JACC: CARDIOONCOLOGY VOL. 8, NO. 3, 2026

EDITORIAL COMMENT

Clonal Hematopoiesis and Cardiometabolic Disease

Expanding Beyond a Hematologic Phenomenon

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Clonal hematopoiesis (CH), defined as the expansion of hematopoietic stem cell clones carrying acquired somatic mutations, is increasingly recognized as an age-related phenomenon and may represent a mechanistic link between aging and cardiovascular disease. Its implications extend beyond hematologic disorders to cardiometabolic diseases. The study by D'Mello et al[1] in this issue of *JACC: CardioOncology* provides a comprehensive systematic review and meta-analysis examining the association between CH and incident cardiometabolic outcomes.

Leveraging data from more than 650,000 individuals across 24 cohorts, the authors move beyond prior work focused on composite endpoints and instead examine individual outcomes, including myocardial infarction, stroke, cardiovascular mortality, and type 2 diabetes. By separating individual cardiovascular endpoints, they demonstrate consistent associations between CH and incident myocardial infarction (HR: ~1.14), stroke (HR: ~1.12), cardiovascular mortality (HR: ~1.20), and type 2 diabetes (HR: ~1.20). These findings align with and extend prior foundational observations linking CH of indeterminate potential to atherosclerotic cardiovascular disease and mortality.[2,3] Importantly, the consistency of associations across distinct endpoints supports the concept that CH reflects a systemic process contributing to cardiometabolic risk, rather than being confined to a single vascular phenotype. These observations are consistent with emerging evidence linking CH to a broader spectrum of cardiovascular conditions, including heart failure and atrial fibrillation.[4,5]

Another key strength of this work lies in its characterization of molecular heterogeneity. The observation that *TET2* mutations are more strongly associated with stroke, whereas *ASXL1* mutations are associated with cardiovascular mortality, is concordant with experimental data pointing to distinct inflammatory and thrombotic pathways across clones.[6,7] Similarly, the stronger association observed for larger clones (eg, variant allele frequency ≥ 10%) supports a dose-response relationship, further reinforcing biological plausibility. The inclusion of type 2 diabetes is also noteworthy. Whereas prior epidemiologic evidence has been inconsistent, this analysis supports a modest positive association between CH and incident diabetes, in line with mechanistic studies linking CH, particularly *TET2* mutations, to adipose inflammation and insulin resistance.[8]

Overall, this meta-analysis supports the role of CH as a systemic contributor to cardiometabolic risk, while highlighting its molecular heterogeneity and mutation-specific consequences. Together, these findings support a broader conceptualization of CH as a biological determinant of cardiometabolic disease, rather than a purely hematologic phenomenon.

Although the definition and measurement of CH are heterogeneous across studies, reflecting differences in sequencing platforms, gene panels, and variant allele frequency thresholds, the observation of consistent associations is reassuring and supports the robustness of the findings. Moreover, the use of random-effects models and multiple sensitivity analyses strengthens confidence that the findings are not driven by any single methodological approach. Although the magnitude of the associations is modest, with HRs of 1.1 to 1.2, this is consistent with other established biological cardiometabolic

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The author attests they are in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2026.05.004

JACC: CARDIOONCOLOGY, VOL. 8, NO. 3, 2026
JUNE 2026:243–244

risk factors, such as inflammatory markers (eg, high-sensitivity C-reactive protein).[9] Even modest relative risks may translate into substantial population-level impact, particularly given the increasing prevalence of CH with aging.

Beyond association, CH captures biological processes, particularly inflammation, that are not fully reflected in traditional risk factors, raising the possibility of additive or complementary value in risk stratification.

At present, no guidelines recommend routine screening for CH, and no therapies have been specifically validated to mitigate CH-associated cardiovascular risk.[10] Nevertheless, CH appears to be a reproducible marker of cardiometabolic risk across populations. The questions moving forward are how CH screening could be integrated into clinical practice, including whether CH improves risk prediction beyond established factors; how thresholds of clone size or mutation subtype should be defined; and whether the detection of CH could guide therapeutic decision-making.

Importantly, CH-related pathways may represent actionable targets for therapeutic intervention. Anti-inflammatory strategies, such as IL-1β inhibition, have demonstrated cardiovascular benefit, and it is plausible that individuals with CH, particularly those with inflammation-driven mutations, may achieve greater benefit from such therapies.[11] This raises the possibility that CH could serve not only as a biomarker of risk, but also as a tool for precision prevention.

Looking ahead, several priorities emerge. Standardization of CH definitions and measurement will be essential to facilitate comparability and clinical translation. Integration of CH with other layers of biology, including genomics, epigenomics, proteomics, and metabolomics, may enhance cardiovascular risk stratification and provide deeper insight into disease mechanisms. Longitudinal studies with repeated measures will be necessary to understand clonal dynamics over time, and interventional studies will ultimately be required to determine whether targeting CH-related pathways can reduce cardiometabolic risk. Studies in large, well-characterized multiethnic cohorts will be essential to better define the generalizability of these associations across populations. These efforts will be essential to determine whether CH represents a modifiable driver of cardiovascular disease or a biomarker of underlying cardiovascular risk.

In this context, the work by D'Mello et al[1] represents an important and timely contribution. By providing a comprehensive synthesis of the available evidence and highlighting both epidemiologic consistency and biological heterogeneity in the associations between CH and cardiometabolic outcomes, the authors help clarify the role of CH in cardiometabolic diseases. Their findings reinforce the view of CH as a meaningful component of cardiovascular risk. As the field advances, CH may increasingly serve as a novel avenue for risk assessment and precision prevention.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The author has reported that she has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS coronary artery disease, diabetes, genetics, ischemic disease