1. **Full Title:**
Matrix metalloproteinases and Incident Heart Failure in a Population Based Cohort

2. **Abbreviated Title (Length 26 characters):** Matrix metalloproteinases and Heart Failure

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. O.B. [please confirm with your initials electronically or in writing]

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4. **Timeline:**
Analysis to start immediately; Manuscript to be written and sent for publication within one year of approval

4. **Rationale:**
The link between inflammation and heart failure (HF) was first recognized in 1990, when elevated levels of tumor necrosis factor (TNF) were first reported in HF patients.¹ Both innate and adaptive immune responses are activated in the heart in response to tissue injury (e.g.,
ischemia or hemodynamic overloading). When the inflammatory response becomes dysregulated and chronic in nature, it can lead to collateral myocardial damage which eventually lead to progressive LV dysfunction and adverse LV remodeling.\textsuperscript{2} Numerous reports of an increasing number of cytokines, chemokines, and matrix metalloproteinases (MMPs) have since established a link between inflammatory mediators and tissue injury and myocardial response to stress in the etiology of HF.\textsuperscript{3-7} Elevated levels of inflammatory mediators have also been reported in HF with preserved ejection fraction (EF) HFrEF and those with reduced EF (HFrEF) and in acute decompensated HF,\textsuperscript{8,9} suggestive of a role for an ongoing inflammatory response in all manifestations of clinical HF.

The extracellular matrix provides a skeleton for myocytes and influences their size and shape. Changes in the extracellular matrix may be causally related to remodeling of the ventricles, resulting in progression of HF. One of the biological effects of inflammatory mediators is the activation of MMPs and tissue inhibitors of MMPs (TIMPs), which regulate collagen turnover in the extracellular matrix, and may play a key role in ventricular remodeling and myocardial fibrosis. Matrix metalloproteinases (MMPs) are a family of 25 proteolytic enzymes that regulate extracellular matrix (ECM) turnover and inflammatory signaling. They have a strategic role in the regulation of collagen turnover, which, in the heart, is crucial for keeping the most efficient shape of the ventricles. MMPs present in the myocardium are capable of degrading all the matrix components of the heart, and are the driving force behind myocardial matrix remodeling. This remodeling is responsible for progressive worsening of the pump function and heart failure development following serious injury (i.e., Ischemia, viral infections, ventricular overloading).\textsuperscript{10-12} A clear cause/effect relationship between MMPs and the LV remodeling process has been demonstrated through the use of animal models of developing HF with transgenic models and through the use of pharmacological MMP inhibition studies.\textsuperscript{13-15} Moreover, in pathological specimens of human HF, the level of MMPs, and their induction and activation systems are increased.\textsuperscript{16} Also, MMPs levels were shown to have prognostic value in HF.\textsuperscript{17} Cardiac repair after a myocardial infarction (MI) is a highly complex process that involves temporarily overlapping phases which comprehend inflammation, new tissue formation, and tissue remodeling.\textsuperscript{18} MMPs process cytokine and ECM substrates to regulate the inflammatory and fibrotic components of the wound healing response to MI.\textsuperscript{19} In the setting of MI, MMPs are significantly increased within hours of the infarction, following the local activation of cytokines and infiltration of inflammatory cells.\textsuperscript{20} However, as the healing process continues, the MMP concentrations decrease, but then are followed by a second wave of activation, which is associated with more ventricular dilation and progression toward heart failure.\textsuperscript{21} An important cause of clinical heart failure is diastolic dysfunction secondary to LV hypertrophy.\textsuperscript{22} Abnormalities in the structure and the composition of the ECM have been demonstrated to contribute to myocardial compliance and, in turn, to influence specific determinants of diastolic function.\textsuperscript{23,24} Evidence exists supporting the concept that alterations in myocardial MMP activity can facilitate collagen accumulation in developing hypertrophy.\textsuperscript{25,26}

In summary, although these aforementioned studies support the hypothesis that ECM biomarkers are expressed in HF, data are lacking on the association between these biomarkers in asymptomatic individuals and incident HF.

5. Main Hypothesis/Study Questions:
Main hypothesis: Plasma levels of MMPs/TIMPs are associated with incident HF hospitalizations in ARIC cohort
Study Aims:
  a. To assess whether MMPs and TIMPs predict incident HF hospitalizations in ARIC cohort

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodological limitations or challenges if present).

Study Design, Inclusion/exclusion:

Study design: We will investigate the associations of levels of MMPs/TIMPs with incident hospitalization for HF in ARIC cohort.

Inclusions: Participants in ARIC Carotid MRI Study who have MMP measures available will be included in the analysis. Previous studies have examined the association between MMPs and carotid MRI characteristics.

Exclusions: Standard ARIC exclusions (race exclusions for different communities) will apply. Subjects will also be excluded for missing information on MMP measurement, those with prevalent heart failure and those with missing information for heart failure data.

Summary of data analysis:
Participant characteristics and cardiac parameters will be reported as means and standard deviations, as medians and inter-quartile ranges (IQR), or as frequencies and percent, where appropriate. If lack of normality is not a concern and transformation is not required then conventional statistics will be used. For non-normal data, transformations and/or non-parametric testing will be used. Chi-square analyses will be used for comparison of categorical variables and analysis of variance (ANOVA) will be used for continuous variables. Heart failure hazard ratios across MMP categories will be calculated using Cox-proportional hazards models. The proportionality assumption of all Cox models will be assessed by inspecting the log (-log [survival function]) curves. Follow up time will begin at entry into the study (until December 2012). Regression models will be first adjusted for age, sex and race. Secondary models will be adjusted for additional variables used in ARIC HF model (model 1 plus SBP, BP meds, current smoking, diabetes, BMI, heart rate). The following MMPs and TIMPs were measured as previously reported and will be used for analyses; MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9 and TIMP-1.

Provide some limitations here: Small sample size of the ARIC MRI study, missing heart failure treated as an outpatient.

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes ___X___ No

   b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? _____ Yes _____ No

8.a. Will the DNA data be used in this manuscript? _____ Yes ___X___ No
8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ Yes  ____ No

9. The lead author of this manuscript proposal has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.

   ____ Yes  ____X____ No

References


