Preventing heart failure: a position paper of the Heart Failure Association in collaboration with the European Association of Preventive Cardiology

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Abstract

The heart failure epidemic is growing and its prevention, in order to reduce associated hospital readmission rates and its clinical and economic burden, is a key issue in modern cardiovascular medicine. The present consensus document aims to provide practical evidence-based information to support the implementation of effective preventive measures. After reviewing the most common risk factors, an overview of the population attributable risks in different continents is presented, to identify potentially effective opportunities for prevention and to inform preventive strategies. Finally, potential interventions that have been proposed and have been shown to be effective in preventing HF are listed.

Keywords

Arterial hypertension, Diabetes mellitus, Heart failure, Epidemiology, Prevention, Population attributable risks

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Introduction

Heart failure (HF) is a growing problem, in terms of both the number of patients affected, its associated clinical consequences and its implications for health care expenditure.[1] Despite the development of beneficial treatments for HF, clinical outcome remains poor. Importantly, rapid ageing of the population means that the incidence of HF shall increase further in the coming years. Preventing the development of this condition in the population at large, in order to reduce hospital readmission rates, its other clinical sequelae and its economic consequences, is a key issue in modern medicine. These considerations drive the decision to provide practical evidence-based information to support the implementation of preventive measures.

This document focuses on the primary prevention of the development of HF and, thus, not on preventing its complications, including HF-related hospitalizations, in those with established HF. The latter is dealt with in the new European Society of Cardiology (ESC)/Heart Failure Association (HFA) guidelines on Heart Failure, as a key complementary publication. This prevention document accompanies the publication of those guidelines. The health care community is well aware of the important risk factors for cardiovascular disease (CVD) that favours the development and maintenance of HF, specifically hypertension, type 2 diabetes mellitus (T2DM) and a sedentary lifestyle. In addition to cardiovascular (CV) risk factors, other behavioural risk indicators are increasingly important, because of the pervasive aspects of economic transition, rapid urbanization and 21st-century lifestyles (in particular concerning unhealthy diet habits, and the harmful use of alcohol, in addition to smoking).

After reviewing the most common risk factors leading to HF, an overview of the population attributable risks (PAR; i.e. the proportion of HF cases in a population attributable to a specific risk factor) in different continents is presented in this article. In doing so we identify potentially effective opportunities for prevention that will then inform preventive strategies. In general, analyses from European as well North American

populations have provided evidence that implementation of healthy behaviours lowers the risk of HF development in both men and women.[2,3]

In this document, the most recent recommendation on healthy lifestyle from the European Guidelines of cardiovascular prevention in clinical practice,[4] and more recent ESC Guidelines for the management of dyslipidaemias[5] are incorporated (*Tables 1 and 2*). Finally, potential interventions that have been proposed and have been shown to prevent the development of HF are presented.

Classical modifiable risk factors

Arterial hypertension

Arterial hypertension is the most common modifiable risk factor for HF and is one which has been increasing in importance over time among patients with HF: a history of hypertension was present in 66% of patients during 1985–1990 and in 74% from 1997 to 2002.[6]

With nearly 30–45% of the general population afflicted by hypertension and the lifetime probability of developing hypertension >75%,[7] strategies to control hypertension are a vital part of any public health effort to prevent HF.

Hypertensive subjects have a substantially greater risk for developing HF than normotensive men and women.[8] Elevated levels of diastolic and especially systolic blood pressure are major risk factors for incident HF. The PAR for HF conferred by hypertension has been estimated at 20%.[9]

A bidirectional effect of arterial hypertension in the context of HF with reduced (HFrEF) vs. HF with preserved ejection fraction (HFpEF) has been advocated. Arterial hypertension is a potent risk factor for HFrEF through incident coronary artery disease (CAD), where hypertension represents the initial exposition triggering, and CAD is the real clinical event terminating in the development of decompensated HF. In the context of HFpEF, which is not triggered by CAD, hypertension may be considered a direct cause through hypertension-mediated organ damage and, specifically, left ventricular (LV) hypertrophy.

Long-term treatment of hypertension reduces the risk of HF by ~50% and is associated with lower HF mortality. In the ARIC (Atherosclerosis Risk in Communities study) cohort, 28 cases of incident HF/100 000 persons/year and 19/100 000 persons/year in African-Americans and in Caucasians, respectively,[10] could be prevented with a 5% proportional reduction in the prevalence of hypertension (*Table 3*). The effect of hypertension treatment on the development of HF has been evaluated in several clinical trials. A network meta-analysis showed that three classes of antihypertensive drugs were the most effective medications to reduce the incidence of HF compared with placebo, with odds ratio (OR) of 0.59 for diuretics, 0.70 for angiotensin-converting enzyme inhibitors, and 0.76 for angiotensin II receptor blockers.[11] These drugs were more effective than calcium-channel blockers, beta-blockers, and alpha-blockers. Another meta-analysis evaluating the effect of beta-blockers found that the degree of blood pressure reduction was the main determinant of success in reducing subsequent HF: beta-blockers did not seem to have a significant effect on reducing HF beyond blood pressure reduction.[12]

Diabetes mellitus

Heart failure is one of the most frequent CV complications of T2DM, regardless of the baseline CV risk[13,14] and contemporary treatment of T2DM has emerged as a viable strategy for preventing the development of HF.

In a recent community-based study of 1.9 million people without CVD (with a median follow-up of 5.5 years), HF was a frequent first CV presentation in T2DM, second only to peripheral arterial disease.[13] The adjusted hazard ratio (HR) for incident HF was 1.56 [95% confidence interval (CI) 1.45–1.69] in people with T2DM as compared to those without.[13] Similarly, in a meta-analysis including placebo arms of 16 CV outcome trials in T2DM, HF hospitalization occurred more frequently than stroke and only slightly less frequently than myocardial infarction (MI) both in patients with and without prior CVD.[14] Development of HF in T2DM is likely multifactorial, with a variable contribution from myocardial ischaemia, hypertension, non-CV comorbidities (e.g. obesity, chronic kidney disease), and a possible direct myocardial impairment caused by T2DM.[15–17]

Earlier strategies aimed at tight glycaemic control (i.e. targeting normal levels of glycosylated haemoglobin), mostly using insulin secretagogues and insulin have not been

proven effective in reducing the likelihood of developing HF.[18] Moreover, intensive glycaemic control has been shown to increase mortality,[19] whereas the use of some medications (e.g. rosiglitazone) may increase the risk of HF.[20]

Nevertheless, a major breakthrough in HF prevention has come from recent CV outcome trials with a novel class of glucose-lowering medications, sodium–glucose contransporter-2 (SGLT2) inhibitors. In multiple clinical trials of patients with T2DM and either established CVD or with multiple risk factors, SGLT2 inhibitors (empagliflozin, canagliflozin, dapagliflozin, and ertugliflozin) have shown a consistent risk reduction in HF hospitalization, while the effect on mortality and other outcomes of interest varied among the trials[21–24] (*Table 4*). In addition, a beneficial effect on HF prevention was also observed among high-risk individuals with T2DM and nephropathy,[25] which was later confirmed in a broader population of patients with chronic kidney disease with and without T2DM.[26] A meta-analysis of the pivotal trials with dapagliflozin, canagliflozin, and empagliflozin has shown a significant risk reduction for CV death or hospitalization for HF (HR 0.77, 95% CI 0·71–0·84; $P < 0.0001$), as well as hospitalization for HF (HR 0.69, 95% CI 0.61–0.79; $P < 0.0001$), regardless of the presence of CVD.[27] The beneficial effect on HF hospitalizations has been confirmed in recent VERTIS-CV trial (Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease), a non-inferiority study on the CV safety of ertugliflozin. In this study, CV mortality was similar in the ertugliflozin and placebo groups.[24] These findings strengthen the role of SGLT2 inhibitors in the prevention of HF in T2DM, and recommendations on their use have been provided in recent practice guidelines,[28] and expert consensus documents.[29–31] A mediation analysis of clinical trial data on empagliflozin has suggested that an improvement in outcomes was primarily attributable to an increase in haematocrit and haemoglobin levels, likely reflecting a reduction in intravascular volume, although other mechanisms (e.g. on metabolism with reduction in uric acid, fasting glycaemia and glycosylated haemoglobin A1c levels, on inflammation, adipose tissue and adipokines, fluid excretion, tubuloglomerular feedback, and nephroprotection) may have also been involved.[32]

Unlike SGLT2 inhibitors, dipeptidyl-peptidase-4 (DPP4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have not proven effective for the prevention of HF in T2DM. In their respective CV outcome trials, DPP4 inhibitors were associated with either no effect[33–35] or with a higher risk (saxagliptin, vildagliptin, and non-statistically significant trend with alogliptin) for HF hospitalization,[36,37] whereas the use of GLP-1 agonists had a neutral effect on HF risk.[38–42]

In addition to SGLT2 inhibition, patients with T2DM may benefit from a comprehensive management of risk factors and comorbidities in the prevention of HF. Indeed, in T2DM nephropathy, treatment with irbesartan reduced the incidence of HF compared with placebo (HR 0.72, 95% CI 0.52–1.00; $P = 0.048$) or amlodipine (HR 0.65, 95% CI 0.48–0.87; $P = 0.004$).[43] However, real-world data suggest that this approach may be insufficient for many patients, given that a recent cohort study of >270 000 individuals with T2DM demonstrated that among those who had five risk factors (elevated glycosylated haemoglobin level, elevated low-density lipoprotein cholesterol level, albuminuria, smoking, and elevated blood pressure) within guideline-directed target ranges, the risk of HF remained elevated (HR 1.45, 95% CI 1.34–1.57) despite a reduction in other CV outcomes (MI, stroke, and mortality).[44] In contrast, real-world data corroborate findings of CV outcomes trials with SGLT2 inhibitors regarding their effectiveness in risk reduction for HF compared with other glucose-lowering agents.[45,46]

Sedentary habits

There is an evidence that individuals that are physically active have significantly lower risk of HF when compared to those with low exercise tolerance and that the risk reduction may be dose sensitive.[47,48] A simple metric such as (self-reported) ability to walk at pace (>5 km or 3 miles per hour) was related to a reduced HF risk. In the Women's Health Initiative, the incidence of HF ranged from 1.55 per 1000 person-years for physically active individuals (defined as >150 min/week of moderate physical activity, or >75 min/week of vigorous physical activity) to 2.15 for those who were somewhat active (less than the activity thresholds for active but >0), to 3.29 per 1000 person-years for those who were inactive. After adjustment for other risk factors, the HF risk for active adults was 0.66 (95% CI 0.58–0.75) and 0.77 (95% CI 0.67–0.87) for somewhat active adults compared with inactive adults.[49]

Endocrine and metabolic factors

Lipid concentrations

In the Framingham Heart Study (6860 participants, mean age 44 years; 54% women) free of baseline CAD, during a mean follow-up period of 26 years, 680 participants (49% women) developed HF.[50] Participants with high baseline non-high-density lipoprotein cholesterol (non-HDL-C > 190 mg/dL) and those with low HDL-C (<40 mg/dL in men, <50 mg/dL in women) experienced a 29% and 40% higher HF risk, respectively, compared to those in the desirable lipid categories; the PARs for high non-HDL-C and low HDL-C were 7.5% and 15%, respectively. Hazards associated with non-HDL-C and HDL-C remained statistically significant after additional adjustment for interim MI. The more recent Multiethnic Study of Atherosclerosis showed that lipid measures were associated with incident HF, but only in individuals with T2DM.[51]

It is well established that hydroxymethylglutaryl-CoA reductase inhibitors (statins) reduce CV events also in patients without previously diagnosed CVD and consequently may prevent HF development, although the net benefit (i.e. absolute risk reduction) is proportional to the baseline CV risk, and lipid blood level. Caution has been recommended, however, in initiating drug therapy in old individuals.[5]

A collaborative meta-analysis of unpublished data from major randomized trials has shown that statins modestly reduce the occurrence of a first non-fatal HF hospitalization not preceded by MI (relative risk (RR) 0.91, 95% CI 0.84–0.98).[52]

Obesity

The risk of HF development is related to body weight and body mass index (BMI).[53,54] It was estimated that risk of HF development increases by 5–7% with each increment of 1 kg/m^2 in BMI.[53] Although the contribution of obesity (BMI > 30 kg/m^2) to the development of HFpEF is greater than for HFrEF, body weight is a risk factor in both scenarios.[55] In a population study from Rochester, Minnesota, obesity was present in 20.5% of newly diagnosed patients with HF during 1985 to 1990 compared with 29.5% from 1997 to 2002 ($P = 0.003$ for trend). The average time from onset of obesity to the development of HF was 16 years.[53] The population attributable risk (PAR) of obesity for

incident HF was estimated at 12%. In a study from the Women's Health Initiative, the incidence of HF increased from 1.32 per 1000 person-years for patients with a BMI between 18.5 and 25 kg/m^2, to 1.72 per 1000 person-years for those with a BMI between 25 and 30 kg/m^2, and 3.37 per 1000 person-years for those with a BMI >30 kg/m^2.[53] After adjustment for classical and acquired risk factors, the risk developing HF for patients with a BMI between 18.5 and 25 kg/m^2 was 0.43 (95% CI 0.38–0.48), and 0.50 (95% CI 0.45–0.56) for those with a BMI between 25 and 30 kg/m^2 compared with those with a BMI >30 kg/m^2.

The precise mechanisms causing obesity-related HF are unknown. Excessive adipose accumulation results in an increase in circulating blood volume. A subsequent, persistent increase in cardiac output, cardiac work, and systemic blood pressure[56] along with lipotoxicity-induced cardiac myocyte injury and myocardial lipid accumulation[57] and oxidative stress have been implicated as potential mechanisms leading to overt HF.[58] There is a pathophysiological link between excess fat tissue, metabolic syndrome and HF at the molecular, neurohormonal, and central haemodynamics level.[57,59] Weight loss is related to favourable haemodynamic effects. There are no large-scale studies of the safety or efficacy of weight loss with diet, exercise, or bariatric surgery in obese patients with HF. However, weight control has been confirmed to reduce the risk of the HF in large cohort analyses.[60]

Thyroid diseases and other endocrine disorders

Multiple endocrinopathies may occasionally be associated with HF (*Table 5*).[61,62] Endocrine disease may be a truly reversible factor of cardiac dysfunction, thus offering the possibility of aetiological treatment of HF or even prevention.

Thyroid dysfunction may predispose to HF. Hypothyroidism is frequent, as it affects 4–10% of the general population but the prevalence of subclinical hypothyroidism is ∼5–15%.[62] It affects the heart as it may trigger rhythm disturbances, including sinus bradycardia, QT prolongation or atrioventricular block, diastolic hypertension, low cardiac output with narrow pulse pressure, and hypercholesterolaemia with accelerated atherosclerosis. Heart failure in this case may be related to diastolic LV dysfunction and low cardiac output.[63] Indeed, the Healthy Aging and Body Composition study, a population-based study of 2730 men and women aged 70–79 years, found that subclinical

hypothyroidism [thyroid-stimulating hormone (TSH) from 7.0 to 9.9 mIU/L] was associated with a 2.6-fold increased risk to develop HF compared to normal TSH values; this relative risk increased to 3.3 folds in patients with TSH ≥10 mIU/L.[62] Subsequent studies such as the Cardiovascular Health Study confirmed these findings.[63]

Hyperthyroidism results in an increased heart rate due to sinus tachycardia or atrial fibrillation and a decrease in systemic vascular resistance with subsequent renin–angiotensin–aldosterone system activation and increased preload; these changes lead in turn to increased cardiac output (increased preload and decreased afterload) and systolic hypertension (increased heart rate and cardiac output), with subsequent LV hypertrophy and diastolic LV dysfunction.[63] These abnormalities may predispose to HF.[62]

Toxic factors

Alcohol abuse

Excessive alcohol consumption is one of the most important causes of dilated cardiomyopathy (defined as alcoholic cardiomyopathy, ACM), and it has been estimated that 40% of dilated cardiomyopathy can be attributed to excessive alcohol consumption.[64] Mild alcohol consumption was reported to be protective against HF development,[65] but this concept has been challenged by the observation that low-volume drinkers may appear healthy only because the 'abstainers' with whom they are compared are biased towards ill health.[66]

In contrast, consuming >40 g of alcohol daily (~2.5–3 standard drinks per day) for >5 years has been associated with higher risk.[65] This is confirmed by a large combined analysis of individual participant data from more than half a million current drinkers; this study showed that the risk of mortality increased over the entire range of alcohol intake above 45 g daily.[67] It is suggested that individual genetic susceptibility plays an important role in the pathogenesis of ACM in patients who consume alcohol above recommended levels.[68]

The clinical diagnosis ACM is suspected when biventricular dysfunction and dilatation are persistently observed in a heavy drinker in the absence of other known causes for myocardial disease. Alcoholic cardiomyopathy most commonly occurs in men 30–

55 years of age who have been heavy consumers of alcohol for >10 years. Women represent ~14% of the ACM cases but may be more vulnerable with less lifetime alcohol consumption.[69]

Recovery of LV function after cessation of drinking has been reported,[70] and in this case, ACM has a better prognosis than dilated cardiomyopathy in alcohol abstainers.[64] Although more evidence is needed, taken together, the available data support that to prevent HF, lower limits for alcohol consumption than those recommended in many current guidelines should be recommended and that ACM patients should be advised to stop drinking.[71]

Smoking

Smoking is a strong modifiable risk factor for CVD. In multiple studies, smoking has been associated with a higher risk of developing HFrEF independently of other lifestyle risk factors.[49,72–75] In the Women's Health Initiative the adjusted risk of incident HFrEF for never smokers was 0.43 (95% CI 0.33–0.55) and 0.47 (95% CI 0.37–0.60) for past smokers compared with current smokers.[49] In this study, smoking was also associated with HFpEF with similar HRs.

Smoking causes HF both indirectly, due to ischaemic heart disease, but also due to a direct effect on cardiac structure and function: in healthy individuals, greater LV mass, poorer systolic function of the left and right ventricle and also worse diastolic function as reflected by a higher E/e′ were observed in smokers compared to non-smokers.[76–80] In a recent meta-analysis, continued smoking after HF had been diagnosed was associated with 38% increased mortality risk and 45% increased risk of hospital readmission.[81]

E-cigarettes have been proposed as a potential tool to facilitate smoking cessation and could thus be helpful to prevent CVD including HF. Their use is, however, discouraged, for several reasons including a higher risk of CVDs among dual users of e-cigarettes plus combustible cigarettes compared with smoking alone.[82,83]

The increasing use of waterpipe (Hookah/Shisha/Hubble bubble) is worrying, because this form of smoking exposes smokers to significantly higher levels of constituents of cigarette smoke, many of which are known to be harmful to CV health.[84,85]

Cocaine

Cocaine is the second most widespread illicit drug in Europe, after cannabis, estimated to be used by ∼13 million Europeans at least once in their lifetime (3.9% of adults aged 15–64 years).[86] Cocaine increases the activity of monoamine neurotransmitters in the central and peripheral nervous system, blocking the reuptake of dopamine, norepinephrine, and serotonin, and modulates endogenous opioid receptors leading to a sensation of increased energy, alertness, euphoria, and decreased tiredness.[87]

Sympathetic-mediated CV complications of cocaine use include coronary and peripheral vasoconstriction, tachyarrhythmias, increased myocardial oxygen consumption, and hypertension. Cocaine induces also a proinflammatory and prothrombotic state by activating mast cells, platelets, and the coagulation cascade. Moreover, it exerts a direct damage on endothelial cells (by blocking nitric oxide synthase and promoting endothelin-1 release), on vascular smooth muscle cells (by impairing acetylcholine-induced vasorelaxation and intracellular calcium handling), and on cardiomyocytes (by directly blocking sodium, potassium and calcium channels, with direct negative inotropic and pro-arrhythmic effects). Cocaine promotes also early-onset atherosclerosis, cystic medial necrosis, and a hypersensitivity reaction (enhanced by contaminants such as amphetamine, sugars, or talc) that may further aggravate CV damage. All these mechanisms are responsible for acute coronary syndromes, early-onset atherosclerosis, but also non-ischaemic complications such as Takotsubo cardiomyopathy, myocarditis, cardiac hypertrophy, dilated cardiomyopathy, arrhythmias, endocarditis, hypertensive crises, aortic dissection or rupture, ischaemic and haemorrhagic stroke, pulmonary hypertension, and vasculitis.[87]

Cocaine abuse is considered responsible for 25% of MI occurring in adults aged 18–45 years.[88] Reduced LV function has been reported in 4–18% of cocaine abusers without HF symptoms, and independently of CAD. Several CV magnetic resonance studies confirm the presence of myocardial oedema in up to 47% and fibrosis in up to 73% of asymptomatic cocaine users.[89] Figure 1 summarizes the pathophysiology and clinical manifestations of CV related to acute and chronic cocaine abuse.

Cardiotoxic and nutritional factors

Many toxic factors have been associated with HF development, such as chloroquine, cobalt, clozapine, and catecholamines, but any list will likely be incomplete. It is worth mentioning here that several pharmacologic agents may also be linked with a true toxic cardiomyopathy, most notably anticancer drugs (see also below), antiretroviral agents, and thiazolidinedione antidiabetic drugs.[90] Also, some substances, prescribed for athletic performance enhancement (e.g. anabolic steroids), and weight loss (e.g. ephedra, amphetamine), are associated with LV dysfunction and sudden cardiac death.

Severe nutritional deficiencies such as those occurring in anorexia nervosa can also account for the development of cardiomyopathy.[91]

Chemotherapy

The considerable improvement in the long-term survival of patients with cancer, caused by aggressive anticancer treatment, is associated with an increased risk of both short and long adverse CV effects. Cardiotoxicity of some of these drugs has an important impact on the patient's survival and quality of life independent of the oncologic process. Cardiotoxicity related to chemotherapy leads mainly to LV dysfunction. LV dysfunction and HF are known consequences associated with exposure to several chemotherapy agents. The classic description of cardiomyopathy related to chemotherapy stems from anthracyclines. With this class of drugs, the typically dose-related onset of cardiomyopathy can occur acutely (even during or shortly after treatment), sub-acutely (days or weeks after treatment), or chronically (months to years after treatment).

Newer agents such as trastuzumab appear to have a different pattern of cardiac dysfunction that are not necessarily dose-related and thought to be due to alterations in myocardial signalling without apoptosis, which in many cases is reversible. A newer class of chemotherapy drugs that target and inhibit vascular endothelial growth factor (VEGF) very commonly can result in severe hypertension. Typically, this precedes the development of cardiomyopathy and diastolic HF may be an early clinical manifestation. Also, small molecules with anti-VEGF activity (tyrosine kinase inhibitors) can lead to LV dysfunction.[92] Immune checkpoint inhibitors, a newer class of anticancer agents, have further been associated with cardiotoxicity mainly in the form of myocarditis and HF.

The use of CV drugs for cardio-protection of oncological patients has not been recommended so far, but regular exercise training has been associated with protective effects for the prevention of LV dysfunction in breast cancer patients.[93] Baseline risk stratification and regular clinical, imaging, and laboratory follow-up are needed to facilitate prevention and early detection of HF, with the aim of CV optimization, proper design of anticancer regimens, and monitoring of side effects. A baseline risk stratification tool has been proposed by the HFA of the ESC.[94]

Radiotherapy

Radiation therapy to the chest area often is part of the treatment for Hodgkin lymphoma and cancers of the lung, oesophagus, or breast. Cardiotoxicity is a risk when a large volume of heart muscle is exposed to a high dose of radiation. Marked interstitial myocardial fibrosis is common in radiotherapy-induced cardiotoxicity, with lesions of variable volumes and distribution. Studies found a relative risk of fatal CV events between 2.2 and 12.7 in survivors of Hodgkin lymphoma and between 1.0 and 2.2 in patients with breast cancer. Among survivors, the risk of HF was increased 4.9-fold.[95,96] Systolic dysfunction is generally observed when radiotherapy is combined with anthracyclines. A restrictive haemodynamic pattern can occur in the absence of a history of treatment with an anthracycline: at a microscopic level collagen not only increases as a whole but the proportion of type I collagen increases proportionally to type III. This marked alteration in collagen synthesis may contribute to impaired diastolic distensibility of the ventricles seen in this group of patients.[97] Most patients with myocardial involvement have interstitial fibrosis. The loss of myocardium results in renin–angiotensin–aldosterone and adrenergic system-driven myocardial remodelling, which is progressive and results in end-stage symptoms.[98]

Alteration in radiotherapy field or targeted radiation, with avoidance and/or shielding of the heart, remains one of the most important things in prevention of radiation-induced cardiac damage and eventually HF.[99]

Viral infection

Viral infection may cause HF triggering viral myocarditis, a condition which is the result of an exaggerated inflammatory response upon viral infection of the heart. Viruses triggering myocarditis include common upper respiratory tract viruses, enteroviruses, parvovirus-B19, and human herpes virus-4 and -6 among others. An immunogenetic susceptibility along with other factors, e.g. co-infection with other viruses, may trigger myocarditis upon cardiac viral presence.[100]

Viral myocarditis can also be part of other systemic conditions, such as lupus erythematosus, muscle disease, and HIV. Presentation may be acute, with severe haemodynamic failure, such as in acute fulminant cases, or it may be subacute, with a better tolerated status. Prognosis varies, from spontaneous complete resolution, to, in up to 20% of cases, the development of severe HF.

In order to prevent HF recurrences, a yearly follow-up of cardiac function and symptoms is required for at least 4 years after viral myocarditis.[101] In case of recurrent myocarditis, persistent or progressive systolic dysfunction, or suspicion of possible underlying (auto-)immune problems, endomyocardial biopsies (EMB) are recommended.[100,102] Immunosuppressive therapy may prevent HF in those cases with persistent immune activation, and in cases of auto-immune diseases, identified by an increase of cytotoxic T-cells quantified in EMB.[103] Anti-viral therapy in case of high cardiac copy numbers and active viral replication, may help to decrease viral presence, and as such might prevent HF development.[103] Viral serology is not helpful in view of the high prevalence of circulating IgG antibodies to cardiotrophic viruses in the absence of viral myocarditis.

There is no direct data on incidence of *de novo* HF and influenza vaccination in the population at large. In contrast, influenza vaccination has proven to reduce the risk of CV events (including HF hospitalizations) in some populations, but direct evidence of influenza-triggered myocarditis is lacking.[104,105]

The management principles remain based on the preventive strategies and curative modalities for clinically evident viral disease (*Figure 2*).

More recently, coronavirus infective disease 2019 (COVID-19) has been shown to be a possible cause of HF.[106] Myocardial injury is present in a meaningful proportion of patients, 10–60% or more, depending on age and comorbidities. It may be due to non-

specific mechanisms, such as fever and adrenergic activation, as well as mechanism typically related to COVID-19, such as angiotensin II release and the exaggerated inflammatory response causing also pneumonia and the acute respiratory distress syndrome in many patients.[107] Typical histopathological signs of myocarditis have not been demonstrated in most of the cases. However, COVID-19 infection of the myocardium has been shown with the most likely localization in interstitial cells or macrophages rather than in the myocytes.[108] The long-term consequences of COVID-19 on cardiac function have not been fully elucidated, although some abnormalities have been shown by cardiac imaging.[109] Thus, adoption of proper measurements to prevent COVID-19 spreading is essential, also to prevent HF.[107]

Chagas' disease

Chagas' disease is caused by the protozoan parasite *Trypanosoma cruzi*, transmitted by infected faeces of haematophagous insects. Over 5 million people are infected worldwide, that is 7.5 times the number affected by malaria.[110] The vast majority of acute infections are never detected because of mild or atypical flu-like symptoms. Chagas cardiomyopathy is by far the most serious long-term complication of the disease, occurring in up to 30% of infected patients up to 20 years after initial infection. HFrEF, conduction abnormalities, arrhythmias, thromboembolic phenomena, precordial chest pain, and sudden death are the classical clinical presentations. Cardiac dysautonomia, microvascular disturbances, parasite-dependent myocardial damage, and immune-mediated myocardial injury are the main mechanisms. Myocarditis is key and parallels HF development.[111]

The best approach to preventing Chagas' disease-related HF is the prevention of Chagas' disease itself. The insects transmitting *T. cruzi* are mainly present in poor rural regions, mainly in children, and through migration of endemic rural villages to Latin American cities, hundreds of thousands now live in the USA, Spain, and other European countries. Early diagnosis, either by serological or PCR testing, of *T. cruzi* infection is essential. Nifurtimox and benznidazole are the only drugs with proven efficacy against *T. cruzi*, but their efficacy to prevent specifically HF has not been proven. In patients older than 50 years, or with cardiomyopathy already present, treatment will not cure the cardiomyopathy or reduce mortality. The role of concomitant comorbidities or genetics

in the clinical progression from asymptomatic to overt HF is unknown. In the absence of initial cardiac manifestations in infected patients, a yearly follow of cardiac symptoms and electrocardiogram (ECG) seems essential: abnormalities should prompt cardiac work-up, including echocardiography and ECG monitoring. If available, echocardiography to detect LV abnormalities is preferable, since the ECG is normal in ~10% of patients with LV abnormalities.[112]

Rheumatic heart disease

Rheumatic heart disease (RHD) is a downstream result of skin or throat infection with Group A Streptococcal bacteria (Strep A).[113] Severe or recurrent episodes of an abnormal immune reaction to Strep A, termed acute rheumatic fever (ARF), can lead to the permanent heart valve damage of RHD with complications including HF, stroke, arrhythmia, and premature death.[114] RHD affects ~40 million people, causing more than 300 000 deaths each year, almost all in low- and middle-income countries.[115]

The protracted causal pathway of RHD means there are many opportunities to intervene and reduce incident disease. Strategies aimed at preventing RHD must begin with action on the indirect causes of disease and move to strategies which address the direct biomedical causes through primary, secondary, and tertiary prevention approaches.

Strep A spreads through large airborne droplets and through skin to skin contact.[116] Therefore, exposure, transmission, and infection are inextricably tied to the environment in which people live and interact, particularly in households. Action must be taken to address the environmental and socioeconomic causes of Strep A infections leading to ARF and RHD, in particular reducing household crowding and improving hygiene infrastructure.

Primary prevention comprises strategies that improve the assessment and treatment of skin and throat infections to prevent ARF in people at high risk of the disease. Antibiotic treatment of Strep A pharyngitis can significantly reduce the risk of developing subsequent ARF. Treatment with oral penicillin can reduce the attack rate of ARF by ~70%, increasing to 80% if a single intramuscular injection of benzathine benzylpenicillin (BPG) is given.[117]

Secondary prevention focuses on people who are at risk of recurrent ARF because they have had ARF or live with RHD. Antibiotic prophylaxis with three or four weekly intramuscular injections of BPG has been the global standard of care for ARF prevention since the drug's development in the 1950s. This aims to prevent Strep A infections in order to prevent recurrent episodes of ARF, which in turn leads to better clinical outcomes, including reduced overall mortality.[118–122] Receiving more than 80% of scheduled injections appears to be protective against recurrent episodes of ARF.[120] Early and accurate diagnosis of ARF is a critical opportunity to prevent RHD because it allows for disease altering secondary prophylaxis to be initiated as soon as possible. Similarly, early diagnosis of RHD before heart valve damage advances provides an opportunity to begin secondary prophylaxis sooner, reducing the risk of progressive heart damage and allowing regression, or even complete resolution of RHD.

People living with RHD require a range of medical and allied health services to prevent complications and ensure the best possible quality of life. Tertiary care includes monitoring of valve function through clinical review and echocardiography, providing advanced medical and surgical management when appropriate, and other primary and specialist health services.[123,124]

Sleep apnoea

In patients with overt HF, there is a high prevalence of periodic breathing and Cheyne–Stokes respiration with alternating central apnoeas (CAs) and hyperpnoea, not only during sleep (central sleep apnoeas, CSAs), but even at daytime in awake patients.[125,126] The severity of CA is associated with increased mortality.[125–127] Central apnoea, may be considered more a consequence of HF than a cause, being triggered by increased isolated or combined peripheral and central chemosensitivity (increased controller gain), increased lung to chemoreceptor circulatory delay, and reduced damping of blood gas levels (increased plant gain).[128] On the other hand, obstructive sleep apnoeas (OSA) and hypopnoeas result from complete or partial collapse within the upper airways and are associated with increased breathing effort, reduced oxygen saturation, increases in arterial carbon dioxide, LV afterload and wall tension and myocardial oxygen needs, alterations in autonomic nervous tone, and arousals from sleep.[129]

Central sleep apnoea is highly prevalent even in patients with asymptomatic LV dysfunction, where the severity of CSA may not be related to the severity of haemodynamic impairment.[130] Severe CSA is associated with impaired cardiac autonomic control and with increased cardiac arrhythmias.[130] These patients with asymptomatic dysfunction may be considered at risk for progression to overt HF and for sudden death, particularly in the setting of ischaemic cardiomyopathy.

Conversely, data from a nationwide database, covering the entire Danish population (4.9 million individuals included, 53.4 years of age) established that OSA is associated with an increased risk of incident HF in patients of all ages. Another large study, including a total of 1927 men and 2495 women, 40 years of age, and free of CAD and HF at the time of baseline polysomnography over a median 9-year follow-up period has demonstrated an increased risk of incident HF in community-dwelling middle-aged and older men with OSA.[131] Use of continuous positive airway pressure therapy was associated with a lower risk of incident HF in the elderly (>60 years of age).[132]

Environmental and air pollution

According to the World Health Organisation (WHO), more than 20% of all CV deaths is caused by air pollution,[133] while the Global Burden of disease study ranked ambient air pollution ninth among the modifiable risk factors.[134]

Experimental studies suggest that exposure to air pollution can lead to oxidative stress, systemic inflammation, and vasoconstriction, which may increase blood pressure and result in atherosclerosis, ultimately increasing the risk of CVD.[135,136]

The impact of air pollution on CV mortality and hospitalization has been established in epidemiological studies,[137–139] in particular in CAD patients.[140] Evidence is less clear, however, on the effects of air pollution on the development of HF. A systematic review and meta-analysis[141] on the association between acute exposure to air pollution and HF showed that HF hospitalization or death was associated with increases in gaseous components concentrations and with increases in particular matter concentration. The percentage increase in risk for carbon monoxide was 3.52 (95% CI 2.52–4.54) per 1 part per million; for sulphur dioxide 2.36 (95% CI 1.35–3.38) per 10 parts per billion (ppb); for nitrogen dioxide 1.70 (95% CI 125–2.16) per 10 ppb; for ozone 0.46 (95% CI −0.10

to 1.02) per 10 ppb; for $PM_{2.5}$ 2.12 (95% CI: 1.42–2.82) per 10 μg/m^3; and for PM_{10} 1.63 (95% CI: 1.20–2.07) per 10 μg/m^3.

There is a growing evidence regarding long-term exposure to air pollution and HF in a dose–response fashion. One cohort study in the UK found that HRs of HF for a 10 μg/m^3 increase in $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_2, and NO_x were 1.85 (1.34–2.55), 1.61 (1.30–2.00), 1.13 (0.80–1.59), 1.10 (1.04–1.15), and 1.04 (1.02–1.06), respectively.[142] The Ontario Population Health and Environment Cohort (ONPHEC) reported that HRs of incident HF responding with every interquartile range increase in exposure were 1.05 (95% CI 1.04–1.05) for $PM_{2.5}$, 1.02 (95% CI 1.01–1.04) for NO_2, 1.03 (95% CI 1.02–1.03) for O_3, and 1.02 (95% CI 1.02–1.03) for O_x, respectively.[143] A separate study within ONPHEC reported that the HR for each interquartile range increase in ultrafine particle matter exposure was 1.03 (95% CI 1.02–1.05) and exposure to nitrogen dioxide was also independently associated with higher HF incidence (HR for each increase in interquartile range 1.04 (95% CI 1.03–1.06).[144]

Sex-based predispositions

The overall lifetime risk of HF is comparable between the sexes, however, there are marked sex differences in the landscape (*Figure 3*).[145] Men are predisposed to HFrEF, while HFpEF is more prevalent in women (for individuals ≥80 years, HFpEF prevalence is 4–6% in men and 8–10% in women).

There are also important differences with respect to how ‘traditional’ risk factors confer risk between the sexes: for example, T2DM, obesity, hypertension, and tobacco smoking are stronger risk factors in women.

Other sex-specific clinical conditions predispose to HF in women. Peripartum cardiomyopathy, a potentially life-threatening condition in the last month of pregnancy or in the months following delivery in women without other known causes of HF, affects 1:1000 pregnancies. Several factors may contribute including environmental factors (e.g. infections), pregnancy-associated conditions such as pre-eclampsia, mode of delivery, and genetic predisposition. Furthermore, breast cancer is the most common cancer in women and shares common risk factors with CVDs, including age, obesity, and tobacco use. A stable to increasing incidence, coupled with a decrease in mortality has resulted in a growing population of survivors at risk for cardiotoxicity from systemic anticancer

therapies (anthracyclines, radiation, trastuzumab, and endocrine therapy). In epidemiologic studies of breast cancer survivors, late CV mortality exceeds oncologic mortality.

Population attributable risks around the world: opportunities for prevention

Worldwide

According to a 2017 analysis from the Global Burden of Disease study,[146] ischaemic heart disease accounted for the highest proportion (26.5%) of age-standardized prevalence rate of HF, followed by hypertensive heart disease (26.2%), chronic obstructive pulmonary disease (23.4%), other cardiomyopathy (6.5%), non-rheumatic degenerative mitral valve disease (2.7%), other CV and circulatory diseases (2.4%), ACM (2.4%), non-rheumatic calcific aortic valve disease (2.3%), RHD (1.8%), and myocarditis (1.7%). The proportion of age-standardized prevalence rate of HF due to each cause varied widely by age group (*Figure 4*). In children and adolescents aged <20 years, congenital heart anomalies, myocarditis, and other cardiomyopathy accounted for over 80% of the age-standardized prevalence rate of HF. In adults aged 25–69 years, hypertensive heart disease accounted for the most among all causes of HF. The effects of ACM and RHD on HF were mainly concentrated in adults aged 20–59 years. This finding underlines the importance of CV risk factor control in preventive HF occurrence

In different continents and regions, differences in underlying causes of HF were observed.[146]

Africa

Characterizing the antecedents of HF within the diverse peoples (>1 billion) living on the vast continent of Africa remains problematic. The heart health of Africans is challenged by a combination of historical diseases of poverty (including malnutrition and endemic communicable diseases such as tuberculosis), occupational and environmental hazards, and the dynamic lifestyle changes inherent to economic growth and rapid urbanization.[147]

Overall, there are an increasing amount of good quality data from Africa leading to better understanding of the epidemiological profile (and indeed regional heterogeneity) of HF on the continent.

The unique and evolving characteristics of HF in Africa was revealed by the Heart of Soweto Study.[148] Within 5328 *de novo* cardiac presentations (mean age 52 years and 60% women) to a hospital servicing Africa's largest urban enclave, a broad variety of HF cases was revealed. This included hypertensive HF (21.1% of the entire cohort), dilated cardiomyopathies (15.4% comprising idiopathic, HIV-related and peripartum cardiomyopathy, right HF (6.5%), idiopathic cardiomyopathy (3.5%), and valvular HF largely attributable to latent RHD (2.2%). Many of the findings of this study, including a broad spectrum of African-specific forms of HF affecting predominantly younger individuals and women was confirmed by an equivalent study undertaken in Nigeria; the Abeokuta Heart Failure Registry[149] reported 320 HF cases (mean age 59 years, 43% women) confirming the central importance of hypertension as the primary driver of HF on the continent.

The subsequent Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) study was a prospective, multicentre observational survey of 1006 patients (mean age 52 years, 51% women) presenting at 12 university hospitals in 9 African countries with acute HF, with a 6-month mortality of 17%.[150] The recent findings of the PEACE Registry, a prospective, multicentre study of 244 Nigerian women presenting with peripartum cardiomyopathy highlighted that this condition is an important contributor to premature death in a young population in Africa.[151]

The International Congestive Heart Failure Study (INTER-CHF) enrolled 1294 patients residing in Africa. Compared to their international counterparts, African patients were, on average 10 years younger and had the highest proportion of women (48%).[152]

Those data confirm that in Africa HF affects overall a young population. This is in contrast with the United Nations Sustainable Development Goals (UN SDGs) which only records death due to non-communicable disease such as HF in the age range 30–70 and therefore missing a larger part of death due to, e.g. RHD and congenital heart disease.[153]

The more recent Global Burden of Disease study analysis revealed that in 2017 ischaemic heart disease was the major underlying causes in all areas but in North Africa where

hypertension and Western Sub-Saharan where other cardiomyopathies, hypertension, COPD were the leading causes.[146]

In view of the heterogeneity of the causes of HF in Africa and the huge regional differences, in combination with the limited number of (population-based), studies PARs for HF are difficult to quantify and differ considerably across the continent. Consequently, evidence-based preventive measures should be tailored regionally.

Asia

Asia is the world's most populated and fastest ageing region,[153,154] bearing half the global CVD burden.[155] Accordingly, the burden of HF in Asia is huge,[156] with >4 million HF patients living in China alone,[157] another 1.3–4.6 million in India,[122] ∼1 million in Japan,[158] and millions more in the highly populous region of Southeast Asia.[159] Traditional modifiable risk factors have been shown to have high PARs for CVD in Asia (*Table 6*).[160] Specifically among Asian patients with HF, traditional risk factors were highly prevalent, despite Asian patients being relatively young (mean age 60 years) compared to European and American counterparts.[161,162] Of note, traditional risk factor burden in HF varied across Asia, being highest in Southeast Asia compared to Northeast or South Asia (*Figure 5*).[161] Moreover, there was significant interaction between region and ethnicity in Asia, where the odds of a risk factor was higher in patients from higher-income regions, compared to those of the same ethnicity from lower-income regions. For instance, an Indian patient with HF in Singapore (high income) had >5 times the odds of T2DM compared to an Indian patient with HF in India (low income) (*Table 6*). This observation was postulated to be related to rapid epidemiologic transition in Asia, with rapid rise in wealth and adoption of unhealthy lifestyle habits.[161]

Epidemiologic transition is also evident within individual country registries in Asia over time. Whereas RHD was previously highlighted,[163] current HF registries show a predominance of vascular risk factors and ischaemic heart disease. In Japan, the prevalence of ischaemic HF increased from the Chronic Heart Failure Registry and Analysis in the Tohoku District (CHART)-1 (2000–2004) to the CHART-2 (2006–2010) study, as did the prevalence of T2DM and hypertension.[156,164] Of particular concern is the increasing trend of ischaemic heart disease in younger individuals in Asia, calling for urgent public health measures to prevent recurrent events and future HF.[165] This trend is

confirmed by the more recent Global Burden of Disease study analysis which revealed that ischaemic heart disease was the leading causes in Central Asia, while COPD in South and East Asia and hypertension in Southeast (but with ischaemic among the first causes).[146]

Australia

The latest National Health Survey reports 67% of adult Australians are overweight/obese (historically elevated), 22.8% are hypertensive (stable), 16.8% over-consume alcohol (modest decline), 13.8% smoke (large decline) while only ∼15% meet recommended physical exercise levels. According to this survey, the point prevalence of HF is reported to be ∼100 000 (two-thirds aged ≥65 years)/26 million Australians. However, these data are based on self-report.[166]

Overall, the current burden of HF is estimated to be 61 000 incident cases/annum (6.9 cases/1000 person-years); 480 000 prevalent HFrEF cases (6.3%, 95% CI 2.6–10.0%) of those aged ≥45 years; and 496 000 prevalent HFpEF cases (6.6%, 95% CI 2.1–11.1%) of those aged ≥45 years. Critically, in the setting of historically elevated HF antecedents, by 2030 an additional 51% and 65% of Australian men and women, respectively, will be living with HF.[167]

Overall, epidemiological data on the antecedents and incidence of HF in Australia are scarce. To the best of our knowledge, data on PARs for HF are not available for Australia. Two prospective, community-based surveillance studies provide insightful information on the prevalence and common antecedents of HF from an urban-to-remote Australia perspective.

In the urban-dwelling, Canberra Heart Study cohort (2000 randomly selected residents, mean age 69 years and 50% men) the prevalence of clinical HF was 6.3% (95% CI 5.0–7.7%), with a 4.4-fold increase from those aged 60–64 years to 80–86 years. The additional prevalence of asymptomatic LV systolic dysfunction was 5.9% (95% CI 4.7–7.3%). On adjusted basis, the main correlates of pre-clinical HF/LV systolic dysfunction were male sex (2.3-fold more likely), hypertension (1.1-fold), MI (3.0-fold), and CAD (1.6-fold).[168]

Despite being markedly younger (436 randomly selected residents from six dispersed Aboriginal communities in Central Australia, mean age 44 years and 36% men), in the

remote-dwelling Heart of the Heart Study cohort a similar prevalence of clinical HF was reported, i.e. 5.3% (95% CI 3.2–7.5%). Moreover, asymptomatic LV systolic dysfunction was evident in 13% (95% CI 9.4–15.7%). The main age- and sex-adjusted risk factors for HF were CAD (cohort prevalence 7%/9.6-fold more likely), T2DM (40%/5.4-fold), hypertension (41%/4.8-fold), obesity (42%/2.9-fold), and RHD (7%/5.6-fold).[169] The Global Burden of Disease study analysis instead observed the hypertension as the leading cause, followed by lung and ischaemic heart diseases.[146]

Europe

There are a number of established risk factors that significantly contribute to the burden of incident HF in Europe, including hypertension, obesity, blood lipids, T2DM, smoking, alcohol consumption, and prevalent CVD.[170,171] The contribution of these risk factors to HF can be quantified with tPARs (*Table 7*). The PAR can in this case be interpreted as the proportion of incident HF cases in a population that is attributable to a particular risk factor. From a public health and prevention standpoint, trends in PAR are important, especially for modifiable risk factors.

In a recent prospective study including 78 657 individuals from 4 European community-based cohorts in Denmark, Finland, Sweden, and Italy with baseline assessment of the traditional risk factors for HF, women had a lower risk for incident HF (5.9%) than men (7.3%).[173] The difference was confirmed even after adjustment for traditional risk factors.[173] The overall PAR of all risk factors combined (BMI, systolic blood pressure, total cholesterol, daily smoking, T2DM, history of MI, and stroke) was 59% for women and 63% for men.[173] Being overweight, or obese, and having hypertension were the strongest contributors, together accounting for 40% of incident HF in women and 36% in men (*Table 7*). As both obesity and hypertension are highly prevalent risk factors, even modest reductions may translate into a large improvement at the population level.[174]

Similar results were also recently reported in a large linked, clinical database with general practice and hospital data from the UK including 871 687 individuals of whom 5.5% of individuals developed HF.[2] Again, the incidence of HF was higher in men compared to women and increased with age. The highest PAR in this study was observed for obstructive pulmonary disease and atrial fibrillation and this was similar in both men and women (*Table 7*). The total PAR is attenuated with older age, but since (modifiable) risk

factors remain common in the elderly, lifestyle interventions could still play a pivotal role in preventing HF in these individuals.

Beside more traditional risk factors, higher levels of social deprivation were also associated with developing HF.[2,177,178] One study showed that at the time of HF diagnosis, each lower quintile of socioeconomic status was associated with a significant reduction in age at the time of HF onset and a significant increase in the number of comorbidities, BMI, and prevalence of ischaemic heart disease and smoking.[178] These studies indicate an opportunity for more targeted population level prevention strategies.

When considering the risk factor profile of patients already diagnosed with HF (i.e. prevalent, not incident, HF) in Europe, several national observational studies showed a high prevalence of traditional risk factors.[179–182] Moreover, non-cardiac comorbidities are of interest; in the ageing HF population there is a prominent increase in concomitant non-cardiac comorbidities. Several studies have shown that the prevalence of non-cardiac comorbidities is higher in HFpEF compared to HFrEF patients,[182] but the definition of HFpEF remains debated hampering comparisons between individual studies. Nevertheless, strategies to improve the management of non-cardiac comorbidities are likely to have more impact on the occurrence of HFpEF than HFrEF. One study reported the prevalence of risk factors, including comorbidities, separately for 941 patients with HFrEF and 1373 patients with HFpEF.[180] Anaemia (present in 24% of HFrEF and 26% of HFpEF patients) and chronic kidney disease (42% and 40% of HFrEF and HFpEF patients, respectively) were the most important contributors to all-cause mortality in HF patients, both in patients with HFrEF and in those with HFpEF.[180] Alarming, the Global Burden of Disease study analysis revealed that ACM as the second leading cause of HF in eastern Europe.[146]

North America

The USA and Canada are similar in representing industrialized countries with similar geography and economics. Both countries have seen an increase in the prevalence and incidence of HF, although the genetics, ethnicity, and race of both countries are dissimilar.[183] As both USA and Canadian populations age, and survival from CVD improves, the overall burden of HF, particularly HFpEF, is expected to increase further over time.

In the USA, the Centers for Disease Control and Prevention sponsors the National Health and Nutrition Examination Survey (NHANES), a set of studies using both interviews and physical examination producing the health statistics for the country.[184] Using data from 2013 to 2016, it is estimated that 6.2 million Americans >20 years old have HF, an increase from 5.7 million in 2007–2012.[185] Forecasting by the American Heart Association (AHA), projects that by 2030 the prevalence of HF will grow by 46% to >8 million over the age of 18, highest in Blacks, lowest in Hispanic whites with the total percent for the population increasing from 2.42% in 2012 to 2.97% in 2030 (*Figure 6*).[186] In 2006, there were ∼500 000 (population 32.7 million) Canadians >40 years old living with HF, a prevalence of 1.5%, with an annual incidence of 50 000 new cases and more common in the older age groups.[183] Similar to the USA and as reported by the Canadian Chronic Disease Surveillance System in 2017, the prevalence has grown to 669 600 (3.6%) as has the incidence to 92 900 (5.2/1000 per year). Since women live longer than men, they are diagnosed with HF at an older age[187,188] (*Figure 7*).

Most of the risk factors for HF in the USA are the traditional ones, such as hypertension,[185] CAD, T2DM, obesity, and smoking accounting for 52% of incident cases, with ORs of 1.4 for hypertension and 2.7 for T2DM. NHANES data indicate that at least one risk factor is present in 33% of the US population. Racial disparities should be highlighted in the USA, where 68% Blacks vs. 49% Whites present modifiable risk factors for hypertension.[185] NHANES in 2013–2016, using the most recent definition of hypertension, reported the age-adjusted prevalence in adults >20 of age to be 46% (49% for men and 43% for women). Thus, there are 116.4 million adults in the USA with hypertension (*Figure 8*). Canada has done considerably better than the USA; in 2012–2013, the prevalence of hypertension in Canadian adults was 22.6%, an increase from 19.6% in 2009–2011.[189,190] Control of hypertension has improved in Canada from 65.9% in 2007 to 68.1% in 2013. The prevalence and proportion diagnosed, treated, and controlled were higher in men compared to women in 2013 (*Figure 9*).

Given the importance of hypertension as a modifiable risk factor, coupled to the results of the SPRINT trial with significant reduction of HF if hypertension is treated aggressively, has led to the new AHA hypertension guidelines with a national campaign of hypertension awareness to the public.[191,192] Similarly, in Canada, the improvement in

control may be in part due to an increase in antihypertensive therapy and the Canadian Hypertension Education Program campaign.[193]

South America

In the last few decades, South America has witnessed a dramatic rise in CV risk factors, such as obesity, the metabolic syndrome, and arterial hypertension.[194] Seron *et al.*, in a cross-sectional analysis of the CESCAS I Study (Detection and follow-up of CVD and risk factors in the Southern Cone of Latin America) assessed the prevalence of 'Ideal Cardiovascular Health' or Life's simple 7 (LS7), defined by the AHA as simultaneous presence of four favourable CV behaviours (non-smoking, BMI <25 kg/m^2, physical activity, and healthy diet) and three ideal health factors (normal levels of cholesterol, blood pressure and glucose). From 5458 participants between 35 and 75 years old from Argentina, Chile, and Uruguay, only 0.1% (95% CI 0.0–0.2) met LS7, supporting the urgent need of developing strategies to improve the primary prevention of CVD.[195]

Ciapponi *et al.* assessed the burden of HF in Latin America and Caribbean area through a systematic review of the literature and meta-analyses, with most of the studies from South America (92%), mainly in Brazil (64%) and Argentina (22%). To the best of our knowledge, data on PARs for HF are not available for South America. The incidence of HF was found to be 199 cases per 100 000 person-years, the prevalence 1% (95% CI 0.1–2.7%) and 1-year mortality rate 24.5% (95% CI 19.4–30.0%). In-hospital mortality was 11.7% (95% CI 10.4–13.0%), with higher rates in patients with HFrEF, ischaemic heart disease, or Chagas' disease.[196] Chagas' disease is responsible for about half of all HF cases in Latin America,[197] and it is endemic to all continental Latin American countries with strong social and economic implications. It is mostly concentrated in Argentina (1 505 235 cases, prevalence 3.6%), Brazil (1 156 821, 0.6%), Bolivia (607 186, the highest prevalence 6.1% with special figures in Gran Chaco area), Colombia (437 960, 0.9%), and Venezuela (310 000, 1.1%). Luckily, Chagas' disease prevalence in endemic countries decreased from 17 million in 1980, to 5.7 million in 2015 (according to the most recent data from WHO).[198]

Conclusions: how to prevent the development of heart failure?

Overall, modifiable risk factors play an important role and improving the levels of these risk factors is crucial in strategies to prevent HF. Comorbidities are also important contributors to the HF epidemic. A summary list of the risk factors and comorbidities promoting the development of HF with potential interventions is provided (*Table 8*). It should be emphasized, however, that the preventive potential of optimal management of comorbidities, in terms of lowering the incidence of HF, is less straightforward. Finally, pharmacological therapies that have been shown to reduce the risk of HF development are presented (*Table 9*).

Conflict of interest: M.B. reports fees from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Medtronic, Novartis, ReCor, Servier, and Vifor and is supported by the Deutsche Forschungsgemeinschaft (DFG, TTR 219, S-01, project ID 322900939). M.G.C.-L. received research grants to my institution and personal fees for lectures or advisory board meetings from CIBERCV. Novartis, AstraZeneca, Vifor, Pfizer, Astellas Pharma. None of them related to the present manuscript. S.H. has received personal fees for scientific advice to AstraZeneca, Cellprothera, and Merck; unrestricted research grant from Pfizer. C.S.P.L. is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/Steering Committee/Executive Committee for Abbott Diagnostics, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Biofourmis, Boehringer Ingelheim, Boston Scientific, Corvia Medical, Cytokinetics, Darma Inc., Us2.ai, JanaCare, Janssen Research & Development LLC, Medtronic, Menarini Group, Merck, MyoKardia, Novartis, Novo Nordisk, Radcliffe Group Ltd, Roche Diagnostics, Sanofi, Stealth BioTherapeutics, The Corpus, Vifor Pharma, and WebMD Global LLC; and serves as co-founder and non-executive director of Us2.ai. A.M. received personal fees for the participation in committees of studies sponsored by Bayer, Fresenius, Novartis outside the present work. M.F.P. received research grants to his institution and personal fees for lectures or advisory board meetings from Novartis, Vifor, AstraZeneca, and CHF solution. None of them related to the present manuscript. P.M.S. received Medtronic honorarium for lecture, Abbott honorarium for lecture,

Servier honorarium for lecture, Astra Zeneca honorarium for lecture, Respicardia honorarium for lecture, Boehringer Ingelheim consultancy agreement and honorarium for lecture, Novartis consultancy agreement and honorarium for lecture, Vifor Pharma consultancy agreement. All other authors declared no conflict of interest.

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Table 1 Risk factor goals and target levels for important cardiovascular risk factors (reproduced from refs[4,5])

Smoking	No exposure to tobacco in any form
Diet	Healthy diet low in saturated fat with a focus on wholegrain products, vegetables, fruit, and fish
Physical activity	3.5–7 h moderately vigorous physical activity per week or 30–60 min most days
Body weight	BMI 20–25 kg/m^2. Waist circumference <94 cm (men) or <80 cm (women)
Blood pressure	<140/90 mmHg[a]
LDL-C	Very high risk in primary or secondary prevention: – ≤50% reduction from baselineb and a goal of <1.4 mmol/L (<55 mg/dL) – No current statin use: this is likely to require high-intensity LDL-lowering therapy Current LDL-lowering treatment: an increased treatment intensity is required High risk: ≤50% reduction from baseline[b] and a goal of <1.8 mmol/L (<70 mg/dL) Moderate risk: <2.6 mmol/L (<100 mg/dL) Low risk: <3.0 mmol/L (<116 mg/dL)
Non-HDL-C	<2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high, high, and moderate-risk people, respectively
ApoB	<65, 80, and 100 mg/dL for very-high, high, and moderate-risk people, respectively
Triglycerides	No target but <1.7 mmol/L (<150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors
Diabetes	HbA1c <7% (<53 mmol/mol)

Apo, apolipoprotein; BMI, body mass index; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

[a] Lower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated.

[b] The term 'baseline' refers to the LDL-C level in a person not taking any lipid-lowering medication, or to the extrapolated baseline value for those who are on current treatment.

Table 2 Healthy diet characteristics (reproduced from[4])

- Saturated fatty acids to account for <10% of total energy intake, through replacement by polyunsaturated fatty acids
- Trans unsaturated fatty acids: as little as possible, preferably no intake from processed food, and <1% of total energy intake from natural origin
- <5 g of salt per day
- 30–45 g of fibre per day, preferably from wholegrain products
- ≥200 g of fruit per day (2–3 servings)
- ≥200 g of vegetables per day (2–3 servings)
- Fish 1–2 times per week, one of which to be oily fish
- 30 g unsalted nuts per day
- Consumption of alcoholic beverages should be limited to 2 glasses per day (20 g/d of alcohol) for men and 1 glass per day (10 g/d of alcohol) for women
- Sugar-sweetened soft drinks and alcoholic beverages consumption must be discouraged

Table 3 Race-specific estimates of the preventable number of heart failure cases, years of life lost lived with disability that would result from a 5% proportional reduction in the prevalence of five common cardiovascular risk factors in the USA

Exposure	African Americans				Caucasians			
	Period prevalence 1987–1998[a]	Preventable number of heart failure cases[b]	Disability adjusted life years		Period prevalence 1987–1998[a]	Preventable number of heart failure cases[b]	Disability adjusted life years	
			Number of years of life lost[c]	Number of years of life with disability[c]			Number of years of life lost[c]	Number of years of life with disability[c]
Current smoking	32.4	15	28	6	26.8	10	63	19
Diabetes	31	53	65	13	17.1	33	81	24
Elevated LDL	65.4	23	60	12	60.5	11	120	36
Hypertension	71.1	28	68	14	45.3	19	102	31
Obesity	50.2	16	39	8	33.9	15	69	21

ARIC, Atherosclerosis

From the ARIC cohort study, 1987–2008 (reproduced from ref.[10]).

[a] Assessed at baseline and three triennial visits.

[b] Per 100 000 person years.

[c] Per year for all participants with heart failure.

Risk in Communities study; LDL, low-density lipoprotein.

Table 4 Cardiovascular and renal outcome trials with SGTL2 inhibitors in patients with type 2 diabetes mellitus

Medication	Trial	Patients, *n*	Patient characteristics	Follow-up (mean or median), years	Primary outcome (HR, 95% CI; *P*-value)	HF hospitalization (HR, 95% CI; *P*-value)
Empagliflozin	EMPA-REG OUTCOME[21]	7020	Established CVD	3.1	3-point MACEa (0.86, 0.74–0.99, $P < 0.001$ for non-inferiority; $P = 0.04$ for superiority)	0.65, 0.50–0.85; $P = 0.002$
Canagliflozin	CANVAS Program[22]	10 142	Established CVD (66%) CV risk factors (34%)	3.2	3-point MACEa (0.86, 0.75–0.97; $P < 0.001$ for non-inferiority; $P = 0.02$ for superiority)	0.67, 0.52–0.87
Dapagliflozin	DECLARE-TIMI 58[23]	17 160	Established CVD (41%) CV risk factors (59%)	4.2	Coprimary outcome: 3-point MACEa (0.93, 0.84–1.03; $P = 0.17$) Coprimary outcome: CV death or HF hospitalization (0.83; 0.73–0.95; $P = 0.005$)	0.73, 0.61–0.88
Ertugliflozin	VERTIS-CV[24]	8246	Established CVD	3.5	3-point MACE[a] 0.97 (0.85–1.11; $P < 0.001$ for non-inferiority)	0.70, 95% CI 0.54–0.90; $P = 0.006$
Canagliflozin	CREDENCE[25]	4401	Chronic kidney disease (eGFR, 30 to <90 mL per minute per 1.73 m^2 of body-surface area and	2.6	Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of	0.61, 0.47–0.80; $P < 0.001$

			ratio of albumin to creatinine >300–5000 mg/g)		<15 mL per minute per 1.73 m^2), a doubling of the serum creatinine level, or death from renal or cardiovascular causes (0.70, 0.59–0.82; $P < 0.001$)	
Dapagliflozin	DAPA-CKD[26]	4304 (2906 with T2DM)	Chronic kidney disease (eGFR ≥25 and ≤75 mL/min/1.73 m^2; urinary albumin to creatinine ratio between ≥200 mg/g and ≤5000 mg/g)	2.4	Worsening kidney function (defined as >50% sustained decline in eGFR or onset of end-stage kidney disease), or death due to kidney disease or CVD) 0.61 (0.51–0.72; $P < 0.001$)	0.71, 0.55–0.92; $P < 0.001$

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; HR, hazard ratio; MACE, major adverse cardiovascular events; T2DM, type 2 diabetes mellitus.

[a] Three-point MACE: cardiovascular death, non-fatal myocardial infarction, and stroke.

Table 5 Main endocrine disorders that may lead or contribute to development of heart failure (modified from refs[61,62])

Hormone	Endocrinopathy	Main mechanisms of HF
Aldosterone	Hyperaldosteronism	Hypertension, myocardial fibrosis, diastolic LV dysfunction, volume overload
Catecholamines	Pheochromocytoma	Hypertension, catecholamine-induced cardiomyopathy
Cortisol	Cushing's syndrome (endogenous or iatrogenic)	Hypertension, LV hypertrophy, diastolic LV dysfunction, metabolic alterations
GH	Acromegaly	Acromegalic cardiomyopathy
GH	GH deficiency	Reduced LV mass with impaired myocardial contractility and cardiac output
Parathyroid hormone	Hypoparathyroidism	Hypocalcemia-induced myocardial dysfunction (possibly due to disrupted excitation-contraction coupling)
Prolactin	18 kDa prolactin fragment	Peripartum cardiomyopathy
Thyroid hormone	Hypothyroidism	Diastolic LV dysfunction, decreased cardiac output
Thyroid hormone	Hyperthyroidism	Tachyarrhythmia, hypertension, LV hypertrophy, diastolic LV dysfunction, increased cardiac output

GH, growth hormone; HF, heart failure; LV, left ventricle.

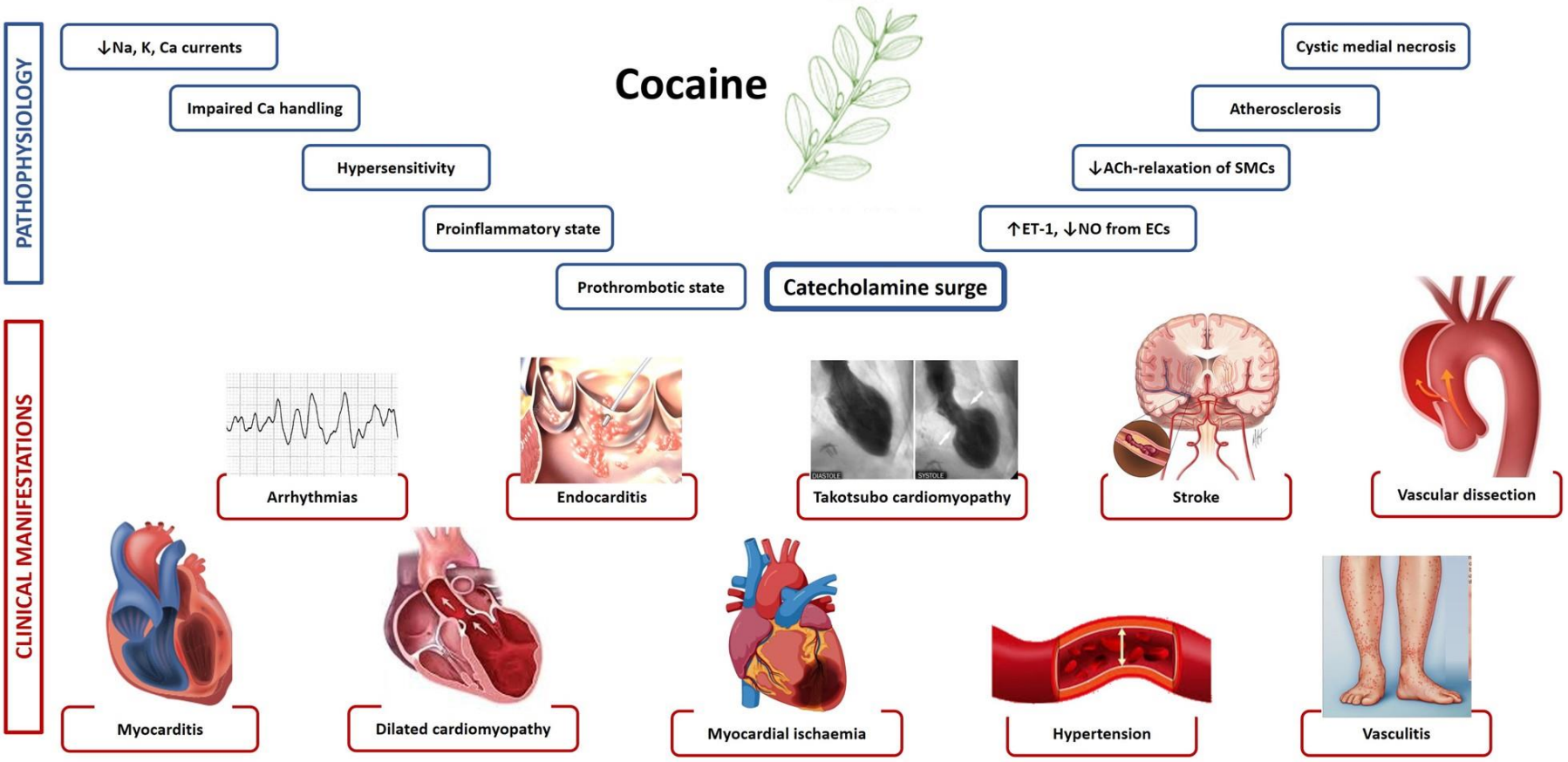

Figure 1 A summary of the pathophysiology and clinical manifestations of cardiovascular involvement of acute and chronic cocaine abuse.

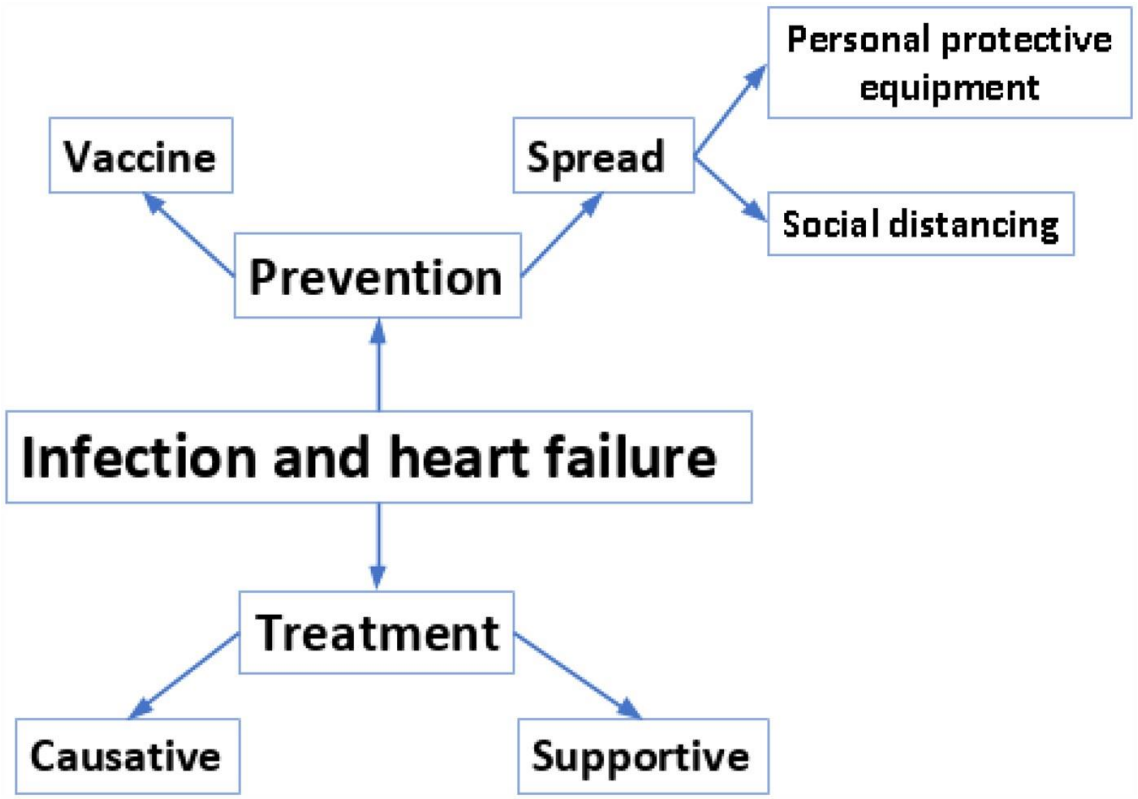

Figure 2 Viral infections: preventive strategies and treatment.

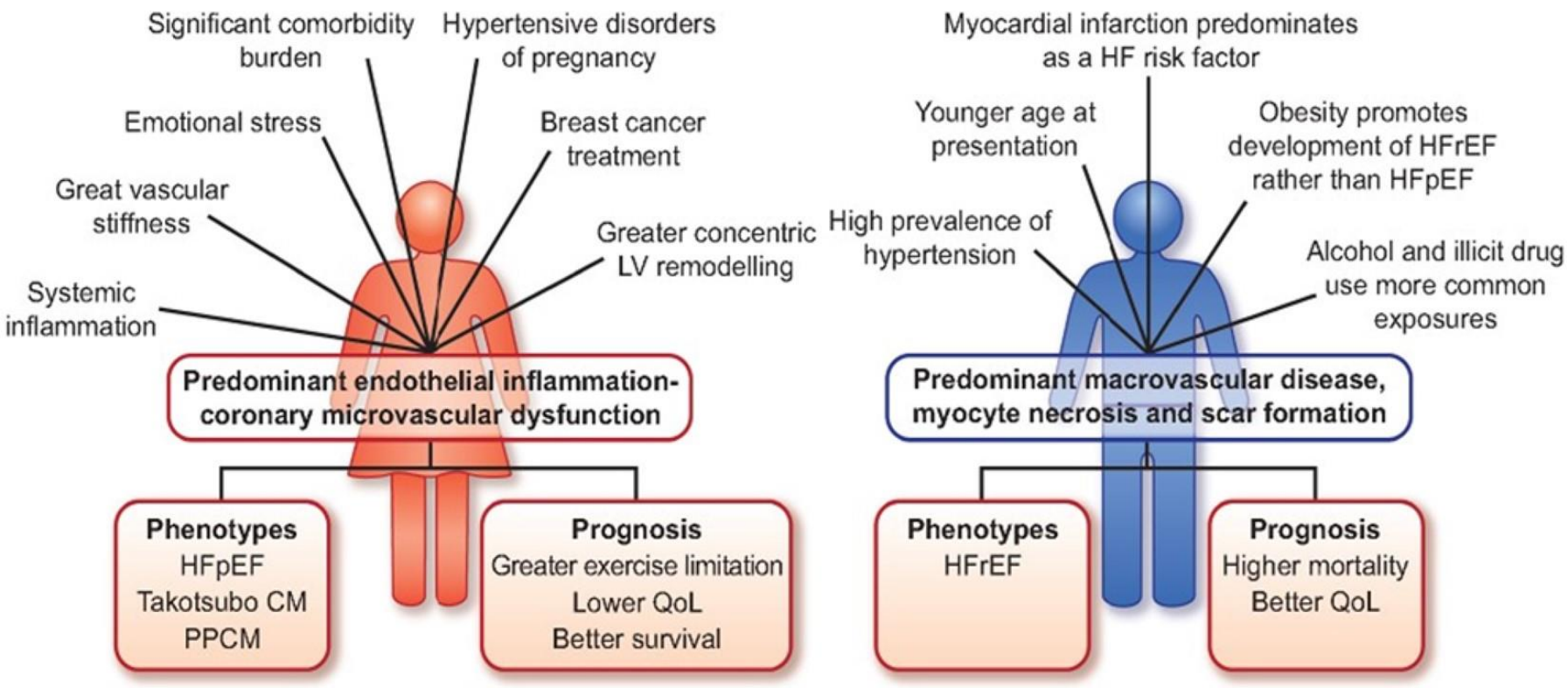

Figure 3 Sex differences in heart failure (from ref.[145]).

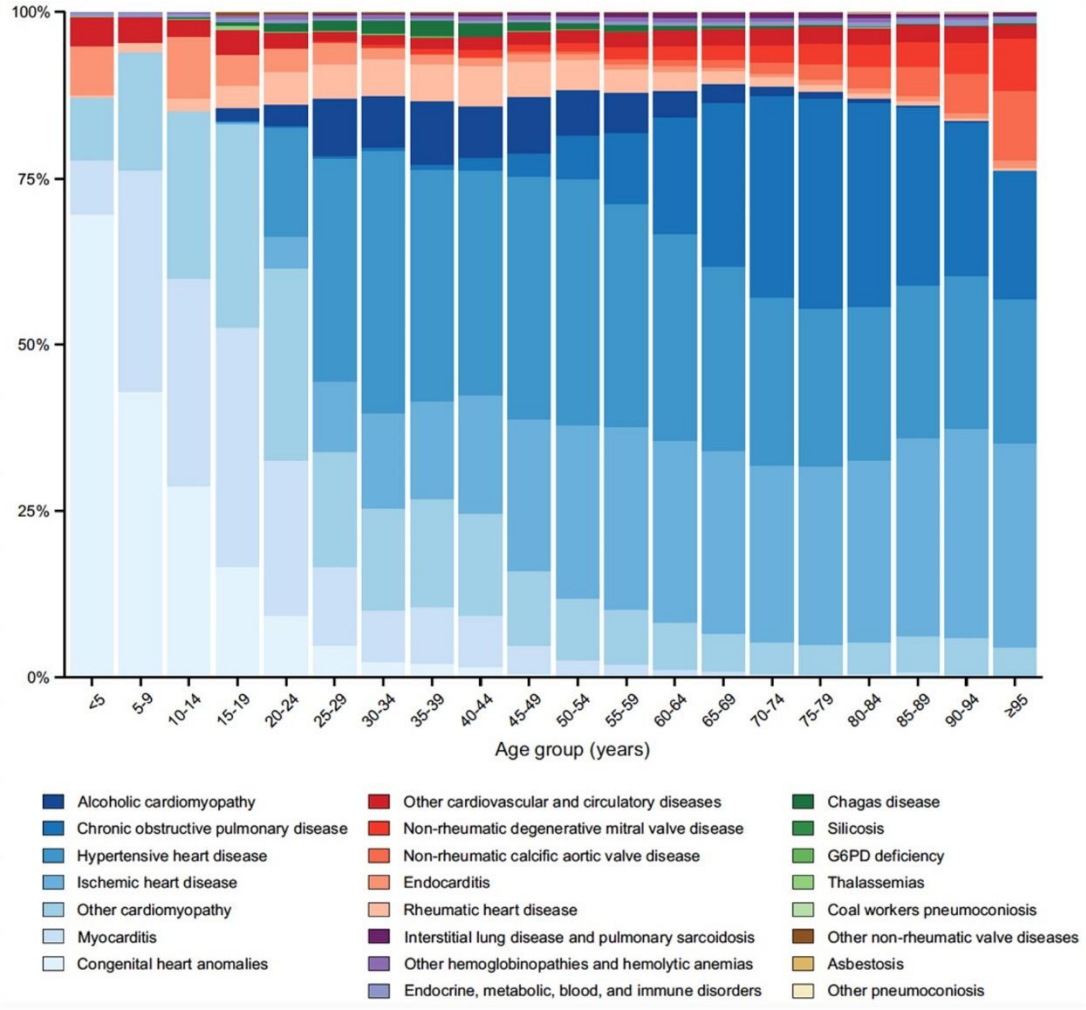

Figure 4 The proportion of age-standardized prevalence rate of heart failure due to each cause by age group, 2017. From ref.[146]

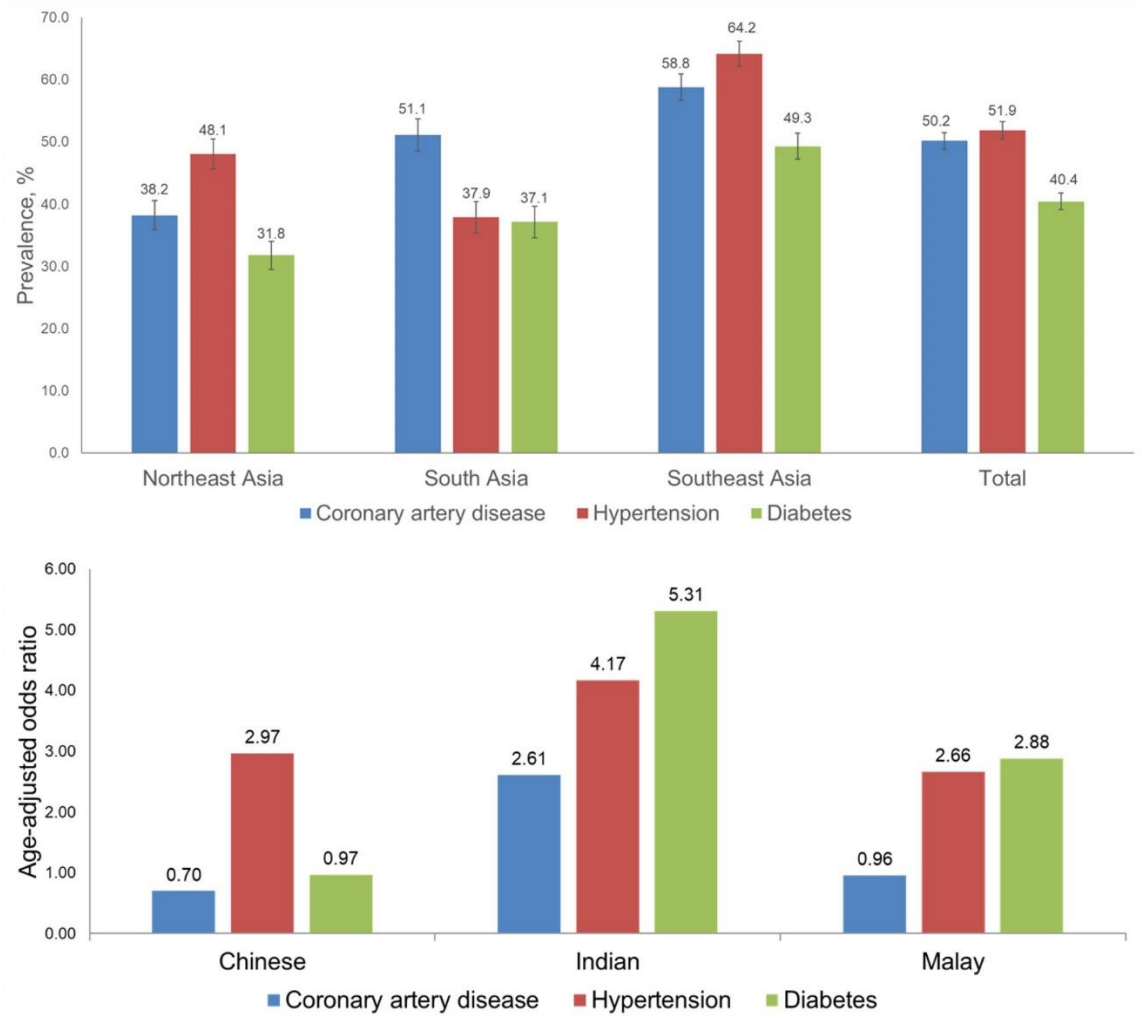

Figure 5 Prevalence of risk factors among Asian patients with heart failure (top) and evidence of interaction between region and ethnicity in Asia (bottom)—from[161]

Table 6 Population attributable risks for modifiable cardiovascular risk factors in Asia

	China (%)	Australia (%)	Taiwan (%)	South Korea (%)	Thailand (%)	Japan (%)	Hong Kong (%)	Singapore (%)
PARs for CVD risk factors (men)								
Obesity	2	4	2	2	2	2	2	2
Smoking	14	6	11	15	12	10	14	8
High cholesterol	5	14	5	7	9	9	5	9
Hypertension	13	8	12	8	14	13	15	11
PARs for CVD risk factors (women)								
Obesity	8	8	8	7	10	6	10	8
Smoking	1	5	1	1	1	3	1	2
High cholesterol	7	11	7	9	12	12	7	13
Hypertension	12	5	10	6	15	9	10	8

Source: EIU Healthcare, WHO prevalence rates for adults over 25.

CVD, cardiovascular disease; PARs, population attributable risks.

Table 7 Populations attributable risks for developing heart failure in Europe

PAR	Schrage et al.[172] (2020)	Magnussen et al.173 (2019)		Uijl et al.[174] (2019)						Pujades-Rodriguez et al.[175] (2015)		Baena-Diez et al.[176] (2010)
	All	Men	Women	Men			Women			Men	Women	All
				55–65 years	65–75 years	>75 years	55–65 years	65–75 years	>75 years			
Hypertension	15.9	13	9	9.2	—	7.5	—	—	—	—	—	50
Diabetes	13	11	8	4.5	3.7	1.6	10.3	4.3	2.3	—	—	—
Obesity	28	22	30	9.1	5.7	2	14.3	7.5	2.3	—	—	43
Smoking	15.1	12.5	8	8	2.9	—	8	3.4	—	7.9	8.3	—
Cholesterol	3.6	0.5	3	—	—	—	—	—	—	—	—	—
Low physical activity	—	—	—	—	5	5.3	6	5.7	6.4	—	—	—
History of MI	—	8	2	—	—	—	—	—	—	—	—	—
History of stroke	—	1	1	—	—	—	—	—	—	—	—	—
History of COPD	—	—	—	17.2	17.1	16.1	23.9	19.6	13.8	—	—	—
History of AF	—	—	—	16.5	11.9	11.4	23.8	16.1	15.6	—	—	—
History of ischemic heart disease	—	—	—	—	—	—	—	—	—	—	—	18.6
Combined PAR %	75.6	63	59	64.5	46.3	43.9	86.3	56.6	40.4	—	—	—

Scharge *et al.*,[172] Magnussen *et al.*,[173] Uijl *et al.*,[174] Pujades-Rodriguez *et al.*,[175] and Baena-Diez *et al.*[176]

AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PAR, population attributable risk.

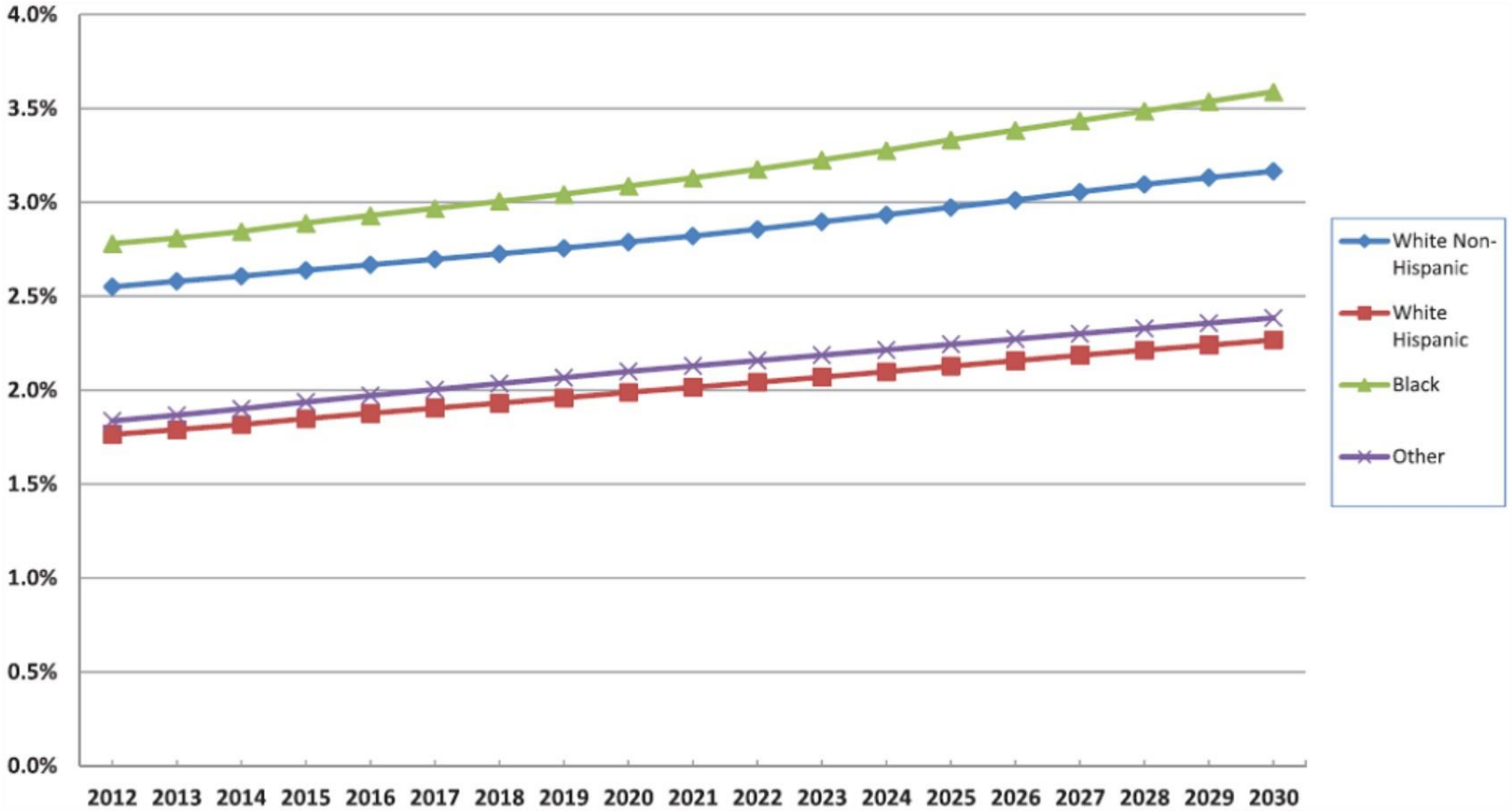

Figure 6 Projected US prevalence of heart failure from 2012 to 2030—from[186]

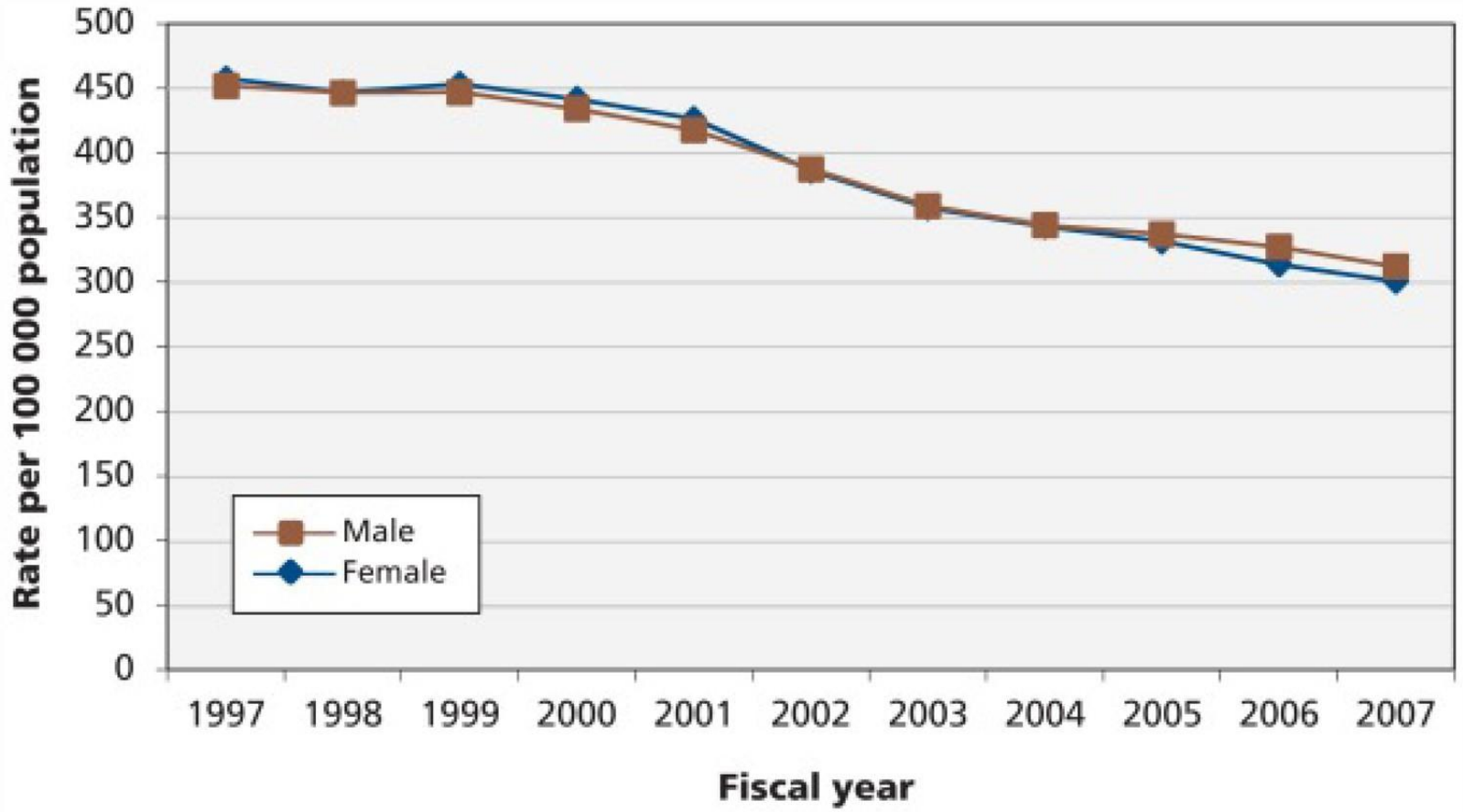

Figure 7 Age-standardized trends in incidence of heart failure, by sex in Canada—from[188]

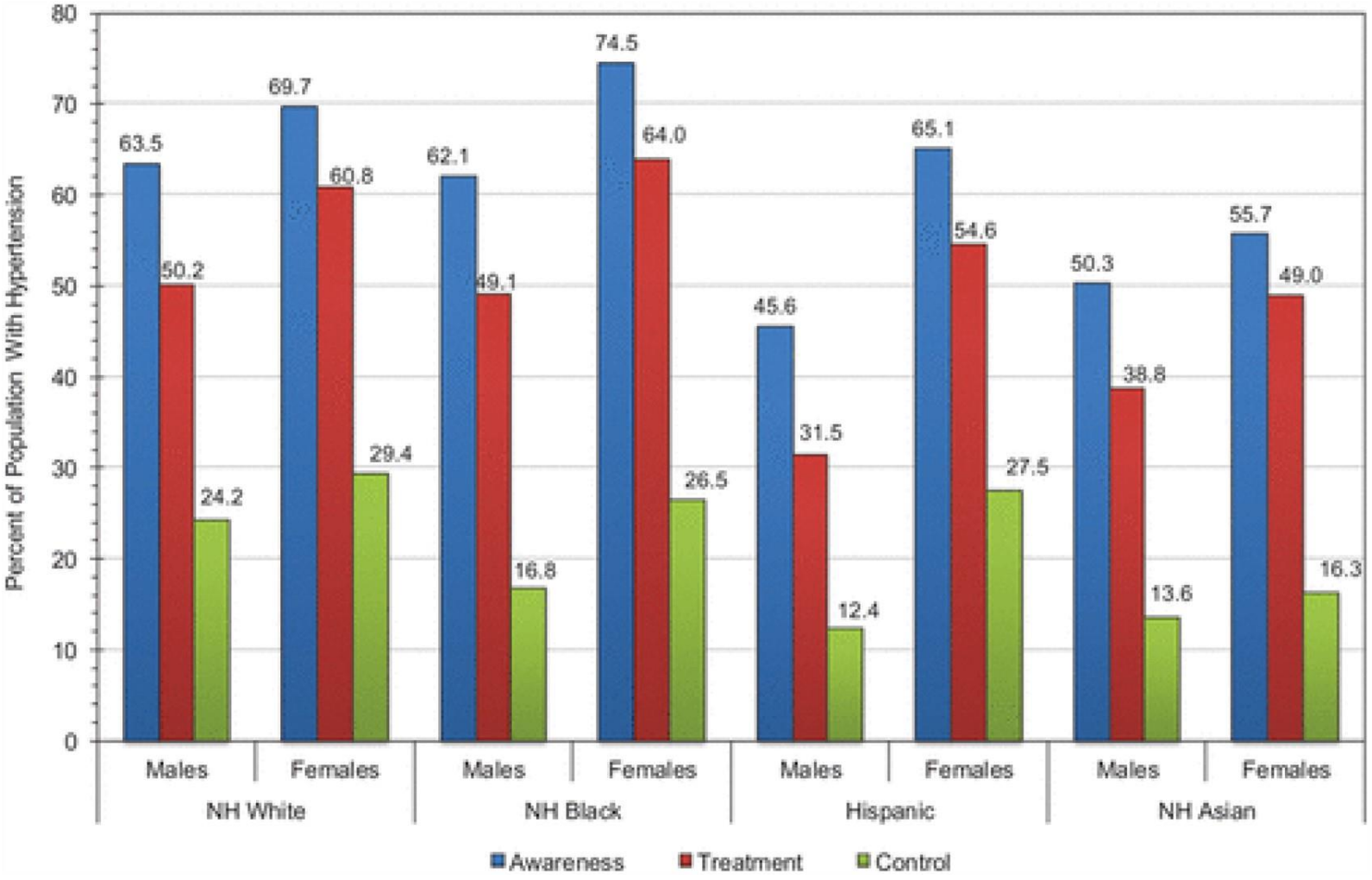

Figure 8 Extent of awareness, treatment, and control of high blood pressure by race/ethnicity and sex, USA (NHANES, 2013–2016)—from[185]

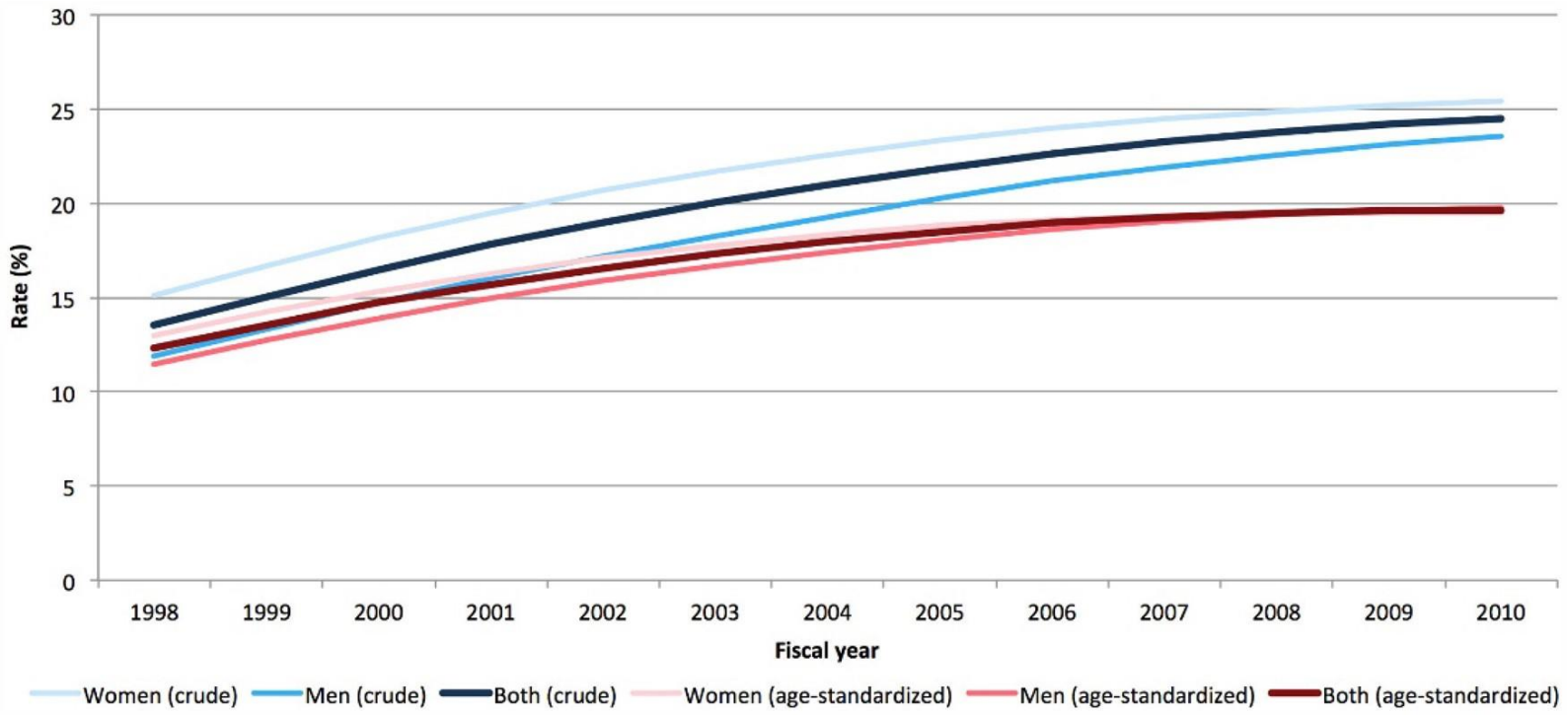

Figure 9 Crude and age-standardized prevalence of diagnosed hypertension by sex in individuals aged 20+ years in Canada—from[189]

Table 8 Risk factors and comorbidities promoting the development of heart failure with potential interventions

Risk factor	Potential interventions
Arterial hypertension	Healthy lifestyle,[a] antihypertensive medications (mainly diuretics and ACEi/ARB)
Diabetes mellitus	Healthy lifestyle,[a] SGLT-2 inhibitor
Sedentary habit	Regular physical activitya
Dyslipidaemia	Healthy diet, statins or other lipid-lowering drugs
Obesity	Healthy diet,[a] bariatric surgery
Endocrine disorders	Early diagnosis, specific therapy for treatment
Alcohol intake/abuse	General population: no or light alcohol intake
	Patients with toxic cardiomyopathy: complete abstention
Smoking	No exposure in any form, nicotine replacement therapy.
Cocaine	Supervised detox and medical treatment
Cardiotoxic drugs (e.g. anabolic steroids, anorectics)	Supervised cessation
Chemotherapy	Dose optimization, monitoring of side effects
Chest radiation	Dose and localization optimization
Viral infections	Influenza vaccination, early diagnosis
Microbe infection (e.g. Chagas' disease, rheumatic heart disease)	Early diagnosis, specific antimicrobial therapy for either prevention or/and treatment
Sleep apnoea	CPAP therapy in individual >60 years of age with obstructive form
Environmental and air pollution	Measures to reduce or prevent pollution
Hypertensive disorders in pregnancy	Early diagnosis, specific therapy for treatment

ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin II receptor blocker; CPAP, continuous positive airway pressure; SGLT2, sodium–glucose-contransporter-2.

[a] Refer to *Tables 1 and 2*.

Table 9 Drugs reducing the risk of heart failure development or hospitalizations

Drugs/interventions	Comments
Diuretics	In patients with hypertension
ACEi/ARB	In patients with hypertension
Statins	In patients at high-risk of cardiovascular disease
SGLT-2 inhibitors	In patients with DM at high risk of cardiovascular disease

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DM, diabetes mellitus; SGLT2, sodium–glucose-contransporter-2