

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

Massimo F. Piepoli ^{1,2,*}, **Marianna Adamo** ³, **Andrea Barison** ^{2,4}, **Reinaldo B. Bestetti**⁵, **Jan Biegus** ⁶, **Michael Böhm**⁷, **Javed Butler**⁸, **Jonathan Carapetis**⁹, **Claudio Ceconi**¹⁰, **Ovidiu Chioncel**^{11,12}, **Andrew Coats**¹³, **Maria G. Crespo-Leiro**¹⁴, **Giovanni de Simone** ¹⁵, **Heinz Drexel** ^{16,17}, **Michele Emdin**^{2,4}, **Dimitros Farmakis**¹⁸, **Martin Halle** ¹⁹, **Stephane Heymans**^{20,21}, **Tiny Jaarsma** ^{22,23}, **Ewa Jankowska**²⁴, **Mitja Lainscak**^{25,26}, **Carolyn S.P. Lam** ²⁷, **Maja-Lisa Løchen** ²⁸, **Yuri Lopatin**²⁹, **Aldo Maggioni**³⁰, **Benedetta Matrone**¹, **Marco Metra**³, **Katharine Noonan**¹⁰, **Ileana Pina**³¹, **Eva Prescott** ³², **Giuseppe Rosano** ³³, **Petar M. Seferovic**³⁴, **Karen Sliwa**³⁵, **Simon Stewart**³⁶, **Alicia Uijl**^{21,37,38}, **Ilonca Vaartjes**²³, **Roel Vermeulen** ³⁷, **W. M. Verschuren**^{39,40}, **Maurizio Volterrani**³³, **Stephan Von Haehling**^{41,42}, and **Arno Hoes**²³

¹Cardiac Unit, Guglielmo da Saliceto Hospital, Piacenza, Italy; ²Institute of Life Sciences, Scuola Superiore Sant'Anna, Pisa, Italy; ³Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy; ⁴Fondazione Toscana Gabriele Monasterio, Pisa, Italy; ⁵Universidade de Ribeirão Preto, Ribeirão Preto, Brazil; ⁶Department of Heart Diseases, Medical University, Wrocław, Poland; ⁷Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Saarland University, Homburg/Saar, Germany; ⁸Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; ⁹Telethon Kids Institute, University of Western Australia and Perth Children's Hospital, Perth, Australia; ¹⁰Department of Translational Medicine, University of Ferrara, Ferrara, Italy; ¹¹University of Medicine Carol Davila, Bucharest, Romania; ¹²Emergency Institute for Cardiovascular Diseases 'C.C. Iliescu', Bucharest, Romania; ¹³University of Warwick, Coventry, UK; ¹⁴Complejo Hospitalario Universitario A Coruña (CHUAC): CIBERCV, Universidade da Coruña (UDC), Instituto Ciencias Biomedicas A Coruña (INIBIC), A Coruña, Spain; ¹⁵Department of Advanced Biomedical Sciences, Federico II University, Naples, Italy; ¹⁶Department of Medicine, Landeskrankenhaus Bregenz, Bregenz, Austria; ¹⁷VIVIT, Landeskrankenhaus Feldkirch, Feldkirch, Austria; ¹⁸University of Cyprus Medical School, Nicosia, Cyprus; ¹⁹Sport and Health Sciences, Policlinic for Preventive and Rehabilitative Sports Medicine, TUM School of Medicine, Munich, Germany; ²⁰Department of Cardiology, Maastricht University, CARIM School for Cardiovascular Diseases, Maastricht, Netherlands; ²¹Centre for Molecular and Vascular Biology, Department of Cardiovascular Sciences, KU Leuven, Belgium; ²²Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden; ²³Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; ²⁴Department of Heart Diseases, Wrocław Medical University, Wrocław, Poland; ²⁵Division of Cardiology, General Hospital Murska Sobota and Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; ²⁶Faculty of Natural Sciences and Mathematics, University of Maribor, Maribor, Slovenia; ²⁷National Heart Centre Singapore, Duke-National University of Singapore, Singapore, Singapore; ²⁸Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway; ²⁹Volgograd State Medical University, Regional Cardiology Centre, Volgograd, Russian Federation; ³⁰ANMCO Research Center, Florence, Italy; ³¹Detroit Medical Center, Detroit, MI, USA; ³²Bispebjerg Frederiksberg Hospital, University of Copenhagen, Copenhagen, Denmark; ³³IRCCS San Raffaele, Roma, Italy; ³⁴Belgrade University Faculty of Medicine, Serbian Academy of Science and Arts, Belgrade, Serbia; ³⁵University of Cape Town, Cape Town, South Africa; ³⁶Torrens University Australia, Adelaide, South Australia, Australia; ³⁷Division of Heart & Lungs, Department of Cardiology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; ³⁸Division of Cardiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden; ³⁹National Institute for Public Health and the Environment, Bilthoven, the Netherlands; ⁴⁰Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands; ⁴¹Department of Cardiology and Pneumology, Heart Center, University of Göttingen Medical Center, Göttingen, Germany; and ⁴²German Center for Cardiovascular Research (DZHK), partner site Göttingen, Germany

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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 dyslipidaemias⁵ 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.

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: <ul style="list-style-type: none"> – ≤50% reduction from baseline^b 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: <ul style="list-style-type: none"> ≤50% reduction from baseline^b and a goal of <1.8 mmol/L (<70 mg/dL) Moderate risk: <ul style="list-style-type: none"> <2.6 mmol/L (<100 mg/dL) Low risk: <ul style="list-style-type: none"> <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.

^aLower treatment targets are recommended for most treated hypertensive patients, provided that the treatment is well tolerated.

^bThe 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 from⁴)

- 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

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

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 Number of years of life lost ^c	Disability adjusted life years Number of years of life with disability ^c	Period prevalence 1987–1998 ^a	Preventable number of heart failure cases ^b	Disability adjusted life years Number of years of life lost ^c	Disability adjusted life years 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).

^aAssessed at baseline and three triennial visits.

^bPer 100 000 person years.

^cPer year for all participants with heart failure.

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

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 cotransporter-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

Table 4 Cardiovascular and renal outcome trials with SGLT2 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 MACE ^a (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 MACE ^a (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 MACE ^a (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 ratio of albumin to creatinine >300–5000 mg/g)	2.6	Composite of end-stage kidney disease (dialysis, transplantation, or a sustained estimated GFR of <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)	0.61, 0.47–0.80; 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.

^aThree-point MACE: cardiovascular death, non-fatal myocardial infarction, and stroke.

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/m² in BMI.⁵³ Although the contribution of obesity (BMI > 30 kg/m²) 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/m², to 1.72 per 1000 person-years for those with a BMI between 25 and 30 kg/m², and 3.37 per 1000 person-years for those with a BMI >30 kg/m².⁵³ After adjustment for classical and acquired risk factors, the risk developing HF for patients with a BMI between 18.5 and 25 kg/m² 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/m² compared with those with a BMI >30 kg/m².

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 pressure⁵⁶ along with lipotoxicity-induced cardiac myocyte injury and myocardial lipid accumulation⁵⁷ 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, neuro-hormonal, 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 \geq 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

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	Hypocalcaemia-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.

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

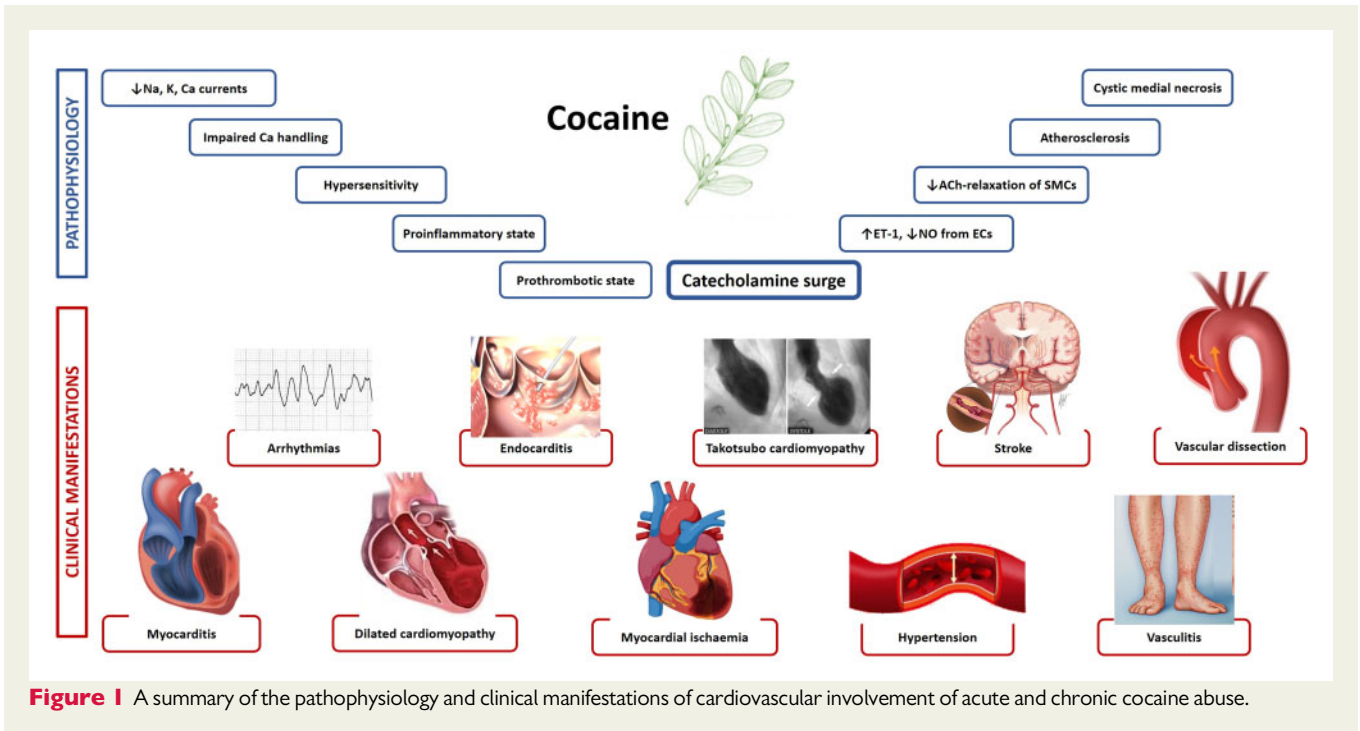


Figure 1 A summary of the pathophysiology and clinical manifestations of cardiovascular involvement of acute and chronic cocaine abuse.

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 cardiotropic 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

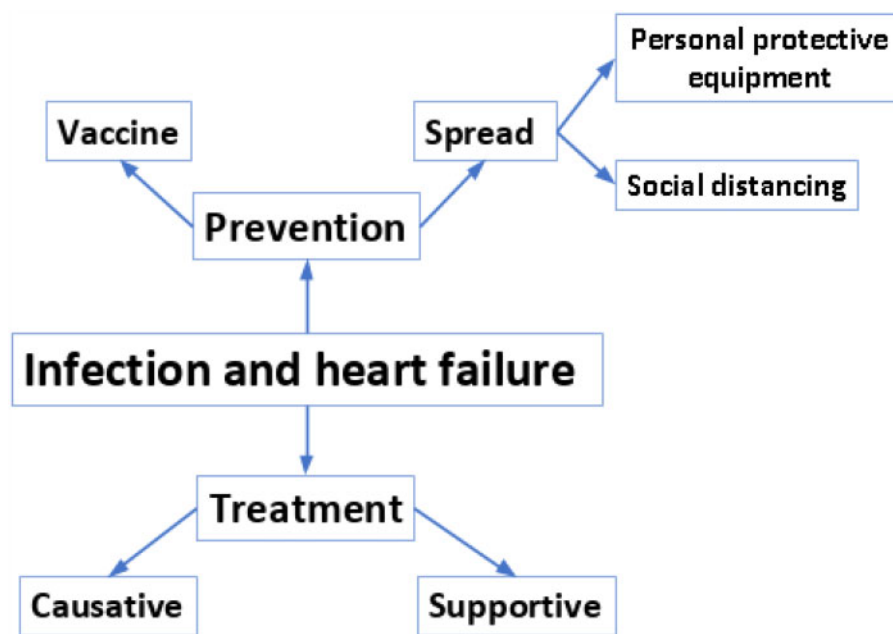


Figure 2 Viral infections: preventive strategies and treatment.

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-analysis¹⁴¹ 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 1.25–2.16) 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/m³; and for PM₁₀ 1.63 (95% CI: 1.20–2.07) per 10 µg/m³.

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/m³ increase in PM_{2.5}, PM₁₀, PM_{2.5–10}, NO₂, 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 NO₂, 1.03 (95% CI 1.02–1.03) for O₃, 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

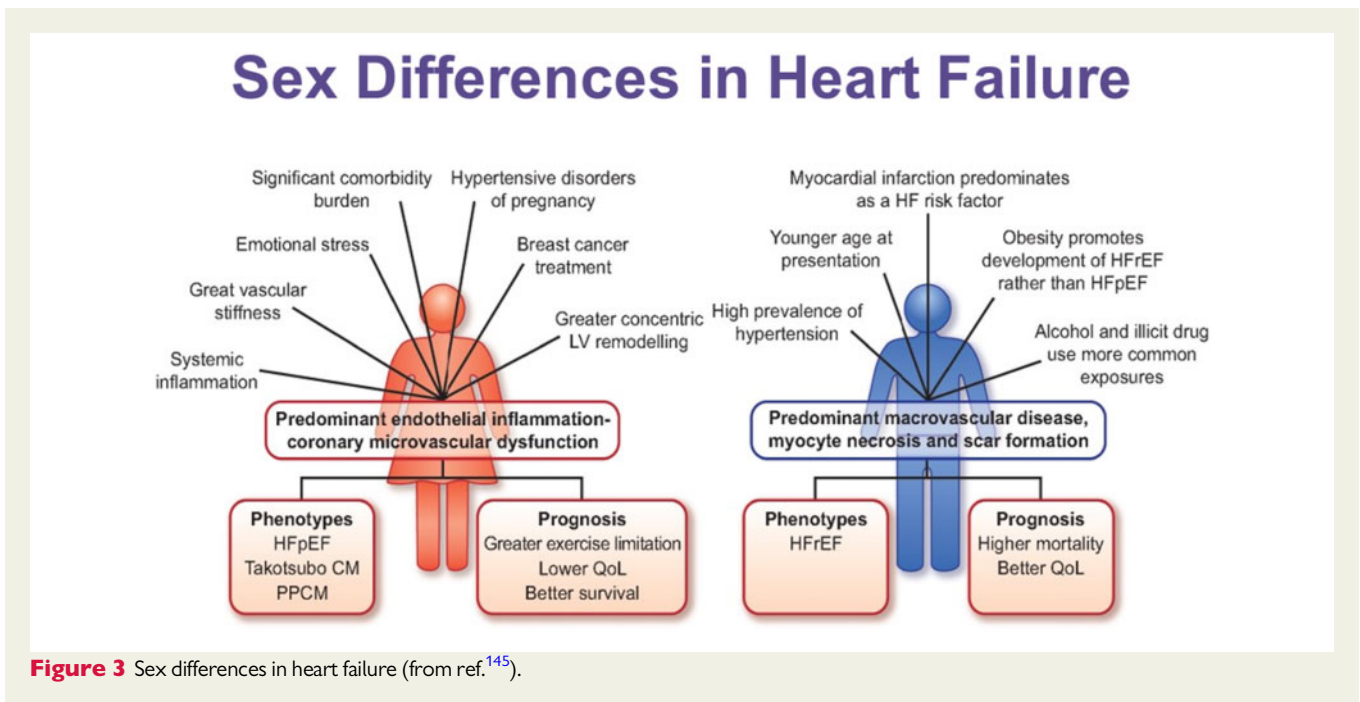


Figure 3 Sex differences in heart failure (from ref.¹⁴⁵).

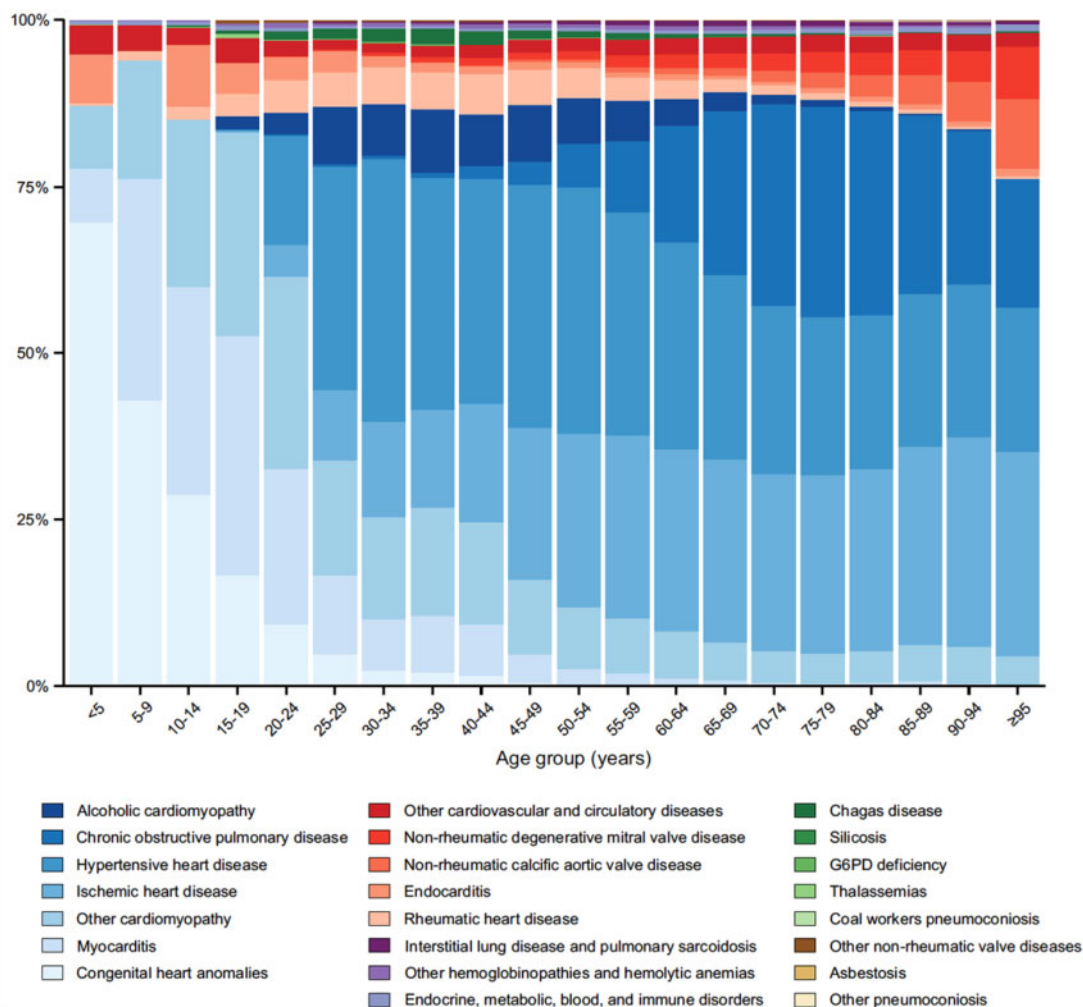


Figure 4 The proportion of age-standardized prevalence rate of heart failure due to each cause by age group, 2017. From ref.¹⁴⁶

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 Registry¹⁴⁹ 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

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.

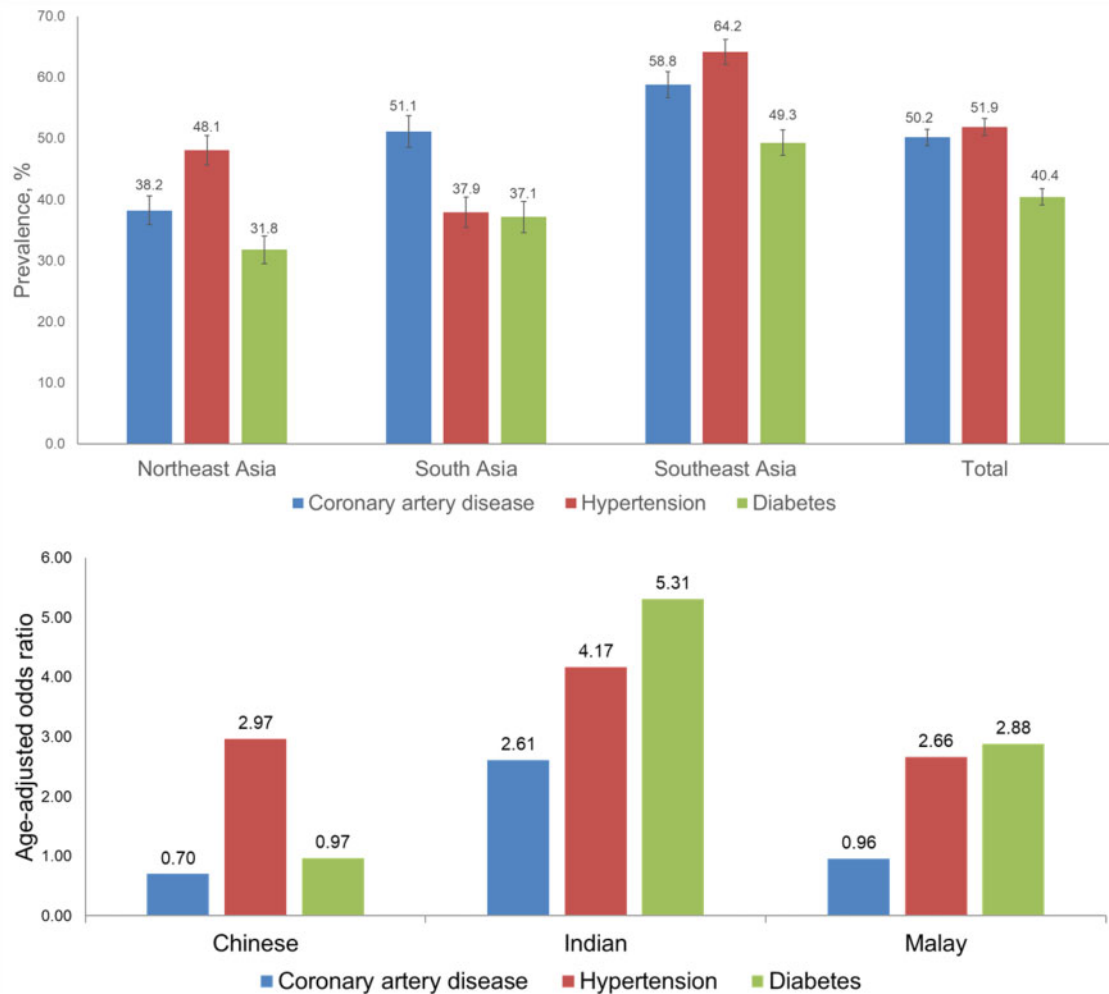


Figure 5 Prevalence of risk factors among Asian patients with heart failure (top) and evidence of interaction between region and ethnicity in Asia (bottom)—from¹⁶¹

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

Table 7 Populations attributable risks for developing heart failure in Europe

PAR	Schrage et al. ¹⁷² (2020)		Magnussen et al. ¹⁷³ (2019)		Ujij et al. ¹⁷⁴ (2019)		Ujij et al. ¹⁷⁴ (2019)		Pujades-Rodriguez et al. ¹⁷⁵ (2015)		Baena-Diez et al. ¹⁷⁶ (2010)	
	All	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	All
Hypertension	15.9	13	9	9.2	—	7.5	—	—	—	—	—	50
Diabetes	13	11	8	4.5	3.7	1.6	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	—	3.4	—	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	—	—	—

Schrage et al.,¹⁷² Magnussen et al.,¹⁷³ Ujij 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.

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/m², 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).

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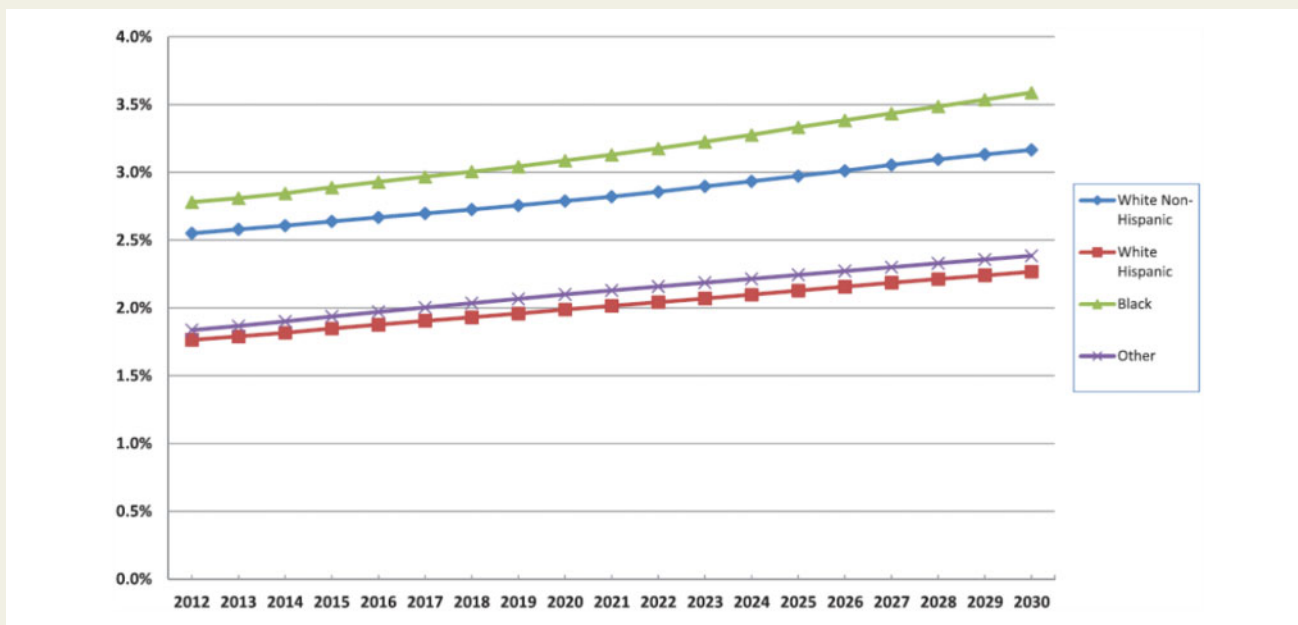


Figure 6 Projected US prevalence of heart failure from 2012 to 2030—from¹⁸⁶

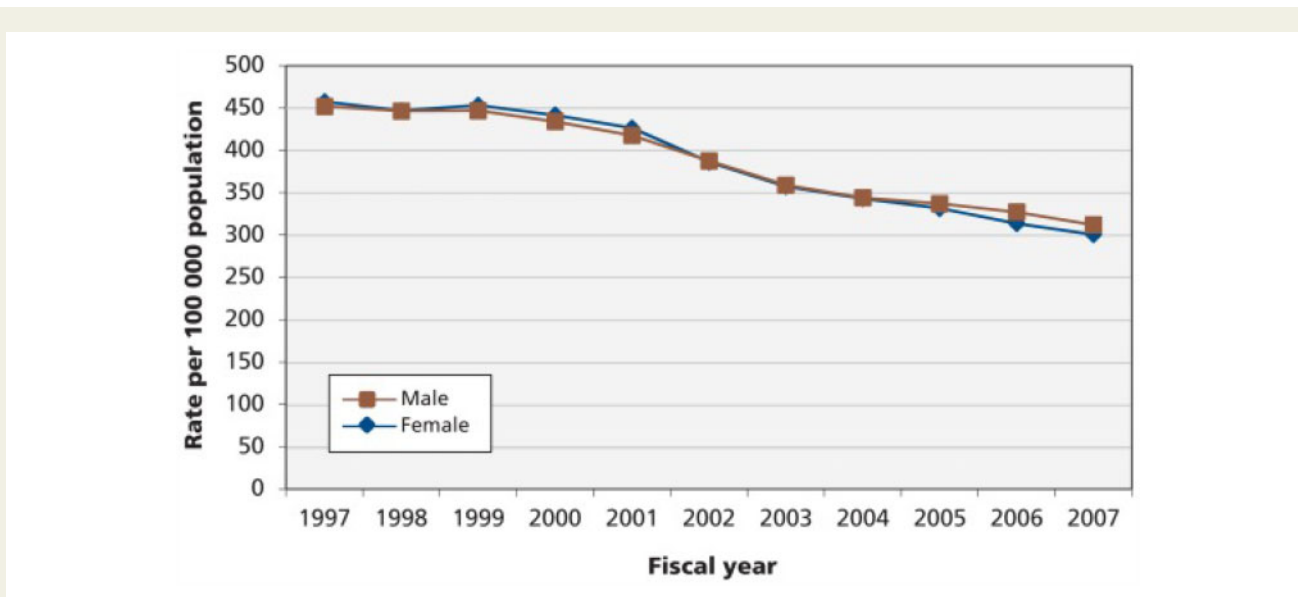


Figure 7 Age-standardized trends in incidence of heart failure, by sex in Canada—from¹⁸⁸

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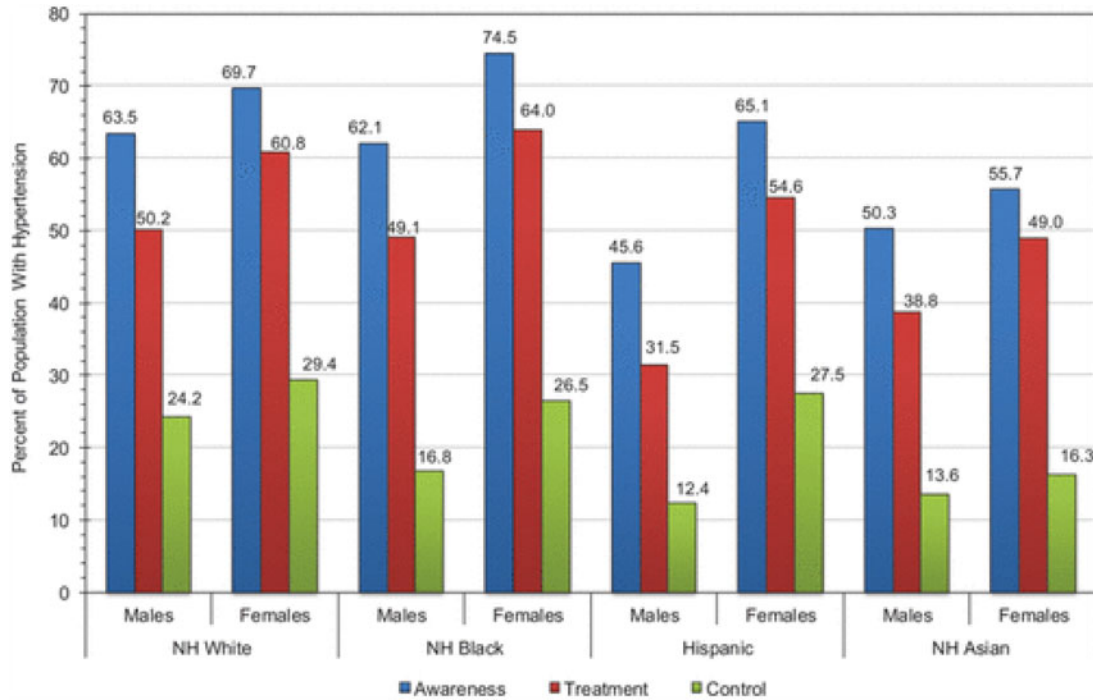


Figure 8 Extent of awareness, treatment, and control of high blood pressure by race/ethnicity and sex, USA (NHANES, 2013–2016)—from ¹⁸⁵

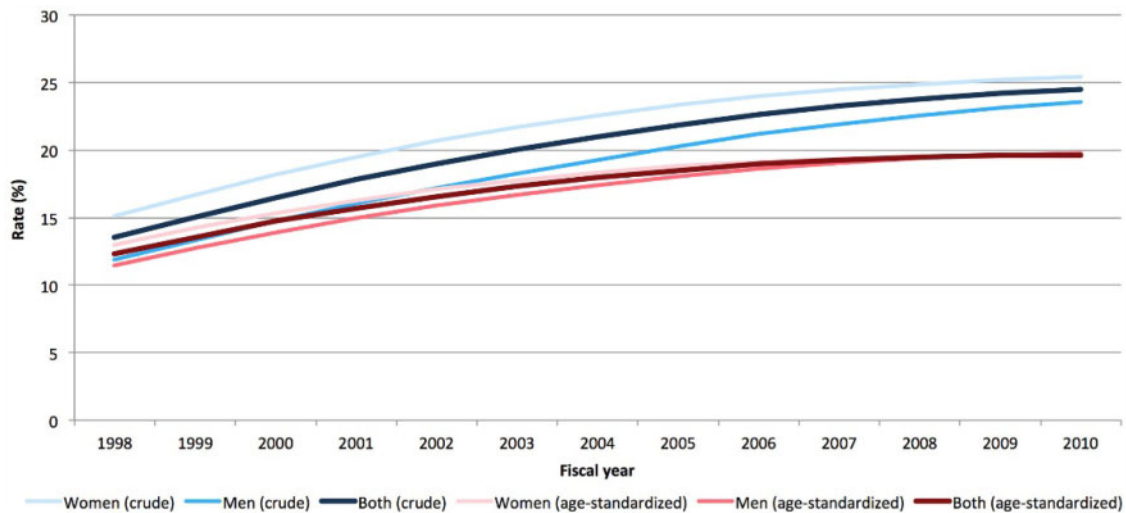


Figure 9 Crude and age-standardized prevalence of diagnosed hypertension by sex in individuals aged 20+ years in Canada—from ¹⁸⁹

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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 activity ^a
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 abstinence
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-transporter-2.

^aRefer 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-transporter-2.

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References

1. Groenewegen A, Rutten FH, Mosterd A, Hoes AW. Epidemiology of heart failure. *Eur J Heart Fail* 2020;**22**:1342–1356.
2. Uijl A, Koudstaal S, Direk K, Denaxas S, Groenewold R, Banerjee A, Hoes AW, Hemingway H, Asselbergs FW. Risk factors for incident heart failure in age- and sex-specific strata: a population-based cohort using linked electronic health records. *Eur J Heart Fail* 2019;**21**:1197–1206.
3. Del Gobbo LC, Kalantarian S, Imamura F, Lemaitre R, Siscovick DS, Psaty BM, Mozaffarian D. Contribution of major lifestyle risk factors for incident heart failure in older adults: the Cardiovascular Health Study. *JACC Heart Fail* 2015;**3**:520–528.
4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, Van der Worp HB, Van Dis I, Verschuren WM, Binno S; ESC Scientific Document Group. European guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016;**37**:2315–2381.
5. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TB, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188.
6. Dunlay SM, Weston SA, Jacobsen SJ, Roger VL. Risk factors for heart failure: a population-based case-control study. *Am J Med* 2009;**122**:1023–1028.
7. Vasani RS, Beiser A, Seshadri S, Larson MG, Kannel WB, D'Agostino RB, Levy D. Residual lifetime risk for developing hypertension in middle-aged women and men: the Framingham Heart Study. *JAMA* 2002;**287**:1003–1010.
8. Levy D, Larson MG, Vasani RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *JAMA* 1996;**275**:1557–1562.
9. Wilhelmens L, Rosengren A, Eriksson H, Lappas G. Heart failure in the general population of men—morbidity, risk factors and prognosis. *J Intern Med* 2001;**249**:253–261.
10. Avery CL, Loehr LR, Baggett C, Chang PP, Kucharska-Newton AM, Matsushita K, Rosamond WD, Heiss G. The population burden of heart failure attributable to modifiable risk factors: the ARIC (Atherosclerosis Risk in Communities) study. *J Am Coll Cardiol* 2012;**60**:1640–1646.
11. Sciarretta S, Palano F, Tocci G, Baldini R, Volpe M. Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk. *Arch Intern Med* 2011;**171**:384–394.

12. Bangalore S, Wild D, Parkar S, Kucin M, Messerli FH. Beta-blockers for primary prevention of heart failure in patients with hypertension insights from a meta-analysis. *J Am Coll Cardiol* 2008;**52**:1062–1072.
13. Shah A, Langenberg C, Rapsomaniki E, Denaxas S, Pujades-Rodriguez M, Gale CP, Deanfield J, Smeeth L, Timmis A, Hemingway H. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Diabetes Endocrinol* 2015;**3**:105–113.
14. McAllister DA, Read SH, Kerstens J, Livingstone S, McGurnaghan S, Jhund P, Petrie J, Sattar N, Fischbacher C, Lund Kristensen S, McMurray J, Colhoun HM, Wild SH. Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes mellitus. *Circulation* 2018;**138**:2774–2786.
15. Shah SJ, Lam CSP, Svedlund S, Saraste A, Hage C, Tan R-S, Beussink-Nelson L, Ljung Faxén U, Fermer ML, Broberg MA, Gan L-M, Lund LH. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFrEF. *Eur Heart J* 2018;**39**:3439–3450.
16. Devereux RB, Roman MJ, Paranicas M, O'Grady MJ, Lee ET, Welty TK, Fabsitz RR, Robbins D, Rhoades ER, Howard BV. Impact of diabetes on cardiac structure and function: the strong heart study. *Circulation* 2000;**101**:2271–2276.
17. Van Melle JP, Bot M, de Jonge P, de Boer RA, van Veldhuisen DJ, Whooley MA. Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease: data from the heart and soul study. *Diabetes Care* 2010;**33**:2084–2089.
18. Rosano GM, Vitale C, Seferovic P. Heart failure in patients with diabetes mellitus. *Card Fail Rev* 2017;**3**:52–55.
19. Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;**358**:2545–2559.
20. Komajda M, McMurray JJ, Beck-Nielsen H, Gomis R, Hanefeld M, Pocock SJ, Curtis PS, Jones NP, Home PD. Heart failure events with rosiglitazone in type 2 diabetes: data from the RECORD clinical trial. *Eur Heart J* 2010;**31**:824–831.
21. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Matthews M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–2128.
22. Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–657.
23. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde AM, Sabatine MS; Declare-TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–357.
24. Cannon CP, Pratley R, Dagogo-Jack S, Mancuso J, Huyck S, Masiukiewicz U, Charbonnel B, Frederich R, Gallo S, Cosentino F, Shih VJ, Gantz I, Terra SG, Cherney DZI, McGuire DK; Vertis CV Investigators. Cardiovascular outcomes with ertugliflozin in type 2 diabetes. *N Engl J Med* 2020;**383**:1425–1435.
25. Perkovic V, Jardine MJ, Neal B, Bompont S, Heerspink HJL, Charytan DM, Edwards R, Agarwal R, Bakris G, Bull S, Cannon CP, Capuano G, Chu PL, de Zeeuw D, Greene T, Levin A, Pollock C, Wheeler DC, Yavin Y, Zhang H, Zinman B, Meininger G, Brenner BM, Mahaffey KW; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–2306.
26. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, Mann JFE, McMurray JJV, Lindberg M, Rossing P, Sjöström CD, Toto RD, Langkilde AM, Wheeler DC; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020;**383**:1436–1446.
27. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Sabatine MS; TIMI Study Group. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Lond Engl* 2019;**393**:31–39.
28. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M, Marx N, Mellbin L, Ostergren J, Patrono C, Seferovic P, Uva MS, Taskinen MR, Tendera M, Tuomilehto J, Valensi P, Zamorano JL, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Document Reviewers De Backer G, Sirnes PA, Ezquerro EA, Avogaro A, Badimon L, Baranova E, Baumgartner H, Betteridge J, Ceriello A, Fagard R, Funck-Brentano C, Gulba DC, Hasdai D, Hoes AW, Kjekshus JK, Knuuti J, Kolh P, Lev E, Mueller C, Neyses L, Nilsson PM, Perk J, Ponikowski P, Reiner Z, Sattar N, Schächinger V, Scheen A, Schirmer H, Strömberg A, Sudzhaeva S, Tamargo JL, Viigimaa M, Vlachopoulos C, Xuereb RG; ESC Committee for Practice Guidelines (CPG). ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2020;**41**:255–323.
29. Seferović PM, Coats AJS, Ponikowski P, Filippatos G, Huelsmann M, Jhund PS, Polovina MM, Komajda M, Seferović J, Sari I, Cosentino F, Ambrosio G, Metra M, Piepoli M, Chioncel O, Lund LH, Thum T, De Boer RA, Mullens W, Lopatin Y, Volterrani M, Hill L, Bauersachs J, Lyon A, Petrie MC, Anker S, Rosano GMC. European Society of Cardiology/Heart Failure Association position paper on the role and safety of new glucose-lowering drugs in patients with heart failure. *Eur J Heart Fail* 2020;**22**:196–213.
30. Seferović PM, Fraggaso G, Petrie M, Mullens W, Ferrari R, Thum T, Bauersachs J, Anker SD, Ray R, Çavuşoğlu Y, Polovina M, Metra M, Ambrosio G, Prasad K, Seferović J, Jhund PS, Dattilo G, Čelutkienė J, Piepoli M, Moura B, Chioncel O, Ben Gal T, Heymans S, de Boer RA, Jaarsma T, Hill L, Lopatin Y, Lyon AR, Ponikowski P, Lainščak M, Jankowska E, Mueller C, Cosentino F, Lund L, Filippatos GS, Ruschitzka F, Coats AJS, Rosano GMC. Sodium-glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:1495–1503.
31. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, de Boer RA, Drexel H, Ben Gal T, Hill L, Jaarsma T, Jankowska EA, Anker MS, Laincsak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G, Coats AJ. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2019;**21**:1169–1186.
32. Inzucchi SE, Zinman B, Fitchett D, Wanner C, Ferrannini E, Schumacher M, Schmoor C, Ohneberg K, Johansen OE, George JT, Hantel S, Bluhmki E, Lachin JM. How does empagliflozin reduce cardiovascular mortality? Insights from a mediation analysis of the EMPA-REG OUTCOME trial. *Diabetes Care* 2018;**41**:356–363.
33. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM, McGuire DK, Pencina MJ, Standl E, Stein PP, Suryawanshi S, Van de Werf F, Peterson ED, Holman RR; Tecos Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2015;**373**:232–242.
34. McGuire DK, Alexander JH, Johansen OE, Perkovic V, Rosenstock J, Cooper ME, Wanner C, Kahn SE, Toto RD, Zinman B, Baanstra D, Pfarr E, Schnaidt S, Meinicke T, George JT, von Eynatten M, Marx N; CARMELINA Investigators. Linagliptin effects on heart failure and related outcomes in individuals with type 2 diabetes mellitus at high cardiovascular and renal risk in CARMELINA. *Circulation* 2019;**139**:351–361.
35. Zannat F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H, White WB; EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet* 2015;**385**:2067–2076.
36. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, Udell JA, Mosenzon O, Im K, Umez-Eronini AA, Pollack PS, Hirshberg B, Frederich R, Lewis BS, McGuire DK, Davidson J, Steg PG, Bhatt DL; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. *Circulation* 2014;**130**:1579–1588.
37. McMurray JJV, Ponikowski P, Bolli GB, Lukashevich V, Kozlovski P, Kothny W, Lewsey JD, Krum H; VIVID Trial Committees and Investigators. Effects of vildagliptin on ventricular function in patients with type 2 diabetes mellitus and heart failure: a randomized placebo-controlled trial. *JACC Heart Fail* 2018;**6**:8–17.
38. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N Engl J Med* 2015;**373**:2247–2257.
39. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, Chan JC, Choi J, Gustavson SM, Iqbal N, Maggioni AP, Marso SP, Ohman P,

- Pagidipati NJ, Poulter N, Ramachandran A, Zinman B, Hernandez AF; EXSCEL Study Group. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2017;**377**:1228–1239.
40. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, Jeppesen OK, Lingvay I, Mosenzon O, Pedersen SD, Tack CJ, Thomsen M, Vilsboll T, Warren ML, Bain SC; for the PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2019;**381**:841–851.
 41. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016;**375**:311–322.
 42. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, Leiter LA, Rosenberg AE, Sigmon KN, Somerville MC, Thorpe KM, McMurray JJV, Del Prato S; Harmony Outcomes Committees and Investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 2018;**392**:1519–1529.
 43. Berl T, Hunsicker LG, Lewis JB, Pfeffer MA, Porush JG, Rouleau JL, Drury PL, Esatjtes E, Hricik D, Parikh CR, Raz I, Vanhille P, Wiegmann TB, Wolfe BM, Locatelli F, Goldhaber SZ, Lewis EJ; Irbesartan Diabetic Nephropathy Trial; Collaborative Study Group. Cardiovascular outcomes in the Irbesartan Diabetic Nephropathy trial of patients with type 2 diabetes and overt nephropathy. *Ann Intern Med* 2003;**138**:542–549.
 44. Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, Zethelius B, Miftaraj M, McGuire DK, Rosengren A, Gudbjörnsdóttir S. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2018;**379**:633–644.
 45. Kosiborod M, Lam CSP, Kohsaka S, Kim DJ, Karasik A, Shaw J, Tangri N, Goh S-Y, Thuresson M, Chen H, Surmont F, Hammar N, Fenici P, Kosiborod M, Cavender MA, Fu AZ, Wilding JP, Khunti K, Norhammar A, Birkeland K, Jørgensen ME, Holl RW, Lam CS, Gulseth HL, Carstensen B, Bollow E, Franch-Nadal J, García Rodríguez LA, Karasik A, Tangri N, Kohsaka S, Kim DJ, Shaw J, Arnold S, Goh S-Y, Hammar N, Fenici P, Bodegård J, Chen H, Surmont F, Nahrebne K, Blak BT, Wittbrodt ET, Saathoff M, Noguchi Y, Tan D, Williams M, Lee HW, Greenbloom M, Kaidanovich-Beilin O, Yeo KK, Bee YM, Khoo J, Koong A, Lau YH, Gao F, Tan WB, Kadir HA, Ha KH, Lee J, Chodick G, Melzer Cohen C, Whitlock R, Cea Soriano L, Fernández Cantero O, Riehle E, Ilomaki J, Magliano D; CVD-REAL Investigators and Study Group. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. *J Am Coll Cardiol* 2018;**71**:2628–2639.
 46. Paterno E, Pawar A, Franklin JM, Najafzadeh M, Déruaz-Luyet A, Brodovicz KG, Sambeski S, Bessette LG, Santiago Ortiz AJ, Kullendorff M, Schneeweiss S. Empagliflozin and the risk of heart failure hospitalization in routine clinical care. *Circulation* 2019;**139**:2822–2830.
 47. Pandey A, Garg S, Khunger M, Darden D, Ayers C, Kumbhani DJ, Mayo HG, de Lemos JA, Berry JD. Dose-response relationship between physical activity and risk of heart failure: a meta-analysis. *Circulation* 2015;**132**:1786–1794.
 48. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. *Arch Intern Med* 2001;**161**:996–1002.
 49. Agha G, Loucks EB, Tinker LF, Waring ME, Michaud DS, Foraker RE, Li W, Martin LW, Greenland P, Manson JE, Eaton CB. Healthy lifestyle and decreasing risk of heart failure in women: the Women, Health Initiative Observational study. *J Am Coll Cardiol* 2014;**64**:1777–1785.
 50. Velagaleti RS, Massaro J, Vasan RS, Robins SJ, Kannel WB, Levy D. Relations of lipid concentrations to heart failure incidence: the Framingham Heart Study. *Circulation* 2009;**120**:2345–2351.
 51. Ebong IA, Goff DC Jr, Rodriguez CJ, Chen H, Sibley CT, Bertoni AG; Multiethnic Study of Atherosclerosis. Association of lipids with incident heart failure among adults with and without diabetes mellitus. *Circ Heart Fail* 2013;**6**:371–378.
 52. Preiss D, Campbell RT, Murray HM, Ford I, Packard CJ, Sattar N, Rahimi K, Colhoun HM, Waters DD, LaRosa JC, Amarencio P, Pedersen TR, Tikkanen MJ, Koren MJ, Poulter NR, Sever PS, Ridker PM, MacFadyen JG, Solomon SD, Davis BR, Simpson LM, Nakamura H, Mizuno K, Marfisi RM, Marchioli R, Tognoni G, Athyros VG, Ray KK, Gotto AM, Clearfield MB, Downs JR, McMurray JJ. The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials. *Eur Heart J* 2015;**36**:1536–1546.
 53. Kenchaiah S, Evans JC, Levy D, Wilson PW, Benjamin EJ, Larson MG, Kannel WB, Vasan RS. Obesity and the risk of heart failure. *N Engl J Med* 2002;**347**:305–313.
 54. Chen X, Thunström E, Hansson P-O, Rosengren A, Mandalenakis Z, Zhong Y, Ergatoudes C, Caidahl K, Fu M. High prevalence of cardiac dysfunction or overt heart failure in 71-year-old men: a 21-year follow-up of “The Study of men born in 1943”. *Eur J Prev Cardiol* 2020;**27**:717–725.
 55. Eaton CB, Pettinger M, Rossouw J, Martin LW, Foraker R, Qudus A, Liu S, Wampler NS, Hank Wu WC, Manson JE, Margolis K, Johnson KC, Allison M, Corbie-Smith G, Rosamond W, Breathett K, Klein L. Risk factors for incident hospitalized heart failure with preserved versus reduced ejection fraction in a multiracial cohort of postmenopausal women. *Circ Heart Fail* 2016;**9**:e002883.
 56. Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. *Am J Med Sci* 2001;**321**:225–236.
 57. Marfella R, Di Filippo C, Portoghesi M, Barbieri M, Ferraraccio F, Siniscalchi M, Cacciapuoti F, Rossi F, D'Amico M, Paolisso G. Myocardial lipid accumulation in patients with pressure-overloaded heart and metabolic syndrome. *J Lipid Res* 2009;**50**:2314–2323.
 58. Aimo A, Castiglione V, Borrelli C, Saccaro LF, Franzini M, Masi S, Emdin M, Giannoni A. Oxidative stress and inflammation in the evolution of heart failure: from pathophysiology to therapeutic strategies. *Eur J Prev Cardiol* 2020;**27**:494–510.
 59. Reddy YNV, Anantha-Narayanan M, Obokata M, Koepf KE, Erwin P, Carter RE, Borlaug BA. Hemodynamic effects of weight loss in obesity: a systematic review and meta-analysis. *JACC Heart Fail* 2019;**7**:678–687.
 60. Wang Y, Tuomilehto J, Jousilahti P, Antikainen R, Mähönen M, Katzmarzyk PT, Hu G. Lifestyle factors in relation to heart failure among Finnish men and women. *Circ Heart Fail* 2011;**4**:607–612.
 61. Favuzzi AMR, Venuti A, Bruno C, Nicolazzi MA, Fuorlo M, Dajko M, De Waure C, Landolfi R, Mancini A. Hormonal deficiencies in heart failure with preserved ejection fraction: prevalence and impact on diastolic dysfunction: a pilot study. *Eur Rev Med Pharmacol Sci* 2020;**24**:352–361.
 62. Bielecka-Dabrowa A, Godoy B, Suzuki T, Banach M, von Haehling S. Subclinical hypothyroidism and the development of heart failure: an overview of risk and effects on cardiac function. *Clin Res Cardiol* 2019;**108**:225–233.
 63. Rhee SS, Pearce EN. Update: systemic diseases and the cardiovascular system (II). The endocrine system and the heart: a review. *Revista Espa de Cardiologia* 2011;**64**:220–231.
 64. Guzzo-Merello G, Segovia J, Dominguez F, Cobo-Marcos M, Gomez-Bueno M, Avellana P, Millan I, Alonso-Pulpon L, Garcia-Pavia P. Natural history and prognostic factors in alcoholic cardiomyopathy. *JACC Heart Fail* 2015;**3**:78–86.
 65. Larsson SC, Orsini N, Wolk A. Alcohol consumption and risk of heart failure: a dose-response meta-analysis of prospective studies. *Eur J Heart Fail* 2015;**17**:367–373.
 66. Stockwell T, Zhao J, Panwar S, Roemer A, Naimi T, Chikritzhs T. “Moderate” drinkers have reduced mortality risk? A systematic review and meta-analysis of alcohol consumption and all-cause mortality. *J Stud Alcohol Drugs* 2016;**77**:185–198.
 67. Wood AM, Kaptoge S, Butterworth AS, Willeit P, Warnakula S, Bolton T, Paige E, Paul DS, Sweeting M, Burgess S, Bell S, Astle W, Stevens D, Koulman A, Selmer RM, Verschuren WMM, Sato S, Njølstad I, Woodward M, Salomaa V, Nordestgaard BG, Yeap BB, Fletcher A, Melander O, Kuller LH, Balkau B, Marmot M, Koenig W, Casiglia E, Cooper C, Arndt V, Franco OH, Wennberg P, Gallacher J, de la Cámara AG, Völzke H, Dahm CC, Dale CE, Bergmann MM, Crespo CJ, van der Schouw YT, Kaaks R, Simons LA, Lagiou P, Schoufour JD, Boer JMA, Key TJ, Rodriguez B, Moreno-Iribas C, Davidson KW, Taylor JO, Sacerdote C, Wallace RB, Quiros JR, Tumino R, Blazer DG, Linneberg A, Daimon M, Panico S, Howard B, Skeie G, Strandberg T, Weiderpass E, Nietert PJ, Psaty BM, Kromhout D, Salamanca-Fernandez E, Kiechl S, Krumholz HM, Grioni S, Palli D, Huerta JM, Price J, Sundström J, Arriola L, Arima H, Travis RC, Panagiotakos DB, Karakatsani A, Trichopoulos A, Kühn T, Grobbee DE, Barrett-Connor E, van Schoor N, Boeing H, Overvad K, Kauhanen J, Wareham N, Langenberg C, Forouhi N, Wennberg M, Després J-P, Cushman M, Cooper JA, Rodriguez CJ, Sakurai M, Shaw JE, Knuiman M, Voortman T, Meisinger C, Tjønneland A, Brenner H, Palmieri L, Dallongeville J, Brunner EJ, Assmann G, Trevisan M, Gillum RF, Ford I, Sattar N, Lazo M, Thompson SG, Ferrari P, Leon DA, Smith GD, Peto R, Jackson R, Banks E, Di Angelantonio E, Danesh J; Emerging Risk Factors Collaboration/EPIC-CVD/UK Biobank Alcohol Study Group. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599912 current drinkers in 83 prospective studies. *Lancet* 2018;**391**:1513–1523.
 68. Ware JS, Amor-Salamanca A, Taya U, Govind R, Serrano I, Salazar-Mendiguchía J, García-Pinilla JM, Pascual-Figal DA, Nuñez J, Guzzo-Merello G, Gonzalez-Vioque E, Bardaji A, Manito N, López-Garrido MA, Padron-Barthe L, Edwards E, Whiffen N, Walsh R, Buchan RJ, Midwinter W, Wilk A, Prasad S, Pantazis A, Baski J, O'Regan DP, Alonso-Pulpon L, Cook SA, Lara-Pezzi E, Barton PJ, Garcia-Pavia P. Genetic etiology for alcohol-induced cardiac toxicity. *J Am Coll Cardiol* 2018;**71**:2293–2302.
 69. Faris R, Henein M, Coats A. Influence of gender and reported alcohol intake on mortality in nonischemic dilated cardiomyopathy. *Heart Dis* 2003;**5**:89–94.

70. Pavan D, Nicolosi GL, Lestuzzi C, Burelli C, Zardo F, Zanuttini D. Normalization of variables of left ventricular function in patients with alcoholic cardiomyopathy after cessation of excessive alcohol intake: an echocardiographic study. *Eur Heart J* 1987;**8**:535–540.
71. Golder C, Gaziano JM. Should people with heart failure avoid alcohol? An evidence review. *Nursing Times* 2018;**114**:43–45.
72. Agarwal SK, Chambless LE, Ballantyne CM, Astor B, Bertoni AG, Chang PP, Folsom AR, He M, Hoogeveen RC, Ni H, Quibrera PM, Rosamond WD, Russell SD, Shahar E, Heiss G. Prediction of incident heart failure in general practice. *Circ Heart Fail* 2012;**5**:422–429.
73. Gopal DM, Kalogeropoulos AP, Georgiopoulou VV, Smith AL, Bauer DC, Newman AB, Kim L, Bibbins-Domingo K, Tindle H, Harris TB, Tang WW, Kritchevsky SB, Butler J. Cigarette smoking exposure and heart failure risk in older adults: the Health, Aging, and Body Composition Study. *Am Heart J* 2012;**164**:236–242.
74. Kamimura D, Cain LR, Mentz RJ, White WB, Blaha MJ, DeFilippis AP, Fox ER, Rodriguez CJ, Keith RJ, Benjamin EJ, Butler J, Bhatnagar A, Robertson RM, Winniford MD, Correa A, Hall ME. Cigarette smoking and incident heart failure: insights from the Jackson Heart Study. *Circulation* 2018;**137**:2572–2582.
75. Aune D, Schlesinger S, Norat T, Riboli E. Tobacco smoking and the risk of heart failure: a systematic review and meta-analysis of prospective studies. *Eur J Prev Cardiol* 2019;**26**:279–288.
76. Ambrose JA, Barua SR. The pathophysiology of cigarette smoking and cardiovascular disease an update. *J Am Coll Cardiol* 2004;**43**:1731–1737.
77. Nadruz W Jr, Claggett B, Gonçalves A, Querejeta-Roca G, Fernandes-Silva MM, Shah AM, Cheng S, Tanaka H, Heiss G, Kitzman DW, Solomon SD. Smoking and cardiac structure and function in the elderly: the ARIC Study (Atherosclerosis Risk in Communities). *Circ Cardiovasc Imaging* 2016;**9**:e004950.
78. Moreira HT, Armstrong AC, Nwabuo CC, Vasconcellos HD, Schmidt A, Sharma RK, Ambale-Venkatesh B, Ostovaneh MR, Kiefe CI, Lewis CE, Schreiner PJ, Sidney S, Ogunyankin KO, Gidding SS, Lima JAC. Association of smoking and right ventricular function in middle age: CARDIA study. *Open Heart* 2020;**7**:e001270.
79. Hendriks T, van Dijk R, Alsabaan NA, van der Harst P. Active tobacco smoking impairs cardiac systolic function. *Sci Rep* 2020;**10**:6608.
80. Rosen BD, Saad MF, Shea S, Nasir K, Edvardsen T, Burke G, Jerosch-Herold M, Arnett DK, Lai S, Bluemke DA, Lima JAC. Hypertension and smoking are associated with reduced regional left ventricular function in asymptomatic individuals: The Multi-Ethnic Study of Atherosclerosis. *J Am Coll Cardiol* 2006;**47**:1150–1158.
81. Son YJ, Lee HJ. Association between persistent smoking after a diagnosis of heart failure and adverse health outcomes: a systematic review and meta-analysis. *Tob Induc Dis* 2020;**18**:1–11.
82. Kim C-Y, Paek Y-J, Seo HG, Kim CY, Paek YJ, Gwan Seo H, Cheong YS, Lee KM, Park SM, Won Park D, Lee K. Dual use of electronic and conventional cigarettes is associated with higher cardiovascular risk factors in Korean men. *Sci Rep* 2020;**10**:1–10.
83. Kavousi M, Pisinger C, Barthelemy JC, Smedt D, Koskinas K, Marques-Vidal P, Panagiotakos D, Prescott EB, Tiberi M, Vassiliou VS, Løchen ML. Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Association of Preventive Cardiology (EAPC). *Eur J Prev Cardiol* 2020.
84. Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Dardari ZA, DeFilippis AP, Bhatnagar A, Blaha MJ. The association between e-cigarette use and asthma among never combustible cigarette smokers: behavioral risk factor surveillance system (BRFSS) 2016 & 2017. *BMC Pulm Med* 2019;**19**:180.
85. Rezk-Hanna M, Benowitz NL. Cardiovascular effects of hookah smoking: potential implications for cardiovascular risk. *Nicotine Tob Res* 2019;**21**:1151–1161.
86. The State of the Drugs Problem in Europe. *European Monitoring Centre for Drugs and Drug Addiction*. Publications Office of the European Union; 2009. 99 pp.
87. Havakuk O, Rezkalla SH, Kloner RA. The cardiovascular effects of cocaine. *J Am Coll Cardiol* 2017;**70**:101–113.
88. Qureshi AI, Suri MF, Guterman LR, Hopkins LN. Cocaine use and the likelihood of nonfatal myocardial infarction and stroke: data from the Third National Health and Nutrition Examination Survey. *Circulation* 2001;**103**:502–506.
89. Aquaro GD, Gabutti A, Meini M, Prontera C, Pasanisi E, Passino C, Emdin M, Lombardi M. Silent myocardial damage in cocaine addicts. *Heart* 2011;**97**:2056–2062.
90. Hantson P. Mechanisms of toxic cardiomyopathy. *Clin Toxicol (Phila)* 2019;**57**:1–9.
91. Becker AE, Grinspoon SK, Klibanski A, Herzog DB. Eating disorders. *N Engl J Med* 1999;**340**:1092–1098.
92. Totzeck M, Mincu R-I, Mrotzek S, Schadendorf D, Rassaf T. Cardiovascular diseases in patients receiving small molecules with anti-vascular endothelial growth factor activity: a meta-analysis of approximately 29,000 cancer patients. *Eur J Prev Cardiol* 2018;**25**:482–494.
93. Howden EJ, Bigaran A, Beaudry R, Fraser S, Selig S, Foulkes S, Antill Y, Nightingale S, Loi S, Haykowsky MJ, La Gerche A. Exercise as a diagnostic and therapeutic tool for the prevention of cardiovascular dysfunction in breast cancer patients. *Eur J Prev Cardiol* 2019;**26**:305–315.
94. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GYH, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM; ESC Scientific Document Group. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines | European Heart Journal | Oxford Academic. *Eur Heart J* 2016;**37**:2768–2801.
95. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, van 't Veer MB, Baaijens MH, de Boer JP, Hart AA, Klokman WJ, Kuenen MA, Ouwens GM, Bartelink H, van Leeuwen FE. Late cardiotoxicity after treatment for Hodgkin lymphoma. *Blood* 2007;**109**:1878–1886.
96. Hooning MJ, Botma A, Aleman BMP, Baaijens MHA, Bartelink H, Klijn JGM, Taylor CW, van Leeuwen FE. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *JNCI J Natl Cancer Inst* 2007;**99**:365–375.
97. Chello M, Mastroberto P, Romano R, Zofrea S, Bevacqua I, Marchese AR. Changes in the proportion of types I and III collagen in the left ventricular wall of patients with post-irradiative pericarditis—ScienceDirect. *Cardiovasc Surg* 1996;**4**:222–226.
98. Veinot JP, Edwards WD. Pathology of radiation-induced heart disease: a surgical and autopsy study of 27 cases. *Hum Pathol* 1996;**27**:766–773.
99. Menezes KM, Wang H, Hada M, Saganti PB. Radiation matters of the heart: a mini review. *Front Cardiovasc Med* 2018;**5**:83.
100. Heymans S, Eriksson U, Lehtonen J, Cooper LT Jr. The quest for new approaches in myocarditis and inflammatory cardiomyopathy. *J Am Coll Cardiol* 2016;**68**:2348–2364.
101. Ammirati E, Frigerio M, Adler ED, Basso C, Birnie DH, Brambatti M, Friedrich MG, Klingel K, Lehtonen J, Moslehi JJ, Pedrotti P, Rimoldi OE, Schultheiss HP, Tschöpe C, Cooper LT Jr, Camici PG. Management of acute myocarditis and chronic inflammatory cardiomyopathy: an expert consensus document. *Circ Heart Fail* 2020;**13**:e007405.
102. Tschöpe C, Cooper LT, Torre-Amione G, Van Linthout S. Management of myocarditis-related cardiomyopathy in adults. *Circ Res* 2019;**124**:1568–1583.
103. Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss HP, Seggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott PM; European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013;**34**:2636–2648, 2648a–2648d.
104. Wu H-H, Chang Y-Y, Kuo S-C, Chen Y-T. Influenza vaccination and secondary prevention of cardiovascular disease among Taiwanese elders—a propensity score-matched follow-up study. *PLoS One* 2019;**14**:e0219172.
105. Kadoglou NPE, Bracke F, Simmers T, Tsioudras S, Parisis J. Influenza infection and heart failure-vaccination may change heart failure prognosis? *Heart Fail Rev* 2017;**22**:329–336.
106. Barison A, Aimo A, Castiglione V, Arzilli C, Lupón J, Codina P, Santiago-Vacas E, Cediél G, Emdin M, Bayes-Genis A. Cardiovascular disease and COVID-19: les liaisons dangereuses. *Eur J Prev Cardiol* 2020;**27**:1017–1025.
107. Zhang Y, Coats AJS, Zheng Z, Adamo M, Ambrosio G, Anker SD, Butler J, Xu D, Mao J, Khan MS, Bai L, Mebazaa A, Ponikowski P, Tang Q, Ruschitzka F, Seferovic P, Tschöpe C, Zhang S, Gao C, Zhou S, Senni M, Zhang J, Metra M. Management of heart failure patients with COVID-19: a joint position paper of the Chinese Heart Failure Association & National Heart Failure Committee and the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail* 2020;**22**:941–956.
108. Lindner D, Fitzek A, Bräuninger H, Aleshcheva G, Edler C, Meissner K, Scherschel K, Kirchhof P, Escher F, Schultheiss HP, Blankenberg S, Püschel K, Westermann D. Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases. *JAMA Cardiol* 2020;**5**:1281–1285.
109. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, Shcherygina A, Escher F, Vasa-Nicotera M, Zeiher AM, Vehreschild M, Nagel E. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;**5**:1265–1273.
110. Bern C. Chagas' disease. *N Engl J Med* 2015;**373**:456–466.
111. Marin-Neto JA, Cunha-Neto E, Maciel BC, Simões MV. Pathogenesis of chronic Chagas heart disease. *Circulation* 2007;**115**:1109–1123.

112. Echeverría LE, Rojas LZ, Villamizar MC, Luengas C, Chaves AM, Rodríguez JA, Campo R, Clavijo C, Redondo AM, López LA, Gómez-Ochoa SA, Morillo CA, Rueda-Ochoa OL, Franco OH. Echocardiographic parameters, speckle tracking, and brain natriuretic peptide levels as indicators of progression of indeterminate stage to Chagas cardiomyopathy. *Echocardiography* 2020;**37**:429–438.
113. Carapetis JR, McDonald M, Wilson NJ. Acute rheumatic fever. *Lancet* 2005;**366**:155–168.
114. Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis* 2005;**5**:685–694.
115. GBD 2017—Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1789–1858.
116. Xu R, Wyber R. How is group A Streptococcus transmitted from person to person? A systematic review. PROSPERO 2019; CRD42019138472.
117. Robertson KA, Volmink JA, Mayosi BM. Antibiotics for the primary prevention of acute rheumatic fever: a meta-analysis. *BMC Cardiovasc Disord* 2005;**5**:11.
118. Mota CC, Meira ZM, Graciano RN, Graciano FF, Araújo FD. Rheumatic fever prevention program: long-term evolution and outcomes. *Front Pediatr* 2015;**2**:141.
119. Mirabel M, Tafflet M, Noël B, Parks T, Axler O, Robert J, Nadra M, Phelippeau G, Descloux E, Cazorla C, Missotte I, Gervolino S, Barguil Y, Rouchon B, Laumond S, Jubeau T, Braunstein C, Empana JP, Marijon E, Jouven X. Newly diagnosed rheumatic heart disease among indigenous populations in the Pacific. *Heart* 2015;**101**:1901–1906.
120. de Dassel JL, de Klerk N, Carapetis JR, Ralph AP. How many doses make a difference? An analysis of secondary prevention of rheumatic fever and rheumatic heart disease. *J Am Heart Assoc* 2018;**7**:e010223.
121. Okello E, Longenecker CT, Beaton A, Kanya MR, Lwabi P. Rheumatic heart disease in Uganda: predictors of morbidity and mortality one year after presentation. *BMC Cardiovasc Disord* 2017;**17**:20.
122. WHO Study Group on Rheumatic Fever and Rheumatic Heart Disease (Geneva, Switzerland, World Health Organization. Rheumatic Fever and Rheumatic Heart Disease: Report of a WHO Expert Consultation, Geneva, 20 October–1 November 2001. World Health Organization Technical Report Series; no. 923. 2001.
123. Carapetis JR, Beaton A, Cunningham MW, Guilherme L, Karthikeyan G, Mayosi BM, Sable C, Steer A, Wilson N, Wyber R, Zühlke L. Acute rheumatic fever and rheumatic heart disease. *Nat Rev Dis Primers* 2016;**2**:15084.
124. Bowen A, Currie B, Katzenellenbogen J, Marangou J, Noonan S, Ralph A, Roberts K, Steer A, Vaughan G, Wade V, Wyber R. *The 2020 Australian Guideline for Prevention, Diagnosis and Management of Acute Rheumatic Fever and Rheumatic Heart Disease*. RHD Australia, Menzies School of Health Research. *Med J Aust*. 2021;**214**:220–227.
125. Ponikowski P, Anker SD, Chua TP, Francis D, Banasiak W, Poole-Wilson PA, Coats AJ, Piepoli M. Oscillatory breathing patterns during wakefulness in patients with chronic heart failure: clinical implications and role of augmented peripheral chemosensitivity. *Circulation* 1999;**100**:2418–2424.
126. Emdin M, Mirizzi G, Giannoni A, Poletti R, Ludice G, Bramanti F, Passino C. Prognostic significance of central apneas throughout a 24-hour period in patients with heart failure. *J Am Coll Cardiol* 2017;**70**:1351–1364.
127. Lanfranchi PA, Braghiroli A, Bosimini E, Mazzuero G, Colombo R, Donner CF, Giannuzzi P. Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. *Circulation* 1999;**99**:1435–1440.
128. Giannoni A, Morelli M, Francis D. *The Breathless Heart—Apneas in Heart Failure*. Michele Emdin—Springer—Pathophysiology of Ventral Apneas in Heart Failure. Switzerland: Springer-Verlag; 2016. p91–124.
129. Bradley TD, Floras JS. Sleep apnea and heart failure: part I: obstructive sleep apnea. *Circulation* 2003;**107**:1671–1678.
130. Lanfranchi PA, Somers VK, Braghiroli A, Corra U, Eleuteri E, Giannuzzi P. Central sleep apnea in left ventricular dysfunction: prevalence and implications for arrhythmic risk. *Circulation* 2003;**107**:727–732.
131. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, Redline S, Resnick HE, Tong EK, Diener-West M, Shahar E. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation* 2010;**122**:352–360.
132. Holt A, Bjerre J, Zareini B. Sleep apnea, the risk of developing heart failure, and potential benefits of continuous positive airway pressure (CPAP) therapy. *J Am Heart Assoc Cardiovasc Cerebrovasc Dis* 2018;**7**:e008684.
133. World Health Organization. WHO | Ambient Air Pollution: A Global Assessment of Exposure and Burden of Disease. <https://apps.who.int/iris/bitstream/handle/10665/250141/9789241511353-eng.pdf?sequence=1&isAllowed=y> (28 August 2021) 2016.
134. Cohen AJ, Brauer M, Burnett R, Anderson HR, Frostad J, Estep K, Balakrishnan K, Brunekreef B, Dandona L, Dandona R, Feigin V, Freedman G, Hubbell B, Jobling A, Kan H, Knibbs L, Liu Y, Martin R, Morawska L, Pope CA, Shin H, Straif K, Shaddick G, Thomas M, van Dingenen R, van Donkelaar A, Vos T, Murray CJL, Forouzanfar MH. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017;**389**:1907–1918.
135. Du Y, Xu X, Chu M, Guo Y, Wang J. Air particulate matter and cardiovascular disease: the epidemiological, biomedical and clinical evidence. *J Thorac Dis* 2016;**8**:E8–E19.
136. Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. *J Air Waste Manag Assoc* 2006;**56**:709–742.
137. Brook RD, Rajagopalan S, Pope CA, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC, Whitsel L, Kaufman JD; American Heart Association Council on Epidemiology and Prevention, Council on the Kidney in Cardiovascular Disease, and Council on Nutrition, Physical Activity and Metabolism. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* 2010;**121**:2331–2378.
138. Hoek G, Brunekreef B, Goldbohm S, Fischer P, van den Brandt PA. Association between mortality and indicators of traffic-related air pollution in the Netherlands: a cohort study. *Lancet* 2002;**360**:1203–1209.
139. Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 2004;**109**:71–77.
140. Cohen G, Steinberg DM, Keinan-Boker L, Yuval, Levy I, Chen S, Shafran-Nathan R, Levin N, Shimony T, Wittberg G, Bental T, Shohat T, Broday DM, Kornowski R, Gerber Y. Preexisting coronary heart disease and susceptibility to long-term effects of traffic-related air pollution: A matched cohort analysis. *Eur J Prev Cardiol* 2020.
141. Shah AS, Langrish JP, Nair H, McAllister DA, Hunter AL, Donaldson K, Newby DE, Mills NL. Global association of air pollution and heart failure: a systematic review and meta-analysis. *Lancet* 2013;**382**:1039–1048.
142. Atkinson RW, Carey IM, Kent AJ, Staa TP, van Anderson HR, Cook DG. Original article: long-term exposure to outdoor air pollution and the incidence of chronic obstructive pulmonary disease in a national English cohort. *Occup Environ Med* 2015;**72**:42–48.
143. Bai L, Shin S, Burnett RT, Kwong JC, Hystad P, van Donkelaar A, Goldberg MS, Lavigne E, Copes R, Martin RV, Kopp A, Chen H. Exposure to ambient air pollution and the incidence of congestive heart failure and acute myocardial infarction: A population-based study of 5.1 million Canadian adults living in Ontario. *Environ Int* 2019;**132**:105004.
144. Bai L, Weichenthal S, Kwong JC, Burnett RT, Hatzopoulou M, Jerrett M, van Donkelaar A, Martin RV, Van Ryswyk K, Lu H, Kopp A, Chen H. Associations of long-term exposure to ultrafine particles and nitrogen dioxide with increased incidence of congestive heart failure and acute myocardial infarction. *Am J Epidemiol* 2019;**188**:151–159.
145. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, Ky B, Santema BT, Sliwa K, Voors AA. Sex differences in heart failure. *Eur Heart J* 2019;**40**:3859–3868.
146. Bragazzi NL, Zhong W, Shu J, Abu Much A, Lotan D, Grupper A, Younis A, Dai H. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. *Eur J Prev Cardiol* 2021;**2021**:28:1682–1690.
147. Keates AK, Mocumbi AO, Ntsekhe M, Sliwa K, Stewart S. Cardiovascular disease in Africa: epidemiological profile and challenges. *Nat Rev Cardiol* 2017;**14**:273–293.
148. Stewart S, Carrington M, Pretorius S, Methusi P, Sliwa K. Standing at the crossroads between new and historically prevalent heart disease: effects of migration and socio-economic factors in the Heart of Soweto cohort study. *Eur Heart J* 2011;**32**:492–499.
149. Ogah OS, Sliwa K, Akinyemi JO, Falase AO, Stewart S. Hypertensive heart failure in Nigerian Africans: insights from the Abeokuta Heart Failure Registry. *J Clin Hypertens (Greenwich)* 2015;**17**:263–272.
150. Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, Dzudie A, Kouam CK, Suliman A, Schrueder N, Yonga G, Ba SA, Maru F, Alemayehu B, Edwards C, Davison BA, Cotter G, Sliwa K. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries. *Arch Intern Med* 2012;**172**:1386–1394.
151. Fatema N, Banerjee SK, Ahmed CM, Habib AA, Rahman F, Ahsan SA, Hoque H, Debnath RC, Hashem S, Arzu J. Clinical profile and outcome of peripartum cardiomyopathy—a study in a tertiary cardiac hospital of Bangladesh. *Mymensingh Med J* 2018;**27**:298–303.
152. Dokainish H, Teo K, Zhu J, Roy A, AlHabib KF, ElSayed A, Palileo-Villaneuva L, Lopez-Jaramillo P, Karaye K, Yusoff K, Orlandini A, Sliwa K, Mondo C, Lanas F, Prabhakaran D, Badr A, Elmaghawry M, Damasceno A, Tibazarwa K, Bellef-Cote E, Balasubramanian K, Islam S, Yacoub MH, Huffman MD, Harkness K, Grinvalds A, McKelvie R, Bangdiwala SI, Yusuf S; INTER-CHF Investigators.

- Global mortality variations in patients with heart failure: results from the International Congestive Heart Failure (INTER-CHF) prospective cohort study. *Lancet Glob Health* 2017;**5**:e665–e672.
153. United Nations, Department of Economic and Social Affairs, Population Division. World Population Prospects 2019: Highlights. ST/ESA/SER.A/423. 2019. https://population.un.org/wpp/Publications/Files/WPP2019_Highlights.pdf (28 August 2021).
 154. Asia Pacific Risk Center. Advancing into the golden years. Costs of Healthcare for Asia Pacific's Elderly. Revision 2016. <https://www.mmc.com/content/dam/mmc-web/insights/publications/2018/dec/healthy-societies/Advancing-into-the-Golden-Years/APRC%20Ageing%20report.pdf>.
 155. Ohira T, Iso H. Cardiovascular disease epidemiology in Asia: an overview. *Circ J* 2013;**77**:1646–1652.
 156. Shimokawa H, Miura M, Nochioka K, Sakata Y. Heart failure as a general pandemic in Asia. *Eur J Heart Fail* 2015;**17**:884–892.
 157. Jiang H, Ge J. Epidemiology and clinical management of cardiomyopathies and heart failure in China. *Heart* 2009;**95**:1727–1731.
 158. Sakata Y, Shimokawa H. Epidemiology of heart failure in Asia. *Circ J* 2013;**77**:2209–2217.
 159. Lam CSP. Heart failure in Southeast Asia: facts and numbers. *ESC Heart Fail* 2015;**2**:46–49.
 160. Dalai R. *The Cost of Silence: Cardiovascular Disease in Asia*. The Economist Intelligence Unit (EIU); https://eiu.com/content/dam/eiu/perspectives/economist.com/sites/default/files/The_cost_of_silence.pdf (28 Aug 2021).
 161. Lam CS, Teng TK, Tay WT, Anand I, Zhang S, Shimizu W, Narasimhan C, Park SW, Yu CM, Ngarmukos T, Omar R, Reyes EB, Siswanto BB, Hung CL, Ling LH, Yap J, MacDonald M, Richards AM. Regional and ethnic differences among patients with heart failure in Asia: the Asian sudden cardiac death in heart failure registry. *Eur Heart J* 2016;**37**:3141–3153.
 162. Reyes EB, Ha JW, Firdaus I, Ghazi AM, Phrommintikul A, Sim D, Vu QN, Siu CW, Yin WH, Cowie MR. Heart failure across Asia: Same healthcare burden but differences in organization of care. *Int J Cardiol* 2016;**223**:163–167.
 163. Grover A, Vijayvergiya R, Thingam ST. Burden of rheumatic and congenital heart disease in India: lowest estimate based on the 2001 census. *Indian Heart J* 2002;**54**:104–107.
 164. Shiba N, Nochioka K, Miura M, Kohno H, Shimokawa H; CHART-2 Investigators. Trend of westernization of etiology and clinical characteristics of heart failure patients in Japan—first report from the CHART-2 study. *Circ J* 2011;**75**:823–833.
 165. Jones JQ. *The Cost of Inaction: Secondary Prevention of Cardiovascular Disease in Asia-Pacific*. The Economist Intelligence Unit (EIU); https://eiu.com/content/dam/eiu/perspectives/economist.com/sites/default/files/eiu_amgen_cvd_secondary_prevention_whitepaper_0319.pdf (28 August 2021).
 166. National Health Survey: First Results, 2017-18 Financial Year | Australian Bureau of Statistics. 2018. <https://www.abs.gov.au/statistics/health/health-conditions-and-risks/national-health-survey-first-results/latest-release> (28 August 2021).
 167. Chan YK, Tuttle C, Ball J, Teng TK, Ahamed Y, Carrington MJ, Stewart S. Current and projected burden of heart failure in the Australian adult population: a substantive but still ill-defined major health issue. *BMC Health Serv Res* 2016;**16**:501.
 168. Abhayaratna WP, Smith WT, Becker NG, Marwick TH, Jeffery IM, McGill DA. Prevalence of heart failure and systolic ventricular dysfunction in older Australians: the Canberra Heart Study. *Med J Aust* 2006;**184**:151–154.
 169. McGrady M, Krum H, Carrington MJ, Stewart S, Zeitz C, Lee GA, Marwick TH, Haluska BA, Brown A. Heart failure, ventricular dysfunction and risk factor prevalence in Australian Aboriginal peoples: the Heart of the Heart Study. *Heart* 2012;**98**:1562–1567.
 170. Ponikowski P, Anker SD, Al-Habib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H, Rastogi V, Rohde LE, Samal UC, Shimokawa H, Budi Siswanto B, Sliwa K, Filippatos G. Heart failure: preventing disease and death worldwide. *ESC Heart Fail* 2014;**1**:4–25.
 171. Ferreira JP, Kraus S, Mitchell S, Perel P, Piñeiro D, Chioncel O, Colque R, de Boer RA, Gomez-Mesa JE, Grancelli H, Lam CSP, Martinez-Rubio A, McMurray JJV, Mebazaa A, Panjath G, Piña IL, Sani M, Sim D, Walsh M, Yancy C, Zannad F, Sliwa K. World Heart Federation roadmap for heart failure. *Glob Heart* 2019;**14**:197–214.
 172. Schrage B, Geelhoed B, Niiranen TJ, Gianfagna F, Vishram-Nielsen JKK, Costanzo S, Söderberg S, Ojeda FM, Vartiainen E, Donati MB, Magnussen C, Di Castelnuovo A, Camen S, Kontto J, Koenig W, Blankenberg S, de Gaetano G, Linneberg A, Jørgensen T, Zeller T, Kuulasmaa K, Tunstall-Pedoe H, Hughes M, Iacoviello L, Salomaa V, Schnabel RB. Comparison of cardiovascular risk factors in European Population cohorts for predicting atrial fibrillation and heart failure, their subsequent onset, and death. *J Am Heart Assoc* 2020;**9**:e015218.
 173. Magnussen C, Niiranen TJ, Ojeda FM, Gianfagna F, Blankenberg S, Vartiainen E, Sans S, Pasterkamp G, Hughes M, Costanzo S, Donati MB, Jousilahti P, Linneberg A, Palosaari T, de Gaetano G, Bobak M, den Ruijter HM, Jørgensen T, Söderberg S, Kuulasmaa K, Zeller T, Iacoviello L, Salomaa V, Schnabel RB; BiomarCaRE Consortium. Sex-specific epidemiology of heart failure risk and mortality in Europe: results from the BiomarCaRE consortium. *JACC Heart Fail* 2019;**7**:204–213.
 174. Uijl A, Koudstaal S, Vaartjes I, Boer JMA, Verschuren WMM, van der Schouw YT, Asselbergs FW, Hoes AW, Sluijs I. Risk for heart failure: the opportunity for prevention with the American Heart Association's Life's Simple 7. *JACC Heart Fail* 2019;**7**:637–647.
 175. Pujades-Rodriguez M, George J, Shah AD, Rapsomaniki E, Denaxas S, West R, Smeeth L, Timmis A, Hemingway H. Heterogeneous associations between smoking and a wide range of initial presentations of cardiovascular disease in 1937360 people in England: lifetime risks and implications for risk prediction. *Int J Epidemiol* 2015;**44**:129–141.
 176. Baena-Diez JM, Byram AO, Grau M, Gómez-Fernández C, Vidal-Solsona M, Ledesma-Ulloa G, González-Casafont I, Vasquez-Lazo J, Subirana I, Schroder H. Obesity is an independent risk factor for heart failure: Zona Franca Cohort study. *Clin Cardiol* 2010;**33**:760–764.
 177. Lawson CA, Zaccardi F, Squire I, Okhai H, Davies M, Huang W, Mamas M, Lam CSP, Khunti K, Kadam UT. Risk factors for heart failure: 20-year population-based trends by sex, socioeconomic status, and ethnicity. *Circ Heart Fail* 2020;**13**:e006472.
 178. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, Allison M, Hemingway H, Cleland JG, McMurray JJV, Rahimi K. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet* 2018;**391**:572–580.
 179. Van Deursen VM, Urso R, Laroche C, Damman K, Dahlström U, Tavazzi L, Maggioni AP, Voors AA. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2014;**16**:103–111.
 180. Iorio A, Senni M, Barbati G, Greene SJ, Poli S, Zamboni E, Di Nora C, Cioffi G, Tarantini L, Gavazzi A, Sinagra G, Di Lenarda A. Prevalence and prognostic impact of non-cardiac co-morbidities in heart failure outpatients with preserved and reduced ejection fraction: a community-based study. *Eur J Heart Fail* 2018;**20**:1257–1266.
 181. Christiansen MN, Køber L, Torp-Pedersen C, Gislason GH, Schou M, Smith JG, Vasan RS, Andersson C. Preheart failure comorbidities and impact on prognosis in heart failure patients: a nationwide study. *J Intern Med* 2020;**287**:698–710.
 182. Chioncel O, Lainscak M, Seferovic PM, Anker SD, Crespo-Leiro MG, Harjola V-P, Parissis J, Laroche C, Piepoli MF, Fonseca C, Mebazaa A, Lund L, Ambrosio GA, Coats AJ, Ferranti R, Ruschitzka F, Maggioni AP, Filippatos G. Epidemiology and one-year outcomes in patients with chronic heart failure and preserved, mid-range and reduced ejection fraction: an analysis of the ESC Heart Failure Long-Term Registry. *Eur J Heart Fail* 2017;**19**:1574–1585.
 183. Blair JE, Huffman M, Shah SJ. Heart failure in North America. *Curr Cardiol Rev* 2013;**9**:128–146.
 184. Glynn P, Ning H, Bavishi A, Shah S, Yancy C, Jones DL, Khan S. Heart failure risk distribution and trends in the united states population from 1999-2014: results from Health and Nutrition Examination survey. *J Am Coll Cardiol* 2019;**73**(9 Suppl 1):785.
 185. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S, Delling FN, Djousse L, Elkind MSV, Ferguson JF, Fornage M, Khan SS, Kissela BM, Knutson KL, Kwan TW, Lackland DT, Lewis TT, Lichtman JH, Longenecker CT, Loop MS, Lutsey PL, Martin SS, Matsushita K, Moran AE, Mussolino ME, Perak AM, Rosamond WD, Roth GA, Sampson UKA, Satou GM, Schroeder EB, Shah SH, Shay DK, Spartano NL, Stokes A, Tirschwell DL, VanWagner LB, Tsao CW; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics—2020 update: a report from the American Heart Association. *Circulation* 2020;**141**:e139–e596.
 186. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O, Konstam MA, Maddox TM, Nichol G, Pham M, Piña IL, Trogon JG; American Heart Association Advocacy Coordinating Committee; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular Radiology and Intervention; Council on Clinical Cardiology; Council on Epidemiology and Prevention; Stroke Council. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail* 2013;**6**:606–619.
 187. Heart Disease in Canada: Highlights from the Canadian Chronic Disease Surveillance System, 2017—Canada.ca. Public Health Agency of Canada. 2017. <https://www.canada.ca/en/public-health/services/publications/diseases-conditions/heart-disease-canada-fact-sheet.html> (28 Aug 2021).
 188. Yeung DF, Boom NK, Guo H, Lee DS, Schultz SE, Tu JV. Trends in the incidence and outcomes of heart failure in Ontario, Canada: 1997 to 2007. *CMAJ* 2012;**184**:E765–E773.

189. Padwal RS, Bienek A, McAlister FA, Campbell NR; Outcomes Research Task Force of the Canadian Hypertension Education Program. Epidemiology of hypertension in Canada: an update. *Can J Cardiol* 2016;**32**:687–694.
190. Daskalopoulou SS, Rabi DM, Zarnke KB, Dasgupta K, Nerenberg K, Cloutier L, Gelfer M, Lamarre-Cliche M, Milot A, Bolli P, McKay DW, Tremblay G, McLean D, Tobe SW, Ruzicka M, Burns KD, Vallée M, Ramesh Prasad GV, Lebel M, Feldman RD, Selby P, Pipe A, Schiffrin EL, McFarlane PA, Oh P, Hegele RA, Khara M, Wilson TW, Brian Penner S, Burgess E, Herman RJ, Bacon SL, Rabkin SW, Gilbert RE, Campbell TS, Grover S, Honos G, Lindsay P, Hill MD, Coutts SB, Gubitz G, Campbell NR, Moe GW, Howlett JG, Boulanger JM, Prebtani A, Larochelle P, Leiter LA, Jones C, Ogilvie RI, Woo V, Kaczorowski J, Trudeau L, Petrella RJ, Hiremath S, Stone JA, Drouin D, Lavoie KL, Hamet P, Fodor G, Grégoire JC, Fournier A, Lewanczuk R, Dresser GK, Sharma M, Reid D, Benoit G, Feber J, Harris KC, Poirier L, Padwal RS. The 2015 Canadian Hypertension Education Program recommendations for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. *Can J Cardiol* 2015;**31**:549–568.
191. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbigele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018;**71**:1269–1324.
192. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. *N Engl J Med* 2015;**373**:2103–2116.
193. Feely A, Lix LM, Reimer K. Estimating multimorbidity prevalence with the Canadian Chronic Disease Surveillance System. *Health Promot Chronic Dis Prev Can* 2017;**37**:215–222.
194. Ruilope LM, Nunes Filho ACB, Nadruz W Jr, Rodríguez Rosales FF, Verdejo-Paris J. Obesity and hypertension in Latin America: current perspectives. *Hipertens Riesgo Vasc* 2018;**35**:70–76.
195. Seron P, Irazola V, Rubinstein A, Calandrelli M, Ponzo J, Olivera H, Gutierrez L, Elorriaga N, Poggio R, Lanás F. Ideal cardiovascular health in the southern cone of Latin America. *Public Health* 2018;**156**:132–139.
196. Ciapponi A, Alcaraz A, Calderón M, Matta MG, Chaparro M, Soto N, Bardach A. Burden of heart failure in Latin America: a systematic review and meta-analysis. *Rev Esp Cardiol (Engl Ed)* 2016;**69**:1051–1060.
197. Van Riet EE, Hoes AW, Wagenaar KP, Limburg A, Landman MA, Rutten FH. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. *Eur J Heart Fail* 2016;**18**:242–252.
198. Echeverría LE, Marcus R, Novick G, Sosa-Estani S, Ralston K, Zaidel EJ, Forsyth C, Ribeiro ALP, Mendoza I, Falconi ML, Mitelman J, Morillo CA, Pereiro AC, Pinazo MJ, Salvatella R, Martínez F, Perel P, Liprandi AS, Piñeiro DJ, Molina GR. WHF IASC roadmap on Chagas disease. *Glob Heart* 2020;**15**:26.