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# Clonal hematopoiesis and ischemic stroke

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**In this issue of *Blood*, Arends et al find an association between mutations causing clonal hematopoiesis (CH) and large artery atherosclerosis and white matter lesions in patients with ischemic stroke.[1] In a prospective study, patients with CH showed an increase in recurrent vascular events, stroke, and death compared with those without CH. The event rate is related to clone size, specific CH mutations, and the presence of multiple mutations. The study supports a causal role of CH in large artery atherosclerotic cardiovascular disease (CVD).**

CH has recently emerged as a major genetic risk factor for CVD.[2] CH arises when somatic mutations in leukemogenic genes endow a fitness advantage to hematopoietic stem and progenitor cells, leading to the clonal expansion of blood cells. CH is common among older people, occurring in >10% of people aged >70 years old.[2,3] CH commonly involves mutations in genes mediating epigenetic modifications (*TET2*, *DNMT3A*, and *ASXL1*), DNA damage response (*PPM1D* and *TP53*), or hematopoietic cytokine signaling ($JAK2^{V617F}$).[3] Although increasing the risk of hematologic malignancies, CH is much more commonly associated with the development of CVD,[2,3] including premature myocardial infarction and heart failure, and the causal role of CH in CVD has been demonstrated using atherosclerosis or heart failure mouse models with CH.[2,4] The association of CH with coronary heart disease and myocardial infarction in humans and with accelerated atherosclerosis in Tet2 or $Jak2^{V617F}$ CH mouse models suggests a potential association of CH with large artery ischemic stroke. One previous study showed an association of CH of indeterminate potential (CHIP, defined as CH-driving mutation variant allele frequency [VAF] >2% in the absence of clinical findings of hematopoietic malignancy) with ischemic stroke.[3] However, in another large population-based study using whole genome sequencing, CH was associated with hemorrhagic stroke or small vessel occlusive stroke but not large vessel atherosclerotic stroke.[5] Here, the authors assessed CH in 581 patients with first-ever ischemic stroke using targeted sequencing and its association with recurrent vascular events, including ischemic stroke and death, prospectively; the composite end point increased among patients with CH. However, this finding appeared to be driven by increased mortality, and a specific association of CH with ischemic stroke was not shown. Consistent with both earlier studies, the authors have provided evidence linking CH with large artery atherosclerotic disease and white matter lesions that are thought largely to reflect small vessel disease. However, the relative importance and etiology of different subtypes of stroke in patients with CH will require further study. Previous studies indicate increased CVD risk in CHIP with a VAF of >10%. Consistently, this article also demonstrates an increased component end point in a clone size–dependent fashion, with the highest risk of CH with a VAF of >10%. Interestingly, CH with a relatively low VAF of 1% to 10% is also associated with increased risk, suggesting that CH with a low VAF may also promote CVD risk.

In CH, a common underlying mechanism promoting atherosclerosis, heart failure, and other diseases appears to be increased myeloid cell inflammation, and common variants appear to uniformly increase coronary artery disease risk by about twofold. However, here, *TET2* and *PPM1D* CH, but not the commonest *DNMT3A* CH variants, were associated with the composite end point. The different impacts of various CH mutations on disease are mirrored by emerging evidence that shows distinct disease impacts and mechanisms for different genetic variants. For example, *DNMT3A* CHIP is associated with osteoporosis[6] but not with incident heart failure,[7] whereas its association with atherosclerotic CVD seems to be relatively weak as compared with some other common CH mutations such as *TET2* and $JAK2^{V617F}$. Although *Tet2* CHIP promotes atherosclerosis and heart failure by NLRP3 inflammasome activation, *Jak2V617F* CHIP worsens atherosclerosis by AIM2 inflammasome activation, highlighting the role of different underlying inflammatory mechanisms and potential treatments in CHIP.[4]

This study shows increased levels of the inflammatory biomarkers high-sensitivity C-reactive protein (CRP) and interleukin 6 (IL-6) as well as the endothelial activation biomarker VCAM-1. Consistent with previous reports, IL-1β levels were increased in individuals with *TET2* CH. IL-1β is a key inducer of IL-6, and increased signaling through the IL-1β/IL-6 axis may contribute to atherosclerotic CVD. In the canakinumab anti-inflammatory thrombosis outcome study, IL-1β antibodies reduced CVD in patients who achieved lower on-treatment IL-6 levels but not in patients whose IL-6 levels were above the study median value.[8] Furthermore, individuals with a common IL-6 receptor (IL-6R) variant, D358A, which limits IL-6 action, displayed both reduced CRP and CVD events. The role of IL-6 signaling in CVD in CH is supported by a study that showed that IL-6R D358A attenuated CVD event risk among participants with large CH clones but not in individuals without CH.[8] Although IL-6R D358A was not associated with recurrent events in the prospective cohort, stratification by CH mutation showed attenuated risk in patients with *TET2* CH, confirming a protective effect of IL-6R D358A in a specific subset of patients with CH.

This study showed the expansion of CH clones in most of the patients as time passed. In view of increased inflammatory biomarkers and recent evidence that atherosclerosis may accelerate CH via

associated dyslipidemia and inflammation,[9] the authors suggested a self-perpetuating cycle of inflammation and clonal expansion. However, specific evidence, such as a relationship between inflammatory biomarkers and rate of clonal expansion, was not provided, presumably because of limited sample size. In contrast, Weinstock et al developed a method called PACER to measure clonal expansion rate from single time point data and then performed a genome-wide association study that revealed a common polymorphism in the *TCL1A* promoter that is associated with reduced expression and a slower clonal expansion rate, indicating germ line genetic determination of clonal expansion rate.[10] Further studies are needed to unravel the complex relationships between CH, inflammation, and CVDs. In the meantime, this study establishes that CH greatly increases the risk of recurrent vascular events and death after an initial ischemic stroke and suggests that targeted anti-inflammatory interventions, for example with IL-6 or IL-1β neutralizing antibodies, might be particularly beneficial in this setting.

*Conflict-of-interest disclosure: A.R.T. is a member of the scientific advisory boards of TenSixteen Bio, Staten Biotechnology, and Beren Pharmaceuticals. N.W. declares no competing financial interests.* ■

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