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Risk factors for the development of heart failure in patients with or without prior myocardial infarction

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This article refers to ‘Comparing and contrasting risk factors for heart failure in patients with and without history of myocardial infarction: data from HOMAGE and the UK Biobank’ by T. Rastogi et al., published in this issue on pages 976–984.

One in five men and women will develop heart failure (HF) during their lifetime.¹ Once patients have developed HF, their mortality and morbidity are high.² Identifying those patients at risk for the development of HF is therefore important. In particular, modifiable risk factors – like hypertension, hypercholesterolaemia, obesity, smoking and diabetes mellitus – have the potential to prevent HF and are cost-effective public health interventions.³,⁴ Cardiac ischaemia, through either a previous myocardial infarction (MI) or coronary artery disease (CAD), is among the chief risk factors for developing HF.⁵,⁶ From studies in patients with prevalent HF we learned that patients with ischaemia and HF have unique characteristics: they are more often men, rather have HF with reduced ejection fraction (HFrEF) than HF with preserved ejection fraction (HFpEF), and have more comorbidities.⁷ Importantly, network analysis of proteins highlighted activation of unique pathophysiological pathways in patients with ischaemia, relating to inflammation, endothelial dysfunction, coagulation and atherosclerosis.⁸ Whether cardiac ischaemia influences the association of risk factors for incident HF is important to design effective prevention strategies.

Against this background, in this issue of the Journal, the study by Rastogi et al.⁹ provides new insights into the modifying effects of MI on risk factors for HF. The authors used data from 26,478 participants of the Heart ‘OMics’ in AGEn (HOMAGE) database to investigate whether a previous history of MI modified the association between risk factors and incident HF hospitalization. Their results were validated in 500,001 participants from the UK Biobank study. The authors found that male sex, older age, and higher heart rate were associated with incident HF, regardless of prior MI. In participants with a prior MI, smoking status, diabetes, and a worse renal function were associated with new-onset HF, but not those without a previous MI. Higher body mass index, elevated systolic blood pressure, and higher blood glucose levels were significantly associated with HF onset in participants without prior MI, but not in participants with a previous MI. The authors observed similar associations in multivariable models and external validation in the UK Biobank cohort.

Rastogi and colleagues need to be complimented for their study. Their results support personalized primary and secondary prevention strategies depending on the presence of a prior MI. Strengths of the study include the large sample size and use of a large validation cohort. The study results should also be interpreted in light of various limitations. First, MI was defined by history alone. No data were available regarding the timing of MI, whether it was transmural or subepicardial, or if it occurred multiple times or only once. The timing and extent of a previous MI might impact the risk of developing HF. There was a notable difference in the proportion of patients developing HF after MI in the derivation and validation cohort. The incidence of new-onset HF was almost three-fold higher in the participants with a prior MI in the validation than in the derivation cohort. This significant difference in the risk of new-onset HF in patients with a history of MI suggests that MI in participants from the validation cohort was perhaps more recent, more severe, or both. Furthermore, participants in the validation cohort were younger and had fewer comorbidities, such as diabetes and hypertension, than the derivation cohort. In addition, the prevalence of prior MI was 27% in the derivation cohort compared to 0.91% in the validation cohort. This could be attributed to a younger study population but could also be due to a higher percentage of smokers (30% vs. 10%) and men (70% vs. 45%) in...
the validation and derivation cohort, respectively. The abovementioned differences might have influenced the modifying effect of a prior MI. Furthermore, data about the type of HF (i.e., HFrEF vs. HFpEF) were unavailable in this study. Risk factors for incident HFrEF and incident HFpEF are different. For example, smoking and a previous MI are more important risk factors for HFrEF. Obesity, atrial fibrillation and hypertension are generally considered more important risk factors for HFpEF. However, a prior MI is also found in patients with HFpEF, especially in the setting of a subepicardial infarction. Therefore, the incident HF cases in the study by Rastogi et al. were likely a mixed bag of patients with HFpEF and HFrEF with ischaemic and non-ischaemic aetiology.

Regardless of the limitations, Rastogi et al.’s study adds to compelling evidence that excess HF risk conferred by comorbidities should not be considered individually. Instead, we should recognize the intimate shared links between comorbidities and risk factors that determine HF risk. Rarely do elderly individuals have only one comorbidity. Indeed, more than 54% of individuals aged >65 years living in the United Kingdom will have more than two comorbidities by 2035. Studies from patients with prevalent HF demonstrated that comorbidities cluster in unique patterns, which differ according to geographic region and possibly determine whether patients have HFrEF or HFpEF. This is likely due to common risk factors of comorbidities, which ultimately lead to HFrEF or HFpEF. In the present study, a history of smoking was associated with an increased risk of HF in patients with a prior MI. Simultaneously, smoking is a significant risk factor for CAD and, therefore, MI might ultimately be a shared risk factor. On the other hand, obesity was more strongly related to new-onset HF in participants without a prior MI. This effect could be mediated by obesity-related hypertension and diabetes, both identified as comorbidities for incident HF in this group. Unfortunately, comorbidities are subject to compound interest: the odds of developing new conditions are higher in people with pre-existing comorbidities than in those without. Identifying relevant interactions between comorbidities deepens our understanding of shared risk factors and can aid in identifying the first tipping stone leading to a common final pathway of HFrEF or HFpEF (Figure 1). Furthermore, identifying risk factors that contribute most to new-onset HF in the context of prior MI versus no prior MI can guide preventive strategies in these patients. On a pathophysiological level, interactions between comorbidities cause the activation of multiple complex disease pathways leading to HF. Disentangling disease pathways requires consideration of these interactions. Multi-omic approaches enable linking specific

![Figure 1](https://via.placeholder.com/150)

**Figure 1** The interplay between multimorbidity, number of involved pathophysiological pathways and the risk of new-onset heart failure (HF).
phenotypical features to underlying pathophysiological pathways, giving more insight in the interplay between comorbidities and the risk of new-onset HF. Future research should consider the complex interplay between comorbidities in preventing HF to identify shared risk factors for prevention. Studies identifying pathophysiological pathways and treatment targets in patients with prevalent HF should consider the interaction between multiple comorbidities, pathophysiological pathways and left ventricular ejection fraction phenotypes.

In conclusion, the study by Rastogi and colleagues provides crucial new evidence highlighting the interplay between risk factors, multimorbidity, and the risk of new-onset HF. The present study results add to the existing evidence of shared links between comorbidities and the risk of new-onset HF. The present study crucially highlights evidence of related shared evidence of shared links between comorbidities, risk factors, multimorbidity, and the risk of new-onset HF. The present study adds to the existing evidence of shared links between comorbidities and the risk of new-onset HF. The present study crucially highlights new evidence of shared links between comorbidities, risk factors, multimorbidity, and the risk of new-onset HF. The present study crucially highlights new evidence of shared links between comorbidities, risk factors, multimorbidity, and the risk of new-onset HF. 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