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EDITORIAL COMMENT

Exploring the Impact of Clonal Hematopoiesis on Heart Failure and Remodeling in Aortic Stenosis

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Clonal hematopoiesis of indeterminate potential (CHIP) has garnered significant attention in cardiovascular research due to its association with adverse outcomes, particularly in aging individuals with an increased prevalence of cardiovascular diseases (CVDs). CHIP refers to the acquisition of somatic mutations in hematopoietic cells, particularly in genes involved in epigenetic regulation and inflammatory pathways, such as *DNMT3A*, *TET2*, and *ASXL1*. These mutations are linked to age-related cardiovascular pathologies, including coronary artery disease and heart failure (HF).[1-4] However, there is limited research on CHIP's role in aortic stenosis (AS), particularly in patients undergoing transcatheter aortic valve implantation (TAVI), which is an increasingly utilized treatment for elderly, high-risk patients. Prior studies, such as those by Mas-Peiro et al, have demonstrated that CHIP is associated with increased post-TAVI mortality, providing essential understanding of its clinical significance.[5]

Building upon this finding, the study by Yao et al[6] in this issue of *JACC: Advances* is valuable for identifying CHIP's influence on HF hospitalizations (HFH) and for conducting the analysis within an Asian population. The authors report a CHIP prevalence of 36.4%, predominantly involving DNMT3A and TET2 mutations, which is notably consistent with frequencies observed in Western populations, despite differences in genetic predispositions and cardiovascular profiles within the Asian population.[5,7] This study by Yao et al[6] contributes to the evolving understanding of CHIP's clinical significance by focusing on its role in patients with severe AS undergoing TAVI. Through a comprehensive assessment of CHIP's relationship with inflammatory biomarkers, left ventricular (LV) remodeling, and subsequent adverse outcomes, the study highlights the implications of CHIP on the long-term outcomes of patients with AS.

A particularly critical finding of this study is its examination of CHIP's association with inflammatory markers and LV remodeling. The authors observed higher serum ferritin levels among CHIP carriers, indicating a pro-inflammatory state linked to adverse cardiovascular outcomes. This is consistent with the hypothesis that CHIP contributes to adverse remodeling processes via systemic inflammation, potentially exacerbating the pathophysiology of AS. By linking CHIP to both structural and functional cardiac changes, the study provides a more comprehensive understanding of CHIP's impact on patients with AS, suggesting that CHIP may influence clinical outcomes through mechanisms that extend beyond mortality alone. Although differences in C-reactive protein and interleukin-6 levels were not statistically significant, the elevated ferritin levels among CHIP carriers support the role of inflammation in cardiac remodeling. The insignificant changes in C-reactive protein and interleukin-6 levels could reflect the specific inflammatory profile of CHIP in AS or might be a limitation of the study's sample size, highlighting the need for larger cohorts to confirm these findings.

Additionally, the authors report significant associations between CHIP and echocardiographic markers of LV hypertrophy and a reduced LV chamber size. These structural changes may be indicative of a maladaptive response that exacerbates LV diastolic

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dysfunction. The finding that CHIP-positive patients exhibited a trend toward a higher E/e' ratio and an increased prevalence of grade 2 or 3 diastolic dysfunction suggests that CHIP may contribute to elevated LV filling pressures. This observation supports the hypothesis that CHIP promotes maladaptive remodeling, potentially through inflammatory pathways that alter myocardial structure and function.

While this study offers valuable insights, certain limitations warrant consideration. The retrospective, single-center design may limit the generalizability of findings, particularly given the homogeneity of the study population. Additionally, although the study successfully identifies associations between CHIP, HFH, and LV remodeling, the lack of cardiac magnetic resonance imaging data restricts the ability to assess myocardial fibrosis, a key feature of pathological remodeling in AS. Future studies incorporating cardiac magnetic resonance could investigate whether CHIP-positive patients exhibit greater degrees of myocardial fibrosis, potentially explaining the reduced capacity for reverse remodeling observed in this cohort.

This study's findings highlight the potential utility of CHIP as a biomarker for risk stratification in patients with AS, particularly those undergoing TAVI. Given that HFH is a major burden in this population, identifying patients at higher risk could enable more targeted follow-up and intervention strategies. While CHIP-related inflammation has been implicated in adverse cardiac remodeling, therapeutic interventions targeting CHIP itself may be more effective in slowing disease progression or preventing further deterioration rather than reversing established damage. For example, anti-inflammatory therapies could help modulate the inflammatory response driven by CHIP, potentially reducing its harmful impact on cardiac structure and function and lowering the risk of additional complications.

A recent study used data from the UK Biobank and Geisinger MyCode Community Health Initiative cohorts to perform two-sample Mendelian randomization, assessing the relationship between CHIP mutations and CVD.[8] Unlike previous studies, this study reported no causal association between CHIP and CVD and concluded that CHIP does not predict CVD in longitudinal risk evaluations.[8] However, it is important to note that the study only included coronary artery disease as a category of CVD, excluding heart failure and valvular heart disease. Well-designed prospective studies in this field are warranted to establish the causal relationship between CHIP and AS or LV remodeling and to evaluate therapies that may delay this pathological process.

In summary, the study by Yao et al[6] provides valuable insights into the role of CHIP in patients with AS undergoing TAVI, highlighting its association with outcomes such as HFH and adverse LV remodeling. Future investigations should focus on identifying effective interventions that address the underlying inflammatory processes associated with CHIP, with the goal of improving long-term outcomes in this high-risk patient population. This work represents an important step toward integrating genetic and molecular insights into personalized strategies for managing AS and related cardiovascular conditions.

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