, especially our SPRINT study,[7] the underlying theme is that lower is better to decrease the risk of cardiovascular disease including HF. What do you see as a feature for clinicians to be able to identify these patients earlier and start treatment?

DR MCCULLOUGH: There is a critical concept that needs to be in every clinical mind when seeing a patient with diabetes and it's called a heat map. A heat map organizes patients according to their estimated glomerular filtration rate (GFR), which is calculated by creatinine, sex, age, and race on one axis and urine albumin-creatinine ratio on the other axis, which is just done from a urine sample. In that heat map, the lower the GFR and the higher the albumin-creatinine ratio the greater the risk. They actually have calculated risks not only for the progression of kidney disease but cardiovascular outcomes including HF. We've published and organized, as an example, the SGLT-2 inhibitor trials along one of these heat maps to really show where the patients were recruited, and the epidemiology of the heat map is exactly matching what we're seeing in clinical trial outcomes.[8] So, that is a great way to size up a patient's risk and then to take it from there in terms of clinical suspicion, and, if patients have effort intolerance and some of the other cardinal features of HF, I think a clinician really needs to move forward with natriuretic peptide testing and echocardiography to identify patients.

DR PUNZI: Great. You mentioned that when you look at the microalbumin-creatinine ratio, this is a marker of inflammation within the blood vessel, which should be considered one of the earliest and easiest risk factors to assess. This correlates nicely with what you just said, Dr McCullough.

Dr Verma, would you care to give us your perspective on those HF risk prediction tools?

DR VERMA: So, first and foremost, I think there is no perfect score in people with diabetes to say this is how we predict who's going to develop HF. I think there have been two recent approaches. One is based on clinical features and they sort of divided this into diabetes-specific risk factors and then general risk factors, and when you're dealing with a patient with diabetes, duration of diabetes of more than 10 years, people who are insulin-requiring diabetics, those who have any evidence of microvascular disease—again, not just nephropathy but also retinopathy and neuropathy—are good surrogates for HF, and then those who have persistently elevated hemoglobin A_{1c}. From a general standpoint, elderly patients, people who have multiple risk factors such as hypertension and obesity, people who have a history of coronary disease, people with atrial fibrillation—those are other ways of identifying people at risk for developing HF. Also people with sleep apnea, for example.

So, we've written about this sort of a general guide to predicting HF in people with diabetes, but more recently there's been the thrombolysis in myocardial infarction (TIMI) diabetes HF risk score that has been published from the DECLARE-TIMI 58 trial.[9] It was developed through the SAVOR-TIMI 53 study[10] and then validated in DECLARE. That has identified, I believe,5 risk factors[11] and assigned a numeric risk score—a number for each one. If you have a prior history of HF, you get 2 points. That's pretty straightforward, right? You don't need to be a rocket scientist to say this patient is at risk for HF because he had a prior HF event, right? But, then the other ones are quite informative and that is if you have microalbuminuria, macroalbuminuria, reduced GFR, atrial fibrillation, then you get, in some cases 2 points, in some cases 1 point. This is essentially just like all of us using the $CHADS_{2\text{-}VASc}$ score or other types of scoring systems to determine risk and other situations. This is a numeric score that tracks for a higher risk of HF.

What was also apparent with the TIMI HF risk score was that it didn't matter whether a patient was at low, intermediate, or high risk for developing HF, the strategy that was used in the trial, which was an SGLT-2, dapagliflozin, had a similar relative risk reduction across the entire spectrum. So, I think you don't really have to identify patients at high risk—everybody can derive benefit.

> ***"I think we're seeing a similar phenomenon now with the SGLT-2 inhibitors, specifically with dapagliflozin, that there is a possible mechanistic action that is similar to renin-angiotensin system blockers and that's why we're seeing significant benefit."***
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> *~ Henry Punzi, MD*

DR PUNZI: Very good.So, the issue that we are still dealing with when looking at data from the AHA, they break down the causes of the 647,457 people who die yearly from cardiovascular disease: coronary heart disease 43%, cerebrovascular accident 17%, and then HF is 9.3%. It always seems to be that HF is going to be at the lower spectrum of what is at the forefront in clinicians' minds. My question to you is: what is it that we have to do or should do to make clinicians more aware? Dr Verma, you just mentioned the issue of the spectrum, right? So, if you treat these diabetic hypertensive individuals with an SGLT-2 inhibitor such as dapagliflozin, we now know we can reduce that risk. The question there is, should we be telling clinicians that for the diabetic hypertensive individual, they need to use dapagliflozin to decrease that risk of HF?

DR MCCULLOUGH: That's a fair statement, as Dr Verma pointed out, that the SGLT-2 inhibitors are associated with a reduced risk for incident HF as well as HF hospitalizations and cardiovascular death in those treated. So, I think that's a fair point that HF can clearly be prevented. I think this new genre of drugs plays a big role. I can tell you that blood pressure control as you implied from the SPRINT trial and others have shown in clinical trials, that HF is a blood pressure–responsive end point. Far more responsive than coronary heart disease end points. There are some emerging data now that are quite interesting that HF with preserved EF appears to have a large preventable fraction based on maintenance of a normal body weight and cardiovascular fitness, both cardiorespiratory fitness and strength training.[12] So, I think being lean and fit through the course of life really drops the risks for HF with preserved EF fairly dramatically.

DR VERMA: I would add to that and ask, should people with diabetes be treated with an SGLT-2 inhibitor if they have multiple risk factors? The answer to that, in my opinion is, yes, yes, and yes, because what are the other alternatives? You have to treat diabetes. We now know that there's no threshold. If you look at the TIMI HF risk score it doesn't matter whether you have a high or low score, the bandwidth of these agents is quite broad. If you start with a patient who's older than 55 who has multiple risk factors, who has preserved renal function, or if you end up with a CREDENCE[13]-like patient who actually has significant renal disease and an GFR that's low and is macroalbuminuric, or someone like in DAPA-HF[14] who has established HF, it doesn't matter where in that continuum you intersect with an SGLT-2 inhibitor, the relative benefits seem to

be the signature of preventing HF and preventing renal disease are observed. So, I think that it is, in my opinion, the European Society of Cardiology guidelines[15] that came out in 2019 suggesting that people with risk factors or those with established atherosclerotic cardiovascular disease, the use of these agents should be considered even potentially ahead of metformin. There's been sort of two camps where some people have actually questioned the evidence base for that, and others think it's an appropriate recommendation to be using these therapies early as disease-modifying therapies in patients with diabetes.

DR PUNZI: Wonderful. Right, I think we're in agreement on that. So, in the hypertension realm I've been a lead investigator in numerous clinical trials. We mentioned the SPRINT trial. We know that when it comes to BP, lower is better. If we look at a BP reduction of only 2 mm Hg, you reduce ischemic heart disease by 7%, you reduce stroke by 10%, and you further reduce HF by 15%. As you mentioned, Dr McCullough, HF improvement is really related to that BP reduction. So, for the last comments here, can you just give me a perspective on what you both think the potential mechanism of action is, because I think we established that we've got to intervene early in these patients. If we're going to treat their diabetes, now the question is metformin or SGLT-2 inhibitor, and in this case with dapagliflozin, should we utilize it first?

DR MCCULLOUGH: Dapagliflozin, like all SGLT-2 inhibitors, causes a loss of glucose and sodium in the urine and predictably lowers BP. There's also a predictable reduction in body weight, and body weight reductions in patients with T2DM work to improve glycemic control from other agents. So, weight loss is very assistive in the T2DM condition. However, my view is that the cardiovascular benefits, the really large reductions we've seen in HF hospitalizations and cardiovascular death, and I'd also parenthetically say that the large reduction in the progression of chronic kidney disease with SGLT-2 inhibitors, cannot be explained just by reductions in hemoglobin A_{1c}, BP, and body weight. So, there's great interest in searching for additional mechanisms by which these drugs confer the benefits.[16]

DR PUNZI: We have been collaborating with Dr Gabby Navar from the physiology department at Tulane University performing the first-in-human experiments. In their studies in spontaneously hypertensive rats that subsequently developed diabetes they observed an upregulation of intra-renal angiotensinogen with suppressed systemic renin levels. Even though diabetic hypertensive patients are characteristically low renin, we found in their 24-hour urine collections increased angiotensinogen. This may be another potential mechanism of action of the SGLT-2 blocking intra-renal angiotensinogen with an effect similar to renin-angiotensin system blockers, which would make sense because—as you mentioned, Dr McCullough—all of this is tied to the issue of the kidney, the issue of HF, the issue of BP.

What do you think is a possible contributing factor to the HF benefit that is seen with dapagliflozin? The FDA has required manufacturers to include a black-box warning (increase cardiovascular morbidity and mortality) on all sulfonylurea drugs. As part of the drug approval process, the FDA has the pharmaceutical companies do long-term clinical outcome trials with the SGLT-2 class with these showing an improvement rather than a neutral effect on cardiovascular disease. Dr Verma, can you give us your opinion on from where you think that benefit derives?

DR VERMA: So there have been a lot of mechanisms and hypotheses that

Clinical Implications

- **Type 2 diabetes mellitus is a major risk for heart failure.**
- **Heart failure is a common occurrence in patients with type 2 diabetes mellitus.**
- **It is important to treat early and aggressively in patients with type 2 diabetes mellitus**
- **Sodium-glucose cotransporter-2 inhibitors are associated with a reduced risk for incident heart failure as well as heart failure hospitalizations and cardiovascular death in treated patients. Therefore, the sodium-glucose cotransporter-2 class has brought with it significant cardiovascular morbidity and mortality improvements in patients with type 2 diabetes mellitus.**
- **Embracing these new therapies will lead to significant long-term cardiovascular benefits in patients with type 2 diabetes mellitus.**

have been put forward, ranging from natriuresis to diuresis, which occur with these agents. There is the recent concept that there may be differential regulation of the intravascular and interstitial component, where SGLT-2 inhibitors may have greater reductions on interstitial vs intravascular volume. Then there has been the hypothesis that these agents may have a direct effect on the sodium hydrogen exchanger by inhibiting exchange—they may have effects to reduce intracellular cardiomyocyte sodium and calcium. There is the ketone hypothesis that by raising beta-hydroxybutyrate, they provide an alternative fuel source for the myocardium, and through that mechanism improve myocardial energetics potentially.

Then, of course, there is the hypothesis that these agents are primarily working at the level of the kidney, which I believe is probably the most cogent hypothesis in that they cause the hemodynamic effect at the level of the kidney, which explains the renal benefit through either tubuloglomerular feedback and afferent arteriole constriction. More importantly, that benefit appears to occur both in people with and without diabetes because in DAPA-HF, even in the nondiabetic population, the GFR decline ocurred similarly to what is seen in people with diabetes and that may trigger a reduction in efferent sympathetic activation. The kidneys are closely associated with central sympathetic activation, and through improving renal function and reducing renal stress, these agents may reduce sympathetic tone, and that may be one of the mechanisms. So, there have been many hypotheses and theories that have been put forward, but I think the bottom line is that the fact that they worked similarly in people with and without diabetes in DAPA-HF really suggests that glucose is off the table with respect to a key mechanism of HF and renal protection.

DR PUNZI: When you look at the clinical trials with diabetic hypertensive patients, microvascular disease seems to be significantly improved when compared with macrovascular disease. I think that relates back to what you were just saying. If you look at the HOPE trial[17] with ramipril (2.5 mg, 10 mg, or placebo) given at bedtime, along with vitamin E, what they found in that clinical trial was that a significant benefit was derived in the diabetic patients (38% of patients). This is when clinicians started using renin-angiotensin system blockers in their diabetic cohort even though, when looking at the pathophysiology of diabetic hypertensive patients they are volume repleted, so they're low-renin hypertensive patients. Numerous guidelines warrant the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in these patients.

I think we're seeing a similar phenomenon now with the SGLT-2 inhibitors, specifically with dapagliflozin, that there is a possible mechanistic action that is very similar to these renin-angiotensin system blockers and that's why we're seeing significant benefit. I think, once again, that clinicians today don't really think that the diabetic patient would be at risk for developing HF. Is there anything that we can do to shift that thinking, to make them more aware? The impetuous behind this thinking is that we now have treatment that is going to benefit these patients early on as well as long term. So, Dr McCullough, are there any closing comments that you want to make with regards to this or anything else that we left out?

DR MCCULLOUGH: I would conclude by saying that, in my view, we are in the middle of an HF and T2DM pandemic. I think the opportunity that you've outlined in terms of general risk factor control, of blood pressure reduction, and now treatment with SGLT-2 inhibitors has the potential to markedly reduce the burden of HF, which currently is the leading cause of nontraumatic adult hospitalization certainly in the United States. I think there is a bright future for this new class of antidiabetic agents and believe they will play a large role in the future treatment of patients with and without diabetes at risk for HF hospitalization and cardiovascular death.

DR PUNZI: Great, thank you, Dr McCullough. Would you like to summarize, Dr Verma?

DR VERMA: My comments are similar in that HF and renal disease remain recalcitrant problems in diabetes and we for many years have been, for lack of a better term, wondering why glucose-lowering strategies have not moved the needle.

So now we've generated the evidence to suggest that these agents have not just a significant but a profound effect on prevention and treatment of HF and an even bigger effect on prevention and treatment of renal disease. Therefore, we just need to overcome clinical inertia. We need to find a way to get past the fact that although the metformin and DPP-4 inhibitor combination is a safe and neutral combination, it doesn't really change someone's prognosis. So, if you are the gate keeper of your patients' outcomes, then we need to remember that we have strategies that can actually prevent and treat these two important and interrelated complications. Clinical practice guidelines are really echoing the results of the trials in that regard.

DR PUNZI: Dr McCullough and Dr Verma, thank you. I think that we've tried to emphasize the point that we've got to start our treatment early. We can't just start these diabetic individuals with medications where the only goal is to lower glucose (sulfonylureas are the most commonly prescribed drug in the United States for diabetes). With diabetes being a coronary heart disease equivalent, I think that the use of the SGLT-2 inhibitors should be utilized earlier in the algorithm. I think that, as Dr McCullough and Dr Verma

well described, with dapagliflozin, not only do we help to lower blood sugar but also decrease BP and decrease the risk of HF hospitalizations. When utilizing dapagliflozin, the BP reduction is about 5 mm Hg. With a drop of 2 mm Hg in clinical trials there is a reduction of ischemic heart disease of 7%, stroke 10%, and then HF of about 15%. The key take-home message is to treat early and be very aggressive and assertive with your therapies. The SGLT-2 class has brought with it significant cardiovascular morbidity and mortality improvements in patients. Embracing these new therapies now will lead to significant cardiovascular benefits that these patients are going to have long term. With that we will conclude this roundtable. Thank you very much, gentlemen.

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