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# **Comparing and contrasting risk factors for Heart failure in patients with and without history of myocardial infarction:**

## **Data from HOMAGE and the UK Biobank**

Tripti Rastogi<sup>1</sup>, Frederick K. Ho<sup>2</sup>, Patrick Rossignol<sup>1</sup>, Thomas Merklings<sup>1</sup>, Javed Butler<sup>3</sup>, Andrew Clark<sup>4</sup>, Timothy Collier<sup>5</sup>, Christian Delles<sup>6</sup>, J Wouter Jukema<sup>7</sup>, Stephane Heymans<sup>8,9,10</sup>, Roberto Latini<sup>11</sup>, Alexandre Mebazaa<sup>12</sup>, Pierpaolo Pellicori<sup>13</sup>, Peter Sever<sup>14</sup>, Jan A Staessen<sup>15,16</sup>, Lutgarde Thijs<sup>17</sup>, John G Cleland<sup>13,18</sup>, Naveed Sattar<sup>19</sup>, Faiez Zannad<sup>1</sup>, Nicolas Girerd<sup>1</sup>

### **Affiliations**

<sup>1</sup> Université de Lorraine, Centre d'Investigations Cliniques Plurithématique 1433, Institut Lorrain du Cœur et des Vaisseaux Louis Mathieu, CHRU de Nancy, INSERM DCAC, F-CRIN INI-CRCT, Nancy, France.

<sup>2</sup> Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK.

<sup>3</sup> Department of Medicine, University of Mississippi School of Medicine, Jackson.

<sup>4</sup> Hull York Medical School, Castle Hill Hospital, Cottingham, United Kingdom.

<sup>5</sup> London School of Hygiene and Tropical Medicine, London, UK.

<sup>6</sup> Institute of Cardiovascular and Medical Sciences, University of Glasgow, Scotland, United Kingdom.

<sup>7</sup> Department of Cardiology, Leiden University Medical Center, Leiden; Netherlands Heart Institute, Utrecht, the Netherlands.

<sup>8</sup> Department of Cardiology, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, the Netherlands.

<sup>9</sup> Department of Cardiovascular Research, University of Leuven, Belgium.

<sup>10</sup> Netherlands Heart Institute, Utrecht, the Netherlands.

<sup>11</sup> IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy.

<sup>12</sup> Université de Paris; APHP, University Hospitals Saint Louis Lariboisière; Inserm 942 MASCOT, Paris, France.

<sup>13</sup> Robertson Centre for Biostatistics and Clinical Trials, Institute of Health and Wellbeing, Glasgow, United Kingdom.

<sup>14</sup> International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, England.

<sup>15</sup> Research Institute Alliance for the Promotion of Preventive Medicine, Mechelen, Belgium.

<sup>16</sup> Biomedical Sciences Group, Faculty of Medicine, University of Leuven, Leuven, Belgium.

<sup>17</sup> Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Diseases, University of Leuven, Leuven, Belgium.

<sup>18</sup> National Heart and Lung Institute, Royal Brompton and Harefield Hospitals, Imperial College, University of Glasgow, London, United Kingdom.

<sup>19</sup> Institute of Cardiovascular and Medical Sciences, University of Glasgow, United Kingdom.

**Corresponding author:** Nicolas Girerd

Centre d'Investigation Clinique Pierre Drouin -INSERM - CHRU de Nancy, Institut lorrain du cœur et des vaisseaux Louis Mathieu, Nancy, France.

**Address:** 4, rue du Morvan. 54500 Vandœuvre-Lès-Nancy

**E-mail:** n.girerd@chru-nancy.fr Phone: +33 383157496 Fax: +33383157324

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## Introduction

Heart failure (HF) is one of the leading causes of morbidity and mortality throughout the world. With  $\geq 37$  million people already affected worldwide, the number will continue to rise for the next 20 years<sup>1,2</sup>. Increasing life expectancy and prevalence of risk factors such as hypertension, diabetes, obesity and coronary artery disease, especially in younger populations, will further add to the steadily increasing number of HF patients<sup>3</sup>. Despite advances in treatment, mortality rates remain particularly high with poor 5-year survival<sup>4</sup>. Hence, early identification and management of risk factors is critical for preventing or delaying the onset of HF.

The implementation of preventive measures relies on the correct identification of individuals at higher risk. Several scores have been developed with the aim of identifying populations at higher risk taking into account variables such as age, sex, body mass index (BMI), lipid levels, kidney function and other comorbidities including diabetes and hypertension<sup>5,6</sup>. These scores assess HF risk irrespectively of the presence of prior myocardial infarction (MI) i.e., these risk score assess the HF risk based on a fixed value assigned to each risk factor including MI. However, the strength of a relation between a risk factor and outcome might depend upon whether a patient has previously had an MI.

Different aetiologies, risk factors and pathophysiological mechanisms, in combination with concomitant diseases, renders HF a complex and heterogeneous syndrome with several phenotypes<sup>7,8</sup>. However, HF with history of prior MI appears distinct from HF without prior MI in many aspects including: ischemic injury, inflammation and neurohormonal pathways involved in cardiac remodelling<sup>9</sup>. Importantly, ischemic/non-ischemic HF is often the only characterization reported in large registries regarding HF aetiology, thus emphasizing the cardinal importance of MI history. Given the different pathophysiological background of HF with and without prior MI, classical risk factors (such as age, blood pressure, diabetes, dyslipidemia, kidney disease, etc.) may contribute differentially

to HF onset in patients with and without MI. History of MI is known to be associated with worse outcomes in patients with overt HF and could be related to MI history rather than the intrinsic prognosis of ischemic HF<sup>10,11</sup>.

We compared the clinical characteristics associated with the progression to HF in patients with or without a history of MI in patients at higher risk of HF in the HOMAGE database and validated our results in the UK Biobank population-based cohort.

## **Methods**

**Derivation cohort:** Patients included in the Heart ‘OMics’ in AGEing (HOMAGE) merged database were studied. Briefly, the HOMAGE database included 52 631 study participants from 21 studies from eight European countries which enrolled subjects with overt cardiovascular (CV) disease or at risk of CV disease or healthy individuals. A detailed description of the database is provided elsewhere<sup>12,13</sup>.

Among this large database, patients identified to be at a higher risk for HF (i.e. without HF but with significant risk for HF based on their comorbidities/clinical history) were included in the analysis reported here<sup>12,13</sup>. Patients included were originally from four separate cohorts (ASCOT, DYDA, HVC, PROSPER) in which included patients had higher risk of HF and provided sufficient follow-up to assess the incidence of HF onset (Supplementary figure 1). Patients were included if the baseline data on age, sex, body weight and height was available. Patients who had HF at baseline or for whom follow-up data on outcome was unavailable were excluded.

**Outcomes:** The objective of the study was to identify whether the risk factors for HF onset differed depending on the presence (MI+) or absence of prior MI (MI-). For this objective, the selected outcome was time to HF onset as defined by hospitalization for HF. The endpoints for each study were

adjudicated in the respective cohort and trials and the committee within the HOMAGE consortium retrospectively assessed the quality of endpoint adjudication for each study (supplementary table 1)<sup>5,13</sup>.

**Validation cohort:** The results of our analysis were replicated in UK Biobank, a large population-based, prospective observational study with 502,493 middle-aged and elderly participants from the United Kingdom<sup>14,15</sup>. The health outcomes were ascertained through data linkage to hospitalization records and incident HF was defined according to the International Classification of Diseases-10 codes. Subjects with prevalent heart failure at baseline were excluded from this analysis. Brief study design and baseline characteristics of the study participants included from the UK Biobank are presented in the supplementary material and supplementary table 2.

All of the studies were conducted in accordance with Good Clinical Practice guidelines and applicable national regulations and all study participants provided written informed consent.

**Statistical analysis:** For the descriptive analyses, continuous variables are expressed as mean  $\pm$  standard deviation (SD) for normally distributed data or as median (Q1-Q3) for skewed data. Categorical variables are expressed as proportions (%).

Univariable Cox regression models were used to calculate the hazard ratio (HR) for HF onset associated with each risk factor. Due to differences in duration of follow-up between each cohort, the cohorts were added as strata in the Cox regression models for the HOMAGE database. The stratified Cox-proportional hazard models were used because the baseline risk and hazards in each cohort constituting HOMAGE cohort were different and unrelated<sup>16</sup>. Age, systolic blood pressure (SBP) and estimated glomerular filtration rate (eGFR) were categorized due to non-linearity. A backward selection procedure was applied to determine the variables to be included in the multivariable models. Total cholesterol, body weight and height were not included in the backward selection due to their high collinearity with other variables (only low density lipoprotein-cholesterol (LDL-c) and BMI were

considered). The variables found to be significantly associated with either the patients with prior MI or the patients with cardiovascular risk factors but no prior MI were then included in the final multivariable model with same variables for each group. Interactions between each risk factor and history of MI were examined in both backward selection model (interaction for unadjusted model) and fully adjusted model (additive and multiplicative interaction for adjusted model), adding multiplicative interaction terms to survival models. The discriminative value of multivariable models for HF onset was assessed using Harrell's c-index. We also ran sensitivity analyses with ACEi/ARBs and Beta-blockers use, forced in the Cox regression models. The competing risk analysis with non-HF death as competing event was conducted using Fine and Gray modification of Cox-proportional hazard models. For validation analysis, a dedicated adjustment was performed to calculate hazard ratios of risk factor associated with HF onset in UK Biobank.

Population attributable risk percentage (PAR) was calculated using the formula  $PAR = Pd * (HR - 1) / HR$  where Pd is the proportion of cases (i.e., HF onset) exposed to a risk factor<sup>17</sup>. Using Bonferroni inequality, 95% confidence intervals (CI) for PAR percentage were calculated from the general PAR formula using the lower and upper limits of the 97.5% CI for Pd and HR (Supplementary Figure 2). This metrics could be calculated for categorical variables.

Statistical analyses were performed using R 3.6.1 and 3.5.3 (URL <https://www.R-project.org/>). A two-sided p value of less than 0.05 was considered statistically significant.

## 1 **Results**

### 2 *HOMAGE cohort results*

3 A total of 26 478 subjects was included for analysis, out of whom 7 241 (27%) had a history of  
4 MI. During a median follow-up time of 5.2 (3.5–5.9) years, 2.44% (N=177/7 241) of participants with  
5 a history of MI and 1.92% (N=370/19 237) without a history of MI developed HF.



1 *Baseline characteristics (Table 1)*

2 Participants with HF onset were older than those without, irrespective of prior MI status.  
3 Participants without prior MI who developed HF had higher SBP than participants without HF (167.5  
4 (23.0) for HF versus 161.3 (19.9) for non-HF) whereas the opposite was observed in patients with MI  
5 history (154.0 (23.8) for HF vs. 159.2 (19.3) for non-HF) (Table 1).

6 *Predictors of HF with or without history of MI (Supplementary Table 3)*

7 In multivariable analysis, male sex, older age and higher heart rate were significantly associated  
8 with increased risk of HF onset both in participants with, and those without, prior MI. However, older  
9 age had a stronger association with the risk of HF in participants with prior MI, as compared to those  
10 without prior MI.

11 Active smoking status was significantly associated with HF onset (HR=2.00 (1.36 - 2.94)  
12  $p<0.001$ ) in participants with prior MI, while the association was neutral in univariable analysis in  
13 those with no prior MI. Similarly, diabetes was a predictor of HF onset only in those with prior MI.  
14 Also, worsening renal function was associated with increased risk of HF only in participants with prior  
15 MI (HR = 2.0 (0.96-4.14) for 60-75ml/min/1.73m<sup>2</sup>; HR= 3.13 (1.54-6.37) for <60ml/min/1.73m<sup>2</sup>;  
16 overall  $p=0.002$ ). In participants with no prior MI the association was non-linear (HR = 0.81 (0.55-  
17 1.18) for 60-75 ml/min/1.73m<sup>2</sup>; HR= 1.3 (0.9-1.87) for <60ml/min/1.73m<sup>2</sup>; overall  $p=0.006$ ). In  
18 contrast, higher BMI, higher SBP and higher blood glucose levels were significantly associated with  
19 HF onset and retained in multivariable models in participants without prior MI but not in participants  
20 with prior MI.

21 *Head-to-head comparison of HF risk factors in multivariable models*

22 When predictors of HF were simultaneously included in multivariable models to allow a direct  
23 comparison of the magnitude of associations in participants with and without prior MI (Figure 1 and

1 graphical abstract), a similar pattern of results was observed: SBP, blood glucose and BMI were more  
2 strongly associated with incident HF in participants without prior MI (p value for interaction  
3 respectively 0.003, 0.006 and 0.027) whereas, smoking status (p value for interaction 0.021) and worse  
4 renal function (p value for interaction 0.002) were associated with incident HF in patients with prior  
5 MI.

6 The c-index of the model improved when the interaction terms of variables were added to the  
7 model (delta C-index = 0.02 (from 0.70 to 0.72); p-value = 0.001). Similarly, a modest, but still  
8 significant, improvement of C-index was observed in the validation cohort (delta C-index = 0.004  
9 (from 0.797 to 0.802); p-value = 0.01).

10 Forcing for ACEi/ARBs and beta-blockers use into the model did not affect the results  
11 (Supplementary Table 4).

12 In the competing risk analysis model, the pattern of association of variable and HF-onset was  
13 similar to multivariable model without competing risk. However, sex was neutrally associated with HF-  
14 onset in patients without prior MI in the competing risk model (Supplementary Table 6).

15 The attributable risk of high SBP was markedly higher in patients without prior MI (Supplementary  
16 Figure 2).

#### 17 *Validation analysis in the UK Biobank study*

18 From the UK Biobank study, 500 001 subjects were included in the validation analysis, of  
19 whom 4 555 (0.91%) had a history of MI at baseline. The validation cohort participants were younger (–  
20 9 years) and fewer participants had hypertension and diabetes compared to participants in the  
21 HOMAGE database. Among people with prior MI, 14.9% (680/4555) developed incident HF while  
22 2.7% (13536/495446) participants without prior MI developed HF over a median (Q1 – Q3) follow-up  
23 of 11.8 (11.1-12.5) years. Increasing age and smoking were significantly associated with increased risk

1 of HF in people with and without prior MI. A higher BMI, HbA1c, diabetes and hypertension had a  
2 stronger association with HF onset in participants without prior MI compared to participants with prior  
3 MI (p value of interaction: 0.0005, 0.03, 0.03 and 0.0005 respectively – Table 2 and supplementary  
4 Table 5). In addition, male sex was significantly associated with a higher risk of HF onset only in  
5 participants with prior MI but not in participants without MI (p for interaction <0.0001) and lower  
6 eGFR was more strongly associated with higher risk of HF onset in patients with prior MI (HR: 0.73  
7 (0.67-0.81) vs 0.67 (0.66-0.69), p value of interaction <0.0001).

## 8 **Discussion**

9 In this pooled cohort study of patients at higher risk of developing HF, we found that the pattern  
10 of association of risk factors with HF was dependent on the presence of prior MI. Increasing age, male  
11 sex and higher heart rate were associated with HF onset irrespective of MI history, and should  
12 consequently be perceived as stable and ubiquitous risk factors for HF onset. Poorer renal function  
13 predisposed to HF onset more in patients with MI. Blood pressure/hypertension, BMI and blood  
14 glucose/HbA1c were more strongly associated with HF onset in participants with cardiovascular risk  
15 but no prior MI both in the HOMAGE cohort and UK Biobank cohort. Our results are in line with  
16 previous reports suggesting that metabolic factors and hypertension are more associated with heart  
17 failure with preserved ejection fraction (HFpEF) than heart failure due to reduced ejection fraction  
18 (HFrEF)<sup>18,19</sup>. Importantly, despite the differences in baseline characteristics and risk factors in the  
19 HOMAGE (participants at high risk of HF) and UK Biobank study (population-based cohort), we saw a  
20 strikingly similar pattern of association between metabolic- and hypertension- related factors and new  
21 onset HF in patients without MI.

22 These results consequently suggest that, as in patients with overt HF, prior MI should be a  
23 variable systematically emphasized in epidemiological studies focusing on the prediction of HF onset.  
24 Importantly, metabolic- and hypertension- related factors have a greater impact on HF onset in the

1 absence of prior MI, and their prevention/treatment should consequently be particularly optimized in  
2 people who have not had an MI.

3 *Risk factors more associated with HF onset in the participants with prior MI*

4 Diabetes, renal dysfunction and smoking status were strong predictors of HF onset in the prior  
5 MI group in the HOMAGE cohort. Our results are in keeping with previous studies where diabetes and  
6 renal dysfunction were found to be an important determinant of HF onset (2- fold increase in risk of  
7 HF) in post-MI patients<sup>20,21</sup>. This differential impact is not currently captured in the risk scores  
8 calculated with multivariable risk models where diabetes is associated with a fixed risk estimate  
9 irrespectively of MI history. However, it is noteworthy to mention that diabetes was more strongly  
10 associated with participants with no prior MI in the validation cohort. The difference of association of  
11 diabetes in derivation and validation may be due to differences in the population requiring insulin for  
12 management of diabetes. Previous studies have shown that cardiovascular mortality is substantially  
13 higher in patients with prior-MI and insulin-treated diabetes compared to patients with prior MI and  
14 diabetes treated with oral medications due to more frequent presence atherosclerotic disease in patients  
15 with diabetes requiring insulin<sup>22</sup>. Yet, we did not had access to diabetes treatment in the HOMAGE  
16 cohort, and could consequently not verify this hypothesis.

17 Smoking is significantly associated with new onset HF following MI, possibly due to increased  
18 myocardial injury and myocardial haemorrhage, even though the smokers seemingly had a better risk  
19 profile than non-smokers<sup>23,24</sup>. However, smoking status was similarly associated with incident HF  
20 regardless of prior MI in the validation cohort and the pattern of association seen for smoking in  
21 HOMAGE (p-interaction=0.021) was not replicated in the UK Biobank (p-interaction=0.59). This  
22 difference was perhaps due to differences in the baseline smoking behaviour of the participants in the  
23 two cohorts.

1           The pattern of association between male sex and HF onset was dissimilar between the two  
2 cohorts. In the HOMAGE cohort, male sex was similarly associated with higher risk in both the groups  
3 whereas, in the UK Biobank, male sex was associated significantly with participants with CV risk but  
4 no prior MI. The difference in the statistical association could be due to an overall higher proportion of  
5 men in the HOMAGE compared to UK Biobank (60% vs 45%).

6           Renal impairment/CKD is frequently associated with patients with prior MI. Although the exact  
7 mechanism linking HF and CKD is not known, it has been speculated that neurohormonal activation,  
8 renal hypoperfusion, increased inflammatory markers involved in myocardial repair, anaemia and  
9 volume overload contribute towards progressive HF, especially post-MI. Similar findings were  
10 reported in an observational study where patients with HFrEF and CKD had higher frequency of a prior  
11 MI compared to patients with HFpEF<sup>25</sup>. Further, CKD was more strongly associated with HFrEF in  
12 comparison of HFpEF. Besides pathophysiological mechanisms, CKD restricts the use of optimal  
13 dosage of renin-angiotensin inhibitors post-MI, thereby increasing the risk of HF. These findings imply  
14 that reno-protection is particularly important in patients with prior MI.

15 *Risk factors more strongly associated with HF onset in participants with cardiovascular risk but no*  
16 *prior MI*

17           Our study found hypertension as a strong risk factor for HF onset in patients with  
18 cardiovascular risk but no prior MI. Similarly, an analysis of the Framingham Heart study cohort  
19 previously demonstrated that hypertension is the most important risk factor associated with HF onset<sup>26</sup>.  
20 Our results highlight that the magnitude of the association between blood pressure and incident HF is  
21 far greater in patients without prior MI than in patients with prior MI. There was no relation between  
22 SBP and incident HF in patients with prior MI, perhaps because low SBP was due to reduced left  
23 ventricular function and hence, greater risk of HF onset<sup>27</sup>. Importantly, in the present analysis, higher  
24 SBP (in HOMAGE) and history of hypertension (in the UK Biobank study) was not associated with an

1 increased risk of incident HF in patients with a prior MI. Previous studies have shown that lower BP  
2 could be related to greater LV dilation following MI, thus increasing the risk of subsequent HF<sup>27,28</sup>.  
3 There is a BP paradox in patients with HFrEF: higher BP appears to be ‘protective’<sup>29,30</sup>. However, the  
4 paradox has been described only *after* HF onset, whereas we focus here on the pre-HF period.

5 Metabolic factors such as BMI and blood glucose were stronger predictors of HF onset in  
6 patients with cardiovascular risk but no prior MI in our study. Similarly, the validation analysis found  
7 that hypertension, diabetes and higher BMI were more strongly related to HF onset without prior MI.  
8 Similar findings were observed in a study combining data from middle-aged men and women from four  
9 different American cardiovascular disease cohorts<sup>31</sup>, in which participants who did not have any of the  
10 three risk factors (hypertension, obesity and diabetes) had a substantially lesser risk of HF, thus placing  
11 greater emphasis on metabolic factors in the genesis of HF in patients without MI. In the presence of a  
12 prior MI, a lower prevalence of metabolic risk factors is perhaps sufficient to trigger remodelling and  
13 tip the patient in to HF. In addition, previous studies have reported an obesity paradox where lower to  
14 normal BMI is associated with poorer CV outcome post-MI compared to overweight patients perhaps  
15 due to a younger age of disease presentation and other confounding variables such as smoking and  
16 cardiorespiratory fitness<sup>32,33</sup>.

17 Diabetes, hypertension and obesity are associated with impaired myocardial energy  
18 consumption, cardiac hypertrophy and oxidative damage. These mechanisms play a role in impaired  
19 relaxation leading to diastolic dysfunction<sup>34</sup>. Further, a recent study found that diabetes/elevated blood  
20 sugar is reported to be associated with increased levels high sensitive cardiac troponin-T suggesting  
21 sub-myocardial damage<sup>35</sup>. It seems that even in absence of direct myocardial damage (prior MI),  
22 considerable injury to heart is caused by cardiometabolic risk factors.

23 *Risk scores and risk prediction models*

1 A number of scores have been developed for predicting the risk of HF. The Framingham Study  
2 CHF (1999) risk score based on key clinical features was the first to provide estimates of the 4-year  
3 probability of heart failure<sup>36</sup>. Subsequently, the ARIC heart failure risk calculator, the Health ABC risk  
4 score, the PCP-HF calculator and the HOMAGE score were developed based on clinical and laboratory  
5 features<sup>5,6,37,38</sup>. Importantly, however, none of these scores differentiates HF prediction according to the  
6 history of MI. Having access to a large dataset enabled us to assess interactions with MI history  
7 efficiently. Interaction p values were significant (for both additive and multiplicative interaction) for  
8 many factors and addition of interaction terms led to a modest but significant improvement of the c-  
9 index in both derivation and validation cohort. Further, we found similar pattern of association and  
10 significant interaction-p values in competing risk model with non-HF death as competing risk factor.  
11 Fine and Gray competing risk model may have predicted an upward bias in estimating HRs for each  
12 risk factor however, directionality of the association and relative magnitudes of the risk factors can be  
13 inferred<sup>39</sup>. Overall, these findings suggest substantial differences between the association of each risk  
14 factor in patients with or without prior MI – something that has not been previously emphasized.

### 15 *Limitations*

16 There are several limitations to our study. First, the results are subject to biases inherent to all  
17 observational cohort studies. Second, the included cohorts featured certain differences in the inclusion  
18 criteria and length of the follow up-period. For example, the DYDA study considered MI as an  
19 exclusion criterion while the ASCOT cohort had a longer follow-up time than the other 3 cohorts.  
20 However, all models were adjusted for clinical characteristics. Third, the diagnosis of HF was not  
21 based on the Framingham criteria but rather on hospitalization of HF. Hence, non-hospitalized HF  
22 patients were not labelled as HF in the current analysis. Moreover, differences in HF hospitalization  
23 due to different hospital admissions policy, treating physicians, adherence to guidelines for therapy  
24 occur in different cohorts. Further, we do not have data regarding how long ago MI happened before

1 the recruitment in the cohort and if there were recurrent MIs during follow-up. Fourth, it is possible  
2 that the some of the patients enrolled had had clinically silent MIs and were consequently included in  
3 the cardiovascular risk but no prior MI group, thus diluting the difference between the two groups. In  
4 addition, the overall SBP in the HOMAGE database was high due to the phenotype of patients included  
5 in the original cohorts aggregated within the HOMAGE consortium. Therefore, we used a cut-off of  
6 160 mm Hg in the HOMAGE cohort given the structure of the data. However, the results were similar  
7 in the UK Biobank using the classic definition for hypertension. Finally, LVEF at the time of HF onset  
8 was not available; we cannot consequently provide HFrEF- or HFpEF- specific associations. Whether  
9 the pattern of association we observed is primarily driven by a subtype of HF (i.e. HFrEF or HFpEF)  
10 should be further studied in future.

#### 11 *Research and clinical implications*

12 Our results suggest that “classical” risk factors for HF carry a different weighting depending on  
13 the clinical setting. This fact has not been sufficiently emphasized previously. In light of our results, a  
14 history of prior MI should be particularly highlighted in epidemiological studies focusing on predictors  
15 of HF onset, as is done in studies performed in patients with overt HF. In addition, the modifying  
16 impact of MI on HF predictors should be systematically assessed in future reports. A personalized HF  
17 risk stratification may help in designing preventive strategies depending on the clinical setting. In  
18 patients without MI, hypertension treatment and the control of metabolic features appear to be of much  
19 greater importance. These results could help in the prioritization of healthcare interventions in the  
20 prevention of HF.

#### 21 *Conclusions*

22 The importance of clinical risk factors and the increase in subsequent mortality risk following  
23 HF onset is dependent on the presence or absence of a history of prior MI. These results suggest that



1 patients should be differentiated in terms of risk assessment based on their history of prior MI and may  
2 ultimately benefit from different targeted interventions to prevent HF.

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23 Government and the British Heart Foundation.

24

**Table 1: Baseline characteristics in relation to history of MI and the occurrence of HF during follow-up in the HOMAGE cohort**

	Overall (N= 26 478)	N available	Patients with a history of MI		Patients without a history of MI*		p
			No HF onset during FU (N=7 064)	HF onset (N=177)	No HF onset during FU (N=18 867)	HF onset (N=370)	
<b>Clinical data</b>							
Sex (Female)	8095 (30.6)	26478	2822 (39.9)	66 (37.3)	5090 (27.0)	117 (31.6)	<0.001
Age (years)	65.6 (9.3)	26478	63.9 (10.3)	73.4 (7.6)	66.1 (8.8)	71.1 (7.7)	<0.001
Smoking status		26413					<0.001
Non-smoker	11146 (42.2)		3513 (49.8)	114 (64.4)	7368 (39.2)	151 (41.4)	
Smoker	7734 (29.3)		1806 (25.6)	43 (24.3)	5789 (30.8)	96 (26.3)	
Ex-smoker	7533 (28.5)		1733 (24.6)	20 (11.3)	5662 (30.1)	118 (32.3)	
Alcohol consumption	17547 (67.5)	25993	4751 (68.0)	98 (56.0)	12480 (67.6)	218 (61.6)	0.001
Hypertension	23711 (89.5)	26478	6087 (86.2)	115 (65.0)	17185 (91.1)	324 (87.6)	<0.001
Diabetes	6779 (25.6)	26478	1096 (15.5)	34 (19.2)	5513 (29.2)	136 (36.8)	<0.001
SBP (mmHg)	160.8 (19.9)	26407	159.2 (19.3)	154.0 (23.8)	161.3 (19.9)	167.5 (23.0)	<0.001
Heart rate (bpm)	70.8 (12.6)	26352	70.6 (12.9)	68.8 (11.8)	70.9 (12.5)	71.8 (13.0)	0.022
BMI (kg/m <sup>2</sup> )	27.8 [25.2, 30.8]	26477	27.7 [25.2, 30.7]	27.2 [25.4, 30.5]	27.8 [25.2, 30.8]	28.3 [25.3, 31.6]	0.042
<b>Laboratory data</b>							
Blood glucose (mmol/L)	5.5 [5.0, 6.4]	24546	5.4 [4.9, 6.0]	5.3 [4.8, 5.9]	5.6 [5.0, 6.6]	5.6 [5.0, 7.4]	<0.001
Total cholesterol (mmol/L)	5.8 (1.1)	26435	5.9 (1.1)	5.7 (1.0)	5.8 (1.1)	5.8 (1.0)	<0.001

			Patients with a history of MI		Patients without a history of MI*		p
	Overall (N= 26 478)	N available	No HF onset during FU (N=7 064)	HF onset (N=177)	No HF onset during FU (N=18 867)	HF onset (N=370)	
LDL-cholesterol (mmol/L)	3.7 (0.9)	24273	3.8 (0.9)	3.7 (0.8)	3.7 (0.9)	3.7 (0.9)	<0.001
HDL-cholesterol (mmol/L)	1.2 [1.0, 1.5]	26431	1.3 [1.1, 1.5]	1.2 [1.0, 1.4]	1.2 [1.0, 1.5]	1.2 [1.0, 1.5]	<0.001
Triglycerides (mmol/L)	1.5 [1.1, 2.1]	24648	1.5 [1.1, 2.1]	1.4 [1.1, 2.0]	1.5 [1.1, 2.1]	1.5 [1.2, 2.1]	0.286
Serum creatinine (µmol/L)	96.0 [86.0, 108.0]	20252	96.0 [85.0, 108.0]	113.0 [92.2, 132.8]	97.0 [86.0, 108.0]	99.0 [87.0, 117.0]	<0.001
eGFR CKD-EPI (ml/min/1,73 m <sup>2</sup> )	65.3 [55.1, 75.6]	20252	64.9 [54.8, 75.3]	48.9 [41.4, 62.7]	65.7 [55.6, 76.0]	59.6 [47.3, 71.0]	<0.001
<b>Medications</b>							
Use of ACEI/ARBs	7947 (34.8)	22821	1933 (33.1)	62 (36.0)	5814 (35.3)	138 (40.4)	0.003
Use of beta blockers	8017 (35.1)	22821	2256 (38.6)	54 (31.4)	5610 (34.1)	97 (28.4)	<0.001
Use of statins	352 (37.7)	933	0 (NA)	0 (NA)	351 (37.7)	1 (50.0)	1

ACEI: Angiotensin-converting enzyme inhibitor; ARBs: Angiotensin receptor blocker; BMI; Body Mass Index; FU: follow-up; HF: Heart failure; MI: Myocardial Infarction; SBP: Systolic Blood Pressure;

eGFR: estimated Glomerular Filtration Rate (calculated using CKD-EPI formula)

\*patients with cardiovascular risk factors but no prior MI

**Table 2: Multivariable Cox regression models for HF event with or without history of MI in UK biobank study**

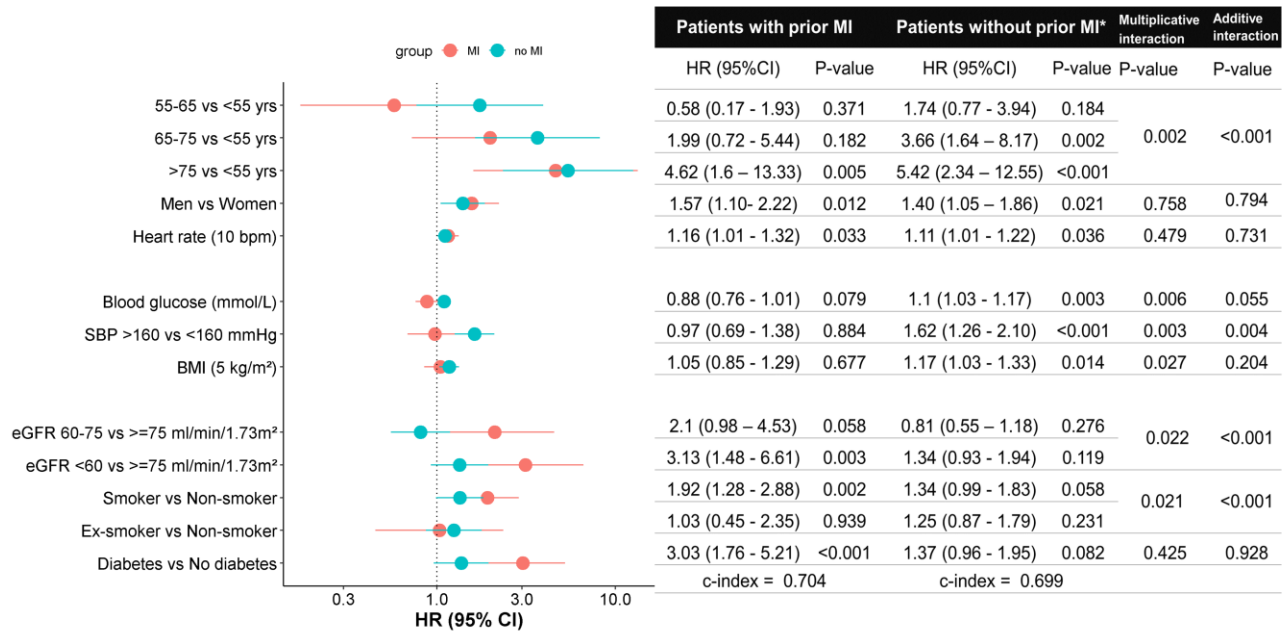
	Patients with history of MI		Patients without history of MI		P- value of interaction
	HR (95% CI)	P	HR (95% CI)	P	
<b>Age in year</b>	1.04 (1.03-1.05)	< 0.0001	1.12 (1.11-1.12)	< 0.0001	< 0.0001
<b>Male</b>	1.00 (0.83-1.21)	0.97	2.06 (1.99-2.13)	< 0.0001	< 0.0001
<b>eGFR</b>	0.73 (0.67-0.81)	< 0.0001	0.67 (0.66-0.69)	< 0.0001	< 0.0001
<b>HbA1c</b>	1.13 (1.07-1.20)	< 0.0001	1.19 (1.17-1.20)	< 0.0001	0.03
<b>Hypertension</b>	1.14 (1.08-1.22)	0.29	1.61 (1.54-1.69)	< 0.0001	0.0005
<b>BMI</b>	1.22 (1.12-1.33)	< 0.0001	1.49 (1.46-1.51)	< 0.0001	0.0005
<b>Smoker</b>	1.88 (1.48-2.38)	< 0.0001	1.97 (1.87-2.08)	< 0.0001	0.59
<b>Ex-smoker</b>	1.36 (1.13-1.63)	0.0009	1.32 (1.27-1.37)	< 0.0001	0.74
<b>Type2 diabetes</b>	1.50 (1.22-1.84)	0.0001	1.81 (1.72-1.91)	< 0.0001	0.03

Continuous variables were standardized to per-SD increase

Detailed adjustment model is presented in supplementary table 4

**Figure legends**

**Figure 1: Forest plot of the head-to-head comparison of risk factors for HF onset in multivariable survival models in participants with and without a history of MI in the HOMAGE cohort**



CI: Confidence Interval; HR: Hazard Ratio; MI: Myocardial Infarction; SBP: Systolic Blood Pressure; eGFR: estimated Glomerular Filtration Rate

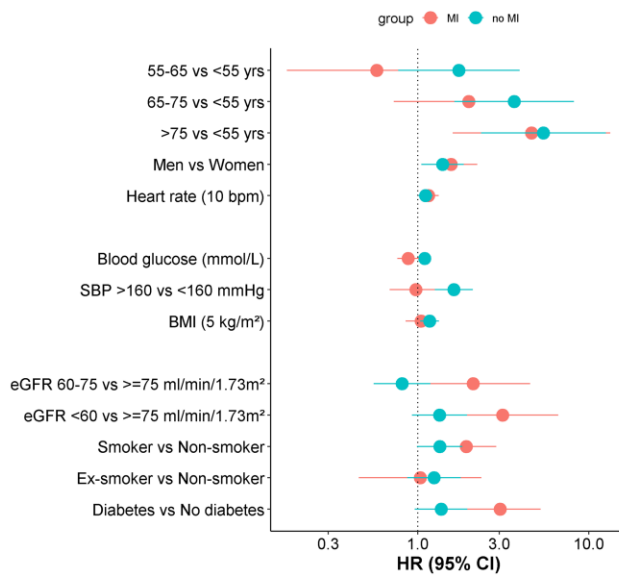
\*patients with cardiovascular risk factors but no prior MI

## Predictors of HF onset in patients with or without a history of MI

### Cohorts used in the analysis

In **HOMAGE cohort** (Derivation cohort)  
Participants at high risk of HF (N=26 478)

In **UK BIOBANK** (Validation cohort)  
Population-based cohort (N= 500 001)



	Patients with history of MI	Patients without history of MI
	HR (95% CI)	HR (95% CI)
<b>Age in year</b>	1.04 (1.03-1.05)	1.12 (1.11-1.12)
<b>Male</b>	1.00 (0.83-1.21)	2.06 (1.99-2.13)
<b>HbA1c</b>	1.13 (1.07-1.20)	1.19 (1.17-1.20)
<b>Hypertension</b>	1.14 (1.08-1.22)	1.61 (1.54-1.69)
<b>BMI</b>	1.22 (1.12-1.33)	1.49 (1.46-1.51)
<b>eGFR</b>	0.73 (0.67-0.81)	0.67 (0.66-0.69)
<b>Smoker</b>	1.88 (1.48-2.38)	1.97 (1.87-2.08)
<b>Ex-smoker</b>	1.36 (1.13-1.63)	1.32 (1.27-1.37)
<b>Diabetes</b>	1.50 (1.22-1.84)	1.81 (1.72-1.91)

**Predictors of HF are dependant on MI status:**  
**Blood pressure/hypertension, BMI , Blood glucose/HbA1c**  
 more strongly associated with HF onset in participants **without prior MI**

## References

1. Ziaeeian B, Fonarow GC. Epidemiology and aetiology of heart failure. *Nat Rev Cardiol* 2016;**13**:368-378. doi: 10.1038/nrcardio.2016.25
2. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* 2017;**14**:591-602. doi: 10.1038/nrcardio.2017.65
3. Andersson C, Vasani RS. Epidemiology of cardiovascular disease in young individuals. *Nat Rev Cardiol* 2018;**15**:230-240. doi: 10.1038/nrcardio.2017.154
4. Shah KS, Xu H, Matsouka RA, *et al.* Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol* 2017;**70**:2476-2486. doi: 10.1016/j.jacc.2017.08.074
5. Jacobs L, Efremov L, Ferreira JP, *et al.* Risk for Incident Heart Failure: A Subject-Level Meta-Analysis From the Heart "OMics" in AGEing (HOMAGE) Study. *J Am Heart Assoc* 2017;**6**. doi: 10.1161/jaha.116.005231
6. Khan SS, Ning H, Shah SJ, *et al.* 10-Year Risk Equations for Incident Heart Failure in the General Population. *J Am Coll Cardiol* 2019;**73**:2388-2397. doi: 10.1016/j.jacc.2019.02.057
7. Shah SJ, Kitzman DW, Borlaug BA, *et al.* Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. *Circulation* 2016;**134**:73-90. doi: 10.1161/circulationaha.116.021884
8. Ho JE, Enserro D, Brouwers FP, *et al.* Predicting Heart Failure With Preserved and Reduced Ejection Fraction: The International Collaboration on Heart Failure Subtypes. *Circ Heart Fail* 2016;**9**. doi: 10.1161/circheartfailure.115.003116
9. Bhatt AS, Ambrosy AP, Velazquez EJ. Adverse Remodeling and Reverse Remodeling After Myocardial Infarction. *Curr Cardiol Rep* 2017;**19**:71. doi: 10.1007/s11886-017-0876-4
10. Kapoor JR, Kapoor R, Ju C, *et al.* Precipitating Clinical Factors, Heart Failure Characterization, and Outcomes in Patients Hospitalized With Heart Failure With Reduced, Borderline, and Preserved Ejection Fraction. *JACC Heart Fail* 2016;**4**:464-472. doi: 10.1016/j.jchf.2016.02.017
11. Fonarow GC, Abraham WT, Albert NM, *et al.* Factors identified as precipitating hospital admissions for heart failure and clinical outcomes: findings from OPTIMIZE-HF. *Arch Intern Med* 2008;**168**:847-854. doi: 10.1001/archinte.168.8.847
12. Ferreira JP, Girerd N, Pellicori P, *et al.* Renal function estimation and Cockcroft-Gault formulas for predicting cardiovascular mortality in population-based, cardiovascular risk, heart failure and post-myocardial infarction cohorts: The Heart 'OMics' in AGEing (HOMAGE) and the high-risk myocardial infarction database initiatives. *BMC Med* 2016;**14**:181. doi: 10.1186/s12916-016-0731-2
13. Jacobs L, Thijs L, Jin Y, *et al.* Heart 'omics' in AGEing (HOMAGE): design, research objectives and characteristics of the common database. *J Biomed Res* 2014;**28**:349-359. doi: 10.7555/jbr.28.20140045
14. Fry DAR, Moffat S, Gordon M, Singh UK Biobank Biomarker Project: Companion Document to Accompany Serum Biomarker Data. doi: [https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/serum\\_biochemistry.pdf](https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/serum_biochemistry.pdf). Published online ahead of print.
15. Ho FK, Celis-Morales C, Gray SR, *et al.* Child maltreatment and cardiovascular disease: quantifying mediation pathways using UK Biobank. *BMC Med* 2020;**18**:143. doi: 10.1186/s12916-020-01603-z

16. Rossello X, González-Del-Hoyo M. Survival analyses in cardiovascular research, part II: statistical methods in challenging situations. *Rev Esp Cardiol (Engl Ed)* 2022;**75**:77-85. doi: 10.1016/j.rec.2021.07.001
17. Natarajan S, Lipsitz SR, Rimm E. A simple method of determining confidence intervals for population attributable risk from complex surveys. *Stat Med* 2007;**26**:3229-3239. doi: 10.1002/sim.2779
18. Elgendy IY, Mahtta D, Pepine CJ. Medical Therapy for Heart Failure Caused by Ischemic Heart Disease. *Circ Res* 2019;**124**:1520-1535. doi: 10.1161/circresaha.118.313568
19. Pfeffer MA, Shah AM, Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. *Circ Res* 2019;**124**:1598-1617. doi: 10.1161/circresaha.119.313572
20. Patel N, Chen O, Donahue C, *et al.* Impact of diabetes on heart failure incidence in adults with ischemic heart disease. *J Diabetes Complications* 2017;**31**:1597-1601. doi: 10.1016/j.jdiacomp.2017.07.011
21. Wellings J, Kostis JB, Sargsyan D, Cabrera J, Kostis WJ. Risk Factors and Trends in Incidence of Heart Failure Following Acute Myocardial Infarction. *Am J Cardiol* 2018;**122**:1-5. doi: 10.1016/j.amjcard.2018.03.005
22. Rossello X, Ferreira JP, McMurray JJ, *et al.* Editor's Choice- Impact of insulin-treated diabetes on cardiovascular outcomes following high-risk myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2019;**8**:231-241. doi: 10.1177/2048872618803701
23. Haig C, Carrick D, Carberry J, *et al.* Current Smoking and Prognosis After Acute ST-Segment Elevation Myocardial Infarction: New Pathophysiological Insights. *JACC Cardiovasc Imaging* 2019;**12**:993-1003. doi: 10.1016/j.jcmg.2018.05.022
24. Gerber Y, Rosen LJ, Goldbourt U, Benyamini Y, Drory Y. Smoking status and long-term survival after first acute myocardial infarction a population-based cohort study. *J Am Coll Cardiol* 2009;**54**:2382-2387. doi: 10.1016/j.jacc.2009.09.020
25. Löfman I, Szummer K, Dahlström U, Jernberg T, Lund LH. Associations with and prognostic impact of chronic kidney disease in heart failure with preserved, mid-range, and reduced ejection fraction. *Eur J Heart Fail* 2017;**19**:1606-1614. doi: 10.1002/ejhf.821
26. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. *Jama* 1996;**275**:1557-1562. doi: 10.1016/j.jacc.2009.09.020
27. Regnault V, Lagrange J, Pizard A, *et al.* Opposite predictive value of pulse pressure and aortic pulse wave velocity on heart failure with reduced left ventricular ejection fraction: insights from an Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) substudy. *Hypertension* 2014;**63**:105-111. doi: 10.1161/hypertensionaha.113.02046
28. Dobre D, Kjekshus J, Rossignol P, *et al.* Heart rate, pulse pressure and mortality in patients with myocardial infarction complicated by heart failure. *Int J Cardiol* 2018;**271**:181-185. doi: 10.1016/j.ijcard.2018.05.017
29. Ambrosy AP, Vaduganathan M, Mentz RJ, *et al.* Clinical profile and prognostic value of low systolic blood pressure in patients hospitalized for heart failure with reduced ejection fraction: insights from the Efficacy of Vasopressin Antagonism in Heart Failure: Outcome Study with Tolvaptan (EVEREST) trial. *Am Heart J* 2013;**165**:216-225. doi: 10.1016/j.ahj.2012.11.004
30. Ather S, Chan W, Chillar A, *et al.* Association of systolic blood pressure with mortality in patients with heart failure with reduced ejection fraction: a complex relationship. *Am Heart J* 2011;**161**:567-573. doi: 10.1016/j.ahj.2010.12.009



31. Ahmad FS, Ning H, Rich JD, *et al.* Hypertension, Obesity, Diabetes, and Heart Failure-Free Survival: The Cardiovascular Disease Lifetime Risk Pooling Project. *JACC Heart Fail* 2016;**4**:911-919. doi: 10.1016/j.jchf.2016.08.001
32. Lavie CJ, Arena R, Alpert MA, Milani RV, Ventura HO. Management of cardiovascular diseases in patients with obesity. *Nat Rev Cardiol* 2018;**15**:45-56. doi: 10.1038/nrcardio.2017.108
33. Stienen S, Ferreira JP, Girerd N, *et al.* Mean BMI, visit-to-visit BMI variability and BMI changes during follow-up in patients with acute myocardial infarction with systolic dysfunction and/or heart failure: insights from the High-Risk Myocardial Infarction Initiative. *Clin Res Cardiol* 2019;**108**:1215-1225. doi: 10.1007/s00392-019-01453-7
34. von Bibra H, Paulus W, St John Sutton M. Cardiometabolic Syndrome and Increased Risk of Heart Failure. *Curr Heart Fail Rep* 2016;**13**:219-229. doi: 10.1007/s11897-016-0298-4
35. Selvin E, Lazo M, Chen Y, *et al.* Diabetes mellitus, prediabetes, and incidence of subclinical myocardial damage. *Circulation* 2014;**130**:1374-1382. doi: 10.1161/circulationaha.114.010815
36. Kannel WB, D'Agostino RB, Silbershatz H, *et al.* Profile for estimating risk of heart failure. *Arch Intern Med* 1999;**159**:1197-1204. doi: 10.1001/archinte.159.11.1197
37. Butler J, Kalogeropoulos A, Georgiopoulou V, *et al.* Incident heart failure prediction in the elderly: the health ABC heart failure score. *Circ Heart Fail* 2008;**1**:125-133. doi: 10.1161/circheartfailure.108.768457
38. Agarwal SK, Chambless LE, Ballantyne CM, *et al.* Prediction of incident heart failure in general practice: the Atherosclerosis Risk in Communities (ARIC) Study. *Circ Heart Fail* 2012;**5**:422-429. doi: 10.1161/circheartfailure.111.964841
39. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med* 2017;**36**:4391-4400. doi: 10.1002/sim.7501