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Title: Treating Maladaptive Cardiac Fibrosis and Preventing Symptomatic Heart Failure Among C-AYA Cancer Survivors

Background: Mitigating late-effects from cancer therapy among survivors diagnosed in childhood, adolescence, or young adulthood (C-AYAs) is a recognized national research priority supported by the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act (Public Law# 117-350). Heart failure (HF) is a leading cause of death among C-AYAs. Subclinical (Stage B) HF occurs in one third of C- AYA cancer survivors by 30 years of age,3 and 11% of survivors with Stage B heart failure will have overt heart failure within 10 years.4 C-AYAs who receive anthracyclines have a four times greater risk for HF compared with those who do not.5,6 The Nod-like receptor protein 3 (NLRP3) inflammasome contributes to maladaptive fibrosis in the setting of anthracycline mediated HF.7 In animal models sacubitril-valsartan, an FDA approved therapy for many populations with HF, has been shown to reduce NLRP3 activation.8-10 However, it remains unproven whether early intervention can mitigate NLRP3 signaling and maladaptive cardiac fibrosis among C-AYAs with anthracycline mediated Stage B HF.
Hypothesis: Sacubitril-valsartan will more effectively reduce markers of inflammation that lead to cardiac fibrosis among adult-age C-AYAs with anthracycline mediated Stage B HF than valsartan alone.

Specific Aims: 1) Correlate imaging markers of cardiac fibrosis and blood-based markers of NLRP3 signaling prior to intervention among C-AYA survivors with Stage B HF. 2) Determine the ability of sacubitril-valsartan to impact markers of cardiac fibrosis and NLRP3 signaling among C-AYA cancer survivors with Stage B HF.

Methods/Study Design: This study will leverage the TREATHF clinical trial supported by the Robert A. Winn Diversity in Clinical Trials Career Development Award, to examine mechanistic underpinnings of maladaptive cardiac fibrosis among C-AYA cancer survivors with Stage B HF who are randomized in a 1:1 fashion to sacubitril-valsartan or valsartan. Cardiac magnetic resonance imaging (CMR) will be utilized at study entry and after completion of 6 and 12 months of sacubitril-valsartan or valsartan to quantify cardiac fibrosis. NLRP3 activation will be quantified at these time points through measurements of interleukin (IL) -18 and IL-1β. The impact of sacubitril-valsartan will be determined by comparing measurements of cardiac fibrosis at baseline and follow up exams.

Cancer Relevance: The goal of this research is to identify the best intervention to prevent Stage B HF related to cancer therapy from progressing to symptomatic heart failure. The proposed study will quantify the correlation between imaging and blood-based markers of maladaptive cardiac fibrosis and examine the ability of sacubitril-valsartan to impact cardiac fibrosis among C-AYA with Stage B HF. The results of this study will provide the foundation for a multi-site trial supported by an R01-type funding mechanism.