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State-of-the-Art Review

Preventing new-onset heart failure: Intervening at stage A

Bharathi Upadhya [a,*], Shriram Hegde [b], Manasi Tannu [a], R . Brandon Stacey [c], Andreas Kalogeropoulos [d], Douglas D . Schocken [a]

[a] Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA
[b] Stony Brook University, Long Island, NY, USA
[c] Section on Cardiovascular Medicine, Department of Internal Medicine, Wake Forest School of Medicine, Winston-Salem, NC, USA
[d] Division of Cardiology, Department of Medicine, Stony Brook University School of Medicine, Long Island, NY, USA

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ABSTRACT

Heart failure (HF) prevention is an urgent public health need with national and global implications. Stage A HF patients do not show HF symptoms or structural heart disease but are at risk of HF development. There are no unique recommendations on detecting Stage A patients. Patients in Stage A are heterogeneous; many patients have different combinations of risk factors and, therefore, have markedly different absolute risks for HF. Comprehensive strategies to prevent HF at Stage A include intensive blood pressure lowering, adequate glycemic and lipid management, and heart-healthy behaviors (adopting Life's Essential 8). First and foremost, it is imperative to improve public awareness of HF risk factors and implement healthy lifestyle choices very early. In addition, recognize the HF risk-enhancing factors, which are nontraditional cardiovascular (CV) risk factors that identify individuals at high risk for HF (genetic susceptibility for HF, atrial fibrillation, chronic kidney disease, chronic liver disease, chronic inflammatory disease, sleep-disordered breathing, adverse pregnancy outcomes, radiation therapy, a history of cardiotoxic chemotherapy exposure, and COVID-19). Early use of biomarkers, imaging markers, and echocardiography (noninvasive measures of subclinical systolic and diastolic dysfunction) may enhance risk prediction among individuals without established CV disease and prevent chemotherapy-induced cardiomyopathy. Efforts are needed to address social determinants of HF risk for primordial HF prevention.

* Corresponding author at: Division of Cardiology, Department of Medicine, Duke University School of Medicine, 2301 Erwin Rd, Durham, NC 27710, USA.
E-mail address: Bharathi.upadhya@duke.edu (B. Upadhya).

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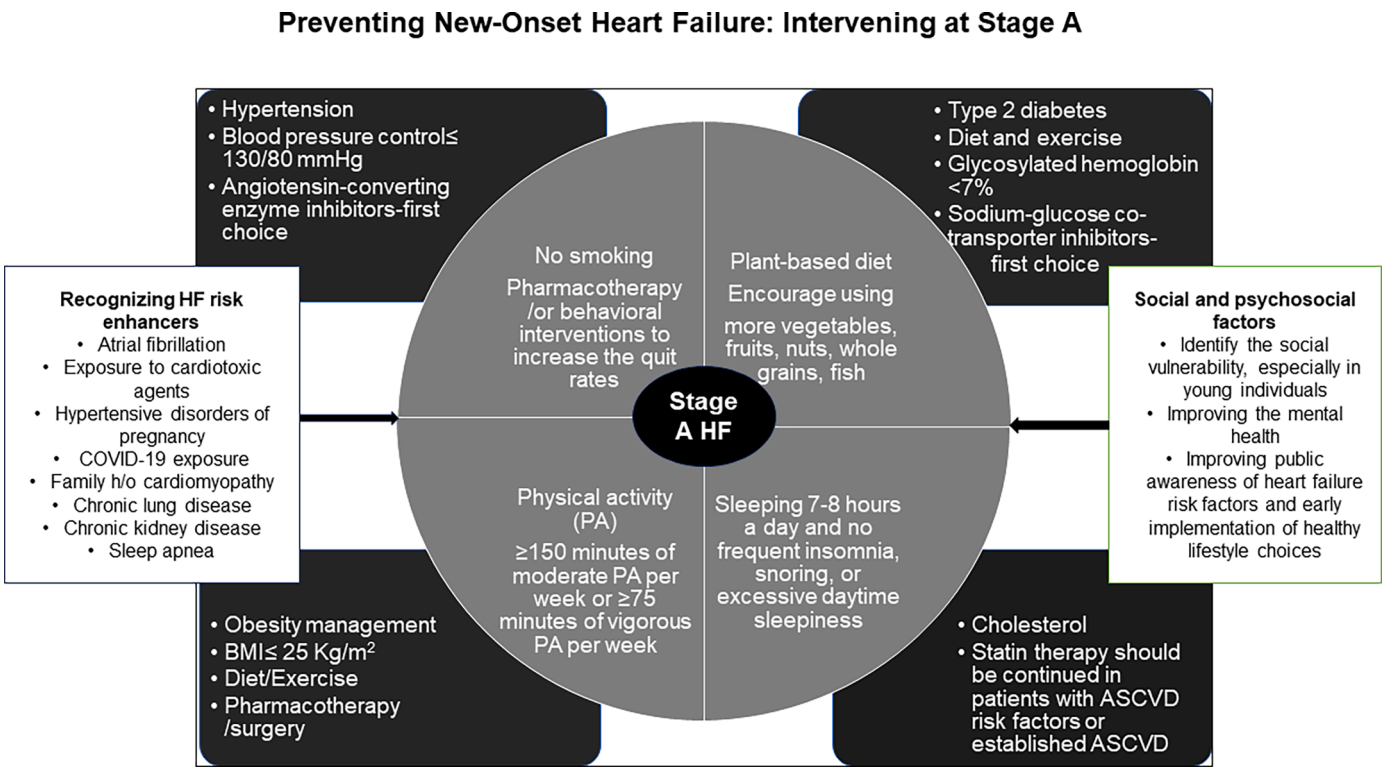

Policies developed by organizations such as the American Heart Association, American College of Cardiology, and the American Diabetes Association to reduce CV disease events must go beyond secondary prevention and encompass primordial and primary prevention.

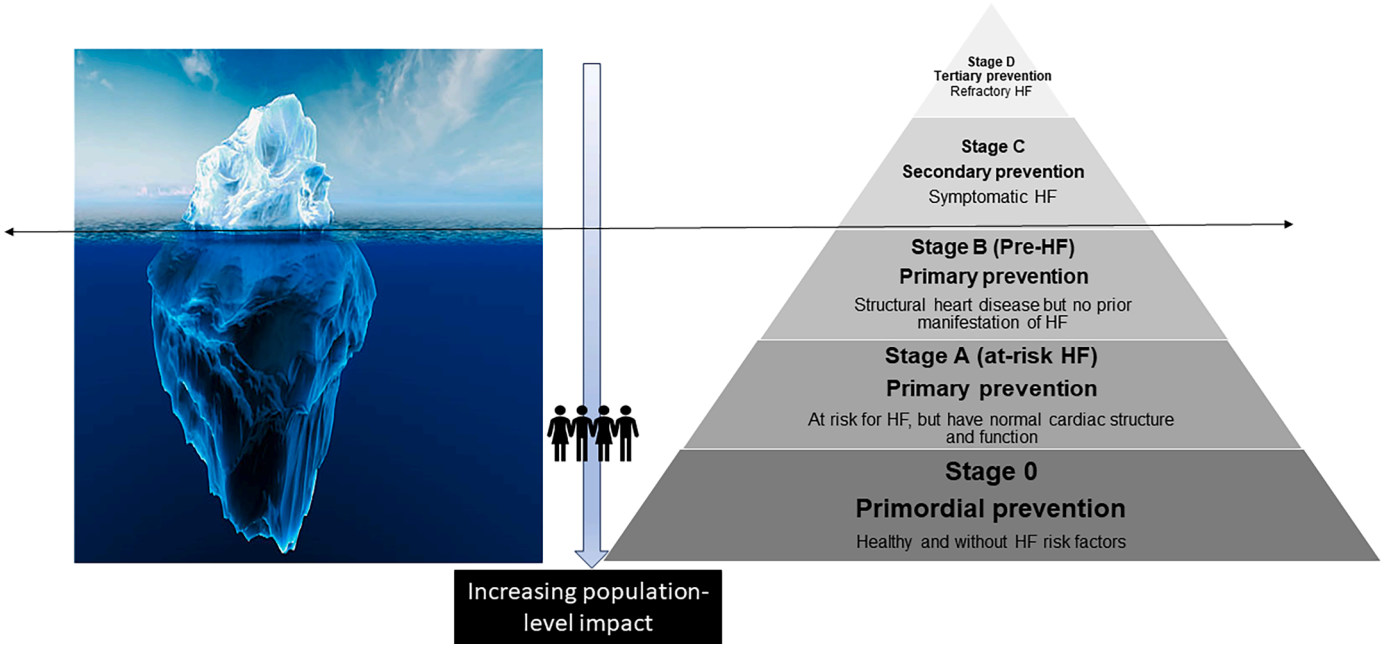

Fig. 1. Clinical significance of Stage A heart failure (HF).

1. Clinical significance

Recognizing the clinical continuum of heart failure (HF), The American College of Cardiology (ACC) and the American Heart Association (AHA) introduced the concept of HF stages and described the HF stages from Stages A to D based on the development and progression of the structural and functional changes and symptoms (Fig. 1) [1]. Stage 0 is defined as healthy and without HF risk factors or abnormal ventricular structure or function [1]. Stage A patients do not show HF symptoms or structural heart disease, or cardiac biomarkers of stretch or injury but have comorbid diseases with a high risk of progressing to HF, such as hypertension (HTN), diabetes (DM), obesity, atherosclerotic cardiovascular (CV) disease (ASCVD) and exposure to cardiotoxins. Survival steeply decreases from Stage A to D, with estimates of a 9-fold increase in mortality once Stage C HF develops [2].

Unlike the NYHA classification, the stages are progressive; a patient may progress from Stage A to Stage D but cannot return to Stage A. Thus, it is even more critical to address Stage A HF as the best means of preventing eventual progression to overt HF, such as Stages C and D. Additionally, from a population-level perspective, the effective prevention strategy identifies the at-risk population before developing the disease (ACC Stage 0/A and B HF) who were primarily managed by primary care providers and general or preventive cardiologists, rather than advanced HF practitioners. As shown by multiple prior cross-sectional population-based community studies, the population at risk (prevalence of Stage A or B HF) is much larger than those with clinical signs or symptoms (Stage C or D) (Fig. 2) [2–8]. Our ceaseless efforts focus on secondary and tertiary prevention in Stage C and Stage D HF, respectively, to mitigate the residual risk; however, they only constitute a small population of HF (Figs. 1 and 2), representing the tip of the iceberg [2–8]. Despite many advances in therapies and immense resources spent on treatment for symptomatic HF, the onset of symptomatic HF remains associated with a poor prognosis [9]. Once HF symptoms and signs develop (Stages C and D), there is no cure for HF, and at that point, we can only try to stabilize the problem. Therefore, our prevention efforts must go beyond secondary prevention and encompass primordial prevention [preventing the development of CV risk factors Stage 0)] and the primary prevention of HF (preventing the onset of disease in people at high risk -Stage A) before irreversible myocardial changes that cause symptomatic HF begin (Stage C and D). This review summarizes the evidence supporting the primary prevention of HF and identifies potential approaches to intervene at Stage A HF.

2. Preventing new-onset HF: intervening at stage 0/A

To prevent the development of CVD, including HF, the AHA introduced Life's Simple 7 (LS7) to help people achieve ideal cardiovascular health (CVH) [10]. Recently, AHA enhanced LS7 by adding sleep; hence they introduced life's essential 8 (LE8) as a more optimal tool to assess CVH [11]. LS7 and LE8 metrics are a simple way to identify higher-risk individuals (Stage A) and focus on reducing modifiable risk factors and optimizing health behaviors.

Several studies have established the relationship between LS7 and incident HF, showing that reduced risk for HF was achieved with a more favorable LS7 score (Table 1) [12–16]. A prospective study that included 250,825 participants (median follow-up of 10.4 years) showed that individuals with a lower LE8 score experienced more CVD events, driven primarily by incident HF [17]. Studies showed that an inadequate

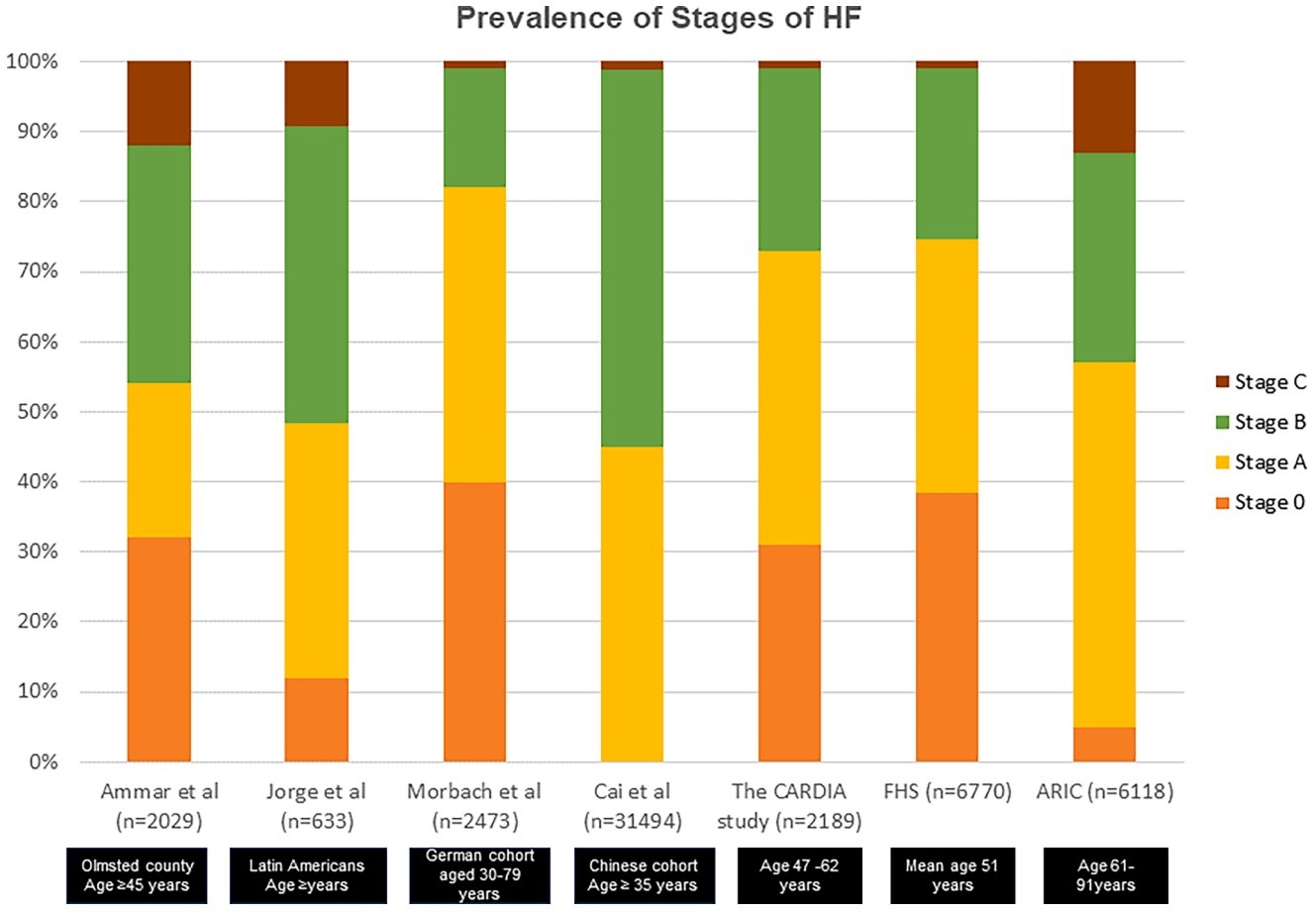

Fig. 2. Prevalence of stages of heart failure (HF).
CARDIA=Coronary Artery Risk Development in Young Adults, FHS=Framingham Heart Study ARIC=Atherosclerosis Risk In Communities.

healthy lifestyle to an intermediate healthy lifestyle is beneficial in lowering HF incidence [16]. Furthermore, studies have demonstrated significant benefits in adopting healthy behaviors even if they start later in life [18].

Of LS7, diet- and activity-related habits can be influenced at an earlier stage in life and, therefore, are the keys to the primordial prevention of CVD. Plant-based diets are high in antioxidants, micronutrients, dietary nitrate, and fiber but low in saturated and trans fats, and sodium is associated with decreased HF incidence [19]. These dietary features might contribute to decreased oxidative stress, reduced inflammation, increased nitric oxide bioavailability, and gut microbiome modulation [19]. Overall, the Mediterranean-style and dietary approaches to stop hypertension (DASH) diets are rich in plant-based foods and low in processed foods and red meat. The AHA presidential advisory group supports pursuing DASH- and Mediterranean-style eating patterns for optimal CVH [11].

Effects of physical activity (PA) are broad and pleiotropic; they decrease blood pressure (BP), improve metabolic health, improve vascular function, decrease markers of inflammation, improve oxidative stress, decrease vascular stiffness, improve endothelial function, prevent age-related cardiac remodeling, prevent systolic and diastolic dysfunction, and mitigate the maladaptive pro-hypertrophic effect [20–31]. The current guidelines for CVD prevention, which recommend 150 min of moderate PA per week or 75 min of vigorous PA per week, should also be used to prevent HF [11].

Both current and past smoking is a risk factor for HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFrEF), independent of traditional CVD risk factors [32–40]. Epidemiological studies also showed the dose-response relationship between the level of secondhand exposure (as measured by serum cotinine $\geq$ 1 ng/ml) and HTN, left ventricular (LV) hypertrophy, and incident HF [41, 42]. There are no reports of association of incident HF with an e-cigarette or vaping device [11].

The dose of alcohol to cause cardiomyopathy is not well described epidemiologically. Alcohol consumption of 80 to 90 g (≈8 drinks) per day for five years puts one at risk for alcoholic cardiomyopathy [43,44]. Light to moderate alcohol intake (2 drinks or less daily for men or 1 drink or less daily for women) has been associated with a lower risk of coronary artery disease (CAD), HF, and CV mortality [45]. However, considerable limitations exist in the reported literature to establish a

Table 1
Studies that evaluated the relationship between LS7 and incident HF.

Trial	LS7 scoring *	LS7 categories	Population	Duration	Outcomes
MESA[12] (n = 6506)	LS7-graded on a scale of 0 to 2, with 2 indicating "ideal" status, 1 "intermediate" status, and 0 "poor" status. Points were summed; thus the LS7 score ranged from 0 to 14	Ideal (≥11 points), intermediate (9 or 10 points), inadequate (≤8 points)	Mean age 62 years, 53%: women, 26%: AAs	Median 12.2 years	Compared with inadequate scores, HRs with CI for HF were 0.57(0.43–0.76) and 0.31 (0.19–0.49) for intermediate and ideal scores, respectively. No data is available on HF phenotype. AAs participants had the highest incidence of HF and the poorest LS7 status, followed by Hispanic, Caucasian, and Chinese American participants.
FOS[13] (n = 3101)	Each participant assigns a score of 0 (poor status), 1 (intermediate status), or 2 (ideal status) for each of the 7 metrics.	Linear scale: 0–14 points Score can vary from a minimum of 0 (consistent with poor CVH) to a maximum of 14 (indicating ideal CVH)	Mean age 58 years, Predominant Caucasians, 56%: Women	Mean-12.3 years	In age- and sex-adjusted Cox proportional HR models, the CVH score was inversely associated with HF incidence (HR per 1-point higher CVH score 0.77, 95% CI 0.72–0.83) Higher scores were associated with a lower prevalence of concentric remodeling and LV wall thickness, mass, and LA dimension.
ARIC[14] (n = 13,462) [Echo:6538 participants]	Each participant assign a score of 0 (poor status), 1 (intermediate status), or 2 (ideal status) for each of the 7 metrics (range 0–14)	Ideal (≥10 points), intermediate (5–10 points), inadequate (≤4 points)	Mean age 54 years, 55%: women, 24.3%: AA	Median-22.5 years	The lifetime risk was 14.4% for those with an optimal score of 10–14, 26.8% for those with an average score of 5–9, and 48.6% for those with an inadequate score of 0–4. The ideal score was associated with lower LVH and diastolic dysfunction.
Jackson Heart (JHS) [15] (n = 4195)	Score 1 (ideal status) or 0 (nonideal) for each of the LS7 metrics. They used metrics already adjudicated within the JHS (as opposed to ideal, intermediate, and poor categories)	Ideal ≥4 ideal components (≥8 points), intermediate (5–7 points), inadequate 0–2 ideal components (0–4 points)	Mean age 54.4 years, 65%: women, 100%: AAs	Median-9.9-year	Relative to 0 to 2 LS7, AAs with 3 factors had 47% lower incident HF risk (HR, 0.53; 95%CI, 0.39–0.73); and those with ≥4 factors had 61% lower HF risk (HR, 0.39; 95% CI, 0.24–0.64). Achieving ideal BP, BMI, glucose, and smoking was associated with a lower risk of adverse cardiac remodeling.
EPIC—NL[16] (n = 37,803)	All risk factors were scored as ideal (2 points), intermediate (1 point), or inadequate (0 points).	Ideal (≥11 points), intermediate (9 or 10 points), inadequate (≤8 points)	Mean age 49 years, 75%: women, European cohort.	Mean-15.2 years	In Cox proportional hazards models, ideal and intermediate LS7 scores were associated with reduced risk for HF compared with the inadequate category (HR: 0.45 [95% CI: 0.34 to 0.60] and HR: 0.53 [95% CI: 0.44 to 0.64], respectively). Clusters, including glucose, BMI, smoking, or BP, were notably associated with a lower incidence of HF.

* Each metric according to LS7 categories of ideal, intermediate, or poor.[10]

LS7=Life's Simple 7, HF=heart failure, n=number of participants, MESA=Multi-Ethnic Study of Atherosclerosis, AA= African American, HR=hazard ratio, CI =confidence interval, FOS= Framingham Offspring Study, CVH=cardiovascular health, LV =left ventricle; LA =left atrium. ARIC =Atherosclerosis Risk in Communities Study, LVH =left ventricular hypertrophy, EPIC—NL=European Prospective Investigation Into Cancer and Nutrition-Netherlands, BP=blood pressure, BMI=body mass index, BP=blood pressure.

strong protective effect of moderate alcohol consumption [45]. The Guidelines do not recommend that individuals who do not drink alcohol start drinking for any reason.

Several organizations have adopted a population health value of ≈7 to 8 h of habitual sleep for adults [11]. In a study that included 408,802 participants aged 37 to 73 years, healthiest sleep patterns (morning risers, sleeping 7–8 h a day and no frequent insomnia, snoring, or excessive daytime sleepiness) were associated with a 42% reduction in the risk of HF [46].

3. Optimizing healthy behaviors

Education and promoting healthy lifestyle habits to the family should be emphasized very early. What can we do as physicians? One crucial thing is goal setting - helping patients visualize what they need to do to reach their goals may make them more likely to succeed [47]. The next thing is discussing possible obstacles to attaining the goal during visits [48]. Physicians should advise the patients to self-monitor their behavior changes and bring their tracking forms to follow-up visits, review them, celebrate successes, and discuss challenges. Encouraging patients to change their diets can be exhausting. Studies have shown that one way to combat this is to help patients commit to small measurable steps — for example, decrease the number of desserts per week by one and eat one more fruit or vegetable daily [49]. Another is the Plate Method, where their plates split into the following components: 50 percent fruits and non-starchy vegetables, 25 percent protein, and 25 percent grains or starchy foods. Discuss healthy options that would fit each category or combine this method with the small steps described above. Additionally, potential barriers to adhering to a healthy diet should be assessed. Clinicians should act as guides and work with patients to develop personalized PA prescriptions, potentially increasing patients' activity levels. The neighborhood environment and access to facilities for PA should be assessed [50]. The US preventive service task force recommends that clinicians ask all adults about tobacco use, advise them to stop using tobacco, and provide behavioral interventions and FDA-approved pharmacotherapy for cessation to nonpregnant adults [51]. Combining behavioral and pharmacotherapy interventions have been shown to increase tobacco smoking cessation rates compared with either usual care/brief cessation interventions alone or pharmacotherapy alone [52]. Also, individualized and group social support counseling is recommended for people who smoke [53].

4. Optimization of modifiable CVD risk factors for HF

Although a healthy lifestyle could improve CVH, it can be challenging to change one's lifestyle [54]. Thus, attention must be directed toward screening and aggressively treating well-recognized, traditional risk factors for CVD, such as HTN, DM, obesity, and dyslipidemia. Indeed, a pooled, individual-level analysis from 4 cohorts [framingham heart study (FHS), framingham offspring (FOS), Chicago Heart Association Detection Project in Industry, and atherosclerosis risk in communities (ARIC)] showed that the avoidance of HTN (BP≥140/90 mm Hg or treatment), obesity [body mass index (BMI) ≥30 kg/m^2], and DM (fasting glucose ≥126 mg/dl) or treatment by ages 45 years and 55 years might substantially prolong HF–free survival and reduce HF-related morbidity [55]. Recently, Hamo et al. performed a prospective analysis of 13 313 participants in the ARIC study [mean age, 57 years, 55% women, 24% african americans (AAs)] without prevalent HF [56]. They found that the presence of multiple uncontrolled CVD risk factors was linked to markedly increased HF risk [BMI ≥35 kg/m^2, systolic BP (SBP)≥160 mmHg, and glycosylated hemoglobin (HBA1c ≥8%)]. Patients with mildly to moderately uncontrolled risk factors (SBP 130 to <160 mm Hg; HBA1c 7% to 8%; BMI 30 to 35 kg/m2) had a lower incidence of HF than those with severely uncontrolled risk factors, suggesting even partial optimization of a risk factor, is treasured in HF prevention, even if the risk factor is not eliminated. More importantly, the absence of CVD risk factors was associated with the lowest incidence of HF, suggesting the value of primordial prevention.

4.1. Blood pressure management

Hypertension is the single most important modifiable factor for the development of HF and precedes HF diagnosis in up to 85% of persons [57]. The Systolic Blood Pressure Intervention Trial (SPRINT) ($n = 9361$, HTN with increased risk of CVD but without DM) showed the superiority of a SBP target of <120 mmHg compared to <140 mmHg, with a 36% lower rate of acute decompensated HF events [both HFpEF and HFrEF phenotypes] [58,59]. A post hoc analysis of SPRINT demonstrated greater risk reduction in those with the highest baseline CVD risk [60]. The optimal BP levels in DM remain controversial. Both 2017 ACC/AHA HTN and HF guidelines recommend that in adults with HTN and increased HF risk, including DM (Stage A), the optimal BP should be <130/80 mmHg [61,62]. European society of cardiology and european society of HTN (ESC/ESH) guidelines recommend reducing BP to <140/90 mmHg for all patients and, if tolerated, SBP for those aged under 65 should be reduced to between 120 and 129 mmHg [63].

Angiotensin-converting enzyme inhibitors (ACE-Is) should remain the medication class of choice for high-risk ASCVD patients with angiotensin receptor blockers (ARBs) reserved for ACE-Is intolerant individuals [64,65]. A meta-analysis showed that diuretics, ACE-Is, and ARBs were more effective than calcium channel blockers (CCBs) for HF prevention [66]. In The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), although diuretics had a somewhat greater effect on HF events than the doses used for CCB and ACE-I, this was explained by the fact that it significantly reduced SBP [67]. A recent meta-analysis supports that the most significant impact on HF prevention results from the magnitude of BP lowering, independent of the antihypertensive class [68]. Due to the greater morbidity and mortality associated with HTN in AAs, current guidelines for treating HTN in adults incorporate race-specific recommendations, including the initial use of thiazide-type diuretics or CCBs and two or more antihypertensive medications [61]. Emerging therapies for HF treatment, such as sacubitril-valsartan, demonstrate promise in preventing the progression from HTN to HFpEF, especially in older adults [69]. However, the long-term antihypertensive efficacy has not been thoroughly evaluated [70].

4.2. Diabetes management

Both type I DM (T1D) and type 2 DM (T2D) are independent risk factors for developing incident HF [71,72]. In a meta-analysis of 47 cohorts (>12 million individuals), T1D was associated with a 47% greater risk of HF in women compared with men, and T2D was associated with a 9% greater risk of HF in women than men [72]. Furthermore, poor glycemic control independently increases the risk of HF. In a prospective cohort study of 18 084 people without DM at high risk for CVD, a 1-mmol/L higher fasting plasma glucose was associated with a 1.23-fold increased risk of HF hospitalization [73]. However, prior landmark trials found no difference in CVD event rates between intensive management (mean HBA1c 6.4%–7.0%) versus standard management of glycemia (mean HBA1c 7.3%–8.4%) [74–79]. Although HF was not a primary endpoint of these clinical trials, post hoc analyses (37,229 patients from 8 randomized trials, follow-up: 2.3 to10.1 years) suggested that intensive glucose lowering (HBA1c<6%) did not reduce the risk for HF hospitalization [80]. Current DM management guidelines vary in the recommended glycemic targets or ranges. However, most agree on HBA1c thresholds of ≤7.0% for most adults with DM and no significant comorbidities or complications (Stage A) [79,81].

4.3. Choosing diabetes therapy for HF prevention

A plethora of evidence consistently demonstrated that sodium-

glucose cotransporter inhibitors(SGLT2i) in T2D with high-risk CVD patients reduced HF hospitalization irrespective of baseline HF status [70,82–86]. SGLT2i also have been shown to have a similar relative risk reduction of hospitalization for HF across a broad spectrum of baseline CV risk [87,88]. In addition, a meta-analysis suggested that in patients with T2D and no prior history of ASCVD, SGLT2is reduces the risk for HF [89]. Recent meta-analysis showed SGLT2i prevent HF consistently in patients with or without myocardial infarction and CAD (Fig. 3) [90]. Several mechanisms may explain how SGLT2i prevents HF (Fig. 4) [70]. All T2D patients at high risk for ASCVD (Stage A), with established ASCVD, or chronic kidney disease (CKD) with an estimated glomerular filtration rate (eGFR)≥20 ml/min per 1.73 m^2 should be on SGLT2i to prevent incident HF. Use with end-stage renal disease on dialysis, pregnancy, or breastfeeding is under investigation but not currently approved [91]. SGLT2is are considered statins of the 21st century [92].

Studies have consistently revealed that metformin reduces the incident HF in people with DM [93–95]. The cardioprotective actions of metformin in DM patients are not fully understood. Activation of AMP-activated protein kinase inhibits the mechanistic target of rapamycin and represses protein synthesis, which could inhibit cardiac hypertrophy [95]. It is reasonable to use metformin in patients with DM at risk of HF if the eGFR exceeds 30 ml/min/1.73 $m^{2.81}$ Metformin should be discontinued in patients with acute conditions associated with lactic acidosis, such as cardiogenic or distributive shock [81]. Agents like sulfonylureas, thiazolidinediones (TZDs), insulin, some glucagon-like peptide 1 receptor agonists (GLP1RAs), and some dipeptidyl peptidase 4 inhibitors might exacerbate or increase the risk for HF [96,97]. The TZDs promote insulin signaling and have increased the risk of HF in controlled clinical trials. Their use is contraindicated in high-risk HF patients [98].

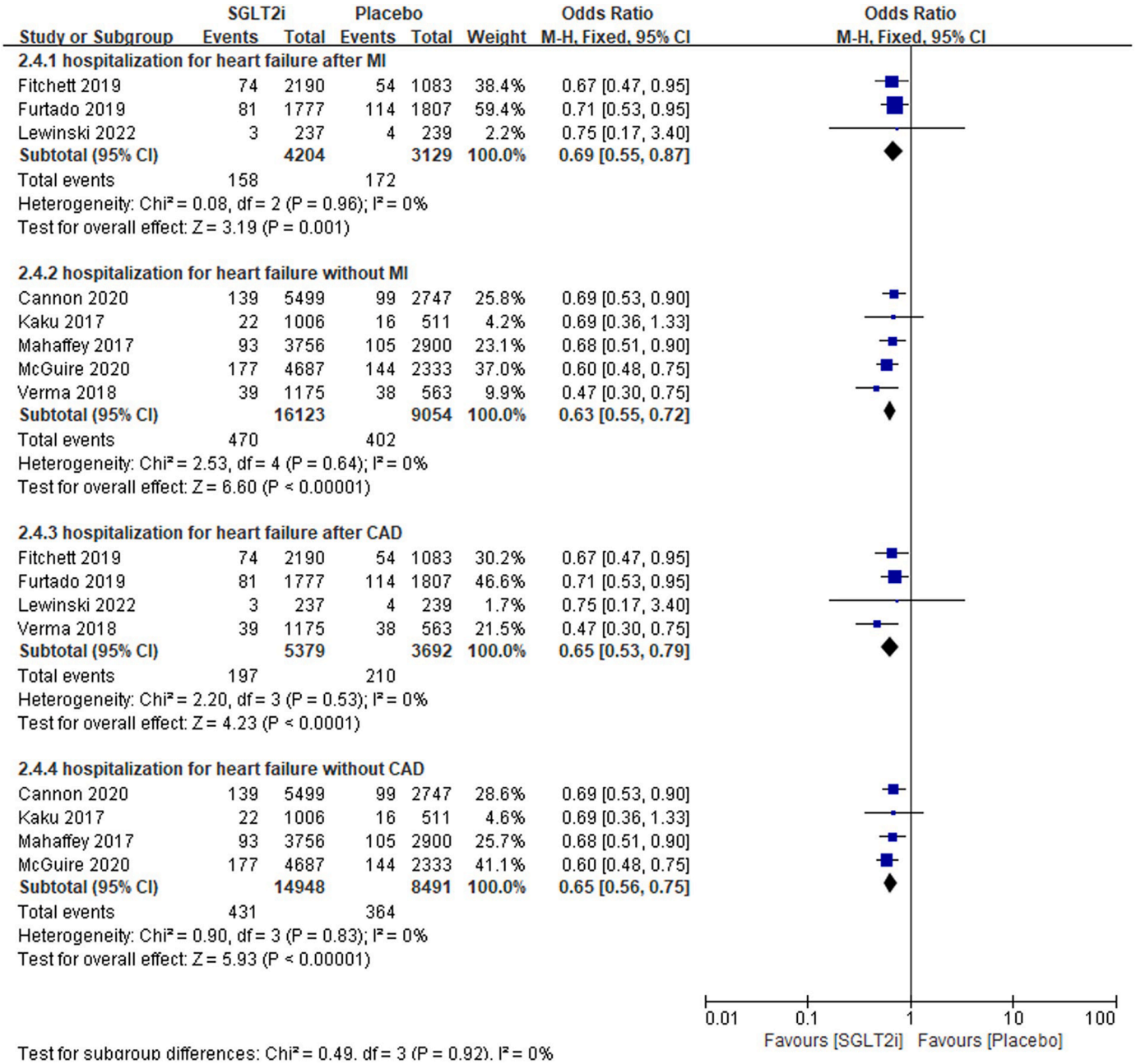

Fig. 3. Mechanism of action of sodium-glucose cotransporter 2 inhibitors.
SGLT2i = sodium-glucose cotransporter 2 inhibitors, LV= left ventricle.

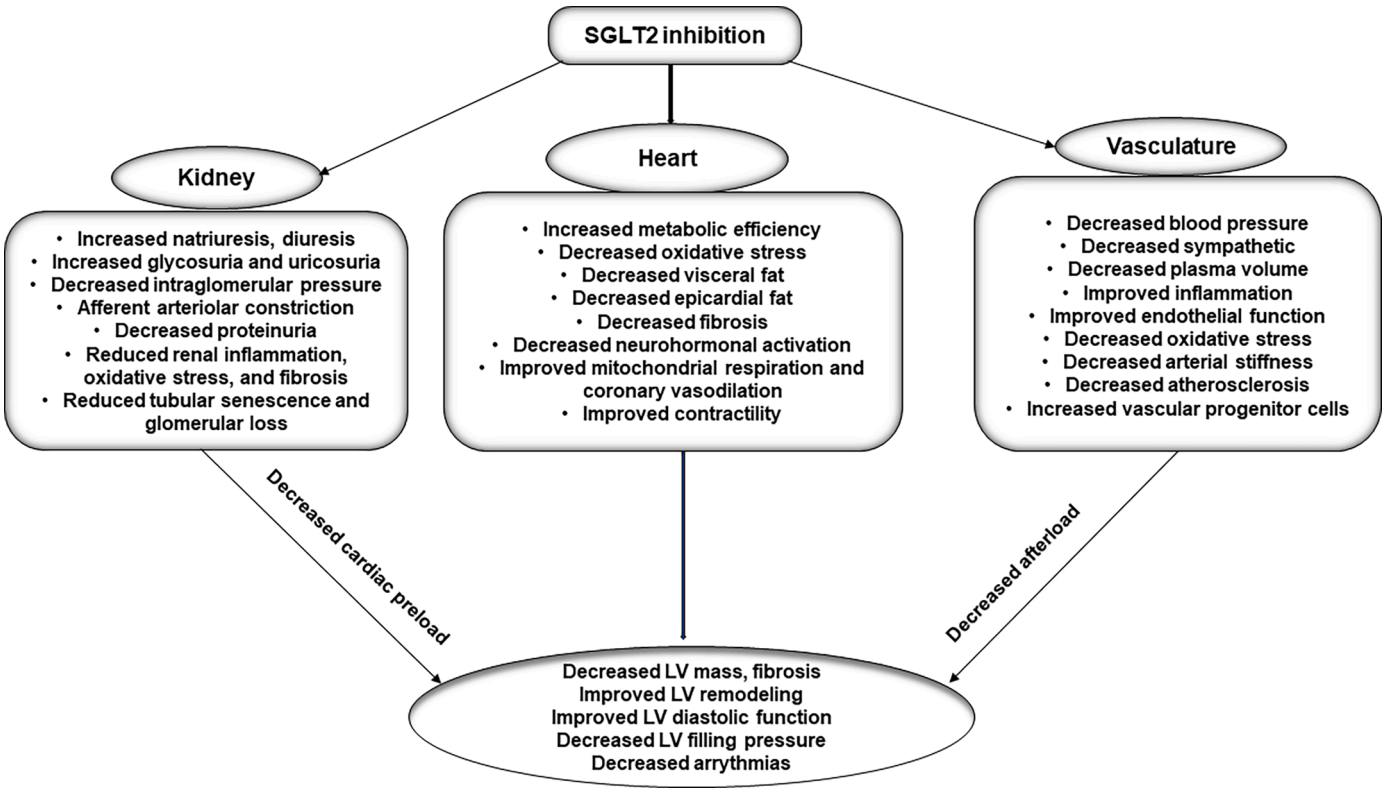

Fig. 4. The forest diagram of the occurrence of MACE.
MACE= major adverse cardiovascular events, MI = myocardial infarction, CAD =coronary atherosclerotic disease, SGLT2i =sodium-glucose cotransporter 2 inhibitors. (Reproduced from *Heart Lung*. 2023;59:109–116).

While there is consistent data for SGLT2is reducing HF risk, the consensus on GLP1RAs has been less clear. One of the primary mechanisms of action of GLP-1 is its ability to enhance glucose-stimulated insulin secretion [99]. GLP-1 stimulates pancreatic islets beta-cell neogenesis, inhibits apoptosis of these cells, slows gastric emptying, increases glucose utilization in muscle and adipose tissues, lowers BP, and reduces HbA1c levels. Also, GLP-1 acts on hypothalamic receptors to promote satiety and reduce food intake [99]. The observations from randomized trials suggest a neutral or modest benefit in preventing HF hospitalizations in those without HF at baseline with GLP1RAs; however, some data from small randomized trials raise a potential safety concern in patients with HFrEF [100]. GLP1RAs have a positive chronotropic effect, causing an increase in heart rate by activating adenylate cyclase in cardiac myocytes of the sinoatrial node, which can deleteriously affect HF [101]. New data showed significant reductions in HF risk with exendin-4–based GLP1RAs [102]. The trial included 4076 patients with T2D with either a history of CVD or current kidney disease plus at least one other CV risk factor [102]. Recent meta-analyses also showed a reduction in new HF hospitalization and mentioned that the possibility of this benefit might be due to a reduction in MI risk [103]. However, the study included patients with previous CVD or kidney disease, which lowers its generalizability in a broader population. The 2019 ACC/AHA CVD prevention guidelines state that the CV benefit of GLP1RA is derived primarily from a reduced rate of ASCVD events as opposed to HF [104]. Thus, physicians can prevent many cases of HF in T2D by careful consideration of agents used to achieve glycemic control. Importantly, these decisions have an immediate effect; changes in risk are seen within the first few months of changes in treatment.

4.4. Obesity prevention and management

Obesity, defined in population studies as a BMI $\geq$30 kg/m^2, is highly prevalent and is associated with an increased risk of HF. Among 5881 participants (mean age, 55 years; 54% women) in the FHS, for every 1 kg/m^2 increase in BMI, the risk of HF during a 14-year follow-up increased by 5% in men, and 7% in women, with graded increases in the risk of HF, noted across all BMI categories [105]. The strongest dose-response relationship between BMI and incident HF is evident for HFpEF [106]. In the multiethnic study of atherosclerosis (MESA) study, BMI, waist circumference, and visceral abdominal adiposity were all identified risks for developing new-onset HFpEF [107]. The excess risk of HF associated with obesity is mainly independent of the traditional CVD risk factors, as shown in Fig. 5 [108–110]. Healthcare providers taking care of obese patients should integrate weight loss treatment in patients' care plans, including lifestyle, pharmacologic, and surgical weight loss strategies.

Although diet and exercise represent the cornerstone of weight management, sustaining weight loss over the long term is challenging. Guidelines suggest adjunctive pharmacotherapy, particularly for adults with a BMI of 30 or greater or 27 or greater in persons with coexisting conditions [111]. As described previously under the DM management section, GLP1RAs are one of the most potent weight-loss agents independent of T2D [99]. Studies have demonstrated that semaglutide and liraglutide effectively reduce body weight in obese patients [99]. In a recent head-to-head randomized controlled trial semaglutide was superior to liraglutide in body mass reduction [112]. Tirzepatide (GIP-GLP-RA) is a new drug that coactivates the glucose-dependent insulinotropic polypeptide (GIP) receptor and GLP-1R. It is a class of drugs that can help with weight loss and blood sugar control by mimicking the effects of two hormones that regulate appetite, insulin secretion, and glucose metabolism. Recent studies showed that tirzepatide was superior to semaglutide and insulin degludec in decreasing HBAIc and body weight [113,114]. Tirzepatide showed a similar safety profile to GLP-1Ras. However, tirzepatide's effects on decreasing incident HF are currently unknown. GLP1RAs should be considered in patients at a high risk of, or with established, ASCVD and in patients with

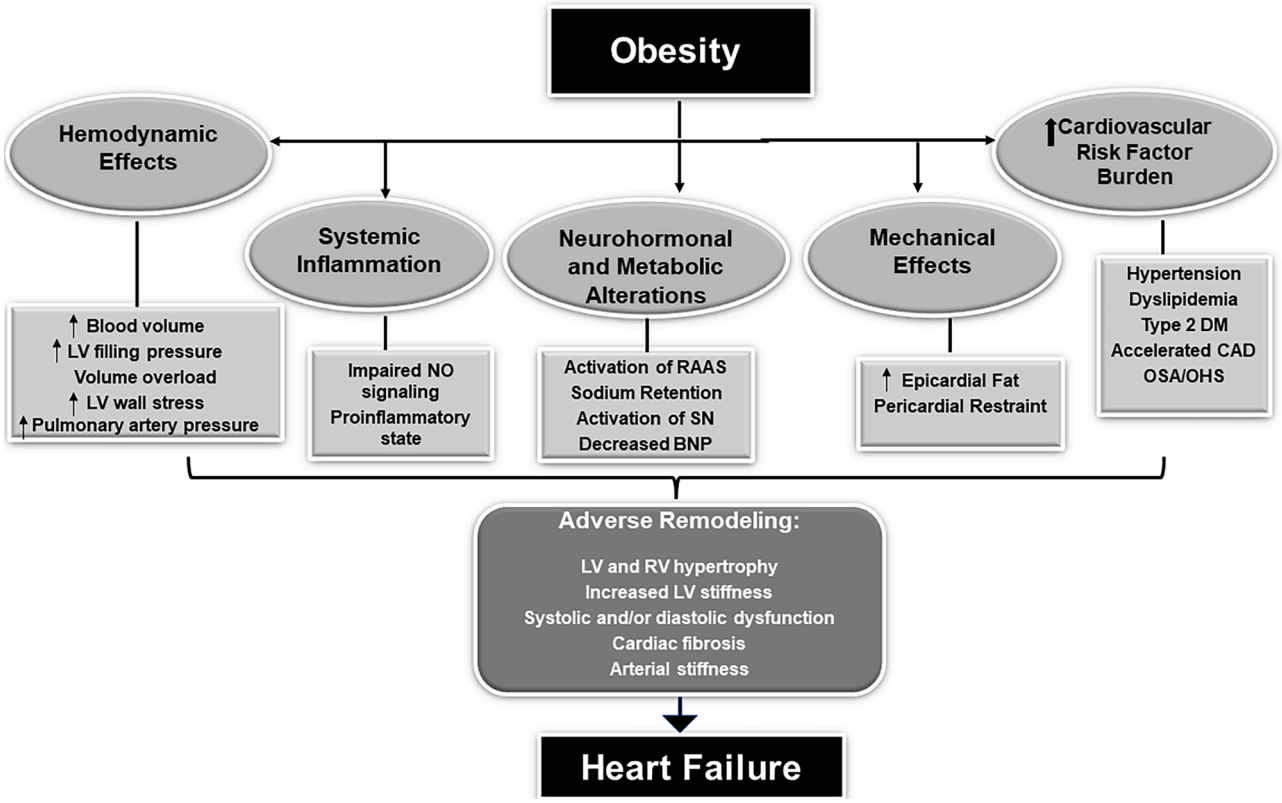

Fig. 5. Obesity and heart failure risk—pathophysiology.
LV =left ventricle, NO=nitric oxide, RAAS = renin-angiotensin-aldosterone system, SN= sympathetic nervous system, BNP=*B* type natriuretic peptide, DM =diabetes, CAD =coronary artery disease, OSA -obstructive sleep apnea, OHS=obesity hypoventilation syndrome, RV=right ventricle.

obesity and overweight with weight-related comorbidities. Gastric bypass surgery was associated with approximately half the incidence of HF compared to intensive lifestyle treatment in a study of nearly 40,000 obese people without HF [115]. They observed a graded association between increasing weight loss and decreasing the risk of HF [115].

4.5. *Lipid management*

Besides its risk for leading to incident CAD, dyslipidemia is also a risk factor for HF [116]. Statin therapy seems beneficial in reducing the incidence of HF (about 20%) in patients with stable CAD or previous acute coronary syndrome, as proven by several randomized clinical trials [117,118]. In a large meta-analysis of up to 17 major primary- and secondary-prevention randomized trials (132,538 participants over 4.3 years), statins modestly reduced the risks of non-fatal hospitalization for HF [118]. The benefit is similar in those with and without a history of CAD at baseline and across both placebo- and standard care-controlled and dose-comparison trials [118]. This indicates statin therapy reduces HF risk through mechanisms partly independent of preventing acute myocardial infarction [118]. However, only a borderline effect was observed in repeated HF hospitalization among HF patients, and the benefit of statins even seems to decline with increasing levels of natriuretic peptides (NP) in HF patients [119,120]. Statin therapy should be continued in patients with ASCVD risk factors or established ASCVD as recommended by guidelines to prevent HF.[121] The thresholds are based on the 2018 Cholesterol Guidelines [121]. ESC guidelines recommend using statins to prevent HF in high-risk individuals [122]. However, we still do not know whether we can start statins in individuals at high risk for HF who are not recommended to initiate statins based on the absolute risk of ASCVD alone.

Proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors target circulating PCSK9, increase hepatic low-density lipoprotein (LDL) receptor expression, and reduce LDL cholesterol levels and ischemic heart disease. When PCSK9 is absent, the expression of critical receptors involved in lipid and lipoprotein uptake increases, resulting in heart cholesterol accumulation, impaired beta-oxidation, and mitochondrial activity, thus affecting cardiac metabolism and function. In an animal study, PCSKP deficiency contributes to the development of HFpEF [123]. Even though long-term LDL-C lowering with PCSK9 inhibitors was associated with persistently low rates of adverse events for more than eight years, the effects on primary prevention of HF events were unknown [124]. Additionally, there was no effect of PCSK9 inhibitor treatment on HF hospitalization in the subgroup of HF patients in the ODYSSEY OUTCOMES study (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab) [125].

5. Assessing and managing HF risk enhancers

Traditional CV risk factors, as mentioned above, are only accountable for 50% of the lifetime risk of HF [126]. HF risk-enhancing factors are nontraditional CV risk factors that identify individuals at high risk for HF (Stage A) [126]. These include a multitude of comorbidities like atrial fibrillation (AF), CKD, chronic liver disease, chronic inflammatory disease, sleep-disordered breathing, adverse pregnancy outcomes, radiation therapy, a history of cardiotoxic chemotherapy exposure, and COVID-19. Notably, the genetic susceptibility for HF is identified as a key risk enhancer (Stage A) [126]. Some representative examples are discussed here.

5.1. *Hereditary cardiomyopathy*

Nearly 20% of the community burden of HF can be attributed to heritable factors [127]. The onset of these hereditary cardiomyopathies,

associated with specific mutations, varies from adolescence to early middle age or even later. Therefore, obtaining a targeted 3-generation family history is crucial to identifying potential asymptomatic individuals at significantly higher risk for HF. When ≥2 family members have been reported to have HF or a first-degree relative has had a premature sudden cardiac death without a well-defined cause, underlying genetic cardiomyopathy should be considered [128]. The next step is a clinical assessment of the patient with ECG, echocardiography, and possibly heart rhythm monitoring. The basis of genetic testing in inherited cardiomyopathies is identifying family members who have inherited the same causal mutation with the proband [129]. This is essential in clinical decision-making since anxiety and unnecessary clinical screening are avoided when the mutation is not detected in family members.

5.2. Atrial fibrillation

AF predisposes to HF through various mechanisms, including tachycardia–related cardiomyopathy, loss of atrial contraction, reduced LV diastolic filling, neurohormonal activation, and ventricular structural and functional myocardial changes [130]. Additionally, modifiable factors such as HTN, DM, obesity, and obstructive sleep apnea (OSA) predispose to AF. Thus, there is a complex inter-relationship between AF and HF. Each adversely affects and complicates the course of the other [130]. Data from Outcomes Registry for Better Informed Treatment of AF showed that among patients with AF, subsequent development of HF was common, with a majority of incident cases being HFpEF [131]. Aggressive risk factors like weight loss, optimum BP control, lipid management, and treatment of OSA have been demonstrated to benefit patients with (lone) AF [130]. Adopting a rhythm control strategy in AF would be expected to benefit HF progression [130]. This is supported by the multicenter randomized trial, which showed that rhythm-control therapy in all patients with early AF and concomitant CV conditions was associated with a lower risk of death from CV causes, stroke, hospitalization for HF, or acute coronary artery syndrome than usual care [132]. Catheter ablation is an effective option to achieve rhythm control without the unfavorable effects of antiarrhythmic drugs [130].

5.3. Exposure to cardiotoxic agents

A full review of the cardiotoxic agents and toxicity mechanisms is beyond this article's scope. Several chemotherapy agents increase the risk for HF (Table 2) [133–136]. Patient-related risk factors (age, HTN, DM, smoking, female sex, and postmenopausal state) and chemotherapy-related risk factors (high-dose chemotherapy, administration as a bolus or in combination with other cancer therapy, prior anthracycline use, mediastinal radiation) can increase the risk of cardiotoxicity [136].

Measurement of LVEF before, during, and after chemotherapy for breast cancer may allow for early detection of CV toxicity related to treatment for early intervention. The European Society of Medical Oncology guidelines recommends LVEF assessment at baseline, the end of treatment, and 6 months after the completion of therapy; annually for 2 or 3 years after that; and then in 3- to 5-year intervals for life [137]. For patients receiving > 250 mg/m^2 of doxorubicin, screening should occur after every 50 mg/m [2,138]. For patients treated with trastuzumab, LVEF assessment is recommended at baseline and every 3 months while on therapy. The global longitudinal strain (GLS) assessment using speckle-tracking echocardiography is an emerging method for detecting and quantifying subtle disturbances in the global long-axis LV systolic function. GLS is essential in diagnosing oncological therapy's cardiotoxicity in the latest ESC guidelines on cardio-oncology. A relative decrease in GLS of >15% during cancer treatment is the recommended cut-off point for suspecting subclinical cardiac dysfunction [139].

Dose reductions represent the first and most apparent primary prevention strategy for anthracycline toxicity [140]. Modifying the structure of the drugs to improve their therapeutic and pharmacological properties is a common strategy [135]. Epirubicin, idarubicin, and mitoxantrone are anthracycline analogs potentially less cardiotoxic than doxorubicin [135]. Risk factors for breast cancer and HF are similar (smoking, obesity, sedentary lifestyle), suggesting these risk factors should be aggressively addressed. Patients receiving trastuzumab and anthracyclines for breast cancer were shown to develop significantly lower rates of cardiotoxicity when treated concomitantly with either lisinopril or carvedilol [141]. Guidelines have supported using β-blockers, ACE-I, dexrazoxane, and statins as prophylactic agents to reduce chemotherapy-induced cardiotoxicity [142]. Introducing these agents in patients with subclinical heart injury (confirmed by increased troponin, decrease in GLS, reduction of LVEF), titrating to the optimal dose for the patient, and monitoring with imaging technology and biomarkers will decrease HF incidence [142].

Hypertensive disorders of pregnancy are associated with a fourfold higher maternal risk of future HF and a higher risk of future HTN and DM [143,144]. Preeclampsia should be prevented by addressing diet, increasing PA, and maintaining a healthy BMI. Professional societies recommend using low-dose aspirin to prevent preeclampsia in high-risk women [145]. Current guidelines suggest that individuals with a strong family history of cardiomyopathy should receive a noninvasive evaluation of LV function [1]. Chronic lung disease is independently associated with an increased risk of HF that may be partly mediated by inflammation [146]. OSA is an independent risk factor for the development of HF, with more impact on men than women [147]. However,

Table 2
Chemotherapy and cardiac dysfunction.

Anthracyclines (doxorubicin)	Irreversible myocardial damage and dose-dependent
Human epidermal growth factor receptor 2-targeted agents (e.g., trastuzumab)	Reversible myocardial damage and dose-independent
Alkylating agents (e.g., cyclophosphamide)	This cardiotoxicity is also dose-dependent The incidence of symptomatic cardiomyopathy is around 22%, and fatal cardiotoxicity is approximately 11% [181].
Taxanes (eg, paclitaxel)	The incidence of left ventricular dysfunction with taxanes is 0.7%, which is comparatively low in comparison with other agents [182].
Platinum-based therapies (e.g., cisplatin)	A weak association has been described.
Tyrosine kinase inhibitors (e.g., dasatinib)	The risk of cardiotoxicity is increased with previous cardiovascular history. It can cause hypertension, acute coronary syndrome, heart failure, and arrhythmias.
Fluoropyrimidines (e.g., Fluorouracil)	The incidence of cardiomyopathy ranges from 1% to 19% [183]. The most frequent cardiotoxicities include heart failure, angina with possible myocardial infarction, arrhythmias, cardiac arrest, pericarditis, and recently reported takotsubo cardiomyopathy.
Vascular endothelial growth factor signaling pathway inhibitors	Known to cause hypertension, ischemia, and left ventricular dysfunction. Bevacizumab is associated with a more than 4-fold increase in heart failure risk [184].
Proteasome inhibitors (e.g., bortezomib and carfilzomib)	There are conflicting data regarding cardiotoxicity in patients on bortezomib.
Immune checkpoint inhibitors (e.g., nivolumab)	Fulminant cases of myocarditis. The incidence is unclear, but it has been reported to range from 0.06% to 1% [185].

continuous positive airway pressure has not been demonstrated to prevent incident HF [148]. Renal insufficiency predicts the occurrence of new cases of HF, showing a graded increase in risk with increasing serum creatinine levels [149]. Notably, about 40–50% of patients with HF have coexisting chronic renal dysfunction (eGFR <60 ml/min/1.73 m^2) [150].

Studies have also shown an increased short- and long-term risk of incident HF after COVID-19 infection [151]. A recent meta-analysis of more than 20 million people (mean age 55 years, 59% males) demonstrated that COVID-19 survivors had an additional 90% risk of developing HF within 9 months from the acute infection [152]. This risk was directly related to age and previous history of HF, especially in the early post-acute phase of the infection [152]. Thus, COVID-19 survivors should be considered at risk for HF and need continuous clinical follow-up.

6. Assessing the social and psychosocial factors and risk of HF

The social determinants (Fig. 6) significantly impact HF risk and outcomes, particularly among marginalized communities. Poverty, lack of education, inability to access health care, low income, low access to healthy food, lousy neighborhood, unsafe home environment, social isolation, discrimination, and early childhood adversity -all these psychosocial stressors can lead to chronic inflammation and neurohormonal modulation and enhance the HF risk and progression [153]. Some social determinants (poverty, lack of education, neighborhood deprivation, social disparities) are consistently associated with incident HF [154–156]. Evidence also suggested that multiple social vulnerabilities have a cumulative effect on HF risk within the same individual, particularly in individuals under 65, independent of traditional risk factors [157]. A meta-analysis found a 62% increase in incident HF with socioeconomic deprivation by any measure of socioeconomic status (income, education, occupation, or area-level measures of neighborhood deprivation) [158]. Thus, a sum of socially determined vulnerabilities may substitute as an additional risk enhancer in patients at increased risk of incident HF, especially among younger individuals. Racial disparities in both the prevalence and incidence of HF are well-established. The prevalence of HF is greater among AAs and develops at younger ages than among non-Hispanic Caucasians [159,160]. Contemporary data suggest that genetic susceptibility, social determinants of health, and implicit bias may play a more significant role in health outcomes than previously appreciated [161].

Fig. 6. Social determinants of heart failure.

Relatively few previous studies have examined associations between psychosocial factors and incident HF. High depressive symptoms were associated with greater risk of incident HF in older adults [162,163]. A European study found a positive association between depression and incident HF but no association between anxiety and incident HF [164]. In MESA, there was no association between several psychosocial factors (i.e., anger, anxiety, chronic stress, depressive symptoms, and hostility) and risk of incident HF; however, there was a relatively small number of incident HF events [165]. Mechanistic links between psychosocial factors and HF include inflammation, heightened sympathetic nervous system activation, endothelial dysfunction, increased platelet activity, hormones, and brain-derived neurotrophic factors [166–168]. People with psychosocial problems are less likely to adhere to medical and behavioral guidelines, which makes them more likely to develop HF [169].

7. Optimizing the adherence to a healthy lifestyle and long-term therapies

Adherence refers to "the extent to which a person carries out lifestyle changes, including medication and dietary habits, according to the agreed recommendations from a health care provider."[170] Many factors influence adherence: socioeconomic factors, healthcare system factors, treatment factors, health condition factors, and patient factors [170]. In primary prevention of HF, patients should follow lifestyle changes or pharmacological therapy for life despite not having any unpleasant symptoms concerning their risk factors, which means that very low adherence is likely. Therefore, it requires a different strategy from the patients hospitalized with HF (secondary prevention). The essential approach is patient-centered clinical communications [171]. Also, counseling should be developed and implemented using motivational strategies and decision-making by patient empowerment [171]. According to the WHO, healthcare systems influence adherence the most [170]. A stronger rapport between a patient and healthcare professional has been found to improve adherence [170]. Successful feasible interventions to improve medication adherence are combination pills to reduce daily pill burden, clinical pharmacist consultation for disease co-management, and medication-taking reminders such as telephone calls to prompt refills [172].

8. HF prediction tools

There are no unique recommendations on detecting Stage A patients. Different patients at Stage A may have different risks of HF because of their different risk factors. In addition, patients in Stage A are heterogeneous; many patients have different combinations of risk factors and, therefore, have a markedly different absolute risk for HF. Several HF risk prediction tools have been developed to address this heterogeneity by combining risk factor levels to facilitate preventive interventions based on absolute risk levels [126]. However, incorporating these models into real-world clinical practice is problematic since these HF prediction models are limited by ethnic diversity and extensive external validation in a population without prevalent CVD [173]. In addition, most risk prediction tools have focused only on the short-term (5–10 years) risk of HF. A contemporary analysis of 33,010 men and women (aged 30–79) from pooled individual-level data from 7 population-based cohorts with long-term follow-up [ARIC, CARDIA (Coronary Artery Risk Development in Young Adults) study, CHS (Cardiovascular Health Study), FOS, and MESA] demonstrated the utility of the sex- and race-specific 10-year Pooled Cohort Equations to Prevent HF risk scores. This scoring system integrates clinical parameters like age, SBP (treated or untreated), fasting glucose (treated or untreated), BMI, cholesterol, smoking status, and QRS duration in EKG (Fig. 7) [174]. The model performed well in

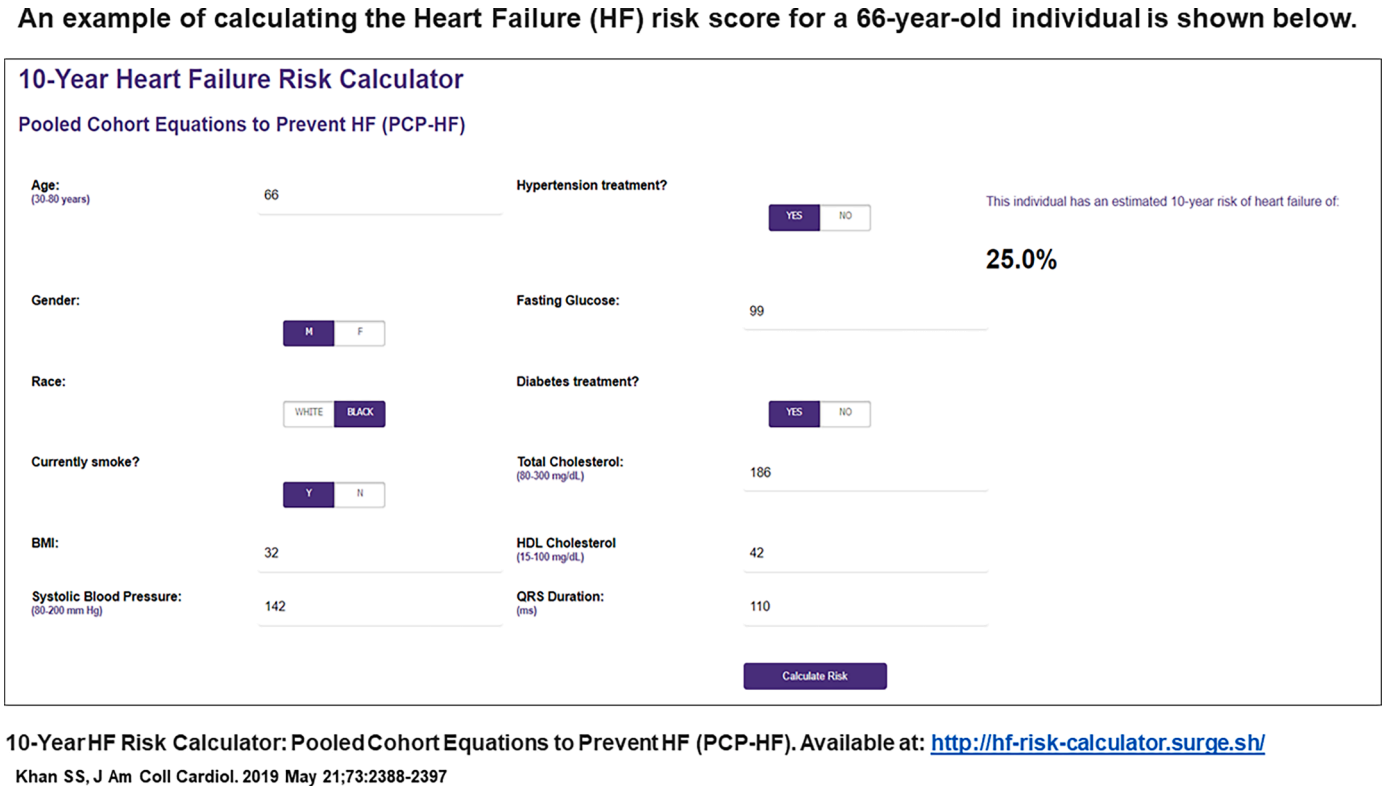

Fig. 7. An example of predicted 10-year HF risk using the online Pooled Cohort Equations to Prevent Heart Failure (PCP-HF) tool. (Reproduced from J Am Coll Cardiol. 2019 May 21;73:2388–2397.

internal and external validation in identifying and discriminating risk of HF. This model has also been validated in real-world data from electronic health records and multiple international populations and endorsed by the 2022 ACC/AHA/HFSA Guidelines in the US (class IIA recommendation to estimate the risk of incident HF) [9,175]. However, nontraditional risk factors have not been included in HF prediction tools. Thus, applying the HF risk model should be undertaken with careful consideration of the population studied and the compatibility of the cohort used to derive the model [176].

9. Role of biomarkers in HF prevention

Biomarkers may help identify subjects at high-risk HF development (Stage A). B-type NP (BNP) and cardiac troponin are well-studied among many biomarkers. St Vincent's Screening to Prevent HF randomized 1374 patients (mean age, 64.8 years) with at least 1 CVD risk factor to receive routine care or screening with BNP-guided care [87]. The participants with 50 pg/mL or higher BNP levels underwent echocardiography and collaborative care between their primary care physician and specialist CV service. BNP-based screening and collaborative care decreased new-onset HF and asymptomatic LV dysfunction.[87] The PONTIAC trial (NT-proBNP Selected Prevention of Cardiac Events in a Population of Diabetic Patients Without a History of Cardiac Disease) randomized 300 subjects with T2D and NT-proBNP >125 pg/mL to regular care in DM care units or intensified care in which renin-angiotensin antagonists and β-blockers were up titrated in a cardiology setting. Intensive treatment significantly reduced the primary endpoint of hospitalization for any cardiac cause; HF hospitalization was a secondary endpoint, and the benefit was modest ($p = 0.07$) [177]. Routine use of these biomarkers is not currently widespread in clinical practice to identify HF risk despite guideline recommendations for BNP-based prevention. Also, these markers are influenced by age, obesity, renal function, etc.

A QRS duration >100 ms was significantly associated with cardiac magnetic resonance imaging (CMRI) measures of cardiac structure and function and incident HF, even after adjustment for demographic covariates, suggesting a potential mechanistic link between structural MRI findings and QRS duration and increased risk of incident HF [178]. Among older adults (70–79 years), baseline and new ECG abnormalities are independently associated with an increased risk of HF [179]. An abnormal ECG or elevated NP level should prompt consideration for an echocardiogram to evaluate for asymptomatic LV dysfunction. GLS may help detect a group of asymptomatic people who need a robust preventive intervention strategy [180]. GLS provided incremental prognostic information beyond the Framingham Risk Score, the Systemic Coronary Evaluation risk chart, and the modified ACCF/AHA Pooled Cohort Equation for the composite outcome and incident HF [180].

These laboratory and imaging biomarkers represent underlying changes to the myocardial structure, which may reflect LV dysfunction and suggest patients transitioning from Stage A to Stage B. Screening markers' contribution to the targeted prevention of HF should be evaluated in clinical trials, particularly with cost-effectiveness in mind.

10. Future directions and conclusions

Table 3 summarizes the take-home points. Comprehensive strategies to prevent HF should identify the individuals with HF at-risk (Stage A) and incorporate intensive BP lowering, adequate glycemic and lipid management, and heart-healthy behaviors (adopting LE8). Our primordial prevention efforts should start with children, adolescents, young adults, and young families to ensure healthy habits are established early in life and sustained throughout life. This will require clinicians to care for not just individual patients but their entire families as well. The key is that healthy parents will have healthy babies.

Efforts to address social determinants of HF risk are very much needed for primordial HF prevention. First and foremost, it is imperative to improve public awareness of HF risk factors and implement healthy lifestyle choices very early. This needs commitment from the whole

Table 3
Take Home points.

"It is never too late" to start LE8 at any age.
Stage A's optimal BP target should be <130/80 mmHg.
ACE-Is or ARBs should remain the medication class for high-risk ASCVD patients.
HBA1c thresholds of ≤7.0% for most adults with DM and no significant comorbidities or complications.
The optimal BP target for DM patients in Stage A is <130/80 mmHg.
ACE-Is or ARBs are the first choice of antihypertensive for DM.
T2D with high risk for or with established ASCVD or CKD with eGFR ≥20 ml/min/1.73 m2 should be on SGLT2i to prevent incident HF.
GLP1RAs should be considered in patients at a high risk of, or with established, ASCVD and in patients with obesity and overweight with weight-related comorbidities.
Statin therapy should be continued in patients with ASCVD risk factors or established ASCVD as recommended by guidelines to prevent HF.
We still do not know whether we can start statins in individuals at high risk for HF who are not recommended to initiate statins based on the absolute risk of ASCVD alone.
A plant-based diet is preferred to prevent incident HF.
Adopting a rhythm control strategy in AF would be expected to benefit HF progression.
COVID-19 survivors should be considered at risk for HF and need continuous clinical follow-up.
Biomarkers and GLS may help detect a group of asymptomatic people who need a robust preventive intervention strategy.

LE8 = life essential 8, BP = blood pressure, ACE-*I* = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blockers, ASCVD = atherosclerotic cardiovascular disease, HbAIc = glycosylated hemoglobin, DM = diabetes, T2D = type 2 diabetes, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, SGLT2i = sodium-glucose cotransporter inhibitors, GLP1Ras = glucagon-like peptide 1 receptor agonists, HF-heart failure, AF = atrial fibrillation, GLS = global longitudinal strain.

family and physicians treating the patients. In addition, as physicians, we must emphasize routine diet, PA, smoking, psychological, and sleep health assessment in clinical practices. Early use of biomarkers, imaging markers, and echocardiography (noninvasive measures of subclinical systolic and diastolic dysfunction) may enhance risk prediction among individuals without established CVD and prevent chemotherapy-induced cardiomyopathy. More research is needed to understand further the efficacy of GLS-guided therapy using cardioprotective drugs such as ACE-Is and ARBs for Stage A HF patients. Studies are needed to assess the use of SGLT2i for the potential new therapeutic strategy for Stage A HF. Studies are needed for integrating machine learning into electronic health records that might provide real-time estimates of a patient's HF risk. Promote behavioral research on improving compliance and adherence to proven therapies for managing risk factors. With the current COVID-19 crisis, telemedicine has become necessary in providing patients with health care, and future studies are needed to evaluate the effect of telemedicine on HF prevention.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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