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RESEARCH ARTICLE

A population-based study of 92 clinically recognized risk factors for heart failure: co-occurrence, prognosis and preventive potential

Amitava Banerjee[1,2,3]*, Laura Pasea[1], Sheng-Chia Chung[1], Kenan Direk[1,4], Folkert W. Asselbergs[1,2,5,6], Diederick E. Grobbee[7], Dipak Kotecha[6,8,9], Stefan D. Anker[10], Tomasz Dyszynski[11], Benoît Tyl[12], Spiros Denaxas[1,5], R. Thomas Lumbers[1,2,5], and Harry Hemingway[1,5,13]

[1]Institute of Health Informatics, University College London, London, UK; [2]University College London Hospitals NHS Trust, London, UK; [3]Barts Health NHS Trust, The Royal London Hospital, London, UK; [4]UCL Energy Institute, London, UK; [5]Health Data Research UK, London, UK; [6]Department of Cardiology, University Medical Center Utrecht, Utrecht, The Netherlands; [7]Julius Center Research Program Cardiovascular Epidemiology, Utrecht University, Utrecht, The Netherlands; [8]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK; [9]Health Data Research UK Midlands, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK; [10]Department of Cardiology, Charité Campus Virchow-Klinikum, Berlin, Germany; [11]Bayer AG, Medical Affairs & Pharmacovigilance, Pharmaceuticals TG Cardio, Thrombosis & Hemophilia Building M084, Berlin, Germany; [12]Center for Therapeutic Innovation, Cardiovascular and Metabolic Disease, Institut de Recherches Internationales Servier, Suresnes Cedex, France; and [13]National Institute for Health Research University College London Hospitals Biomedical Research Centre, London, UK

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Aims Primary prevention strategies for heart failure (HF) have had limited success, possibly due to a wide range of underlying risk factors (RFs). Systematic evaluations of the prognostic burden and preventive potential across this wide range of risk factors are lacking. We aimed at estimating evidence, prevalence and co-occurrence for primary prevention and impact on prognosis of RFs for incident HF.

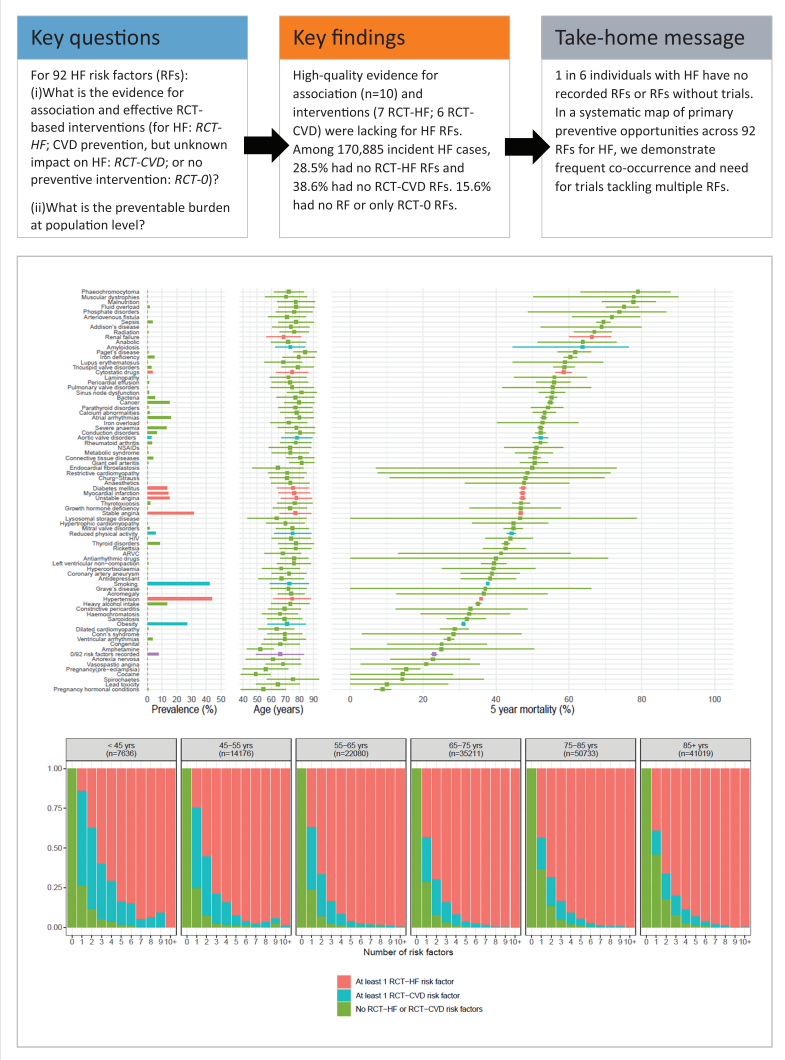
Methods and results We systematically reviewed trials and observational evidence of primary HF prevention across 92 putative aetiologic RFs for HF identified from US and European clinical practice guidelines. We identified 170 885 individuals aged ≥30 years with incident HF from 1997 to 2017, using linked primary and secondary care UK electronic health records (EHR) and rule-based phenotypes (ICD-10, Read Version 2, OPCS-4 procedure and medication codes) for each of 92 RFs. Only 10/92 factors had high quality observational evidence for association with incident HF; 7 had effective randomized controlled trial (RCT)-based interventions for HF prevention (RCT-HF), and 6 for cardiovascular disease prevention, but not HF (RCT-CVD), and the remainder had no RCT-based preventive interventions (RCT-0). We were able to map 91/92 risk factors to EHR using 5961 terms, and 88/91 factors were represented by at least one patient. In the 5 years prior to HF diagnosis, 44.3% had ≥4 RFs. By RCT evidence, the most common RCT-HF RFs were hypertension (48.5%), stable angina (34.9%), unstable angina (16.8%), myocardial infarction (15.8%), and diabetes (15.1%); RCT-CVD RFs were smoking (46.4%) and obesity (29.9%); and RCT-0 RFs were atrial arrhythmias (17.2%), cancer (16.5%), heavy alcohol intake (14.9%). Mortality at 1 year varied across all 91 factors (lowest: pregnancy-related hormonal disorder 4.2%; highest: phaeochromocytoma 73.7%). Among new HF cases, 28.5% had no RCT-HF RFs and 38.6% had no RCT-CVD RFs. 15.6% had either no RF or only RCT-0 RFs.

Conclusion One in six individuals with HF have no recorded RFs or RFs without trials. We provide a systematic map of primary preventive opportunities across a wide range of RFs for HF, demonstrating a high burden of co-occurrence and the need for trials tackling multiple RFs.

*Corresponding author. UCL Institute of Health Informatics, University College London, 222 Euston Road, London NW1 2DA, UK. Tel: +44 20 35495449, Email: ami.banerjee@ucl.ac.uk

[Correction added on 16 May 2022, after first online publication: The author name Folkert Asselbergs has been corrected to Folkert W Asselbergs in this version.]

Graphical Abstract



A population-based study of 92 clinically recognized risk factors for heart failure: co-occurrence, prognosis and preventive potential.

Keywords Heart failure • Primary prevention • Risk factor • Epidemiology

Introduction

Declines in incidence of heart failure (HF) have been slower than for ischaemic heart disease (IHD) and stroke.[1,2] Primary prevention strategies exist for HF in individuals with hypertension, IHD and diabetes mellitus (DM),[3–5] but the European Society of Cardiology (ESC) identifies 89 discrete, frequently overlapping, risk factors (RFs), classified as 'diseased myocardium', 'abnormal loading conditions' and 'arrhythmias' (online supplementary *Table S1*), partly explaining the limited success of HF primary prevention. A further three RFs are mentioned in the American College of Cardiology/American Heart Association (ACC/AHA) primary cardiovascular disease (CVD) prevention guidelines (smoking, reduced physical activity [PA], and reduced cardiorespiratory fitness).[6] However, beyond suggesting broad diagnostic work-up, international HF guidelines neglect prevalence, co-occurrence, relative importance and prognosis by these 92 RFs.[3]

In order to tackle the high and rising global burden of HF,[1,7–11] primary prevention strategies must prioritize evidence-based RF-specific interventions. The only cause-specific interventions for HF supported by randomized controlled trials (RCT) in primary CVD prevention guidelines are sodium–glucose cotransporter 2

inhibitors for DM, and blood pressure (BP)-lowering therapy for hypertension.[6] Canakinumab, an interleukin-1β inhibitor, may have a role in reducing HF events.[12] Other recommendations for HF prevention, such as increased PA,[13] smoking cessation,[14] or 'ideal cardiovascular health' (smoking, cholesterol, BP, blood glucose, weight, diet and PA)[15–17] are not based on RCT evidence, which needs to be reviewed across the 92 RFs.

Effective, impactful prevention relies on knowledge of prevalence, co-occurrence and preventive potential across 92 RFs. However, studies to date have assessed individual RFs,[18] considering neither RFs comprehensively,[9] nor basic HF sub-typing, e.g. with and without antecedent myocardial infarction (MI), hypertension and DM.[19–26] Despite proven validity of electronic health record (EHR) research in HF[27] for detection,[28] prognosis,[29] risk prediction[30] and burden of disease,[1] 'agnostic' approaches have not yet been used in national EHR across a wide range of RFs for incident HF, unlike genomics.[31]

For each of 92 HF RFs reported in clinical guidelines, our objectives were: (i) to classify preventive potential by associated relative risk (RR) from observational studies, and effective interventions from RCTs (for HF: RCT-HF; CVD prevention, but unknown impact on HF: RCT-CVD; or no preventive intervention: RCT-0); (ii) to develop reproducible coding and conduct a population-based, linked EHR study[32] to investigate prevalence and co-occurrence, prognosis, and preventable burden by effective treatments specific to HF and CVD prevention.

Methods

Risk factors

We extracted RFs from guidelines: (i) ESC[8]: 89 RFs for HF (online supplementary *Table S1*), and (ii) ACC/AHA[11]: 3 RFs for primary HF prevention (smoking, reduced PA and reduced cardiorespiratory fitness).

Evidence of preventive potential for 92 risk factors for heart failure

Following literature review of observational studies and RCTs, we investigated RFs by (i) level of evidence (GRADE A-D)[33] and strength of association (RR) for incident HF, and (ii) RF-specific interventions: for primary prevention of HF (RCT-HF), CVD (RCT-CVD), or no interventions (RCT-0), noting RR reduction. GRADE levels of evidence were high (A: ≥2 high-quality cohort studies with consistent results or in special cases: one large, high-quality multicentre trial), moderate (B: one high-quality cohort study and several cohort studies with some limitations), low (C: ≥1 cohort studies with severe limitations) or very low (D: expert opinion, no direct research evidence, ≥1 studies with very severe limitations).

Electronic health record cohort and study population

We used primary care EHRs in Clinical Practice Research Datalink (CPRD-GOLD), hospital admissions (Hospital Episodes Statistics, HES) and death registry (Office for National Statistics, ONS), with prospective recording and follow-up, linked by CPRD and NHS Digital using a unique national healthcare identifier.[32] MHRA (UK) Independent Scientific Advisory Committee [18_029R] approval was under Section 251 (NHS Social Care Act 2006). Eligible individuals were ≥30 years and free from HF at baseline. Patients with diagnosis of incident HF between 1 January 1997 and 1 January 2017, and ≥5 years of medical history available before HF diagnosis were included. Follow-up ceased at the date of death or on 1 January 2017. Incident HF was defined as the first coding of diagnosis after baseline (study entry) of fatal or non-fatal, hospitalized or non-hospitalized HF, identified in primary care (Read clinical terminology systems) and hospital inpatient admission (International Statistical Classification of Diseases, 10th version; ICD-10) using a validated CALIBER phenotype,[28,32] involving ICD-10 I50, I110, I130, I132, I260 codes and Read code equivalents.

Electronic health record phenotypes for 92 risk factors (14 groups) for heart failure

For each of the 92 RFs, phenotyping algorithms (code lists plus logic of how the codes are combined) are available at www.caliberresearch.org/portal (online supplementary *Appendix S1*). Where available (n = 66) we used existing EHR phenotyping algorithms. Hypertension was based on recorded values in primary care according to recent guidelines: ≥140 mmHg systolic BP (or ≥150 mmHg for people aged ≥60 years without DM and chronic kidney disease) and/or ≥90 mmHg diastolic BP.[34] DM was defined at baseline (including type: 1, 2, or uncertain) by coded diagnoses recorded in CPRD or HES at or before study entry.[35] Heavy alcohol intake was defined by most recent record of alcohol consumption in the 5 years before study entry.[36] ESC guidelines list five different IHD sub-types, not directly available in EHR. Based on clinical judgment of two cardiologists (AB and TL), we used available EHR data ('ESC' term) as follows: abnormal coronary microcirculation ('coronary artery aneurysm'), endothelial dysfunction ('vasospastic angina'), unstable angina (UA) ('myocardial stunning'), stable angina (SA) ('epicardial coronary disease') and MI ('myocardial scar'). We developed 36 new phenotypes based on available data and by clinical judgment (AB and TL), using the CALIBER approach,[32] a collaborative, iterative process involving multiple disciplines (e.g. clinicians, epidemiologists, computer scientists, public health researchers, statisticians), using Read codes (Version 2), ICD-10 coding, drugs and procedure (OPCS-4) codes. AB and TL independently agreed all EHR RF definitions and a third reviewer (HH) resolved cases of disagreement.

Follow-up

Participants who developed new-onset RFs during follow-up were analysed according to the baseline status of that RF. We considered RFs as ever (in the 5 years prior to first HF diagnosis), first ever (first RF recorded in the 5 years prior to HF diagnosis), or most recent (last RF recorded prior to or at HF diagnosis). RFs were curated as individual binary variables. Primary endpoint was 1-year all-cause mortality, defined by the record in either ONS or CPRD.

Analysis

For each of 92 RFs for incident HF, we calculated observed frequency for each RF ever in the 5 years prior to HF diagnosis. RFs were not mutually exclusive in the initial analysis, i.e. an individual patient

could have multiple RFs. These analyses were repeated by first ever and most recent RFs. For the 10 most prevalent RFs and the 14 RF groups (IHD; toxic damage; immune-mediated and inflammatory damage; infiltration; metabolic derangements; genetic abnormalities; hypertension; valve and myocardium structural defects; pericardial and endomyocardial pathologies; high output states; volume overload; tachyarrhythmias; bradyarrhythmias; primary prevention) 'ever' in the 5 years prior to HF diagnosis, baseline characteristics were compared. The 92 'ever' RFs were analysed by age at HF diagnosis. The frequency of individuals was analysed by number of risk factors. We compared the observed age- and sex-adjusted and case mix-adjusted 1-year mortality by the 12 most prevalent RFs and the 14 RF groups for HF with Kaplan–Meier estimates and Cox proportional hazards models, adjusted for age and gender. The proportional hazard assumption and model fit was examined by Schoenfeld residuals and c-index. All analyses were performed with SAS (version 9.3) and R (version 3.4.3).

Results

Review of observational evidence and randomized controlled trials

Level of evidence was A for 10/92 RFs (B: $n = 24$ and C: $n = 58$). Associations with incident HF were *very strong* (RR >3.5; $n = 4$: MI, hypertrophic cardiomyopathy, pregnancy (pre-eclampsia), and atrial arrhythmias [atrial fibrillation]); *strong* (RR 2.5–3.5; $n = 5$: hypertension, smoking, reduced cardiorespiratory fitness, connective tissue diseases and sinus node dysfunction); *moderate* (RR 1.5–2.5; $n = 15$: SA, DM, reduced PA, Conn's syndrome, phaeochromocytoma, obesity, acquired valve disease, arteriovenous fistula, severe anaemia, thyrotoxicosis, renal failure and conduction disorders); and *weak* (RR <1.5; $n = 4$: UA, alcohol, metabolic syndrome and parathyroid disorders). The remaining 64/92 RFs (including thyroid disease: 9.1%, iron deficiency: 6.1% and cytostatic drugs: 4.1%) lacked available evidence for strength of association with incident HF (*Table 1*).[13,14,37–139] Only 7/92 RFs were RCT-HF: UA, SA, MI, hypertension, cytostatic drugs, DM and renal failure. Six RFs (smoking, reduced PA, obesity, aortic valve disorders, reduced cardiorespiratory fitness and amyloidosis) were RCT-CVD.

Study population, prevalence and co-occurrence of risk factors

Using 5961 controlled clinical terminology terms, we developed phenotypes for 91/92 RFs (no codes available for cardiorespiratory fitness), including 170 885 individuals with incident HF (online supplementary *Figure S1*, online supplementary *Table S2*). Mean age at HF diagnosis was 73.7 (standard deviation [SD] 14.3) years.

Hypertension (48.5%), smoking (46.4%), SA (34.9%), obesity (29.9%), atrial arrhythmias (17.2%), UA (16.8%), cancer (16.5%), MI (15.8%), DM (15.1%), alcohol (14.9%), severe anaemia (14.3%) and thyroid disorders (9.1%) were commonest. Prevalence was <1% for 63/91 RFs and zero for 3 RFs (endomyocardial fibrosis, immunomodulating drugs and Chagas disease) (*Figure 1*, *Table 2*). 8.0% of those with incident HF had 0/91 RFs. IHD, atrial arrhythmias, hypertension, obesity, DM and cancer had >15% prevalence, among 12 commonest RFs. Bradyarrhythmias, toxic damage, genetic abnormalities and IHD were more common in males than females, unlike high output states and immune-mediated/inflammatory which were more common in females (online supplementary *Table S3*).

When RFs were analysed by age at HF diagnosis, individuals with atrial arrhythmias were oldest (mean age 80.1, SD 10 years) and with none of the 91 RFs were youngest (mean age 67.1, SD 17.1 years). Analysing 'first ever' RFs in the 5 years preceding HF diagnosis, the commonest were hypertension, smoking, SA, obesity, other cause (no history of any of the 91 RFs), heavy alcohol intake, cancer, DM, severe anaemia, atrial arrhythmias and MI. Analysing 'most recent' RFs, the commonest were smoking, hypertension, other cause, SA, atrial arrhythmias, obesity, UA, MI, cancer, severe anaemia and heavy alcohol intake (online supplementary *Figures S2* and *S3*). Among the four commonest RFs overall, for hypertension, SA and obesity, prevalence of CVD and RFs was higher in 'first ever' than 'last ever' classification, whereas for atrial arrhythmias, the opposite trend was true (online supplementary *Table S4*).

Overall, 8.0%, 14.3%, 17.2%, 16.2% and 44.3% of individuals with HF had 0, 1, 2, 3 and ≥4 RFs, respectively. Prevalence of ≥4 RFs increased with age at HF onset (1.2%, 3.0%, 5.8%, 12.9% and 20.5% for <50, 50–59, 60–69, 70–79, and ≥80 years) (online supplementary *Figure S4*). Hypertension, SA and obesity were most commonly associated with other RFs. Almost all ($n = 85$) RFs were comorbid with hypertension. For those with a RF, probability of hypertension was 53.3% (average over 85 RFs). Commonest combinations of 2, 3, 4 and 5 RFs were hypertension and smoking; hypertension, obesity and smoking; hypertension, SA, MI and smoking; and hypertension, smoking, SA, UA, and MI. For the 12 most prevalent RFs, the proportion with 0 and ≥4 RFs in addition to the named RF was 6.8% and 43.4% for hypertension, 6.5% and 46.9% for smoking. 3.6% and 57.1% for SA, 3.9% and 52.1% for obesity, 4.7% and 53.9% for atrial arrhythmias, 0.7% and 72.0% for UA, 4.5% and 54.0% for cancer, 1.0% and 65.1% for MI, 1.7% and 66.7% for DM, and 3.8% and 55.7% for heavy alcohol intake, 4.7% and 56.8% for severe anaemia, and 3.4% and 57.3% for thyroid disorders. For the same RFs, in those *without* the named RF, the proportion of individuals with 0 and ≥4 RFs was 15.5% and 28.9% for hypertension, 14.3% and 27.6% for smoking, 12.3% and 28.7% for SA, 11.4% and 33.7% for obesity, 9.7% and 38.8% for atrial arrhythmias, 9.6% and 35.9% for UA, 9.6% and 39.1% for cancer, 9.5% and 37.5% for MI, 9.4% and 37.5% for DM, and 9.4% and 39.4% for heavy alcohol intake, 9.3% and 39.7% for severe anaemia, and 8.8% and 41.4% for thyroid disorders.

Prognosis

One-year mortality was 16.7%, increasing with number of RFs (8.5%, 10.2%, 12.8%, 16.2% and 23.1% for 0, 1, 2, 3 and ≥4 RFs, respectively). For individual RFs, 1- and 5-year mortality were highest for phaeochromocytoma (73.7% and 79.0%) and lowest for pregnancy-related hormonal disorder (7.6% and 15.4%) (*Figure 2*). Among the commonest RFs, cancer (55.0%), atrial arrhythmias (53.1%) and severe anaemia (52.3%) had worst 5-year prognosis (*Figure 3*).

Table 1 ESC and ACC/AHA risk factors for heart failure: evidence from observational studies and randomized controlled trials, and prevalence in electronic health records

A. Evidence that treating the risk factors reduces risk of incident heart failure (RCT-HF)

Risk factor	Observational level of evidence according to GRADE strength of association RR (95% CI)		Randomized controlled trial treatments (incident HF as outcome) RRR (95% CI)	Diseased myocardium	Abnormal loading conditions	Arrhythmias	ACC/AHA prevention guidelines	Prevalence, *n* (%)	No. of EHR codes, *n*
Hypertension	A[37]	1.61 (1.33–1.96)	Antihypertensive 0.72 (0.67–0.78)[38]		•			82 921 (48.7)	91
Stable angina	A[37]	2.90 (1.85–4.54)	Statins 0.91 (0.84–0.98)[39] ACEI 0.77 (0.67–0.90)[40] Tight BP control 0.76 (0.67–0.86)[41]	•				59 689 (35.1)	71
Unstable angina	A[42]	1.35 (1.02–1.78)	Tight BP control 0.76 (0.67–0.86)[41] Clopidogrel 0.82 (0.69–0.98)[43] ACEI 0.85 (0.78–0.92)[44]	•				28 700 (16.9)	16
Myocardial infarction	A[45]	3.80 (2.10–6.80)	Clopidogrel 0.82 (0.69–0.98)[43] ACEI 0.85 (0.78–0.92)[44]	•				26 994 (15.9)	74
Diabetes mellitus	A[37]	1.94 (1.71–2.19)	ACEI 0.80 (0.66–0.96)[46] ARB 0.59 (0.38–0.92)[47] SGLT2 inhibitors 0.77 (0.71–0.84)[48] Tight BP control 0.44 (0.20–0.94)[49]	•				25 841 (15.2)	225
Cytostatic drugs	B[50]		Dexrazoxane 0.35 (0.27–0.45)[51] Statin 0.31 (0.13–0.77)[51] ACEI/ARB 0.11 (0.04–0.29)[51] BB 0.31 (0.16–0.63)[51]	•				7028 (4.1)	50
Renal failure	B[52]	1.94 (1.49–2.53)	ARB 0.67 (0.47–0.93)[53]		•			556 (0.33)	44

Table 1 (Continued)

B. Evidence that treating the condition reduces risk of cardiovascular disease/mortality or non-RCT evidence for heart failure risk reduction (RCT-CVD)

Risk factor	Observational level of evidence; strength of association RR (95% CI)		Randomized controlled trial treatments (incident CVD as outcome) RRR (95% CI)	Diseased myocardium	Abnormal loading conditions	Arrhythmias	ACC/AHA prevention guidelines	Prevalence, *n* (%)	No. of EHR codes, *n*
Smoking	B[14]	2.82 (1.71–4.64)	Smoking cessation 0.72 (0.57–0.90)[54]				•	79 308 (46.6)	2
Obesity	B[55]	2.12 (1.51–2.97)	Bariatric surgery 0.54 (0.36–0.82)[56,57]	•				51 068 (30.0)	2
Reduced physical activity	A[58]	1.42 (1.37–1.49)	High physical activity 0.74 (0.67–0.80)[13]				•	10 140 (5.9)	1
Aortic valve disorders	B[37]	1.74 (1.07–2.84)	Transcatheter aortic valve implantation 0.55 (0.40–0.74)[59,60]		•			5516 (3.2)	70
Amyloidosis	A[61]		Tafamidis 0.70 (0.51–0.96)[62]	•				65 (0.04)	23
Reduced cardiorespiratory fitness	B[63]	2.70 (2.50–3.57)	High fitness 0.79 (0.75–0.83)[64]				•	–	0

C. No evidence of treatment to reduce heart failure risk (RCT-0)

Risk factor	Observational level of evidence; strength of association RR (95% CI)		Randomized controlled trial treatments RRR (95% CI)	Diseased myocardium	Abnormal loading conditions	Arrhythmias	ACC/AHA prevention guidelines	Prevalence, *n* (%)	No. of EHR codes, *n*
Atrial arrhythmias	A[65]	4.62 (3.13–6.83)	–			•		29 399 (17.3)	27
Cancer	B[66,67]	1.94 (1.66–2.25)	–		•			28 164 (16.6)	1856
Heavy alcohol intake	A[68]	1.20 (1.11–1.33)	–	•				25 425 (14.9)	5
Severe anaemia	B[69]	2.24 (1.15–4.35)	–		•			24 352 (14.3)	208
Thyroid disorders	B[70]		–		•			15 473 (9.1)	150
Conduction disorders	B[71]	2.29 (1.80–2.92)	–			•		12 426 (7.3)	96
Iron deficiency	C[72]		–	•				10 148 (6.0)	22
Bacteria	B[73]		–	•				9703 (5.7)	270
Sepsis	C[74]		–		•			7703 (4.5)	58
Connective tissue diseases	C[75]	3.17 (2.63–3.83)	–	•				7486 (4.4)	111
Ventricular arrhythmias	B[76]	1.72 (1.24–2.37)	–			•		6333 (3.7)	8

Table 1 (Continued)

C. No evidence of treatment to reduce heart failure risk (RCT-0)

Risk factor	Observational level of evidence; strength of association RR (95% CI)		Randomized controlled trial treatments RRR (95% CI)	Diseased myocardium	Abnormal loading conditions	Arrhythmias	ACC/AHA prevention guidelines	Prevalence, *n* (%)	No. of EHR codes, *n*
Rheumatoid arthritis	B[77]	1.56 (1.46–1.66)	–	•				5737 (3.4)	59
Tricuspid valve disorders	B[37]	1.74 (1.07–2.84)	–		•			5618 (3.3)	57
Thyrotoxicosis	A[70]	1.94 (1.01–3.72)	–		•			3387 (2.0)	39
Fluid overload	C[78]		–		•			3081 (1.8)	4
Mitral valve disorders	B[37]	1.74 (1.07–2.84)	–		•			2552 (1.5)	68
Calcium abnormalities	B[79,80]		–	•				2524 (1.5)	91
Pericardial effusion	C[81]		–		•			1667 (0.98)	6
Sinus node dysfunction	B[45]	3.40 (1.10–10.80)	–			•		1530 (0.90)	17
Radiation	B[82–84]	2.70 (1.60–4.80)	–	•				1463 (0.86)	34
Left ventricular non-compaction	C[85]		–	•				1461 (0.86)	4
Dilated cardiomyopathy	B[86]		–	•				1395 (0.82)	3
Giant cell arteritis	C[87,88]	2.40 (0.90–6.00)	–	•				1317 (0.77)	9
Parathyroid disorders	C[89]	1.38 (1.09–1.74)	–	•				1277 (0.75)	71
Metabolic syndrome	C[90]	1.37 (1.02–1.84)	–	•				1061 (0.62)	138
Pregnancy hormonal conditions	B[91]		–	•				818 (0.48)	43
Paget's disease	C[92]		–	•				758 (0.45)	51
Pregnancy(pre-eclampsia)	A[93]	4.19 (2.09–8.38)	–		•			664 (0.39)	196
Rickettsia	C[94]		–	•				637 (0.37)	13
Sarcoidosis	C[95]		–	•				535 (0.31)	21
Antidepressant	C[50]		–	•				513 (0.30)	659
Coronary artery aneurysm	C[96]		–	•				476 (0.28)	11
Non-steroidal anti-inflammatory drugs	B[50]		–	•				459 (0.27)	4
Human immunodeficiency virus/acquired immunodeficiency syndrome	B[97,98]	2.80 (2.00–3.80)	–	•				456 (0.27)	116
Pulmonary valve disorders	B[37]	1.74 (1.07–2.84)	–		•			412 (0.24)	11

Table 1 (Continued)

C. No evidence of treatment to reduce heart failure risk (RCT-0)

Risk factor	Observational level of evidence; strength of association RR (95% CI)		Randomized controlled trial treatments RRR (95% CI)	Diseased myocardium	Abnormal loading conditions	Arrhythmias	ACC/AHA prevention guidelines	Prevalence, *n* (%)	No. of EHR codes, *n*
Malnutrition	C[99]		–	•				408 (0.24)	68
Hypertrophic cardiomyopathy	B[100]	4.31 (3.30–5.62)	–	•				322 (0.19)	5
Anabolic	C[101]		–	•				286 (0.17)	10
Arteriovenous fistula	C[102]	2.24 (1.15–4.35)	–		•			228 (0.13)	37
Phosphate disorders	C[79]		–	•				219 (0.13)	5
Lupus erythematosus	C[103]		–	•				217 (0.13)	23
Laminopathy	C[104]		–	•				214 (0.13)	18
Addison's disease	C[105]		–	•				209 (0.12)	5
Iron overload	C[106]		–	•				187(0.11)	21
Growth hormone deficiency	C[107,108]		–	•				164 (0.1)	18
Arrhythmogenic right ventricular cardiomyopathy	C[109]		–	•				135 (0.08)	2
Hypercortisolaemia	C[110]		–	•				117 (0.07)	16
Anorexia nervosa	C[111]		–	•				115 (0.07)	7
Anesthetics	B[50]		–	•				115 (0.07)	23
Phaeochromocytoma	C[112]	1.94 (1.01–3.72)	–	•				112 (0.07)	9
Haemochromatosis	C[113]		–	•				105 (0.06)	2
Congenital	C[114,115]		–		•			84 (0.05)	135
Cocaine	C[116]		–	•				62 (0.04)	62
Muscular dystrophies	C[117]		–	•				61 (0.04)	14
Constrictive pericarditis	C[118]		–		•			56 (0.03)	4
Vasospastic angina	C[119]		–	•				56 (0.03)	6
Acromegaly	C[108]		–	•				46 (0.03)	3
Conn's syndrome	B[120]	2.05 (1.11–3.78)	–	•				41 (0.02)	11
Restrictive cardiomyopathy	C[121,122]		–	•				31 (0.02)	2
Churg–Strauss	C[123]		–	•				29 (0.02)	2
Amphetamine	C[124]		–	•				25 (0.01)	25
Endocardial fibroelastosis	C[125]		–		•			16 (0.01)	5
Grave's disease	C[126]		–	•				15 (0.01)	49

Table 1 (Continued)

C. No evidence of treatment to reduce heart failure risk (RCT-0)

Risk factor	Observational level of evidence; strength of association RR (95% CI)	Randomized controlled trial treatments RRR (95% CI)	Diseased myocardium	Abnormal loading conditions	Arrhythmias	ACC/AHA prevention guidelines	Prevalence, *n* (%)	No. of EHR codes, *n*
Lead toxicity	C[127]	–	•				11 (0.01)	28
Antiarrhythmic drugs	B[50]	–	•				8 (0)	63
Copper toxicity	C[128]	–	•				7 (0)	9
Spirochaetes	C[129]	–	•				7 (0)	14
Lysosomal storage disease	C[130]	–	•				6 (0)	6
Thiamine deficiency	C[131]	–	•				5 (0)	12
Glycogen storage disease	C[132]	–	•				3 (0)	3
Selenium deficiency	C[133]	–	•				2 (0)	4
Hypereosinophilic syndrome	C[134]	–		•			2 (0)	6
Protozoa	C[135]	–	•				2 (0)	25
Cobalt toxicity	C[127]	–	•				2 (0)	1
Fungi	C[136]	–	•				1 (0)	7
L-carnitine deficiency	C[137]	–	•				1 (0)	3
Chagas disease	C[138]	–	•				0 (0)	19
Immunomodulating drugs	C[50]	–	•				0 (0)	2
Endomyocardial fibrosis	C[139]	–		•			0 (0)	5

Factors are ordered by prevalence (high to low) in the population.
CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; RR, relative risk; RRR, relative risk reduction.
Blank cells: Observational evidence – no estimate for strength of association from literature. •: Randomized evidence – no trial evidence of treatments or interventions to reduce incident HF.
GRADE level of evidence for observational evidence: A (High) – Several high-quality cohort studies with consistent results or, in special cases, one large, high-quality multicentre trial; B (Moderate) – One high-quality cohort study or several cohort studies with some limitations; C (Low) – One or more cohort studies with severe limitations; or D (Very low) – Expert opinion, no direct research evidence or one or more studies with very severe limitations.

Figure 1 Prevalence of risk factors recorded any time in the 5 years before first diagnosis of heart failure in 170 885 patients, classified by mode of action (diseased myocardium, abnormal loading, arrhythmic and other) and evidence for preventive treatment (RCT-HF, RCT-CVD, RCT-0, or 0/92 risk factors). Factors with <100 patients are excluded from this plot. ARVC, arrhythmogenic right ventricular cardiomyopathy; HIV, immunodeficiency virus; NSAID, non-steroidal anti-inflammatory drug.

Preventable burden

Among hypertensive individuals, only 51.7% were on angiotensin-converting enzyme inhibitors (ACEI) and 53.7% on calcium channel blockers. Among those with SA, 73.5% and 63.1% were on antiplatelets and statins, respectively (*Table 1*). Individuals with 0/91 RFs were younger and less likely to be on medications at HF diagnosis. Of the commonest RFs, 5/12 were RCT-HF. Of those with ≥1 RF, most had ≥1 RCT-HF or RCT-CVD (*Table 1* and online supplementary *Figure S5*). Of all new HF cases, 28.5% had no RCT-HF RFs and 38.6% had no RCT-CVD RFs. 15.6% had either no risk factor, or a risk factor without evidence of preventive potential. Individuals >80 years with 1 or 2 RFs in the 5 years prior to HF diagnosis were less likely to have ≥1 treatable RF than individuals aged <65 or 65–75 years (*Figure 4*).

Discussion

We provide the first systematic map of primary prevention opportunities across a wide range of RFs for HF, with four main findings. First, we show poor quality evidence for RCT-supported interventions to prevent HF across 92 RFs. Second, we rank order the prevalence of RFs recorded prior to the first diagnosis of HF (and therefore amenable to primary preventive efforts), of which hypertension, smoking, obesity, atrial arrhythmias, MI, DM and heavy alcohol intake are noteworthy. Third, 1- and 5-year mortality for HF was highly variable, depending on specific causes (e.g. ischaemic vs. non-ischaemic) and the number of co-occurring RFs. Fourth, the majority of individuals with HF (84.4%) had at least one RF amenable to preventive treatment in the 5 years preceding diagnosis (*Graphical Abstract*).

Trials to support preventive interventions are lacking (i.e. of 92 RFs for HF, only 7 were directly supported by RCT data). Moreover, the level of observational evidence (by GRADE criteria) is poor (i.e. of 92 RFs, levels A = 10, B = 24, C = 58), and 64/92 RFs had no available data for strength of association with incident HF. Lack of evidence limits coordinated approaches to HF prevention at individual and population levels, across research, guidelines and practice.

We provide reusable EHR definitions of each of the HF RFs (https://www.caliberresearch.org/portal). Definitions and coding have varied across different study designs (e.g. trial, cohort, EHR, registry) and settings (e.g. community, primary care, hospital), and may not be representative of the population, hampering the transferability and interoperability of definitions. Standardization of these definitions may form the basis of new classifications and sub-phenotypes, 'discovered' by machine learning and other methods. A small number of RFs (n = 12) may explain 81% of 'first' or 65% of 'most recent' HF RFs, providing focus for prevention. However, high burden of co-occurring RFs and complexity of interaction between RFs highlights the need for trials across multiple RFs.

The 14 RF groups and 92 RFs are associated with marked differences in mortality after diagnosis, with implications for early diagnosis, risk stratification, management and clinical prioritization. Number and type of comorbidities are related to mortality as per previous studies,[51,52] but neither have all RFs been studied together, nor have they been studied by different levels of classification

Table 2 Co-occurrence of the 12 most prevalent risk factors ever in the 5 years prior to incident heart failure (n = 170 885 heart failure cases)

Characteristics at time of HF diagnosis	Hypertension	Smoking	Stable angina	Obesity	Atrial arrhythmias	Unstable angina	Cancer	Myocardial infarction	Diabetes	Heavy alcohol intake	Severe anaemia	Thyroid disorders	Other risk factor	0/92 risk factors recorded
N	82 921	79 308	59 689	51 068	29 399	28 700	28 164	26 994	25 841	25 425	24 352	15 473	4331	13 661
RCT evidence for preventive treatment														
RCT-HF	82 921 (100)	63 529 (80.1)	59 689 (100)	42 442 (83.1)	23 392 (79.6)	28 700 (100)	22 623 (80.3)	26 994 (100)	25 841 (100)	20 624 (81.1)	18 944 (77.8)	12 223 (79)	218 (5)	0 (0)
RCT-CVD	59 938 (72.3)	79 308 (100)	40 080 (67.1)	51 068 (100)	19 341 (65.8)	20 739 (72.3)	18 608 (66.1)	18 694 (69.3)	21 697 (84)	19 925 (78.4)	15 752 (64.7)	10 430 (67.4)	785 (18.1)	0 (0)
RCT-0	58 408 (70.4)	55 671 (70.2)	43 465 (72.8)	35 687 (69.9)	29 399 (100)	22 109 (77)	28 164 (100)	19 269 (71.4)	19 479 (75.4)	25 425 (100)	24 352 (100)	15 473 (100)	3678 (84.9)	0 (0)
Demographics														
Age (years)	75.2 (13.1)	73.3 (13.7)	77.1 (11.1)	71.6 (13.4)	80.1 (10)	77.9 (10.9)	80 (10.4)	76.5 (11.3)	75.6 (11.2)	74 (13.6)	78.1 (13.1)	77.9 (12.2)	71.2 (16.8)	67.1 (17.1)
Women	41 001 (49.4)	32 564 (41.1)	25 111 (42.1)	26 107 (51.1)	14 371 (48.9)	12 625 (44)	13 758 (48.8)	9542 (35.3)	11 608 (44.9)	10 175 (40)	15 473 (63.5)	11 985 (77.5)	2718 (62.8)	6818 (49.9)
Cardiovascular diseases														
Stable angina	29 809 (35.9)	31 366 (39.5)	**59 689 (100)**	19 760 (38.7)	12 662 (43.1)	25 114 (87.5)	10 937 (38.8)	23 555 (87.3)	12 682 (49.1)	10 420 (41)	9881 (40.6)	6052 (39.1)	0 (0)	0 (0)
Atrial arrhythmias	15 952 (19.2)	14 793 (18.7)	12 662 (21.2)	9314 (18.2)	**29 399 (100)**	6073 (21.2)	6630 (23.5)	5100 (18.9)	5054 (19.6)	5066 (19.9)	5359 (22)	3646 (23.6)	0 (0)	0 (0)
Unstable angina	15 410 (18.6)	16 336 (20.6)	25 114 (42.1)	10 724 (21)	6073 (20.7)	**28 700 (100)**	5649 (20.1)	12 072 (44.7)	6827 (26.4)	5458 (21.5)	5348 (22)	3162 (20.4)	0 (0)	0 (0)
Myocardial infarction	13 543 (16.3)	15 387 (19.4)	23 555 (39.5)	8715 (17.1)	5100 (17.3)	12 072 (42.1)	4977 (17.7)	**26 994 (100)**	5992 (23.2)	4898 (19.3)	4200 (17.2)	2562 (16.6)	0 (0)	0 (0)
Conduction disorders	6703 (8.1)	6472 (8.2)	7300 (12.2)	3900 (7.6)	4403 (15)	4244 (14.8)	2860 (10.2)	3465 (12.8)	2386 (9.2)	2450 (9.6)	2272 (9.3)	1530 (9.9)	416 (9.6)	0 (0)
Cardiovascular risk factors														
Hypertension	**82 921 (100)**	46 894 (59.1)	29 809 (49.9)	30 720 (60.2)	15 952 (54.3)	15 410 (53.7)	15 571 (55.3)	13 543 (50.2)	15 009 (58.1)	15 619 (61.4)	12 408 (51)	8519 (55.1)	0 (0)	0 (0)
Smoking	46 894 (56.6)	**79 308 (100)**	31 366 (52.5)	30 203 (59.1)	14 793 (50.3)	16 336 (56.9)	14 736 (52.3)	15 387 (57)	16 118 (62.4)	16 624 (65.4)	11 591 (47.6)	7562 (48.9)	0 (0)	0 (0)
Obesity	30 720 (37)	30 203 (38.1)	19 760 (33.1)	**51 068 (100)**	9314 (31.7)	10 724 (37.4)	8402 (29.8)	8715 (32.3)	15 578 (60.3)	9721 (38.2)	7790 (32)	5885 (38)	0 (0)	0 (0)
Cancer	15 571 (18.8)	14 736 (18.6)	10 937 (18.3)	8402 (16.5)	6630 (22.6)	5649 (19.7)	**28 164 (100)**	4977 (18.4)	4785 (18.5)	5083 (20)	5588 (22.9)	2899 (18.7)	0 (0)	0 (0)
Diabetes mellitus	15 009 (18.1)	16 118 (20.3)	12 682 (21.2)	15 578 (30.5)	5054 (17.2)	6827 (23.8)	4785 (17)	5992 (22.2)	**25 841 (100)**	5033 (19.8)	5307 (21.8)	3026 (19.6)	0 (0)	0 (0)
Heavy alcohol intake	15 619 (18.8)	16 624 (21)	10 420 (17.5)	9721 (19)	5066 (17.2)	5458 (19)	5083 (18)	4898 (18.1)	5033 (19.5)	**25 425 (100)**	3438 (14.1)	2374 (15.3)	0 (0)	0 (0)
Severe anaemia	12 408 (15)	11 591 (14.6)	9881 (16.6)	7790 (15.3)	5359 (18.2)	5348 (18.6)	5588 (19.8)	4200 (15.6)	5307 (20.5)	3438 (13.5)	**24 352 (100)**	3618 (23.4)	0 (0)	0 (0)
Thyroid disorders	8519 (10.3)	7562 (9.5)	6052 (10.1)	5885 (11.5)	3646 (12.4)	3162 (11)	2899 (10.3)	2562 (9.5)	3026 (11.7)	2374 (9.3)	3618 (14.9)	**15 473 (100)**	0 (0)	0 (0)
Sepsis	4471 (5.4)	4353 (5.5)	3129 (5.2)	3012 (5.9)	1476 (5)	1724 (6)	1918 (6.8)	1467 (5.4)	1942 (7.5)	1371 (5.4)	1654 (6.8)	844 (5.5)	383 (8.8)	0 (0)
Medication														
Antiplatelet	44 857 (54.1)	44 219 (55.8)	43 882 (73.5)	28 296 (55.4)	20 450 (69.6)	23 414 (81.6)	16 371 (58.1)	21 630 (80.1)	18 724 (72.5)	14 422 (56.7)	14 378 (59)	8922 (57.7)	793 (18.3)	1678 (12.3)

Table 2 (Continued)

Characteristics at time of HF diagnosis	Hypertension	Smoking	Stable angina	Obesity	Atrial arrhythmias	Unstable angina	Cancer	Myocardial infarction	Diabetes	Heavy alcohol intake	Severe anaemia	Thyroid disorders	Other risk factor	0/92 risk factors recorded
Statin	41 279 (49.8)	42 231 (53.2)	37 653 (63.1)	28 771 (56.3)	14 442 (49.1)	20 858 (72.7)	13 212 (46.9)	19 022 (70.5)	20 049 (77.6)	13 961 (54.9)	11 466 (47.1)	7677 (49.6)	319 (7.4)	599 (4.4)
Warfarin	15 304 (18.5)	14 328 (18.1)	13 336 (22.3)	9464 (18.5)	20 049 (68.2)	6342 (22.1)	6570 (23.3)	5467 (20.3)	5344 (20.7)	4881 (19.2)	5378 (22.1)	3522 (22.8)	267 (6.2)	409 (3)
Beta-blocker	38 242 (46.1)	36 276 (45.7)	33 334 (55.8)	25 275 (49.5)	17 240 (58.6)	18 339 (63.9)	13 241 (47)	16 430 (60.9)	13 579 (52.5)	12 255 (48.2)	11 362 (46.7)	7458 (48.2)	785 (18.1)	1814 (13.3)
CCB	44 505 (53.7)	42 203 (53.2)	37 242 (62.4)	29 956 (58.7)	17 030 (57.9)	20 649 (71.9)	15 208 (54)	16 920 (62.7)	17 608 (68.1)	14 253 (56.1)	13 581 (55.8)	8508 (55)	822 (19)	1760 (12.9)
ACEI	42 843 (51.7)	40 964 (51.7)	34 891 (58.5)	29 980 (58.7)	17 644 (60)	17 991 (62.7)	14 431 (51.2)	17 640 (65.3)	19 567 (75.7)	13 647 (53.7)	13 250 (54.4)	8101 (52.4)	766 (17.7)	1673 (12.2)
ARB	14 595 (17.6)	13 395 (16.9)	10 857 (18.2)	10 917 (21.4)	5867 (20)	6034 (21)	5086 (18.1)	5112 (18.9)	6891 (26.7)	4764 (18.7)	4808 (19.7)	3143 (20.3)	214 (4.9)	367 (2.7)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; CVD, cardiovascular disease; HF, heart failure.
Other aetiologic factor – Patients with a risk factor not in the top 12. No recognized risk factor – No history of any of the 91 risk factors in the 5 years preceding incident HF.

(ESC in this case), nor over the long term (20 years).[53–55,58] For example, in our study, individuals with abnormal loading had worse outcomes than those with arrhythmias and diseased myocardium, and those with IHD had worse outcomes than hypertension. Our observations may inform future studies of long-term HF pathophysiology by RF clustering.[56] One-year mortality rates are comparable to acute HF, but higher than rates for chronic HF,[53] probably reflecting the mixed acute and chronic HF study population.

A total of 44.3% of those with HF had ≥4 RFs in the prior 5 years, suggesting major preventive potential. Of all new HF cases, 71.5% had ≥1 of the 7 RCT-HF RFs; 12.9% had ≥1 RCT-CVD RF. By the leading 12 RFs, or by the 14 RF categories, 78%–100% of individuals had ≥1 RCT-HF RF, and 65%–100% had ≥1 RCT-CVD RF. Most incident HF occurs in presence of hypertension, DM and IHD, highlighting need for primordial prevention. In those without the leading 12 RFs, only 5% had ≥1 RCT-HF RF, 18.1% had ≥1 RCT-CVD RF and 84.1% had ≥1 RCT-0 RF.

Strengths and limitations

The key strength of this analysis is to provide a systematic map: RFs for HF have often been studied in isolation,[44,45] restricted populations,[46,47] or specific sub-populations.[48] Associations between RFs, incidence[22,49] and prognosis[50] (including adjustment for comorbidities[47]) have been investigated, but not across all possible causal RFs. We used national, representative, linked EHRs and the most comprehensive list of causes for HF, maximizing the external validity of our findings. Incident cases of HF were considered to study causal RFs, and our inclusion criteria enabled the investigation of RFs over a 5-year period prior to diagnosis.

There are inherent limitations. First, there is no ICD-10 code distinguishing 'systolic versus diastolic', 'acute versus chronic', 'HF with reduced ejection fraction versus HF with preserved ejection fraction', and more recent introduction of a new category of 'HF with mid-range ejection fraction"[29] (terms to denote these distinctions do however exist in ICD-9-CM and ICD-10-CM which are not used in the UK healthcare system). Furthermore, we lacked echocardiographic data as these events rarely get recorded in structured EHRs using ontologies and unstructured data (e.g. clinical text and narrative as not available for research). Second, the validity of the 91 RF phenotypes, while well-established for some (e.g. hypertension, diabetes, obesity, smoking, heavy alcohol), is not known for the new phenotypes. Coding validity is through the use of comprehensive coding lists across linked EHR data, with review by two cardiologists, and prognosis lends some validity. Third, RFs were analysed by 'ever', 'first ever' and 'last ever' but neither every permutation and combination nor duration of RFs could be investigated. Therefore, we concentrated on the most common RFs for secondary analyses.

Research implications

First, our findings outline the need for RCTs that examine single and multiple RFs in HF prevention to establish causal inference, and methods such as trial emulation, may have a role where

Figure 2 Five-year all-cause mortality from time of incident heart failure diagnosis by risk factors ($n = 89$) in 170 855 individuals with incident heart failure. ARVC, arrhythmogenic right ventricular cardiomyopathy; HIV, immunodeficiency virus; NSAID, non-steroidal anti-inflammatory drug

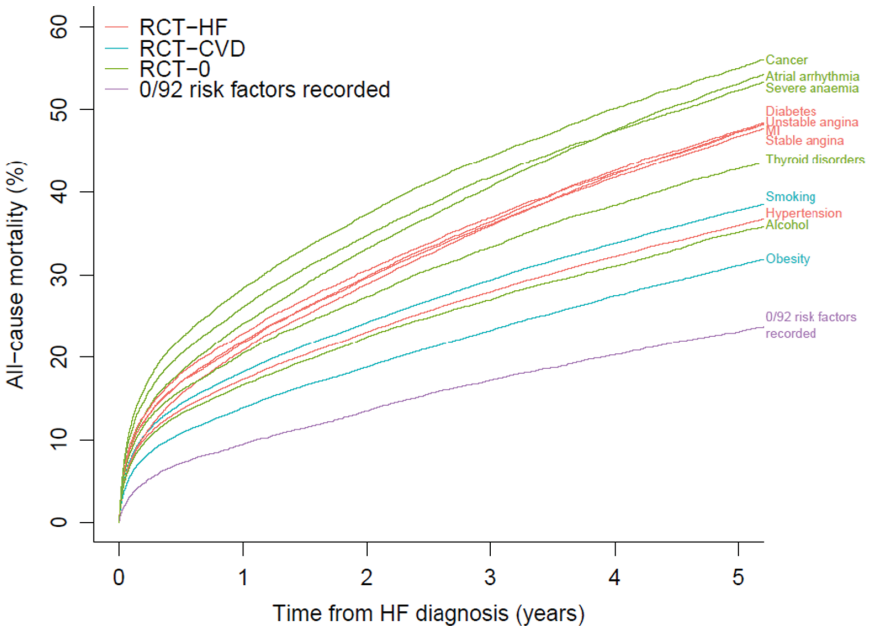


Figure 3 Five-year mortality in patients with incident heart failure (HF) ($n = 170\,885$) by the 12 most common risk factors at any time in the preceding 5 years. MI, myocardial infarction.

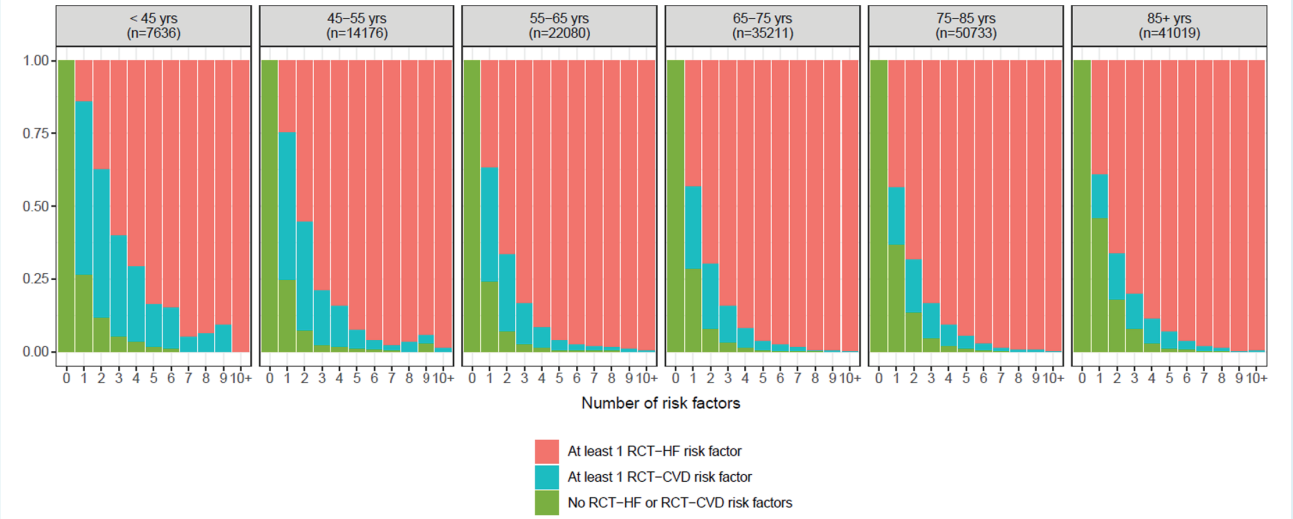


Figure 4 Number of risk factors co-occurring in patients and proportion of patients with at least one risk factor treatable for heart failure prevention or cardiovascular disease prevention, stratified by age group (n = 170 855).

RCTs are unlikely. Second, machine learning may inform distribution and trajectories of HF by different RF combinations, as well as the impact of longitudinal changes in RFs over time. Third, EHR approaches can be used to define HF subtypes and inform genome-wide approaches, which have led to novel biologic[39] but not translational[40] insights for prevention, to date. Fourth, prevention strategies may require modification, based on varying prevalence of HF RFs,[3] and primary versus secondary prevention. Fifth, novel HF prediction models should account for the interplay of the number and type of RFs, where existing risk prediction models for incident HF have only modest discrimination, partly due to lack of external validation, but also incomplete knowledge of HF causes and classification.[46,57]

Clinical implications

Our results have three clinical implications. First, clinician recording and use of better data in EHR is central to understanding and improving HF prevention. Second, in individuals with new and existing HF, RFs by RCT-HF (hypertension, DM and IHD) and RCT-CVD (e.g. smoking, obesity) should be excluded through history, examination and/or investigation and monitored at follow-up, so that evidence-based preventive interventions can be initiated and optimized. Third, HF exemplifies co-occurrence of RFs and multi-morbidity. There are joint clinical guidelines for DM and CVD but more 'joined-up' and 'cross-disease' thinking is required to emphasize and up-titrate existing treatments in the highest-risk individuals.

Conclusion

In the first systematic and comprehensive map of 92 RFs for HF, showing that 44.3% of individuals with HF had ≥4 RFs recorded by the time of diagnosis, and only 8.0% had no coded RF. EHRs can be used to study the whole spectrum of causes of HF and should be used to inform future strategies for primary prevention research, diagnostic work-up of individuals with HF as well as treatment of those at highest risk of HF.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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References 31–139 are in 'Supplemental References' in online supplementary material.