Clonal Hematopoiesis – An Opportunity to Confront the Heart Failure Epidemic

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Clonal hematopoiesis driven by somatic mutations, often termed clonal hematopoiesis of indeterminate potential (CHIP), has emerged as an important and independent cardiovascular risk factor. This condition arises when somatic mutations acquired in certain genes, most frequently the epigenetic regulators *DNMT3A* and *TET2*, confer a competitive advantage to hematopoietic cells, enabling their clonal expansion and the propagation of the mutation to a substantial proportion of immune cells, which can influence inflammatory responses central to cardiovascular pathophysiology. A growing body of evidence has associated CHIP with atherosclerotic disease, heart failure (HF), arrhythmias, and myocarditis/pericarditis.[1-4] Among these conditions, HF stands out for its high prevalence in the aging population, socioeconomic impact, and complex pathophysiology. Now, in this issue of *JAMA Cardiology*, Flynn and colleagues provide new insight into the relationship between CHIP and HF, reporting the results of a large-scale analysis of CHIP and incident HF in approximately 415 000 individuals from the UK Biobank, followed for a median of 11.1 years.[5]

In their work, Flynn et al focused on individuals without prevalent HF, hematologic malignancy, or other CHIP-associated comorbidities. In multivariable-adjusted analyses, CHIP was associated with a higher risk of incident HF. Gene-specific analyses showed a substantially stronger effect for non-*DNMT3A* mutations than for *DNMT3A* mutations, underscoring the gene-specific heterogeneity of this association. Mediation analyses indicated that this relationship was largely, although not completely, independent of CHIP-related comorbidities. Among individual drivers, mutations in *DNMT3A*, *TET2*, *ASXL1*, *JAK2*, and spliceosome genes were significantly associated with increased HF risk. The association was particularly complex for *DNMT3A*, with only dominant-negative R882 hotspot mutations, but not other variants, linked to higher HF incidence. Furthermore, consistent with previous studies,[2,6] *DNMT3A*-mutant CHIP was more frequent in women, and the authors made the novel observation of a significant interaction between biological sex and *DNMT3A* mutations, as *DNMT3A*-mutant CHIP conferred higher HF risk in women, but not in men. As the authors rightfully acknowledge, these sex-related differences must be interpreted cautiously and as hypothesis-generating, as they may reflect differences in statistical power, mutational spectrum or HF phenotype distribution between men and women.

The study by Flynn and colleagues needs to be considered in the context of existing literature linking CHIP to HF development. Previous studies have shown that CHIP is associated both with an increased risk of incident HF and with worse clinical progression in patients with established disease.[3,7,8] However, most studies to date have focused on the most frequently mutated genes, the epigenetic regulatory genes *DNMT3A* and *TET2*, because of statistical power limitations. This left a significant knowledge gap regarding the potential role of less frequent CHIP mutations in HF development. In this setting, the most relevant finding of this new study likely lies in the gene-specific analyses of less frequent CHIP mutations, which reinforce the known associations between *TET2*, *ASXL1*, and *JAK2* and incident HF, while also providing the first robust evidence

of an association between CHIP driven by mutations in spliceosome genes and incident HF. These observations suggest that the contribution of CHIP to HF risk extends beyond the canonical epigenetic regulatory genes that have largely dominated the field to date and may involve a broader repertoire of genetic alterations with potentially distinct biological effects.

The methodological strengths of this work include its very large sample size, which enabled adequately powered gene-specific analyses of less frequent CHIP mutations, and the robust statistical approaches employed. Nonetheless, several important limitations must be considered. The study relies on whole-exome sequencing data, which offers limited sensitivity to detect mutant clones with variant allele fraction (VAF) below 5% (which typically indicates 10% mutant blood cells, assuming monoallelic mutations). These relatively small clones are common in the population and may be clinically relevant. Furthermore, the findings are derived from a single cohort. Therefore, replication in other populations using higher-sensitivity sequencing technologies will be essential to validate these observations and refine the VAF threshold that defines clinically meaningful CHIP in HF. Another critical aspect to consider relates to causality: while the CHIP–HF association is compelling, particularly for some genes, not all associations may reflect direct pathogenic effects. Some CHIP mutations expand faster under specific selective pressures that may independently contribute to HF risk. Disentangling causal effects from such confounding processes remains a key challenge in the field. Notably, Flynn and colleagues reported that less than 30% of the risk associated with non-*DNMT3A* CHIP mutations was mediated by comorbidities, supporting a direct contribution of these mutations to HF risk.

The clinical implications of the current work and of our growing understanding of the relationship between CHIP and HF are substantial. The use of the UK Biobank offers important advantages in this context, as it provides administratively linked clinical data and prolonged follow-up, enabling the investigation of progression toward symptomatic HF. At present, most patients with HF are diagnosed late—nearly 80% during hospitalization for acute decompensation—reflecting both insufficient prevention and delayed recognition of the disease.[9] Moreover, guideline-directed disease-modifying therapies remain largely restricted to patients with symptomatic HF (stages C/D AHA/ACC), mostly HFrEF, while the incidence of HFpEF continues to rise. Achieving a meaningful public health impact will require shifting the focus toward earlier stages of disease (pre-HF: stages A/B AHA/ACC), where prevention is still possible. Lifetime HF risk is now estimated at roughly 1 in 4, with nearly one-third of adults in stage A and up to one-third in stage B, yet therapeutic options at these stages are roughly limited to managing comorbidities.[10]

Considering the findings of Flynn *et al* and the accumulating evidence supporting the robust relationship between CHIP and HF, targeting CHIP or its effects may offer a new avenue for preventive strategies to confront the HF epidemic. The growing number of specialized CHIP clinics illustrates the potential to identify high-risk patients and improve HF prevention. These

clinics have been established in several institutions to improve the care of individuals incidentally found to carry CHIP mutations, often through cancer or cardiovascular genetic testing, and aim to provide risk stratification and counseling. As knowledge of the gene-specific effects of CHIP grows, there may be opportunities to tailor preventive strategies to the underlying biology of each mutated gene. For example, the strong proinflammatory signaling associated with some CHIP mutations may make carriers more likely to benefit from anti-inflammatory interventions. However, the field is still in its early stages, and well-designed clinical trials stratified by CHIP status will be required to determine whether mutation-specific interventions can effectively reduce HF risk.

In summary, this new work expands our understanding of the genetic heterogeneity underlying the CHIP–HF association. By shining light on less frequent CHIP subtypes, the study broadens the conceptual framework for understanding how acquired mutations in hematopoietic cells contribute to cardiovascular disease. These insights may eventually help shape precision prevention strategies. Yet, substantial work remains to validate these findings, clarify the causal contribution of CHIP mutations to HF development, and translate them into actionable clinical interventions to confront this epidemic. The field has advanced remarkably over the past decade, but the path from genetic association to clinical application is long—and we are just at the beginning.

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