have a positive, non-linear association with the development of STEMI at younger ages.

### PROTEOMICS IDENTIFICATION AND EVALUATION OF A COLLAGEN SUB-TYPE WITH POTENTIAL TO SUPPORT IMPROVEMENTS IN DIAGNOSIS AND MANAGEMENT OF HEART FAILURE

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#### Introduction

Heart failure (HF) is an extremely debilitating condition that currently affects at least 16,500 people in Northern Ireland. Ischemic heart disease and cardiac fibrosis are the primary causes of end-stage HF. Greater understanding of molecular changes associated with this underlying pathophysiology could lead to the identification of novel biomarkers and therapeutic targets for improved diagnosis and management of HF.

#### Methods

Unbiased, deep proteomic analysis of individual left ventricular tissue samples from patients with HF (n=30) and patients without HF (NF; n=9) was performed using the diaPASEF workflow on a timsTOF Pro mass spectrometer. Validation of notable protein expression changes were performed by ELISA. Protein expression changes and correlations with clinical data were assessed using appropriate non-parametric testing of log-transformed data. Differentially expressed proteins were identified based on an observed fold change of $\leq 1.5$ or $\geq -1.5$ and q-value $\leq 0.005$.

#### Results

HF patients included patients with hypertrophic obstructive cardiomyopathy (HOCM; n=12), dilated cardiomyopathy (DCM; n=9) and ischemic cardiomyopathy (ISCM; n=9). One hundred and eighteen proteins were identified as being significantly associated with HF, irrespective of the underlying aetiology. Among these, a collagen sub-type, with a reported role in myocardial development, (referred to as ‘COL-CT’), was identified as being significantly elevated in HF (p=0.012), with greatest increase observed in patients with ISCM. Existing transcriptomic data for these samples corroborated these findings at gene level. Measurement of ‘COL-CT’ is more predictive of HF than combined measurement of the cardiac-specific collagen sub-types I and III (AUC 0.847 vs AUC 0.778). HF-associated changes in ‘COL-CT’ protein expression were validated in silico in an independent LV tissue dataset (n=7 NF v n=20 HF, p<0.001), and further confirmed in-house by ELISA-based analysis of serum samples from an independent patient cohort (n=50 NF v N=54 HF, p= 0.0004). ‘COL-CT’ is enriched in atrial regions of the heart and serum levels were found to be significantly positively correlated with left atrial volume (p<0.0001).

#### Conclusions

‘COL-CT’ has yet to be fully investigated in the context of myocardial disease. Here we report a significant association between ‘COL-CT’ and HF. These observations have been validated in multiple independent clinical cohorts, in various sample types. Circulating levels of ‘COL-CT’ in serum provide evidence that ‘COL-CT’ may have clinical utility as a minimally invasive biomarker for HF. Moreover, strong association with ISCM and a likely role in cardiac fibrosis suggest that ‘COL-CT’ should be further investigated as a therapeutic target for management of HF.