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Clonal Hematopoiesis and Atherosclerosis: How Age-Related Mutations in Blood Cells Drive Inflammation

Naeem Hamza*, Rayane Naegels, Timea, Dhina, Chloé and Daniyal Khan

Iuliu Hatieaganu University of Medicine and Pharmacy Cluj-Napoca, Romania

***Corresponding Author:** Naeem Hamza, Iuliu Hatieaganu University of Medicine and Pharmacy Cluj-Napoca, Romania.

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Introduction

Atherosclerosis, the underlying cause of most cardiovascular events, is no longer viewed solely as lipid accumulation. It is now identified as a chronic inflammatory disease of the arterial wall driven by endothelial dysfunction, lipid accumulation, and chronic inflammation [1,2]. Inflammation is central to atherogenesis, with both innate and adaptive immune responses involved. Monocytes and macrophages drive the process at every stage, from endothelial activation and foam-cell formation to plaque growth and rupture [1]. Traditional risk factors like hypertension, smoking, diabetes and dyslipidemia remain central drivers of atherosclerosis, yet they do not fully explain disease progression, especially in older adults, highlighting the need to explore additional mechanisms such as age-related changes in the immune system [3].

Aging is the single greatest risk factor for ASCVD and profoundly alters the hematopoietic system, marked by a decline in HSC function and an increase in somatic mutations, leading to altered hematopoiesis and myeloid bias [3]. This shift results in elevated numbers of circulating myelocytes and neutrophils, which are responsible for heightened inflammatory responses. Somatic mutations accumulate over time, providing mutant clones with a selective advantage, resulting in their expansion and altering immune responses to promote vascular inflammation [4].

Clonal hematopoiesis of indeterminate potential (CHIP), defined by the presence of somatic mutations in hematopoietic cells, is associated with advanced age and increases the risk of both hematological malignancy and cardiovascular diseases. Clonal hematopoiesis arises when a mutation confers a selective growth advantage; the mutated HSC and its progeny expand and dominate [1,5]. CHIP is defined by the presence of a somatic mutation with a variant allele frequency (VAF) ≥ 2% in the absence of criteria for a hematological neoplasm [6]. Subsequent studies have clarified the strong association between aging and CHIP. Fewer than 1% of healthy individuals under 40 exhibit CHIP, whereas the prevalence rises to approximately 10–20% in adults aged 70 and older [5].

The link between CHIP and CVD stems from epidemiological observations showing that CHIP carriers face an increased risk of coronary heart disease, myocardial infarction, and stroke, independent of traditional risk factors. In the BioImage and MDC cohorts, CHIP carriers had a 1.9-fold increased risk of incident coronary heart disease compared with noncarriers (95% CI, 1.4–2.7; P<0.001). In the ATVB and PROMIS cohorts, CHIP was associated with 4.0-fold higher odds of early-onset myocardial infarction (95% CI, 2.4–6.7; P<0.001). Across samples from BioImage, MDC, and three additional prospective cohorts unselected for coronary events, they specifically examined the association between coronary heart disease and mutations in DNMT3A, TET2, ASXL1, and JAK2. Participants with mutations in DNMT3A, TET2, or ASXL1 had a 1.7- to 2.0-fold increased risk of incident coronary heart disease compared with those without mutations, whereas the JAK2 V617F mutation was associated with a 12.1-fold increased risk [2]. These findings indicate that CHIP is strongly associated with increased cardiovascular risk.

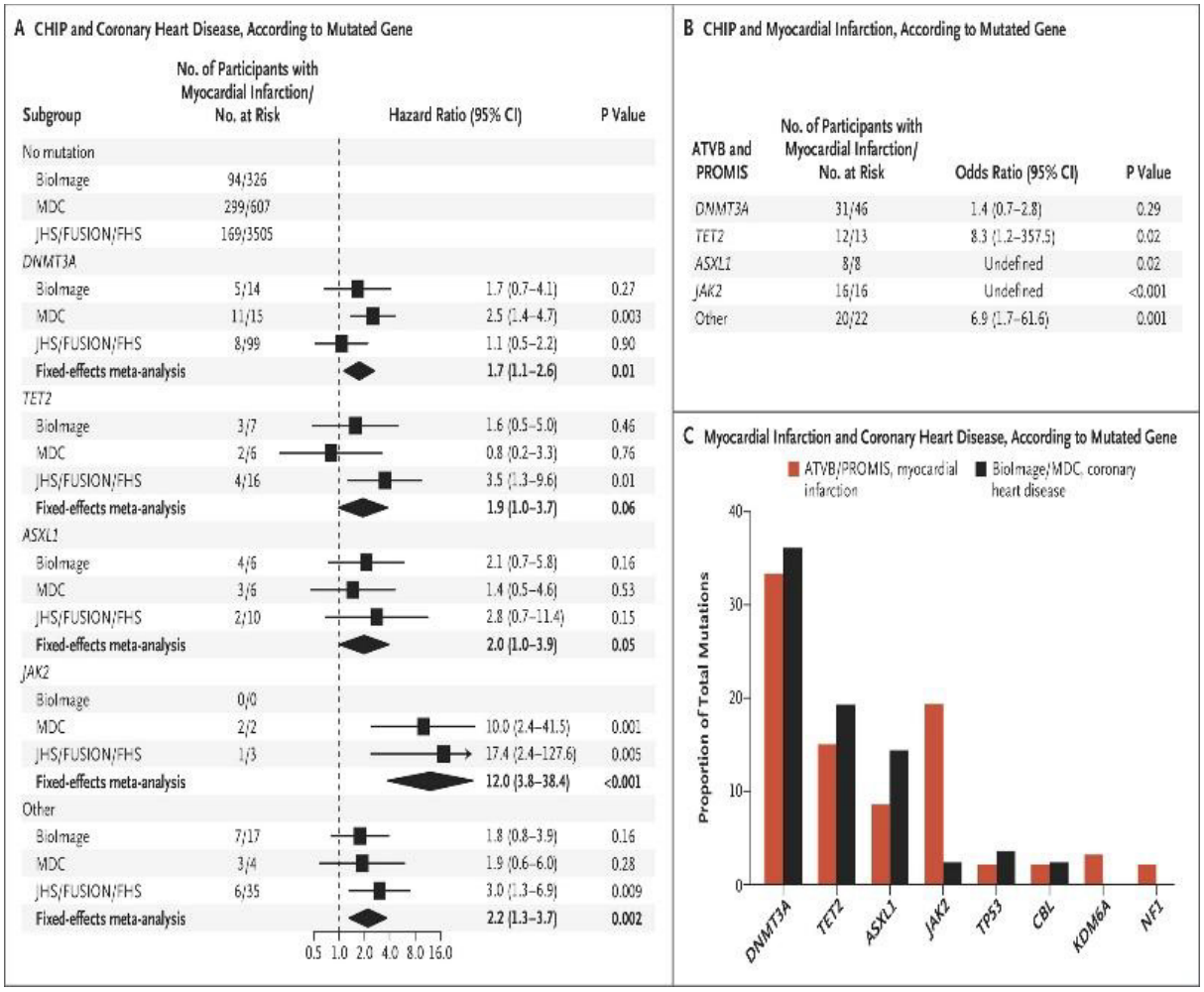

Figure 1: Association between Coronary Heart Disease and Early-Onset Myocardial Infarction among CHIP Carriers, According to Genetic Mutation. (Note: Adapted from [2])

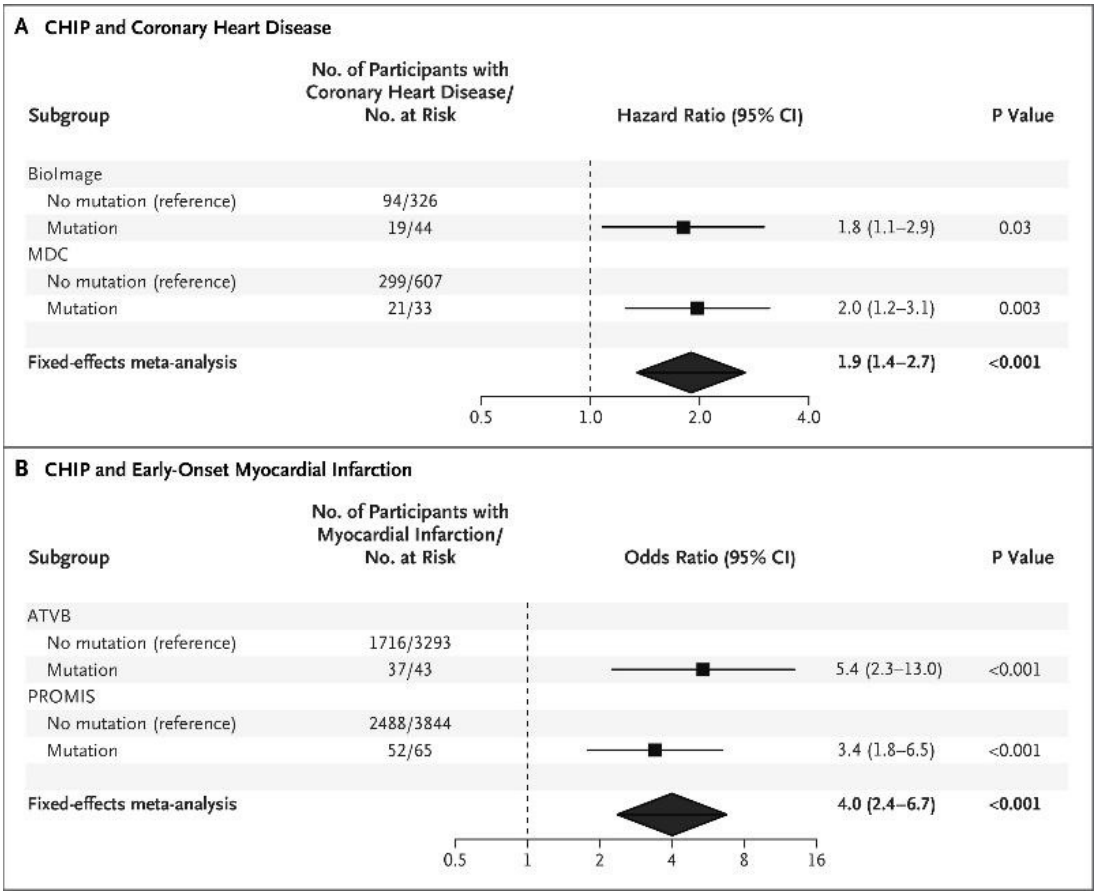

Figure 2: Association between Clonal Hematopoiesis of Indeterminate Potential

(CHIP) and coronary heart disease and Early-Onset Myocardial Infarction. (Note: Adapted from [2])

Biology of Clonal Hematopoiesis

Clonal hematopoiesis of indeterminate potential (CHIP) is defined as the presence of somatic mutations in hematopoietic cells with a variant allele frequency (VAF) ≥2% in peripheral blood, without evidence of hematologic malignancy or cytopenias. Clonal cytogenetic abnormalities of undetermined significance (CCUS) refer to similar clonal expansions driven by chromosomal changes rather than point mutations [2,3,6]. In contrast, myelodysplastic syndromes (MDS) involve CHIP-like mutations alongside dysplasia and cytopenias, progressing to overt malignancy [6]. These terms represent a progression from premalignant states (CHIP/CCUS) to overt disease (MDS), with CHIP being the most common in the general elderly population Somatic mutations in HSCs occur spontaneously during aging, often in epigenetic regulators or signalling genes, disrupting DNA methylation and histone modifications [1]. These mutations confer a proliferative advantage to HSCs, enabling clonal dominance and altering downstream myeloid differentiation toward pro-atherogenic monocytes and macrophages.

The most frequent somatic mutations associated with clonal hematopoiesis occur in the DNMT3A, TET2, ASXL1, JAK2 or TP53 genes that encode for epigenetic regulators involved in the control of hematopoiesis [3]. DNMT3A mutations (20-30%) disrupt de novo DNA methylation, promoting clonal expansion and mild inflammatory skewing, though less atherogenic than TET2 [1]. TET2 (10-20% of cases), which encodes a methyl cytosine dioxygenase, its mutations lead to inflammasome hyperactivation and increased atherosclerosis risk [1,7]). ASXL1 alterations (5-10%) affect chromatin remodelling, associating with higher CVD and type 2 diabetes incidence [8]. JAK2 mutations (V617F, ~2%) activate cytokine signalling, enhancing thrombosis and plaque progression [5]. TP53 mutations (~1-2%) impair DNA repair, linking to advanced atherosclerosis and malignancy risk, though less studied in CVD contexts [8].

Clonal expansion in CHIP occurs when mutations give hematopoietic stem cells a competitive advantage, such as enhanced self-renewal or resistance to cell death, allowing mutant clones to gradually dominate over time [3]. In inflammatory conditions like hypercholesterolemia, TET2-mutant clones expand further due to increased IL-6 sensitivity, driving macrophages toward pro-atherogenic states. This process amplifies systemic inflammation, with higher NLRP3 activity and disrupted calcium handling in cardiomyocytes, contributing to plaque instability and arrhythmias [7].

CHIP prevalence rises exponentially with age, affecting ~1% of individuals under 40 and ~20% of individuals above 70, with higher rates in males and smokers [5]. Most individuals with CHIP harbour only a single driver mutation, commonly in DNMT3A, TET2, ASXL1, or JAK2. While the presence of one mutation increases the risk of acquiring additional somatic mutations and progressing to hematologic malignancy, such progression remains relatively uncommon [4]. Known risk factors for CHIP include older age, smoking, prior cytotoxic therapy, and certain inherited predispositions. In contrast, lifestyle factors and comorbidities likely influence clonal selection, but remain incompletely defined [9].

Mechanistic Links Between Chip and Atherosclerosis

Clonal hematopoiesis arises when hematopoietic stem cells acquire somatic mutations in leukemia-associated genes. Mutations in DNMT3A, TET2 or JAK2 offer selective growth advantages, allowing the mutated cells to outcompete normal stem cells. Age is one of the key elements in this process. As hematopoietic stem cells accumulate DNA damage, they experience inflammatory stress and then undergo functional reduction. All these age-related changes favor the proliferation of mutated clones [10].

An important characteristic of CHIP associated with clonal expansion is the biased differentiation into myeloid cells. The mutant hematopoietic stem cells differentiate mainly into monocytes, macrophages and neutrophils. This differentiation is amplified by the inflammatory signalling and age-related changes occurring in the bone marrow [11].

The expansion of these myeloid-biased clones has significant implications for cardiovascular disease. Myeloid cells play a major role in plaque formation, cytokine production and lipid uptake. As CHIP clones expand, the total number and inflammatory activity of the myeloid cells found in the circulation increase, resulting in a link between age-related clonal hematopoiesis and atherosclerosis [12].

CHIP not only affects the myeloid cell production, but also leads to functional alterations that the cells acquire. Somatic mutations in genes such as TET2 and DNMT3A program a hyper-inflammatory phenotype. Mutated myeloid cells display an increased production of pro-inflammatory cytokines, including IL-1β, TNF-α and IL-6 and increased activation of the NLRP3 inflammasome. The systemic inflammation is amplified and fuels a cycle that sustains CHIP clone expansion and age-related inflammatory states.

In addition, epigenetic changes caused by CHIP mutations alter the transcription in myeloid cells. As an example, the loss-of-function mutations in TET2 lead to an increase in the immune response and chemotaxis. This causes monocytes and macrophages to become hyper-responsive to inflammatory stimuli [13].

The central mechanism that causes this increased inflammatory state is the overactivation of the NLRP3 inflammasome. The NLRP3 inflammasome is a cytosolic protein complex that regulates caspase-1activation and the maturation of pro-

inflammatory cytokines IL-1β and IL-18. The activation follows a two-step process. Firstly, a priming signal induces transcription of NLRP3 and pro-IL-1β through NF-kB and a secondary signal triggered by cellular stress. In the context of CHIP, mutated macrophages show a lower threshold for inflammasome activation and produce larger amounts of IL-1β even under mild inflammatory stimulus.

Disruption of epigenetic regulators causes the further amplification of this response. This allows the inflammasome signalling to become overactive, leading to heightened caspase-1 activation and excessive cytokine production. Cells also produce elevated levels of IL-6, TNF-α and different chemokines, showing a general shift towards a pro-inflammatory transcriptional program.

Together, these changes result in a cytokine-rich environment that reinforces the activation of surrounding immune cells and maintains the chronic systemic inflammation [14].

The persistent inflammatory state has direct effects on the vascular wall. Pro-inflammatory cytokines drive the endothelial cells to a state characterised by increased adhesion molecules, such as VCAM-1 and ICAM-1. These changes will help with adhesion and leukocyte migration into the arterial wall [15].

Once inside the vessel, the immune cells contribute to plaque formation by releasing localized mediators and enzymes that remodel the extracellular matrix. Chronic endothelial activation also enhances vascular permeability, supporting plaque growth. Over time, these changes make lesions more complex and raise the chance of plaque rupture, linking CHIP to the worsening of atherosclerosis [16].

Studies on mice provide evidence that CHIP-associated mutations in hematopoietic stem cells accelerate atherosclerosis independently of traditional risk factors. TET2 or DNMT3A-deficient bone marrow was transplanted into hyperlipidemic mice, which resulted in macrophage-rich plaques compared with the control mice. These experiments separate the role of mutant hematopoietic cells, showing that clonal expansion alone alters plaque development. Histological analysis reveals that plaques in these mice display increased necrotic cores and expanded lesion areas. The study demonstrates that mutated hematopoietic clones amplify the local inflammatory environment within plaques and enhance vascular lesions [13].

Clinical Evidence in Humans

CHIP is recognised as an independent contributor to cardiovascular disease. The frequency of CHIP increases with age, and individuals carrying the CHIP mutation have a higher risk of coronary artery disease(CAD) than non-carriers [17]. Beyond the increased risk of CAD, patients carrying the CHIP mutation have a higher risk of peripheral arterial disease and strokes. These associations remain even after accounting for traditional cardiovascular risk factors(hypertension, diabetes, age or hyperlipidemia), indicating that CHIP is a systemic contributor to cardiovascular morbidity. The increased risk arises from chronic, low-grade inflammation that is associated with the expansion of mutated hematopoietic clones. This accelerates plaque formation and destabilizes the preexisting vascular lesions in cerebral and peripheral arteries [18].

Multiple cohort studies support these findings. In "Clonal hematopoiesis is associated with cardiovascular events in patients with stable coronary artery disease", carriers of CHIP with CAD have shown significantly higher rates of adverse cardiovascular events, concluding that CHIP contributes to residual risk even under therapy [18].

Similarly, in "Clonal hematopoiesis of indeterminate potential predicts adverse outcome in patients with atherosclerotic cardiovascular disease," it was demonstrated that CHIP independently associates with further cardiovascular events and mortality, especially in TET2 and JAK2 mutations [19].

Altogether, these studies demonstrate that CHIP consistently acts as an independent predictor of cardiovascular events. The cardiovascular risk associated with CHIP depends on both the specific gene mutation and the size of the clonal population. The most commonly mutated genes, TET2 and JAK2, have shown a strong association with incident cardiovascular disease. In "Clonal Hematopoiesis of Indeterminate Potential Predicts Adverse Outcomes in Patients With Atherosclerotic Cardiovascular Disease," it was demonstrated that carriers of the TET2 mutation had a higher risk of recurrent atherosclerotic events.

On the other hand, DNMT3A mutations have shown a more moderate cardiovascular risk, though still higher than compared to non-carriers.

Clone size also influences the outcome for all mutation types. Larger variant allele fractions have been consistently associated with greater risk, compared to smaller clones [20].

In conclusion, CHIP-associated cardiovascular risk is influenced by both the affected gene in the extent of clonal expansion.

Diagnostic and Therapeutic Implications

Accurate detection of clonal hematopoiesis of indeterminate potential (CHIP) relies primarily on sequencing-based identification of somatic mutations in leukemia-associated genes within peripheral blood cells from patients free of hematological cancer or of any other non-neoplastic clonal disease (CCUS, MDS) [21]. Genome-wide molecular analysis is performed through next-generation sequencing (NGS), with whole-genome sequencing (WGS) or whole-exome sequencing (WES) analysis, or targeted gene panels in identified pathogenic variants such as DNMT3A, TET2, ASXL1, JAK2 and in DNA damage repair genes, such as TP53/PPM1D, mainly1. Cohort studies usually choose a variant allele frequency (VAF) threshold >2% to classify CHIP. A higher VAF (>10%) defines clinically significant clonal expansion associated with increased risk of cardiovascular events (High-VAF CHIP) [21]. Emerging methods for molecular analysis include ultra-deep error-corrected DNA sequencing, targeted gene sequencing with droplet digital PCR (ddPCR), and single-cell sequencing [22].

CHIP-associated atherosclerosis (ATS) is mediated through dysregulated immune cell function, particularly among monocyte and macrophage populations derived from mutated hematopoietic stem cells. Mutations in TET2, ASXL1, and to a lesser extent DNMT3A and JAK2 induce exaggerated inflammatory signalling, characterized by upregulated IL-1β, IL-6, IL-8, TNF-α, high chemokines CXCL1 and CXCL2, and activation of the NLRP3 and AIM2 inflammasome1. Biomarkers of inflammatory activity and clonal burden include circulating cytokine profiles (eg, IL-1β, IL-6, IL-8, TNF-α), High-sensitivity CRP (hsCRP), which correlates with CHIP-associated inflammation, absolute monocyte counts and monocyte transcriptomic signatures, quantitative VAF, which provides an estimate of clonal size and is associated with a higher cardiovascular risk.

To date, treatment options proven to prevent and reduce cardiovascular risk in patients with CHIP are lacking. Potential therapeutic strategies for CHIP from already existing compounds could target inflammation in TET2 and JAK2 CHIP (Azacytidine, Decitabine, Ruxolitinib), inhibit NLRP3 in TET2 and DNMT3A CHIP (Colchicine, Glyburide, Thiolutin), or target inflammatory cytokines (Canakinumab, IL-1β inhibitor; Anakinra, IL-1 receptor antagonist; Tocilizumab, anti-IL-6 receptor antibody; Ziltivekimab, anti-IL-6 antibody) [21,23]. Compounds in development targeting mutant HSPC clones include TP53 mutation inhibitors and SF3B1 modulators. Other drugs could target the inflammasome, such as Selenoflast and DFV890 (NLRP3 inhibitors), Dapansutrile, Shikonin, and NLRP3/AIM2-IN-3. Additionally, Aspirin could be given to patients with JAK2 CIHP, which is prothrombotic, and Vitamin C could be given to patients with TET2 CHIP, due to the vitamin's role as a cofactor [23].

CHIP arises from age-related somatic mutations in epigenetic regulators (TET2, DNMT3A, ASXL1) affecting DNA methylation, covalent histone modifications, and non-coding RNAs (ncRNAs), as well as altering signalling molecules (JAK2). Further treatment possibilities could target DNA methylation, such as 5-aza-2-deoxycytidine (DNMTi) or Rosiglitazone (DNMT1i), as supported by mouse studies [24]. Histone deacetylase could be targeted by Vorinostat, Valproate, or Trichostatin A (HDACi), by RGFP966 (HDAC3i), statins, curcumin, or GSK126, all supported by either mice or in vitro studies. BET bromodomain, non-coding RNAs such as anti-miRNA-33, or transcription factors, for example, NF-kB or NRF2, or PPARα modulators could be targeted to try and blunt the proliferative advantage of mutated clones. Another possible approach would be the selective targeting of mutated blood cells and eliminating them. However, further pre-clinical studies should assess concerns regarding toxicity and potential interference with normal hematopoiesis [24].

Discussion

Both clinical and animal studies highlight that clonal hematopoiesis of indeterminate potential (CHIP) increases the risk of atherosclerotic cardiovascular disease (ASCVD) independently of variables already assessed by cardiovascular risk prediction models (AHA-PREVENT online calculator, ESC-SCORE2 and SCORE2-OP) [25]. Traditionally, non-modifiable risk factors – age, sex, genetics – are conceptualized as separate from inflammatory drivers of plaque progression. Meanwhile, in CHIP, mutations in DNMT3A, TET2, ASXL1, and JAK2 promote clonal expansion and skew myeloid cell phenotypes toward pro-inflammatory secretion (IL-1β, IL-6, IL-8, and NLRP3 inflammasome activation) [22]. CHIP increases cardiovascular risk to an extent comparable to LDL-C elevation or hypertension, even after adjusting for traditional factors [22]. Integrating CHIP into ASCVD models could be relevant primarily for older adults, people with premature or unexplained atherosclerosis, and individuals with residual inflammatory risk despite optimal lipid-lowering therapy.

The traditional pathway of atherosclerosis development involves a combination of endothelial dysfunction, lipid accumulation, oxidative stress, and adaptive immune activation. CHIP, on the other hand, contributes to atherosclerosis formation through a hematopoietic pathophysiological mechanism. Macrophages with mutated TET2- or DNMT3A-genes release pro-inflammatory cytokines (IL-1, IL-6) and show impaired resolution phenotypes [25]. Those mutated clones amplify foam-cell formation, plaque necrotic core expansion, and thrombosis. Similarly, neutrophils carrying the JAK2 mutation (JAK2V617F) enhance neutrophil extracellular trap (NET) formation and platelet activation, thus enhancing the risk of thrombus formation and acute coronary events. Unlike traditional risk factors for atherosclerosis, which increase the lipid burden, CHIP operates by modifying the immune effector cells that drive plaque progression [24].

Both pre-clinical and clinical studies performed so far link CHIP with an increased risk of atherosclerosis development and, in the end, with more acute cardiovascular events. Some barriers still limit our understanding of the disease course

and prognosis, the clinical significance of variant allele frequency (VAF), and treatment options that might be beneficial. First, the data available to date are limited and come mostly from retrospective cohort studies that are not followed for extended periods of that use incomplete CHIP genotyping. Various screening methods have been used, making studies based on NGS (WES or WGS) difficult to compare with those relying on targeted sequencing, which is more sensitive for detecting CHIP mutations [23]. Some sex- and age-specific differences have been noted for CHIP in mural studies, but their impact on prognosis, phenotypic expression, and potential treatment still needs to be explored. [23] Additionally, CHIP is driven by four main mutated genes, each displaying distinct phenotypical effects and characteristic variant frequencies. Patients may carry one or more mutated clones in different hematopoietic lineages, which complicates data analysis. Actionable and traditional cardiovascular risk factors may also be present and interact with, or confound the effects of, CHIP mutations in atherosclerosis development. [22] Some cases of CHIP have not been linked to any of the main drivers, which may reflect limitations in detection methods or neutral drift within small populations of active HSCs. [26] Further studies are required to determine the appropriate cardiovascular surveillance and risk-reduction or prophylactic strategy (e.g., lifestyle changes and lipid-lowering medication) for patients with CHIP [22].

Current guidelines do not recommend routine screening in the general population [22]. However, a more widespread use of NGS and targeted gene sequencing raises ethical, clinical, and psychological considerations. Most individuals with CHIP are asymptomatic, and the condition might be overdiagnosed. Small clones with low VAF may be detected, even though their prognostic significance is unclear. Further studies are required to distinguish benign age-related mutations from clones conferring meaningful risk. Also, so far, different sequencing techniques have been used, which give variable detection rates of CHIP mutations. On a large scale, these do not influence overall prevalence, but individual screening would benefit from unified sequencing approaches. Furthermore, standardized management and therapeutic strategies are lacking [23]. A better understanding of the prognosis and guidelines on clinical actions is required to reduce the anxiety caused by disclosure of CHIP status and avoid inappropriate interventions. Ethically speaking, patients undergoing sequencing for unrelated reasons (e.g., cardiovascular risk panels, tumor profiling) should be informed about the possibility of identifying CHIP and genetic counselling on its implications should be available.

CHIP is a disease at the crossroads between immunology, hematology, genomics, inflammation, and diseases such as cancer and atherosclerosis. Cardiovascular pathologies induced by CHIP display gene-specific phenotypes, with different mutations leading to varied effects. This highlights the possibility of developing precision medicine strategies for both prevention and treatment of atherosclerosis-related events. Management of CHIP-related pathologies should be based on precision medicine, targeted immunomodulation, and maybe even gene editing to tackle this specific pathophysiological pathway offering multidisciplinary research opportunities [23].

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