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ORIGINAL ARTICLE

Development of a tool to predict the risk of incident heart failure in a general population: the HUNT for HF risk score

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Abstract

Aims Currently, no incident heart failure (HF) risk score that is in regular use in a general population is available. We aimed to develop this and compare with existing HF risk scores.

Methods and results Participants in the third wave (2006–08) of the population-based Trøndelag Health Study 3 (HUNT3) were included if they reported no previous HF. Any hospital diagnoses captured during follow-up (until the end of 2018) of HF, cardiomyopathy, or hypertensive heart disease were assessed by an experienced cardiologist. Valid HF events were defined as symptoms/signs of HF and objective evidence of structural/functional abnormality of the heart at rest. The model was compared with slightly modified HF risk scores (the Health Aging and Body Composition HF risk score, the Framingham HF risk score, the Pooled Cohort equations to Prevent HF risk score, and NORRISK 2). Among 36 511 participants (mean ± SD age of 57.9 ± 13.3 years, 55.4% female), with a mean follow-up of 10.2 ± 1.3 years, 1366 developed HF (incidence rate of 3.66 per 1000 participant years). Out of the 38 relevant clinical variables assessed, we identified 12 (atrial fibrillation being the strongest) that independently predicted an HF event. The final model demonstrated good discrimination (C statistics = 0.904) and calibration, was stable in internal validation, and performed well compared with existing risk scores. The model identified that, at enrolment, 31 391 (86%), 2386 (7%), 1246 (3%), and 1488 (4%) had low, low-intermediate, high-intermediate, and high 10-year HF risk, respectively.

Conclusions Twelve clinical variables independently predicted 10-year HF risk. The model may serve well as the foundation of a practical, online risk score for HF in general practice.

Trial Registration: ClinicalTrials.gov Identifier: NCT04648852.

Keywords Heart failure; Risk score; Epidemiology; General population

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Introduction

Heart failure (HF) is a global pandemic affecting more than 26 million people worldwide[1] and approximately 1–2% of the adult population in developed countries. The prevalence of HF increases with age and in co-morbidities such as hypertension, obesity, and type 2 diabetes mellitus (T2DM).[2] Given the diabetes and obesity epidemic as well as the aging of the population we are currently facing, the prevalence of HF has been suggested to increase dramatically over the next decades.[3] Despite improved survival during the last two to three decades, presumably due to

improved evidence-based treatment,[4] the general prognosis in advanced HF is poor as evidenced by repeated hospitalizations and a 5 year mortality rate of approximately 50%.[5,6] Due to the high burden of the disease in terms of morbidity, mortality, and health care costs, focus on the prevention of HF is important, as acknowledged by international HF guidelines.[2]

Whereas validated risk stratification tools for the risk of cardiovascular events are implemented in routine clinical care, no validated risk score for incident HF is currently routinely used in clinical settings.[7] Some HF risk scores have been developed and validated, but they are often derived from non-generalizable populations such as elderly,[8] or a high-risk population with coronary heart disease, hypertension, or valvular disease,[9] and are not suitable for application in a general practice setting. The Pooled Cohort equations to Prevent HF (PCP-HF) risk score was developed in a pooled sample of several population-based, smaller, multi-ethnic cohorts from the United States and may not be applicable across other regions.[10]

The aim of the current study was to generate a risk score to predict 10 year risk of incident HF by using readily available data, routinely recorded in primary clinical care, collected in a large, population-based sample. Furthermore, we aimed to compare this new HF risk score with existing HF risk scores[8,10] and with an established risk score for cardiovascular events[11] given the large overlap of traditional risk factors for HF and cardiovascular events. Finally, we assessed the mortality risk according to the risk categories as defined by the new risk score.

Methods

Study design and population

The Trøndelag Health Study 3 (HUNT3) was the third wave of the original HUNT study,[12] a population-based, multi-purpose health study in Nord-Trøndelag county in Central Norway. All residents 20 years or older were invited to a screening visit between September 2006 and June 2008. A total of 50 807 participants (54.1% of all invited) responded to a comprehensive health and lifestyle questionnaire and underwent a general health examination. Details on data collection and the cohort profile of the HUNT study have been published previously.[12] In the current analyses, we only included the participants in HUNT3 who also participated in the second wave of the HUNT study (HUNT2) 10 years earlier. Moreover, we excluded participants with a self-reported history of HF at baseline (date of investigation in HUNT3) or a valid HF event prior to baseline. Importantly, emigration from this area is low (historically $<3\%$).

Predictors of heart failure

A clinical examination was conducted by trained study personnel. Height and weight were measured barefoot and wearing light clothing; height was measured to the nearest centimetres and weight to the nearest 0.5 kg. Body mass index (BMI) was calculated as body weight in kilograms divided by the squared value of height in metres. Systolic and diastolic blood pressure (BP) was measured three times using a Dinamap 845XT (GE Healthcare, Milwaukee, WI, USA). Measurements were made after 2 min of rest with the arm on a table, and the mean of the two last measurements was used. The waist circumference was measured horizontally at the height of the umbilicus, and the hip circumference was measured at the thickest part of the hip. Non-fasting blood samples were analysed for glucose, creatinine, triglycerides, high-density lipoprotein cholesterol (HDL-C), and total cholesterol.[13] Estimated glomerular filtration rate (eGFR) was calculated by the Modification of Diet in Renal Disease (MDRD) study formula.[14] Self-reported data obtained at baseline included smoking status (never, former, or current), alcohol consumption (abstainers, light drinkers, moderate drinkers, or heavy drinkers), use of chewing tobacco (never, former, or current), physical activity (do you have at least 30 min of physical activity daily at work or in your leisure time, yes/no), and marital status (single, widowed, married/co-habitant, or divorced/separated). Information on common chronic disorders was self-reported and included history of angina pectoris, myocardial infarction (MI), stroke, diabetes, asthma, chronic bronchitis, emphysema, or chronic obstructive pulmonary disease (COPD), chronic kidney disease, rheumatoid arthritis, ankylosing spondylitis, and sleep apnoea. Other self-reported data included the use of anti-hypertensive medication and previous MI in first degree relative before the age of 60 years. History of atrial fibrillation (AF) was defined as either self-reported AF at baseline or a discharge diagnosis of AF in the hospital records prior to baseline. These results were cross-checked against results from a subset (n = 16 247) of the study population that had all AF events validated,[15] and those events that were judged as 'no AF' were set as 'no AF' also for the predictor variable. In sensitivity analyses, we excluded AF that had occurred <3 and <12 months prior to baseline.

Outcomes and validation of outcomes

The primary outcome in our analyses was time to a first HF event. In Nord-Trøndelag county, there are just two county hospitals from which we had access to full medical records including any information from the collaborating university hospital in Central Norway. By linkage to electronic medical records from the two county hospitals, we extracted data on all participants with an HF diagnosis by the International

Classification of Diseases (ICD)-10 (ICD-9) codes I50 (428) HF, I42 (425) cardiomyopathy, and I11 (402) hypertension with HF, listed in any position (i.e. as primary or subsequent diagnosis), from inpatient and outpatient visits, from October 2006 to December 2018. One experienced cardiologist critically reviewed all patient records and available information and classified events as a valid HF event, unlikely HF event, or uncertain HF event due to lacking information, according to the 2016 European Society of Cardiology (ESC) HF guidelines.[16] In cases where the first event was unlikely or uncertain, subsequent events were judged for valid HF. The term uncertain HF was used in cases where HF was likely but the criteria were not fulfilled based on the available information. Events that were judged to be either valid or uncertain were included as valid HF events in the current analysis.

Informed consent and ethics

All participants in HUNT3 gave written informed consent, and the study was approved by the Regional Committee for Medical and Health Research Ethics and by the Norwegian Data Inspectorate. The present study and protocol were approved by the Regional Committee for Medical and Health Research Ethics in 2018.

Statistics

Baseline characteristics of patients with and without a valid HF diagnosis during follow-up are presented as mean [standard deviation (SD)] or proportion, as appropriate, and were compared using the Student's *t*-tests for continuous variables and χ^2 tests for categorical data. We used univariable Cox regression analyses to assess potential predictors. The variable (or two variables in three cases) from each clinical or demographic category that had the best predictive ability of the outcome was included in the full multivariable model to avoid multicollinearity. Subsequently, a manual backward stepwise elimination procedure with evaluation of the Akaike information criterion at each step was performed. The significance level was set to 5%. The most important predictor variables were determined according to their test statistic (z statistic) in the multivariable model. In addition, we explored non-linearity for the association of continuous variables with incident HF using multivariable fractional polynomial models. After the backward selection, any covariates that were not originally included in the multivariable model were added back into the model, one at a time.

Interaction effects between covariates were checked by including product terms, one at a time, into the models.[3] Only clinically meaningful, significant interactions (P-value < 0.001) were considered for inclusion in the multivariable models.

The essential check of the proportional hazard assumptions was investigated by plotting the logarithm of the integrated hazards (log–log survival plots) and by the Schoenfeld tests.

We assessed the predictive accuracy of the models by calibration and discrimination. Calibration was evaluated by comparing observed vs. predicted probabilities of incident HF. This was done by comparing probabilities across deciles of risk and by plotted smoothed calibration plots. In a plot of observed vs. predicted probabilities, perfect calibration will be on the 45° line. Discrimination, which measures the model's ability to differentiate between those who experienced the outcome of interest and those who did not, was evaluated by Harrell's c-index. If the c-index is >0.7, it can be concluded that the model has an acceptable discriminatory capability.[17] As a sensitivity analysis, we repeated the analyses excluding participants who reported a history of MI, angina, or stroke at inclusion.

Internal validation of the prediction model was evaluated by bootstrapping where samples were drawn with replacement from the original sample until we had a new sample of the same size. To obtain stable estimates, 200 bootstrap samples were drawn. In each bootstrap sample, we developed a model using the exact same modelling approach as in the original sample. The performance of each of the bootstrap sample-derived models was evaluated in the bootstrap sample and in the original sample. Then the optimism, which is the decrease between model performance (i.e. c-index) in the bootstrap sample and that in the original sample, was calculated by the difference between average measure of performance in the bootstrap sample and the performance measure in the original sample. Subsequently, this optimism measure ('shrinkage factor') could be used to adjust the original model for over-fitting if necessary. We validated both the c-index and the slope of the linear predictor of performance of the model. Further, predicted incident HF risk was calculated and stratified into four risk groups (10 year risk) using the following cut-offs: low risk ($<5\%$), low-intermediate risk (5–$<10\%$), high-intermediate risk (10–20%), and high risk ($>20\%$).

The comparison of the new HF risk score with the Health Aging and Body Composition (Health ABC) HF risk score, the Framingham HF risk score, the PCP-HF risk score, and NORRISK 2 was performed by calculation of the prognostic index (PI) of the models, that is, the weighted sum of the covariates in each risk score (the weights are the regression coefficients). Comparisons of the scores were evaluated by calibration and discrimination, as described above.

As a sensitivity analysis to assess the robustness of the data, we applied multiple imputation under the assumption of missing at random. All available data were used (e.g. predictors, outcome status, and follow-up time) to generate 25 imputed datasets using the multiple imputation chained procedure in STATA. The prediction modelling analyses were

repeated in the 25 imputed datasets and results were pooled using Rubin's rules. All analyses were performed using STATA Version 17 (StataCorp LP, College Station, TX, USA). The data management was done using IBM SPSS Statistics Version 27.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

A total of 36 511 people were included in the study. During a mean follow-up time of 10.2 ± 1.3 years, contributing a total of 372 776.2 individuals' years at risk, there were 1366 incident HF cases (648 in women and 718 in men). This yielded an overall incidence rate of 3.66 per 1000 participant years: 3.12 per 1000 participant years in women and 4.35 per 1000 participant years in men.

Baseline characteristics of all participants as well as in those who experienced a valid HF event during follow-up (n = 1366) and in participants who did not (n = 35 145) are shown in *Table 1*. Participants who experienced an HF event were older (74 vs. 57 years) and had higher mean systolic BP (142 vs. 133 mmHg), lower mean eGFR (79 vs. 95 mL/min/1.73 m^2), a worse metabolic profile with higher BMI (28.2 vs. 27.4 kg/m^2), and lower HDL-C (1.3 vs. 1.4 mmol/L). Furthermore, among participants with an HF event, more had co-morbidities such as prior MI or angina (27.9% vs. 5.7%), diabetes (15.6% vs. 4.5%), stroke (8.9% vs. 2.8%), and COPD

Table 1 Baseline characteristics in the overall population and in those who experience a heart failure event during follow-up and those who do not

		No HF diagnosis during follow-up (N = 35 145)		HF diagnosis during follow-up (N = 1366)	
	All (n = 36 511)		N with measured variable		N with measured variable
Age, years	57.9 ± 13.3	57.3 ± 13.0	35 145	74.1 ± 9.4	1366
Male sex, n (%)	16 273 (44.6)	15 555 (44.3)	35 145	718 (52.6)	1366
BMI, kg/m^2	27.4 ± 4.3	27.4 ± 4.3	34 932	28.2 ± 4.6	1344
Waist–hip ratio	0.91 ± 0.08	0.91 ± 0.08	34 937	0.94 ± 0.08	1355
Systolic BP[a], mmHg	133 ± 19	133 ± 19	34 925	142 ± 22	1351
Diastolic BP[a], mmHg	75 ± 11	75 ± 11	34 922	74 ± 12	1351
Use of anti-hypertensive medication, n (%)	9606 (26.3)	8780 (25.0)	35 139	826 (60.5)	1366
Self-reported diabetes[b], n (%)	1807 (5.0)	1594 (4.5)	35 132	213 (15.6)	1365
eGFR, mL/min/1.73 m^2	94.3 ± 23.5	94.9 ± 23.2	34 732	79.1 ± 24.1	1351
Cholesterol, mmol/L	5.6 ± 1.1	5.6 ± 1.1	34 297	5.4 ± 1.2	1337
HDL, mmol/L	1.4 ± 0.4	1.4 ± 0.4	34 296	1.3 ± 0.4	1337
Current smoking, n (%)	8191 (23.2)	7904 (23.2)	34 097	287 (22.3)	1286
Alcohol consumption[c], n (%)			34 131		1278
Never	3259 (8.9)	3012 (8.8)		247 (19.3)	
Light	11 161 (30.6)	10 644 (31.2)		517 (40.5)	
Moderate	20 066 (55.0)	19 590 (57.4)		476 (37.3)	
Heavy	923 (2.5)	885 (2.6)		38 (3.0)	
Marital status, n (%)			35 133		1366
Single	5195 (14.2)	5097 (14.5)			98 (7.2)
Widowed	3667 (10.1)	3262 (9.3)			405 (29.7)
Divorced/separated	3624 (9.9)	3542 (10.1)			82 (6.0)
Co-habitant/married	24 013 (65.8)	23 232 (66.1)			781 (57.2)
Self-reported history of myocardial infarction or angina pectoris, n (%)	2397 (6.6)	2016 (5.7)	35 139	381 (27.9)	1366
Known AF[d], n (%)	3276 (9.0)	2551 (7.3)	35 145	725 (53.1)	1366
Self-reported history of COPD/emphysema/bronchitis, n (%)	1306 (3.6)	1196 (3.4)	35 130	110 (8.1)	1365
Self-reported rheumatoid arthritis, n (%)	1455 (4.1)	1336 (3.9)	33 884	119 (9.3)	1274
30 min daily physical activity, n (%)	27 715 (76.0)	26 788 (76.3)	35 100	927 (68.0)	1364
Myocardial infarction in first degree relative before 60 years of age, n (%)	7571 (21.7)	7239 (21.5)	33 673	332 (26.3)	1261
Self-reported history of cerebral stroke/haemorrhage, n (%)	1113 (3.1)	992 (2.8)	35 138	121 (8.9)	1366

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate.
from independent t-test or χ^2 as appropriate.
[a]Mean of the second and third measurements.
[b]Self-reported in HUNT3.
[c]Never = never drunk alcohol or not the last year, light = one to a few times per month the last year, moderate = from two times per month to three times per week the last year, heavy = four to seven times per week the last year.
[d]Either self-reported AF in HUNT3 or validated AF from Malmo or a discharge diagnosis of AF prior to the HF diagnosis.

(8.1% vs. 3.4%). Strikingly, whereas 53.1% among those with an HF event had known AF, only 7.3% among those without an HF event had this condition. During follow-up, 1281 people died, yielding an overall mortality rate of 3.39 per 1000 person years, 2.74 in women vs. 4.21 in men per 1000 person years.

Independent predictors of HF

A total of 38 variables were tested, and the following variables (one, or two in three cases, from each category) were candidates for the multivariable Cox regression model: age, sex, BMI, systolic BP, use of anti-hypertensive medication, self-reported diabetes mellitus, eGFR, current smoking, alcohol use, marital status, self-reported MI or angina, AF, self-reported COPD, self-reported rheumatoid arthritis, daily physical activity of more than 30 min, and MI in first degree relative before 60 years of age (*Table 2*). The remaining variables tested (including lipids, chewing tobacco, sleep apnoea, asthma, and diastolic BP) were either not significantly associated with the outcome or judged less clinically relevant than the other variable(s) from the same clinical or demographic category and hence not included in subsequent testing.

Table 3 shows the final 12 variables that were independently and significantly associated with incident HF. AF was identified as the strongest predictor associated with higher risk of incident HF [hazard ratio (HR) 5.69, 95% confidence interval (CI) 5.03–6.43]. The results did not change when we excluded AF that had occurred <3 and <12 months prior to baseline. Elderly participants and participants with self-reported diabetes mellitus, with MI in first degree relative before 60 years of age, and who were smokers also had higher risk of incident HF. eGFR was inversely associated with the risk of incident HF event. Investigation of non-linearity for the continuous variables with multivariable fractional polynomial functions showed significant non-linear relationship for age, BMI, and eGFR. The transformations for these variables are given in *Table 3*. The only significant interaction was between age and self-reported AF ($P < 0.001$). However, this interaction was not included in the final model. The model for

Table 2 Univariable analyses of tested predictors (one from each category and two in three cases) of a heart failure event during 10 years of follow-up

	HR (95% CI)	*P*-value
Age, 5 year increase	1.71 (1.67–1.75)	<0.0001
Male sex	1.39 (1.25–1.55)	<0.0001
Adiposity		
BMI, kg/m^2	1.04 (1.03–1.06)	<0.0001
Cardiac disease		
History of MI or angina	6.18 (5.49–6.95)	<0.0001
History of known AF	14.56 (13.09–16.20)	<0.0001
Haemodynamic markers		
Use of BP medications	4.52 (4.05–5.04)	<0.0001
Systolic BP, 10 mmHg increase	1.24 (1.21–1.27)	<0.0001
Diabetes		
History of diabetes	3.79 (3.27–4.38)	<0.0001
Kidney function/disease		
eGFR, 1 mL/min/1.73 m^2 increase	0.97 (0.96–0.97)	<0.0001
Rheumatic disease		
History of rheumatoid arthritis	2.47 (2.04–2.98)	<0.0001
Respiratory disease		
History of COPD	2.47 (2.03–3.00)	<0.0001
Cerebrovascular disease		
History of stroke	3.36 (2.79–4.05)	<0.0001
Use of nicotine		
Current smoking	0.95 (0.83–1.08)	0.453
Alcohol consumption		
No	1	
Light	0.59 (0.50–0.68)	<0.0001
Moderate	0.30 (0.26–0.35)	<0.0001
Heavy	0.53 (0.38–0.74)	<0.0001
Marital status		
Single	1	
Widowed	6.35 (5.09–7.92)	<0.0001
Divorced/separated	1.21 (0.90–1.62)	0.205
Co-habitant/married	1.75 (1.42–2.15)	<0.0001
Physical activity		
30 min daily activity	0.65 (0.58–0.73)	<0.0001
Family history of coronary heart disease		
Myocardial infarction in 1st degree relatives	1.30 (1.15–1.47)	<0.0001

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction.

Table 3 Independent predictors of incident heart failure events (the final model, complete case analysis)

	HR	95% CI	z	*P*-value
Age_1 for 10 year increase	1.06	1.04–1.07	9.29	<0.001
Age_2 for 10 year increase	0.98	0.97–0.98	−8.42	<0.001
Male sex	1.26	1.12–1.42	3.78	<0.001
BMI (kg/m^2) for 10 unit increase	1.01	1.01–1.02	4.56	<0.001
Use of BP medication	1.26	1.11–1.44	3.54	<0.001
Systolic BP for 10 mmHg increase	1.03	1.01–1.06	2.33	0.020
Self-reported diabetes	2.03	1.73–2.38	8.68	<0.001
eGFR (mL/min/1.73 m^2) for 100 unit increase	1.29	1.18–1.41	5.51	<0.001
Self-reported rheumatoid arthritis	1.30	1.06–1.59	2.55	0.011
Current smoker	1.60	1.39–1.84	6.62	<0.001
Self-reported MI or angina	1.69	1.47–1.94	7.48	<0.001
Self-reported AF	5.69	5.03–6.43	27.9	<0.001
Self-reported COPD	1.41	1.14–1.75	3.17	0.002

AF, atrial fibrillation; BMI, body mass index; BP, blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MI, myocardial infarction.
Where Age_1 = Age^3 − 189.03; Age_2 = Age^3 * ln(Age) − 330.3; BMI_1 = BMI^3 − 20.5; and eGFR_1 = 1/eGFR − 1.057.
[Correction added on 27 July 2023, after first online publication: The unit, coefficients and hazard ratios of the variables BMI and eGFR have been corrected in this version.]

Table 4 Predicted vs. observed heart failure incidence and median survival by risk groups

HUNT risk group	*n*	Predicted 10 year HF risk (%)	Number of incident HF (%)	Observed 10 year HF incidence, per 1000 py	Number of deaths (%)	Mean survival (years)	95% CI	Mortality rate per 1000 py
Low	30 678	<5	304 (1.0)	0.95	67 (0.2)	11.39	11.39–11.40	0.21
Low intermediate	2704	5–<10	265 (9.8)	9.82	93 (3.4)	11.26	11.22–11.29	3.31
High intermediate	1419	10–20	266 (18.8)	20.09	193 (13.6)	10.85	10.76–10.93	13.49
High	1710	>20	531 (31.1)	41.18	928 (54.3)	8.67	8.52–8.82	65.54

CI, confidence interval.

incident HF had satisfactory discrimination, C statistics of 0.904 (95% CI 0.896–0.911) in the derivation dataset. The model did not change during internal validation: Harrell's c-index of 0.903 (95% CI 0.895–0.911) with bootstrap-derived samples and corrected for optimism. The estimated optimism measure was only 0.001. The calibration plot of the model (Supporting Information, *Figure S1*) demonstrated good calibration as all the deciles of risk fell on the unity line in the calibration plot. Most of the deciles were clustered at the bottom left, indicating that most of the participants had low risk of HF. In concordance, the slope of the linear predictor during internal validation with bootstrap-derived samples was estimated to 0.999, suggesting good calibration. Thus, because the correction was negligible, we opted not to use the optimism-corrected slope to obtain 10 year estimates. The sensitivity analysis excluding participants with MI, angina, or stroke at inclusion did not change the model's diagnostic accuracy (c-index of 0.903) (data not shown).

Imputation

In the sensitivity analyses performed in 25 multiple imputed datasets, the results after imputation did not differ substantially from the complete case analyses (Supporting Information, *Table S2*). There were no discernible differences between the performance on the multiple imputed datasets and the restricted analysis including only those with complete information of all risk factors [the c-index on the imputed dataset was 0.901 (95% CI 0.893–0.908)].

Risk groups

We were able to divide the patients into four risk groups (low, low intermediate, high intermediate, and high) corresponding to <5%, 5% to <10%, 10–20%, and >20% 10 year risk of incident HF developed from the coefficients in Supporting Information, *Table S1*. *Table 4* shows the HF incidence rate and mortality rate according to these risk groups. Whereas 1.4% of the 'low risk' group had incident HF during follow-up, 30.8% in the 'high risk' group developed HF. The mortality rate increased from 0.67 per 1000 person years of follow-up in the 'low risk' group, to 14.16 in the 'high-intermediate risk' group, and to 61.43 per 1000 person years in the 'high risk' group.

Comparison with other HF risk scores

Supporting Information, *Table S3* provides an overview of the risk scores included in these analyses. Supporting

Information, *Table S4* shows the discriminative performance data for each of the four HF or cardiovascular risk scores that were validated in the HUNT database. Harrell's C statistics were high for both the Framingham and NORRISK 2 models (between 0.82 and 0.87) in both men and women and lower for the Health ABC score (0.72). The PCP-HF showed an acceptable discrimination, although somewhat higher in women than in men (C statistics of 0.78 and 0.72, respectively). Supporting Information, *Figures S2* and *S3* show the calibration plots for each of the four HF or cardiovascular risk scores. Calibration demonstrated that, for all four scores, there was poor agreement between observed and predicted risks across the deciles of risks. There was a consistent under-prediction using the Framingham and PCP-HF risk scores in both women and men, whereas the calibration of the NORRISK 2 demonstrated an over-prediction in both women and men. Using the Health ABC HF score, there was an under-prediction in the lower deciles and an over-prediction for the highest deciles in both women and men.

Discussion

In this study, we developed and internally validated a novel risk score for predicting 10 year risk of incident HF using a large population-based study sample of more than 35 000 participants. The novel risk score (the HUNT for HF risk score) includes variables that are readily available in primary care. It has an excellent discriminative ability and outperforms existing HF risk scores, such as the Framingham HF risk score and the Health ABC HF score, and thus might be a helpful tool for HF risk stratification in the primary care setting. Finally, the high rates of incident HF and mortality we observed in the 'high risk' group according to the novel risk score may suggest that a substantial proportion of these participants may have undiagnosed HF.

The occurrence of HF is increasing worldwide and focuses on early detection, but also risk assessment is of utmost importance as a large body of evidence supports the prevention or delay of HF onset through modification of risk factors.[18,19] Due to subtle and non-specific symptoms, it is often challenging to establish the HF diagnosis early. This was clearly demonstrated in a study using primary care data from the United Kingdom where the authors found that almost 80% of newly diagnosed HF patients were diagnosed in hospital during their first admission for HF.[20] Interestingly, 89% of these had seen their general practitioner (GP) during the year prior to hospital admission and 37% of them had had a record of HF symptoms during the last 5 years. A study by Taylor *et al*. added to this, showing that survival rates following a diagnosis of HF only modestly improved from 2000 to 2017 and patients that did not require a hospital admission around the time of diagnosis lived longer.[21] A simple risk stratification tool such as the HUNT for HF risk score may promote the early detection of HF. Even though standardized screening for HF of the general population is not recommended in practical guidelines, they emphasize prevention of HF[2,19] and recommend the use of validated risk scores to identify people at risk of HF, albeit with a weak 2b recommendation.[19] Despite this, and in contrast to prevention of cardiovascular disease, the use of risk scores is not widely implemented in clinical practice. One reason may be the lack of a risk score that has been based on data from a general population. Two of the existing, most validated risk scores, the Framingham HF risk score and the Health ABC HF score, were derived in populations with either cardiac disease or hypertension (Framingham), or elderly (Health ABC), limiting the generalizability of the scores. Furthermore, both these scores included variables that may often not be recorded in general practice, such as the presence of left ventricular hypertrophy or valvular disease. More recently, Khan *et al*. published a risk score for incident HF (the PCP-HF risk score) using five community-based cohorts in the United States.[10] However, they excluded participants with known cardiovascular disease at baseline and included QRS duration as a predictor, a variable that may not routinely be captured during GP visits.

Thus, the HUNT for HF risk score fills a gap in early detection of HF: It was derived from a large sample from the general population and includes variables that are readily available and usually routinely recorded in the primary care setting and should therefore be easy to implement in general practice. In the present analysis, the variables of disease history were based on self-reported information. Subsequent work demonstrated that, by validation of a total of >2000 acute MI diagnoses, >2000 stroke diagnoses, and 500 AF diagnoses,[15] we found no evidence that misclassification of these diagnoses influenced the presented results.

Guidelines put a clear emphasis on subgroups that are at higher risk of developing HF: People with conditions such as hypertension, diabetes, or cardiovascular disease, but with no symptoms of HF, are classified to be 'at risk for HF' (Stage A) in the American guidelines, with Class 1 recommendations to treat risk.[2,19] Our results support this grading: A history of AF and a history of diabetes were the strongest independent predictors with more than five-fold and two-fold increased risk of developing incident HF over the next 10 years.

The discriminative ability of the HUNT for HF risk score is excellent with a C statistics of 0.90. This appeared robust with no substantial change during internal validation or following imputation. Moreover, the HUNT for HF risk score outperformed existing HF risk scores, including the PCP-HF risk score, as well as NORRISK 2, a Norwegian score estimating the risk of acute stroke and MI.

Importantly, the high-risk participants in our study had a very high risk of incident HF of 4.0 per 100 person years and of death (6.1 per 100 person years at risk). These rates are actually not very different from rates of HF events and deaths in populations with known HF, as shown in data from an epidemiological study utilizing the Swedish HF registry that showed mortality rates of 11 per 100 person years.[22]

Moreover, data from contemporary randomized controlled outcome trials (e.g. participants with HF, type 2 diabetes, and cardiovascular disease in EMPA-REG OUTCOME) had rates of hospitalization for HF of 5.2 per 100 patient years and all-cause mortality rates of 5.5 per 100 patient years.[23] Therefore, these data may suggest that a substantial proportion of the participants in the 'high risk' group may have undiagnosed HF and underscore the importance of risk stratification and early implementation of preventive strategies.

Limitations and strengths of the study

Apart from the clear strengths including large sample size and stringent validation of all HF events, our study has some limitations. Our findings from one county in Norway cannot readily and directly be generalized to the remaining Norwegian population or to countries with different underlying HF risks. Because electrocardiogram (ECG) and biomarkers were not available, potential predictors stemming from these investigations were not tested. Furthermore, because we did not have all data available that were required to calculate risk according to the existing HF risk scores, the comparison of the HUNT for HF risk score and the existing risk scores was done by modifying the risk scores omitting variables that were missing.

Conclusions

We identified 12 clinical, readily available variables that independently predicted 10 year HF risk. The model performed well compared with existing risk scores and is well suited to be the foundation of a practical, online risk score for HF risk assessment in general practice. The risk score needs external validation but could become an instrumental part of a strategy to improve early detection, and enable prevention and early treatment, of HF.

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Conflict of interest

A.P.O. is an employee of Boehringer Ingelheim. C.B. declared no conflict of interest. O.E.J. was previously employed by Boehringer Ingelheim but is now an employee of Nestlé Health Science. B.M., M.W.F., L.E.L., L.L.G., and H.D. also declared no conflict of interest.

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Supporting information

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

Table S1. Cox regression coefficients with 95% CI, model HUNT for HF, for prediction of 10-year risk of incident heart failure [Corrections added on 27 July 2023, after first online publication: The unit, coefficients, and hazard ratios of the variables BMI and eGFR have been corrected in Supplementary Table S1 in this version.]
Table S2. The final prediction model with multiple imputed predictors [Corrections added on 27 July 2023, after first online publication: The unit, coefficients, and hazard ratios of the variables BMI and eGFR have been corrected in Supplementary Table S2 in this version.]
Table S3. Variables going into the Framingham HF risk score, The Health ABC HF risk score, the PCP-HF risk score and the NORRISK 2 risk score for cardiovascular events
Table S4. Discriminative performance of existing models for 10-year heart failure prediction
Figure S1. Calibration plot of the final HUNT for HF model
Figure S2. Calibration plots for existing HF or CV risk scores: A and B) the Framingham HF risk score (from a logistic regression model), C) Health ABC Risk Score
Figure S3. Calibration plots for existing HF or CV risk scores: A and B) NORRISK2, C and D) PCP-HF

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