

## **Supplemental Material**

### **Risk Factors (Expanded)**

Traditionally, the risk factors for HF in both T2D and T1D include diabetes duration, poor glycemic control, uncontrolled hypertension, hyperlipidemia, higher BMI, microalbuminuria, renal dysfunction, ischemic heart disease, and peripheral artery disease (1–3). Current trends suggest control of risk factors is poor in those with diabetes (4), emphasizing importance of careful review for each during clinical visits.

### *Role of Obesity*

Obesity exerts similar adverse effects on the risk of incident HF among individuals with T2D and prediabetes (2,5–7). In several large population-based studies, BMI significantly predicted incident HF among patients with T2D, T1D, and prediabetes (2,5,7).

### *Role of Hypertension*

The risk of HF development is exaggerated with the (common) coexistence of diabetes and hypertension (8) and the frequent combination of poorly controlled hypertension and diabetes is particularly problematic with respect to HF risk. For example, in the UKPDS cohort, risk of incident HF increased by 12% for every 10 mmHg above systolic BP 130 mmHg (9). A meta-analysis including 193,424 individuals with hypertension showed that those with diabetes had a fourfold increased risk of HF development compared with those without diabetes (10), while participants with T2D and hypertension in the Strong Heart Study (11) had a 2.6 higher 12-year risk of HF than those with normal fasting glucose. Conversely, optimal BP control was shown to decrease risk of new HF by ~50% (12).

### *Role of Hyperlipidemia*

Due to genetic factors, excess weight, and insulin resistance, individuals with T2D have a wide spectrum of lipid abnormalities such as increased small dense LDL particles, elevated plasma triglycerides, and decreased HDL cholesterol, all contributing to accelerated atherosclerosis and increased cardiovascular risk (13). In contrast, individuals with T1D with optimal glucose control have normal or slightly decreased plasma LDL cholesterol and triglycerides, and their plasma HDL cholesterol levels are normal or elevated. Despite normal or even increased levels of HDL cholesterol in T1D, the CVD and HF risks are considerable. This paradox could suggest a potential role of functional abnormalities of HDL particles in individuals with T1D (14) (Supplementary Fig. 1).

Hypercholesterolemia is associated with increased risk for the development of HF (15), and lipid-modifying therapy trials have demonstrated that treatment with statins decreases incidence of HF (16). Although large epidemiological studies such as MESA (17) or the Physicians' Health Study (18) failed to show that specific dyslipidemia such as high triglyceride or low HDL cholesterol levels were significant predictors of incident HF in the general population, the risk of incident HF was greater in individuals with diabetes who also had high triglyceride or low HDL cholesterol levels or high total cholesterol-to-HDL cholesterol ratio (19).

### *DKD*

Kidney disease and diabetes are both major and independent risk factors for the development of HF; thus, individuals with DKD are at especially high risk (20). Such individuals not only are more likely to have coronary artery disease and hypertension but also are more likely to have diabetic cardiomyopathy (20). Accordingly, early recognition and management in these individuals are crucial.

Among individuals with DKD, both albuminuria and the level of estimated glomerular filtration rate (eGFR) are predictors of HF in those without HF, as shown in several large longitudinal DKD cohorts (21,22). Individuals with T2D with eGFR 45–60 mL/min/1.73 m<sup>2</sup> have ~25–35% increased risk for HF hospitalization, and this risk increases by 2.0–2.5 times in individuals with eGFR <30 mL/min/1.73 m<sup>2</sup> (23).

In individuals with T1D, the risk of HF hospitalization is double at eGFR 45–60 mL/min/1.73 m<sup>2</sup>, and more than triple at eGFR <30 mL/min/1.73 m<sup>2</sup>, compared with that associated with normal eGFR (24). Moreover, the risk of cardiorenal disease (HF and DKD) may be higher, 1.4- to 3.0-fold, in adults with T1D across various ages compared with adults with T2D (25).

### *CAD*

CAD is a major risk factor for and a common cause of HF in all individuals with diabetes and it is often premature, diffuse, severe, and silent (26–28). In addition, individuals with diabetes and CAD have worse outcomes after acute myocardial infarction (26,29,30). Recently reported evidence from >70,000 individuals admitted with acute myocardial infarction included in the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART) registry shows that HF risk was twice as high among those with diabetes during a mean follow-up of ~3 years compared with individuals without diabetes (31).

### *Sex Differences*

In the Framingham Heart Study, incident HF risk was twofold higher in men and fivefold higher in women with diabetes compared with the respective general population (32). Several more recent large cohort studies subsequently confirmed that women with diabetes have higher

risks of incident HF and hospitalization for HF (1,33) than men with diabetes. In a global meta-analysis of >12 million individuals to examine sex differences in the excess risk of HF associated with diabetes (34), women with T1D and T2D demonstrated a respective 47% and 9% excess risk of HF compared with men with the same diabetes types.

CAD is a major cause of HF in people with T2D, and the excess CAD risk associated with diabetes is greater in women compared with men irrespective of age (35). Evidence highlights that women with diabetes may have overall poorer control for several established cardiovascular risk factors (e.g., blood glucose, blood pressure, cholesterol, and smoking status) than men with diabetes (36). Although it is not yet established whether these discrepancies are due to undertreatment, poorer access to health care, or some other cause (36), recently reported data indicated that women with diabetes are less likely to receive cardioprotective medications such as statins and ACE inhibitors compared with men (37).

### *SDOH*

SDOH affect development and progression of HF (38,39). In both T1D and T2D, low income and low educational attainment increase morbidity and worsen outcomes and mortality risk irrespective of health care access and have a negative impact on health outcomes in individuals with HF (40) through barriers to accessing health insurance, medications, and high-quality foods and maintaining timely follow-up for long-term care. Food insecurity, often viewed as a surrogate marker of low socioeconomic status, poverty, and increased health risk, may represent a major risk factor for increased prevalence of cardiometabolic disorders including HF (41), as it has the potential to propagate a cycle of poor metabolic control, which then precipitates heart disease and HF. People with diabetes who live in insecure or poor housing conditions may

experience up to 70% higher rates of myocardial infarction, stroke, and HF (42) and have increased emergency room visits and hospital admission (43,44).

Although the inequity regarding both CVD and diabetes among the U.S. population has recently been highlighted (42), better understanding of race-specific risk factors for those with diabetes and HF is needed.

#### *Key Points*

- Nonglycemic risk factors amplify risk for HF in those with diabetes.
- Individuals with DKD are at especially high risk of developing HF.
- The increase in risk of HF is greater for women with diabetes than for men in comparisons with individuals without diabetes.
- Women with diabetes may have overall poorer control for the traditional cardiovascular risk factors, potentially further increasing HF risk.
- SDOH play an important role in HF risk.

**Supplementary Figure 1**—Pathophysiology of HF in diabetes. AGEs, advanced glycemc end products; ER, endoplasmic reticulum; FA, fatty acid, CA, calcium.

**Supplementary Figure 2**—Components of cardiac rehabilitation. Adapted with permission from Winnige et al. (45).

**Supplementary Table 1—Prevalence and incidence of HF among individuals with prediabetes and diabetes**

Cohort	Population studied	Duration of follow-up	Findings
Framingham Heart Study (32)	5,209 individuals age 30–62 years, no HF at baseline	18 years	<u>Incident HF</u> : RR vs. no diabetes 1.82 for men with diabetes 3.75 for women with diabetes
NHANES I Epidemiologic Follow-up Study (46)	13,643 individuals, no HF at baseline	19 years	<u>Incident HF</u> : RR vs. no diabetes 1.85 (95% CI 1.51–2.28)
Reykjavik Study (5)	19,381 individuals, age 33–84 years	30 years	a) <u>Prevalent HF rates</u> : 11.8 % in diabetes, 6.0% in IGT 3.2% in no diabetes. b) <u>HF and diabetes</u> , age-adjusted OR 2.8 (95% CI 1.9–4.1) for women, 2.7 (1.9–3.9) for men
Cardiovascular disease research using Linked Bespoke studies and Electronic health Records (CALIBER) (47)	1,921,260 individuals, 1.8% with T2D age ≥30 years; no CVD at baseline	5.5 years*	<u>Incident HF</u> : HR vs. no diabetes 1.56 (95% CI 1.45–1.69);
Scottish diabetes mellitus register (33)	3,066,253 individuals with no diabetes,	3 years	<u>Incident HF</u> : No diabetes, 2.4/1,000 person-years; T2D, 12.4/1,000 person-years;

Saskatchewan Health databases (48)	136,042 T2D individuals 18,240 T1D individuals 12,272 individuals with recent-onset T2D	5.2 years	T1D, 5.6 /1,000 person-years Incident HF: rate ratio vs. no diabetes 2.9 (95% CI 2.6–3.2)
Kaiser Permanente Northwest (6)	8,231 T2D individuals 8,845 age-sex-matched s no diabetes individual; no HF at baseline	6 years	Incident HF: rate ratio vs. no diabetes 2.5 (95% CI 2.3–2.7)
Kaiser Permanente Georgia (49)	359,947 individuals no HF at baseline	1,015,794 person-years	Incident HF diabetes vs no diabetes : Women HR 2.03 (95% CI 1.84–2.37) Men HR 1.71 (1.55–1.89)
Taiwan's National Health Insurance system (50)	34,291 T2D participants 34,291 age- and sex- matched no diabetes; no HF at baseline	7.79 years	Incident HF vs. no diabetes: HR 1.47 (95% CI 1.40–1.54)
Swedish National Diabetes Registry Cohort 1 (2)	20,985 T1D individuals no HF at baseline	9.0 years*	Incident HF (95% CI): 3.38/1,000 person-years (3.12–3.65)
Swedish National Diabetes Registry Cohort 2 (1)	33,402 T1D individuals 166,228 age-, sex-, and county-matched control subjects	7.9 years for T1D cohort, 8.3 years for control cohort	<u>Rates of HF hospitalization</u> (95% CI) no diabetes: 0.97/1,000 person-years (0.91–1.02); T1D: 4.00/1,000 person-years (3.77–4.25) <u>Incident HF</u> : HR vs. no diabetes (95% CI) 4.69 (3.64–6.04)
ARIC study	11,057 individuals with no diabetes at baseline	14 years	Incident HF: HR (95% CI) HbA <sub>1c</sub> 6.0–6.4%: 1.40 (1.09–1.79), HbA <sub>1c</sub> 5.5–6.0%: 1.16 (0.98–1.37). Comparator: HbA <sub>1c</sub> 5.0–5.4%

\*Median duration. HF, heart failure; HR, hazard ratio; OR, odds ratio; T1D, type 1 diabetes; T2D, type 2 diabetes.

**Supplementary Table 2—Prevalence and incidence of diabetes among individuals with HF in population-based analyses and clinical trials**

Cohort	Population studied	Duration of follow-up	Findings
Cardiovascular Health Study (51)	3,748 elderly individuals (age ≥65 years) no diabetes at baseline	3–4 years	<u>Incident diabetes</u> : among those with history of HF OR 2.43 (95% CI 1.38–4.29)

Studies Of Left Ventricular Dysfunction (SOLVD) (52)	291 individuals reduced LV function no diabetes at baseline	2.9 ± 1.0 years	Incident diabetes: 47 cases/1,000 person-years
Candesartan in <i>Heart Failure—Assessment of Reduction in Mortality and Morbidity Program (CHARM)</i> (53)	5,436 individuals reduced LVEF (≤40%) no diabetes at baseline	2–4 years	Incident diabetes: 28 cases / 1,000 person-years
Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) (54)	1,846 individuals mild systolic HF no diabetes at baseline		Incident diabetes: 21 cases/1,000 person-years
Carvedilol Or Metoprolol European Trial (COMET) (55)	2,298 individuals chronic HF no diabetes at baseline	5 years	Incident diabetes: 20 cases/1,000 person-years
PARADIGM-HF (56)	8,442 individuals class II, III, or IV HF reduced EF (≤40%)	27 months*	Incident diabetes: 13 cases /1,000 person-years

EF, ejection fraction; HF, heart failure; LV, left ventricle; OR, odds ratio. \*Median.

**Supplementary Table 3—Lifestyle/nutrition therapies for people with diabetes and HF**

Type of intervention	Consensus recommendations	Notes
Physical activity	<ul style="list-style-type: none"> <li>• Regular structured exercise should be discussed.</li> <li>• Individualize the exercise training for each person, with a targeted tailored plan based on risk stratification, clinical assessment, and cardiopulmonary exercise testing before initiation of exercise training for people with diabetes and HF (57).</li> <li>• Those more deconditioned individuals will need to start at a lower training intensity and with shorter sessions.</li> <li>• In general, a combination of aerobic exercise and resistance training protocols is recommended, preferably throughout entire life.</li> </ul>	<ul style="list-style-type: none"> <li>• Shown to improve exercise capacity, symptoms, and quality of life for people with HF.</li> <li>• Recognize that not all individuals will be able to participate in a structured exercise training program; care providers should identify barriers and facilitators to best support patients.</li> </ul>
Cardiac rehabilitation	<ul style="list-style-type: none"> <li>• Programs include tailored combination of exercise, education on cardiovascular risk factors, psychological support, lifestyle modification, and medical care (with focus on medications with secondary cardiovascular prevention benefits).</li> </ul>	<ul style="list-style-type: none"> <li>• People with diabetes are significantly less likely to be referred for cardiac rehabilitation (59).</li> </ul>



	<ul style="list-style-type: none"> <li>• Cardiac rehabilitation is most effective in persons with HF with reduced ejection fraction and diabetes (58)</li> <li>• Referring eligible individuals with diabetes and HF to cardiac rehabilitation should be a high priority.</li> <li>• Home-based cardiac rehabilitation may be an alternative for selected clinical stable low-to moderate risk individuals</li> </ul>	
Serum potassium	<ul style="list-style-type: none"> <li>• Clinical monitoring of potassium levels in people with diabetes should be part of management plans</li> <li>• Serum potassium should be assessed within 2 to 3 days and again at 7 days. The schedule for subsequent monitoring should be dictated by the clinical stability of renal function and volume status but should occur at least monthly for the first 3 months and every 3 months thereafter</li> <li>• People should be educated to avoid over-the-counter potassium supplements and potassium-based salt substitutes</li> <li>• Limited intake of high-potassium food and beverages</li> <li>• Avoidance of medications that may increase risk for hyperkalemia (such as nonsteroidal anti-inflammatory drugs).</li> </ul>	<ul style="list-style-type: none"> <li>• People with diabetes are at increased risk of developing hyperkalemia in the setting of RAAS blockade including the combination of ARB and neprilysin inhibitors (60,61).</li> <li>• Serum potassium levels were shown to independently predict mortality in HF.</li> </ul>
Smoking	<ul style="list-style-type: none"> <li>• Smoking cessation counseling</li> <li>• Appropriate referrals for smoking support</li> </ul>	
Dietary salt	<ul style="list-style-type: none"> <li>• In general, lowering sodium intake (to &lt;2300 mg/d or even lower, to &lt;1500 mg/d) (3,62)</li> <li>• The DASH diet, the ADA recommendations for medical nutrition therapy, and the AHA/ACC lifestyle management guidelines can all be used to guide dietary sodium recommendations.</li> </ul>	<ul style="list-style-type: none"> <li>• The optimal quantity of salt in the diet is still a subject of debate. The amount should be adapted to the clinical situation, the severity of symptoms, and baseline consumption without interfering with other nutritional content.</li> </ul>
Fluid intake	<ul style="list-style-type: none"> <li>• Restriction of daily fluid intake to approximately 2 L/d should be considered for people with fluid retention or congestion that is not easily controlled with diuretics (3,62,63)</li> <li>• Severely limiting daily fluid intake to &lt; 1.5 L might have adverse consequences on nutrition, renal function, and quality of life without known additional benefit and should be applied selectively.</li> <li>• Special consideration for person with hyponatremia should be applied</li> </ul>	<ul style="list-style-type: none"> <li>• The appropriate quantity of fluid intake is a subject of debate. Strict limits should be imposed when there is clear fluid overload or demonstrated sensitivity to fluid intake.</li> </ul>
Alcohol	<ul style="list-style-type: none"> <li>• Minimize alcohol intake</li> <li>• Promote person education regarding management strategies of hypoglycemia and hypoglycemia unawareness.</li> </ul>	<ul style="list-style-type: none"> <li>• Alcohol intake in individuals with diabetes can increase the risk for delayed hypoglycemia and blunt hypoglycemia awareness.</li> </ul>

Dietary recommendations	<ul style="list-style-type: none"> <li>• Should be individually tailored according to caloric requirements, personal and cultural food preferences, prescribed medications, presence of overweight /obesity and comorbid medical conditions</li> <li>• Decrease of energy density: &lt; 125 kcal/100 g of consumed food is recommended compared to the average values &gt; 160 kcal/100 g in the USA and UK populations.</li> <li>• Reducing the intake of saturated fat (to 5% to 6% of total calories)</li> <li>Eliminating trans fat</li> <li>• Increased intake of dietary fiber</li> <li>• A Mediterranean-style diet high in MUFA is a recommended alternative to consuming a high-carb low-fat diet</li> <li>• Dietary patterns that focus on the intake of vegetables, moderate amounts of fruit and whole grains, poultry, fish, low-fat dairy, legumes, nontropical vegetable oils and nuts.</li> <li>• Intake of sweets, sugar-sweetened beverages and red meats should be limited</li> <li>• DASH diet (vegetables, fruits, whole gains, low fat milk products, nuts, fish, lean poultry)</li> </ul>	<ul style="list-style-type: none"> <li>• The ADA recommendations for medical nutrition therapy and the AHA/ACC lifestyle management guidelines can all be used to guide dietary recommendations (64,65).</li> </ul>
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**Supplementary Table 4—Pharmacological treatment for managing hyperglycemia in individuals with diabetes and HF (66–68)**

Type of intervention	Consensus recommendations	Notes
<b>SGLT2i</b>	<ul style="list-style-type: none"> <li>• Empagliflozin, canagliflozin, and dapagliflozin decreased risk of HF hospitalizations and major CVD outcomes in large randomized trials of individuals with T2D and either established ASCVD or high ASCVD risk (69–72).</li> <li>• Dapagliflozin and empagliflozin have been found to decrease risk of CV death and worsening HF in individuals with HFrEF and are recommended treatments for people with HFrEF with or without diabetes.</li> <li>• Canagliflozin and dapagliflozin are recommended for people with T2D and established CKD with albuminuria (UACR <math>\geq 200</math> mg/g).</li> <li>• Additional data suggest a benefit to SGLT2i therapy in individuals with both HFpEF and HF, and in CKD without significant albuminuria (69–72).</li> <li>• SGLT2i are therefore recommended for individuals with T2D and high ASCVD risk, HF, or CKD irrespective of the need for glucose lowering.</li> </ul>	<ul style="list-style-type: none"> <li>• Mechanisms for cardiorenal benefits include: increased natriuresis with associated decrease in plasma volume and cardiac preload, lower systolic blood pressure, decreased aortic stiffness, weight loss, and reductions in oxidative stress, advanced glycation end products, and inflammation.</li> <li>• Use of SGLT2i may increase risk of urinary and genital infections and dehydration and should not be initiated if people are following a very-low-carbohydrate diet.</li> </ul>

	<ul style="list-style-type: none"> <li>• For people with diabetes and stage B HF, SGLT2i should be started as early as possible, while for those with HF stage C and higher SGLT2i are an expected element of care.</li> </ul>	
<b>GLP-1RA</b>	<ul style="list-style-type: none"> <li>• Benefits of GLP-1RA in individuals with T2D and HF remain less well established in comparison with SGLT2i.</li> <li>• GLP-1RA should be considered for treating hyperglycemia in individuals with T2D at risk for or with established HF if SGLT2i are contraindicated or not tolerated, including in individuals with advanced CKD.</li> <li>• GLP-1RA may also be considered as additional therapy for such persons if adequate glycemic control is not achieved with use of an SGLT2i, as they have indirectly beneficial effects on weight, BP, and CKD with a reduced risk of hypoglycemia.</li> </ul>	<ul style="list-style-type: none"> <li>• Results from meta-analysis of smaller studies indicated that liraglutide may be associated with improvements in LVEF, LVESV, and LV filling pressure (74–76).</li> <li>• Potential cardiovascular effects are likely mediated by reduced RAAS activity, reduced oxidative stress, decreased blood pressure, improved endothelial function, and reduced triglycerides and LDL levels.</li> <li>• GLP1-RA use increases risk for GI-related side effects.</li> </ul>
<b>Metformin</b>	<ul style="list-style-type: none"> <li>• If additional glycemic control is indicated beyond SGLT2i monotherapy for individuals at risk for or with established HF, use of metformin or GLP-1RA should be favored over sulfonylurea therapy.</li> <li>• In the absence of contraindications, metformin is safe and effective, with a reduced risk of hypoglycemia and weight gain (77,78).</li> </ul>	<ul style="list-style-type: none"> <li>• From recent meta-analyses including large cohorts it was reported that metformin was associated with significant reduction in all-cause hospitalization for people with HF.</li> <li>• Metformin was associated with lower risk of HF hospitalization compared with sulfonylureas including in those with reduced EF.</li> <li>• Metformin may increase risk for GI side effects.</li> </ul>
<b>Sulfonylureas</b>	<ul style="list-style-type: none"> <li>• Use of sulfonylureas should be judiciously considered in those situations when therapies with proven benefit for HF are not available (78).</li> </ul>	<ul style="list-style-type: none"> <li>• Sulfonylurea use may increase risk of severe and recurrent hypoglycemia and weight gain.</li> </ul>
<b>Insulin</b>	<ul style="list-style-type: none"> <li>• If insulin is needed for management of hyperglycemia, it should be used judiciously to prevent hypoglycemia, weight gain, and other adverse events (79).</li> </ul>	<ul style="list-style-type: none"> <li>• Insulin use may increase risk of severe hypoglycemia and weight gain.</li> </ul>
<b>DPP-4 inhibitors</b>	<ul style="list-style-type: none"> <li>• DPP-4 inhibitors are not recommended for people with T2D with stage B, C,D HF.</li> </ul>	
<b>TZDs</b>	<ul style="list-style-type: none"> <li>• TZDs are not recommended for use in individuals with stage B HF and are contraindicated for those with stage C or D.</li> </ul>	<ul style="list-style-type: none"> <li>• TZDs increase risk of fluid retention and weight gain.</li> </ul>

CV, cardiovascular; EF, ejection fraction; GI, gastrointestinal; LVESV, left ventricular end-systolic volume; LV, left ventricular; UACR, urine albumin-to-creatinine ratio.

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