Navigating the Major Adverse Cardiovascular Event (MACE)-atherosclerotic Cardiovascular Disease versus Heart Failure

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Concerns about cardiovascular (CV) disease have focused primarily on atherosclerotic vasculo-occlusive events, such as myocardial infarction, stroke, and limb ischemia. However, one of the earliest, most common, and most serious CV disorders is heart failure (HF). Comorbid conditions for HF include insulin resistance, hypertension, diabetes, obesity, coronary artery disease, chronic obstructive pulmonary disease, obstructive sleep apnea, and dysrhythmias. While there are many etiologies for HF, and it can present as HF with reduced ejection fraction or HF with preserved ejection fraction, the primary aim of this editorial is to encourage healthcare providers to begin identifying patients at risk for HF in addition to their focus on macrovascular complications.

Keywords

Heart failure, insulin resistance, hypertension, diabetes, obesity, estimated glomerular filtration rate/mL/min/1.73 m^2 (eGFR), glomerular hyperfiltration, albuminuria, angiotensin receptor neprilysin inhibitor, sodium–glucose cotransporter 2 inhibitor (SGLT2i)

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Heart failure (HF) is a disease that affects about 10% of men and 8% of women over the age of 60 years, and its prevalence increases with age.[1] HF and type 2 diabetes are each characterized by insulin resistance and are accompanied by the activation of neurohormonal systems; 35–45% of patients with HF have diabetes.[2] HF is the second most common reason for hospital admissions in the United States.[2] Despite major improvements in the treatment of virtually all cardiac disorders, HF is a disappointing exception. While there is an encouraging trend showing a decrease in primary HF hospitalizations, this chronic disease still accounts for over 1 million primary hospitalizations each year.[3] Additionally, patients with HF experience over 3 million secondary hospitalizations annually, often due to related comorbid conditions.[3] In total, HF imparts a substantial burden on both patients and the healthcare system.

Over the past three decades several therapies have been developed to reduce hospitalization for HF. Many drugs are used in managing HF including beta blockers, diuretics, aldosterone antagonists, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and most recently, some very positive results with sacubitril/valsartan an angiotensin receptor neprilysin inhibitor.[4] Despite these therapies there continues to be a significant number of HF-related hospitalizations. Standards of medical care for cardiovascular (CV) disease and risk management must include strategies to reduce death and hospitalizations for HF in addition to treating disorders from an atherosclerotic origin.

There is a growing body of literature that shows a strong linear relationship between albuminuria, hospitalization for HF, and CV death at levels well below current guidelines.[5] Also emerging, is a U-shaped relationship between estimated glomerular filtration rate (eGFR) and adverse CV outcomes including HF.[6] Fatal and non-fatal CV events have been reported as similar, but significantly higher in patients with increased (hyperfiltration) or low eGFR versus patients with normal eGFR.[7]

So, what is albuminuria? An elevated urinary albumin-to-creatinine ratio (UACR) excretion is a marker of endothelial dysfunction that suggests the existence of vascular damage. A UACR as low as 5 mg/g increases CV mortality, HF, myocardial infarction, and stroke. The risk gradient is steeper for CV mortality and HF than for myocardial infarction and stroke. In patients with type 2 diabetes on insulin therapy, increasing UACR has been independently associated with an increased risk of 3-major adverse cardiovascular events ([MACE] CV death, non-fatal myocardial infarction, and non-fatal stroke, p=0.006) and all-cause mortality (p=0.007), especially in patients with UACR >300 mg/g. Increasing UACR, however, was not associated with an increased risk of non-fatal myocardial infarction (p=0.554) or non-fatal stroke (p=0.264).[8] In the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) study, albuminuria was independently associated with worse

CV outcomes including all-cause mortality, CV death, and hospitalization for HF.[9] In addition, three landmark CV outcome trials with a sodium-glucose co-transporter-2 (SGLT2) inhibitor have been reported in patients with type 2 diabetes.[10–12] The benefit of these trails was predominantly on hospitalization for HF, suggesting effects primarily on myocardial function, "the pump", and not on "the pipes" (vasculo-occlusive disease).[13] All three of these drugs resulted in a reduction of albuminuria. The greatest CV benefit was observed in patients with a baseline UACR >300 mg/g.[10–12] These clinical trials confirm that albuminuria is a strong predictor of death from CV and hospitalization for HF, and treatments that lower albuminuria appear to have a major impact on reducing the burden of HF in our society. Several clinical trials are ongoing looking at the impact that SGLT2 inhibitors have on HF in patients with and without diabetes.[14]

It is well established that a lower than normal eGFR is a strong and independent predictor of both end-stage renal disease and CV mortality. However, the association between abnormally elevated eGFR, a clinical condition called glomerular hyperfiltration (GHF), and the risk of CV events, remains uncertain. GHF has been associated with medical conditions such as insulin resistance, hypertension, diabetes, prediabetes, and obesity. Pregnancy and smoking are also associated with GHF. To investigate whether GHF is independently associated with risk of adverse CV outcomes, 8,794 participants with an average age 52, 89% of whom had hypertension, were enrolled in eight prospective studies. A meta-analysis of these studies revealed that 626 patients had GHF (eGFR 111.2 mL/min/1.73 m^2), 433 patients had low eGFR (48.2 mL/min/1.73 m^2) and the remaining patients had a normal eGFR of 81.4 mL/min/1.73 m^2.[7] During a mean follow-up of 6.2 years, a first CV event developed in 722 participants. There were 137 CV deaths, 162 non-fatal myocardial infarctions, 232 non-fatal strokes, 97 coronary revascularizations, 42 who experienced HF leading to hospitalization, 39 who had peripheral artery disease, and 13 patients who started dialysis. Event rates were similar but significantly higher for both the high- and low-eGFR groups as compared with the normal eGFR group.[7] Another study showed that patients with type 1 diabetes on an SGLT2 inhibitor with a baseline eGFR >135 mL/min/1.73 m^2 had the greatest drop in eGFR (19.2%) versus only 1–2% in those patients with an eGFR in the normal range.[15] In the patients with GHF there was also 30–40% greater reduction in albuminuria than those with normal eGFR.[15,16] Systolic blood pressure declines were similar between the groups supporting blood pressure independent kidney benefits.

SGLT2 inhibitors increase tubuloglomerular feedback which decreases afferent arteriole constriction, resulting in a decline in interglomerular hypertension, hyperfiltration, and albuminuria. Since there is a paucity of literature on GHF it is difficult to know the prevalence in the general population, including those medical conditions associated with hyperfiltration. To investigate this further, the eGFR levels of 2,100 patients in the database of American Health Care (www.americanhealthcare.com) were collected. GHF was defined as an eGFR >115 mL/min/1.73 m^2. A total of 431 patients (20.5%) had an eGFR >115.0 mL/min/1.73 m^2 (range 115.0–238.2). Surprisingly, many of the ICD-10 codes were not the usual suspects for GHF. The database search was restricted to ICD-10 codes for prediabetes, type 1 diabetes and type 2 diabetes; of which 130 patients were identified. Of these, 63 (48.5%) had an eGFR >115 mL/min/1.73 m^2 (range 115.0–206.7) suggesting that the incidence of GHF in the diabetes population may be much higher than previously recognized.

In conclusion, HF continues to have a huge burden on the US healthcare system as a primary hospitalization or associated with other comorbid conditions. Known interventions that reduce albuminuria and GHF are all established treatments for renal disease, atherosclerotic events, and HF and include drugs interfering with the renin–angiotensin system, weight loss in obese individuals, and smoking cessation. Beyond these interventions, the potential value of targeting albuminuria and hyperfiltration is underscored by the results of SGLT2 inhibitors in patients with diabetes and are now being extended to patients with HF who do not have diabetes. A number of ongoing trials are looking at the impact that SGLT2 inhibitors have in patients with HF with reduced ejection fraction and preserved ejection fraction. There is also a study specifically looking at the effect of SGLT2 inhibition on albuminuria (NCT02547935). Given the blood-pressure lowering and glycemic benefit of these drugs, obese hypertensive patients with or without diabetes that have GHF, represent a category where SGLT2 inhibition may be peculiarly useful. Appropriate clinical trials should be conducted to test this hypothesis.[17] Once a primary care provider identifies a patient with albuminuria and/or GHF, appropriate interventions should be initiated to reduce the burden of HF as well as occlusive vascular disorders. ❑

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