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EDITORIAL COMMENT

The pathophysiological and clinical relevance of combined measurement of natriuretic peptides and cardiac troponins for risk prediction of incident heart failure in community-dwelling individuals

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This article refers to 'Relationship between body mass index, cardiovascular biomarkers and incident heart failure' by N. Suthahar *et al.*, published in this issue on pages 396–402.

Cardiovascular biomarkers, particularly natriuretic peptides (NPs) and cardiac troponins (cTn), are important tools for diagnosis, risk stratification and follow-up of patients with heart failure (HF).[1] It is well known that both sex and body mass index (BMI) influence the relationship between the severity of cardiac disease and circulating levels of cardiovascular biomarkers.[1–3] Therefore, sex and BMI should be regarded as important confounding factors whenever cardiovascular biomarkers are evaluated, including when they are measured for the prediction of incident HF in the general population.[1–3]

From a physiological perspective, circulating levels of NPs are higher (about two-fold) in healthy women than in age-matched men during the fertile period of life.[1–3] This sex-specific difference is predominantly due to the antagonistic action of sex-steroid hormones on the production of cardiac NPs from cardiomyocytes: oestrogens have a positive action, while male steroid hormones (especially testosterone) a negative one.[1–3] On the contrary, circulating levels of cTn are higher in healthy men than in women.[1,4–6] Some authors have suggested that circulating levels of cTn, measured with high-sensitivity (hs-cTn) assays, reflect the turnover of cardiomyocytes.[4–6] According to this hypothesis, the circulating levels of hs-cTn in healthy adults should be considered as a reliable estimate of the physiological renewal of myocardial tissue, which is on average higher in men than in women.[4–6] From a pathophysiological point of view, macrovascular coronary artery disease and myocardial infarction are the leading causes of HF in men, whereas coronary microvascular dysfunction, hypertension and immuno-inflammatory mechanisms are thought to play a greater role in the development of HF in women.[1] Accordingly, the absolute number of incident HF cases was 9% higher in men than in women, but among older individuals (>80 years), the absolute number of HF cases was higher in women.[1] From a clinical point of view, the different cut-off levels recommended for men and women may be confounding for clinicians (in particular for hs-cTn and NP assay).[1]

With respect to BMI, the interplay of obesity, weight loss and HF has not been completely characterized.[2,3,7] A recent meta-analysis indicated that the risk of all-cause mortality is lower in the overweight group and that there is a "J-curve" relationship between BMI and the risk of incident HF.[7] These data confirm the presence of an obesity paradox in patients with HF. This paradox has been attributed to many pathophysiological factors, but the exact mechanisms remain unclear.[2,3,7] It is conceivable that the combined use of some biomarkers, specific for different tissues and related to different pathophysiological mechanisms, should provide more accurate and objective information about several biological or pathological processes related to the obesity paradox in patients with HF.[1]

In this issue of the Journal, Suthahar *et al.*[8] evaluated whether BMI influences the association between 13 cardiovascular biomarkers (NPs, cTn, and other 11 markers such as hormones, cytokines and growth factors) and incident HF in 8202 community-dwelling individuals (mean age 49 ± 13 years, 50% men, 41% overweight, 16% obese) from the Prevention of Renal and Vascular End-stage Disease (PREVEND) study. During a mean follow-up of 11 ± 3 years, a total of 357 incident HF events were recorded in the total population, including 71 events in lean individuals, 178 in overweight

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Table 1 Biochemical and biological characteristics of cardiac troponins and natriuretic peptides

	Molecular weight	Amino acid chain (*n*)	Biological function	Intra-individual variability	Inter-individual variability	Plasma half-life
Cardiac troponins						
cTnI	24 kD	206	Sarcomeric protein	13%	50%	~2 h
cTnT	36 kD	287	Sarcomeric protein	8%	40%	~2 h
Natriuretic peptides						
BNP	3.5 kD	32	Peptide hormone	40–60%	40–60%	15–20 min
NT-proBNP	8.4 kD	76	Inactive peptide	30–50%	40–60%	60–120 min

BNP, B-type natriuretic peptide; cTnI, cardiac troponin I; cTnT, cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

individuals and 108 in obese individuals. Among all the biomarkers considered, only N-terminal pro-B-type NP (NT-proBNP) [hazard ratio (HR) 1.89, 95% confidence interval (CI) 1.55–2.30; $P < 0.001$], mid-regional pro-atrial NP (MR-proANP) (HR 1.49, 95% CI 1.19–1.85; $P < 0.001$), and high-sensitivity cardiac troponin T (hs-cTnT) (HR 1.51, 95% CI 1.32–1.72; $P < 0.001$) independently predicted incident HF.[8] Furthermore, NT-proBNP and MR-proANP displayed negative correlations with BMI after accounting for potential confounders. In a model including also clinical risk factors, only NT-proBNP (HR 1.82, 95% CI 1.41–2.36; $P < 0.001$) and hs-cTnT (HR 1.31, 95% CI 1.13–1.15; $P < 0.001$) remained significantly associated with incident HF. A combination of NT-proBNP and hs-cTnT improved discrimination as well as model fit of the HF risk prediction model in overweight and obese individuals.[8]

Some points should be considered when interpreting these results. First, individuals who developed incident HF during follow-up were not divided into the categories of preserved, mid-range and reduced ejection fraction, as recommended by the European Society of Cardiology (ESC) guidelines.[9] This is relevant because obesity and type 2 diabetes are important risk factors, especially for the development of HFpEF. Indeed, 70–80% of patients with established HFpEF are obese, and nearly half have diabetes.[10] HFpEF is also more frequent in women than in men.[9,10] Second, individuals in the PREVEND cohort[8] were younger than patients with HF considered in a recent meta-analysis evaluating the relation between obesity and incident HF (49 ± 13 years vs. 53 ± 8 years).[7] For these reasons, the conclusions of this study do not automatically apply to other general population settings.

Despite these possible limitations, these results confirm the greater prognostic value of cardiac-specific biomarkers compared to a large group of other markers and clinical risk factors in community-dwelling individuals.[8] Another very important observation is that NPs and hs-cTn yield independent prognostic significance in the general population.[8] This can be attributed to the fact that circulating levels of NPs and hs-cTn may be differently affected by the mechanisms responsible for cardiac dysfunction and/or damage.[11] An increase in both biomarkers suggests that some powerful stressor mechanisms have already caused relevant alterations of cardiac function (increasing NPs), as well as a significant damage of cellular structure (increasing hs-cTn).[11]

Compared with NPs, hs-cTn show more favourable analytical and biological characteristics as a cardiovascular risk marker. In particular, hs-cTn show a considerably lower intra-individual (~8%) than inter-individual variability (~50%) in healthy adult subjects.[12] On the contrary, NPs have similar intra-individual and inter-individual variability (~50%) (*Table 1*). Accordingly, hs-cTn methods are able to estimate a difference between serial (or more) measurements with an error of about 30% for biomarker concentration at the cut-off level (i.e. the 99th percentile of the reference population).[12] This excellent analytical performance of hs-cTn methods is critical for early diagnosis of acute myocardial infarction using algorithms based on serial change in the cardiac biomarker ≤3 h, as suggested by the latest ESC guidelines.[13] Another important example is the estimation of cardiovascular risk in community or general populations, as also indicated by the results from the PREVEND study.[8] Furthermore, two very recent expert documents[12,14] strongly support the use of hs-cTn methods to identify individuals at highest risk of developing symptomatic HF, possibly resulting in early diagnosis and improved outcome.

For cardiovascular risk assessment in the general population, the use of sex-specific cut-offs is well demonstrated for high-sensitivity cardiac troponin I assays, with lower cut-off values in women than men.[14,15] It has been proposed that sex-specific B-type NP and NT-proBNP cut-points (i.e. lower cut-points in men than women) may rule out HF more accurately.[1] However, there is currently no experimental evidence to support this hypothesis, and specific studies are needed to examine the value of cardiac-specific biomarkers in men and women for risk evaluation of incident HF in the general population.[14,15] These studies should specifically evaluate the cost–benefit ratio of a screening in the general population to identify individuals with a higher risk of progression to symptomatic HF. Finally, the opportunity to perform single or multiple measurements, and to dose one or multiple biomarkers should be specifically evaluated.[14,15]

Conflict of interest: none declared.

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