
Article:
Powell, N., Cubbon, R. M., Bailey, M. A. et al. (Accepted: 2026) Clonal haematopoiesis of indeterminate potential (CHIP), vascular somatic mutation, and cardiovascular disease: a narrative review. Vascular Medicine. ISSN: 1358-863X (In Press)

Clonal Haematopoiesis of Indeterminate Potential (CHIP), Vascular Somatic Mutation, and Cardiovascular Disease: A Narrative Review

Nicole Powell[1], Richard M Cubbon[1], Marc A Bailey[1,2], Kathryn J Griffin[1], Lee Roberts[1], Chew Cheng[1,3]

[1]Leeds Institute of Cardiovascular and Metabolic Medicine, School of Medicine, University of Leeds, Leeds, UK

[2]The Leeds Vascular Institute, Leeds General Infirmary, Leeds Teaching Hospitals NHS Trust, Great George Street, Leeds LS1 3EX, United Kingdom

[3]UK Health Security Agency, Virus Reference Department, Immunisation and Diagnostics Unit, London, Colindale, NW9 5EQ

Corresponding Author: Miss Nicole Powell

Light Laboratories, Clarendon Way, University of Leeds, Leeds, LS2 9JT, UK

Email: umnpo@leeds.ac.uk Twitter: @nicolejpowell

Abstract

Somatic cell DNA mutations accumulate with age, and can give cells a survival advantage, resulting in their clonal expansion over time. We know that these mutations can lead to cancer, but the growing application of next-generation sequencing across multiple 'healthy' tissues has revealed their ubiquity and relevance to non-cancer pathology. Indeed, these mutations may play a role in cardiovascular disease (CVD), particularly in the progression of atherosclerosis and other vascular diseases. This review examines the impact of somatic mutations in both blood and cardiovascular tissues, focusing particularly on clonal haematopoiesis of indeterminate potential (CHIP), and its association with systemic inflammation. CHIP mutations, present in haematopoietic stem cells and their progeny, have been associated with increased risk of CVD, possibly by promoting pro-inflammatory pathways that drive atherosclerosis, although some data suggest CHIP may also arise due to an inflammatory milieu. These somatic variants, and non-CHIP variants, have been detected in atherosclerotic plaques, raising questions about their direct role in atherogenesis and vascular remodelling. Understanding the current research on somatic mutations in blood and cardiovascular tissues may uncover new insights into CVD progression and highlight potential therapeutic targets.

Keywords: cardiovascular disease, atherosclerosis, somatic mutations, clonal haematopoiesis, endothelial cells, vascular smooth muscle cells

Introduction

Despite current preventative and therapeutic approaches, cardiovascular disease (CVD) remains the leading global cause of death[1].

This complex, multifactorial disease is caused by genetic and environmental (e.g. diet, smoking, physical inactivity) factors, and mechanisms such as inflammation and endothelial dysfunction. While inherited (i.e. germline) gene mutations, present in all cells, have a causal role in CVD [2], emerging evidence also implicates later-life non-heritable (i.e. somatic) mutations that develop in individual cells. Some cells with somatic mutations gain a survival advantage and accumulate amongst 'normal' cells (called mosaicism), potentially leading to disease. Cancer is the classical example, but the increasing use of DNA sequencing has found somatic mutation in many diseases, including CVD. This review summarises literature proposing that somatic mutation in blood and vascular wall cells causes CVD.

Somatic Mutations in Blood

A prominent example of mosaicism is clonal haematopoiesis of indeterminate potential (CHIP). This arises from somatic mutations in haematopoietic stem cells (HSCs), which confer a survival advantage, enabling them to outcompete other HSCs. The arising 'clones' expand and give rise to mutant circulating immune cells with a pro-inflammatory phenotype. Individuals carrying CHIP mutations experience a > 10-fold greater risk of developing haematological malignancy [3], and are at an increased risk of many cardiovascular diseases (e.g. atherosclerosis, myocardial infarction, and heart failure) [4–7]. In the clinic, CHIP is detected using next generation sequencing (NGS) of blood DNA, focusing on genes of interest rather than the whole genome. Variants are quantified by variant allele fraction (VAF – the percentage of detected alleles with the specified mutation) as an indicator of clone size. Since blood is readily available and routinely sequenced in people with possible blood disorders, substantial clinical data are available. This led haematologists to discover CHIP as detectable somatic mutations linked to myeloid malignancy, but without evidence of malignancy. Identifying CHIP (or other somatic mutation) in vascular tissues is challenging as biopsy is required, meaning routine clinical data are not available.

Somatic Mutation in Cardiovascular Tissues

Beyond the blood, somatic mutations have also been detected in vascular tissues and cells, such as vascular smooth muscle cells (VSMCs), and endothelial cells (ECs), which are also important in the pathology of cardiovascular diseases. Accumulating evidence suggests clonal expansion of somatic mutations (including CHIP variants) in these tissues may contribute to atherosclerosis [8–10], through promotion of inflammation, and vascular remodelling and dysfunction. This adds nuance to the notion of atherosclerosis as a disorder of lipid accumulation and systemic inflammation. However, the temporal relationship between somatic mutation and atherogenesis remains incompletely understood.

Somatic mosaicism has also been implicated in non-atherosclerotic vascular disease (e.g. cavernous vascular malformations (CCM)) [11], where cerebral lesion formation is driven by somatic mutations in genes such as *PIK3CA*, *KRIT1*, *CCM2*, and *PDCD10*. In addition, recent data have suggested that somatic mutations can arise in the heart [12].

Yet despite these emerging insights, many questions remain. This review aims to summarise evidence on the association between somatic mutation, in both the blood and vasculature, and CVD.

It will particularly focus on CHIP mutation, given the larger research literature, but non-CHIP somatic mutation will also be considered.

Beyond exploring potential causal links between somatic mutation and CVD, the review highlights key knowledge gaps and discusses the potential clinical implications for CVD risk stratification and targeted therapies.

Clonal Haematopoiesis of Indeterminate Potential

Somatic mutations were first implicated in the development of cancer [13], but are now known to accrue with age in apparently healthy tissues [14,15]. Many healthy individuals, particularly with advancing age [3,16,17], harbour myeloid malignancy-associated somatic mutations in their blood or HSCs, but without malignancy or abnormal blood cell counts.

When present in blood with VAF ≥ 2%, this is described as CHIP and is associated with increased risk of diverse age-related diseases, including CVD.

Immune alterations also characterise ageing, particularly increases in IL-6 and C-reactive protein (CRP), indicating systemic low-grade inflammation [18]. It is unclear if immune alterations promote ageing or vice versa [19], but recent clinical trial data support inflammation directly causing atherosclerotic cardiovascular disease [20].

Notably, CHIP does not simply represent age-related genomic instability or cumulative stochastic mutation burden; the growth of clones implies specific mutations provide a survival advantage under particular selection pressures, such as during inflammation.

Recent population studies have uncovered CHIP driver mutations in many genes, most commonly *DNMT3A*, *TET2*, and *ASXL1*, with less common examples being *JAK2*, *TP53*, *PPM1D*, and *SF3B1L*; many were associated with CVD [7,21,22]. Some mutations (e.g. nonsense or frameshift variants) cause a non-functioning truncated protein, as often seen with *ASXL1* CHIP. Others (e.g. missense variants) alter protein function via single amino acid changes; *DNMT3A* and *TET2* CHIP can rise from missense or nonsense variants. Pich *et al*. identified over 70 potential CHIP driver genes [23], with key roles in epigenetic programming, haematopoietic differentiation, cytokine signalling, and DNA repair.

The former is a process by which expression of many genes is altered by reversible modifications (e.g. methylation) of DNA and/or its histone proteins, with some CHIP genes (e.g. *DNMT3A*, *TET2*) catalysing these DNA modifications.

Epigenetic changes have widespread impacts on cell biology relevant to CVD pathogenesis, such as skewing haematopoietic differentiation towards pro-inflammatory myeloid cells.

CHIP as a Risk Factor for Cardiovascular Disease

CHIP has been identified as an independent risk factor for a diverse range of cardiovascular diseases [5,7]. Early studies, on small cohorts, reported > 2-fold relative risks of cardiovascular diseases, but subsequent large-scale studies have much smaller (or no evidence of) risk increases, highlighting the need of cautious interpretation of early studies. CHIP is also associated with greater burden of coronary and non-coronary calcification [7,24], processes promoted by chronic inflammation [25], that are linked to arterial stiffening and heightened risk of major cardiovascular events.

Notably, mutations in specific genes may pose different risks of CVD, reflecting the distinct biological roles of these genes and the varying impact of specific mutations on a gene's expression and activity. For example, *TET2* and *DNMT3A* have been associated with the expansion of atherosclerotic plaques in animal models and humans [26–28], possibly through expression of pro-inflammatory cytokines and myeloid cell accumulation.

However, whilst *TET2* mutations confer > 1.5-fold higher risk of coronary heart disease, *DNMT3A* confers smaller relative risk. CHIP involving *TP53*, which participates in the DNA-damage response, is associated with > 2-fold greater risk of atherosclerotic CVD events, with mouse models revealing increased plaque macrophage proliferation [29].

JAK2 mutant CHIP is linked to a > 2-fold higher risk of arterial (e.g. myocardial infarction) and venous thrombotic events [30,31], yet paradoxically also increased bleeding events, especially at higher VAF [32]. *JAK2*^{V617F} (a mutation switching valine to phenylalanine at amino acid 617, leading to JAK2 kinase activation) is a key driver in myeloproliferative neoplasms, such as essential thrombocythemia (ET). Murine models suggest this mutation directly induces production of immature hyper-reactive platelets (i.e. increased agonist-induced aggregation and *in vivo* thrombosis), but also indirectly activates non-mutant platelets via secreted factors [33]. The bleeding risk may reflect associated acquired von Willebrand factor deficiency, but more research is needed [32]. Chromosome 9p21.3, a common germline risk locus for CVD [34], has also been associated with platelet reactivity [35]. Notably, the *CDKN2A* gene resides here, and somatic mutation of this gene is reported in cancer [36] , although there is currently no evidence that somatic mutation of this gene contributes to CHIP or CVD.

Table 1 summarises reported risks of CVD associated with key CHIP-associated genes. Beyond differing biology of CHIP genes and mutations, conflicting data may reflect differences in study methodology, such as sequencing depth, population demographics, and VAF thresholds used to define CHIP. These factors should be addressed in future studies to more confidently define CHIP's role as a CVD biomarker.

Inflammation as a Mechanism Connecting CHIP and CVD

The link between CHIP and CVD is often attributed to an inflammatory state. Somatic mutations in HSCs can promote clonal expansion of pro-inflammatory leukocytes, and cytokine production (e.g. IL-1, IL-6) [4,37–39], altering vascular homeostasis.

CHIP promotes inflammation through gene-specific effects [7,40]. For example, *GNB1* is a direct regulator of the NLRP3 inflammasome [41], whereas *DNMT3A* and *TET2* have broad-based epigenetic effects. Larger clone sizes, often seen with *DNMT3A* and *TET2* CHIP, are linked to increased severity of disease [42,43]. The functional effects of smaller clones (VAF 0.1 – 2.0) is less clear and requires further research [43,44].

Notably, CHIP is associated with non-atherosclerotic inflammatory cardiovascular diseases, such as myopericarditis, and non-cardiovascular inflammatory diseases, emphasising its broad relevance [45].

It is also reported that inflammation may drive CHIP and growth of CHIP clones, rather than vice versa [46]. This could imply that CHIP is simply an epiphenomenon in an inflammatory milieu, rather than directly driving CVD. Some studies have used Mendelian-randomisation to infer causal associations between CHIP and CVD [47]. These inferred causal links between CHIP and atrial fibrillation, with weaker evidence for adverse myocardial remodelling, but no link to atherosclerotic CVD events was elicited. Other data show baseline CHIP is associated with future de novo femoral atheroma development, whereas neither baseline atherosclerosis nor atheroma volume is associated with future CHIP clone expansion [48]. These findings alone cannot confirm or refute causal relationships in isolation and make important assumptions that are difficult to validate.

Further mechanistic research is needed to address this issue at the crux of whether CHIP is a therapeutic target for CVD prevention.

Inflammatory Pathways Linking CHIP to CVD

Ten-Eleven Translocation 2 (*TET2*)

TET2 is an epigenetic regulator that demethylates DNA, promoting gene expression. *TET2* was one of the first described CHIP-associated genes [49], and has been repeatedly linked to CVD risk [40,50,51]. Fuster *et al*. (2017) used competitive bone marrow transplantation in low-density lipoprotein receptor (LDLR)-knockout mice to investigate the role of *TET2*-deficient HSCs in atherosclerosis [52]. They observed a 60% increase in aortic root plaque size with *TET2* deficiency increasing IL-1β expression and NLRP3 inflammasome activation, offering potential mechanistic insight into the atherogenic effect of *TET2* CHIP [52].

In support, *post hoc* analysis of clinical trial data has shown *TET2* CHIP is associated with a larger reduction in cardiovascular events from the anti-IL1β antibody canakinumab [53].

Beyond atherosclerosis, murine haematopoietic *TET2* loss is associated with accelerated heart failure [40].

Clinically, *TET2* CHIP is associated with higher mortality after trans-catheter aortic valve replacement (TAVR) for severe aortic stenosis [54,55], and a longer hospitalisation after coronary artery bypass grafting [56].

DNA Methyltransferase 3A (DNMT3A)

Conversely, *DNMT3A* is an epigenetic regulator that adds a methyl group to DNA, resulting in gene silencing. *DNMT3A* is the most frequently mutated gene in CHIP [16,57] and is again associated with atherosclerotic CVD [7], adverse heart failure outcomes [6,58,59], and mortality after TAVR [55].

Abplanalp *et al* showed that *DNMT3A*-mutant monocytes have increased expression of pro-inflammatory cytokines, such as IL-1β and Il-6, and activate T cells in patients with heart failure [59]. Shumliakivska *et al* showed that *DNMT3A*-deficient monocytes activate cardiac fibroblasts, promoting cardiac fibrosis and heart failure progression [60].

Other Driver Genes

While *TET2* and *DNMT3A* dominate in frequency, many other CHIP genes are associated with CVD risk, including *ASXL1* [61,62], *JAK2* [7,16,63,64], *TP53* [65] and others. Kiefer *et al*. (2021) studied CHIP mutations with VAF > 0.5% in patients with ischaemic heart failure, and found *CBL*, *CEBPA*, *EZH2*, *GNB1*, *PHF6*, *SMC1A*, and *SRSF2* were significantly associated with increased mortality [66]. Though mechanistic insights are limited for these genes, pathway enrichment analysis suggested roles in immune regulation and cytokine production.

As noted earlier, *JAK2* mutants contribute to CHIP and myeloproliferative neoplasms, such as polycythaemia vera or essential thrombocythaemia, with the *JAK2*^{V617F} variant being an independent risk factor for CVD [67]. *JAK2* normally conveys signals from activated type 2 cytokine receptors; the V617F mutant constitutively activates its kinase, increasing onward signalling to STAT transcription factors, altering gene expression akin to pro-inflammatory cytokine signalling [68].

Endothelial Cell Somatic Mutations and CVD

While CHIP-associated low-grade inflammation presumably aggravates atherosclerosis through effects on established plaque, it is also likely to drive early atherogenesis via endothelial dysfunction. Endothelial cells (ECs) line the vasculature, regulating vascular tone, inflammatory cell adhesion, and thrombosis, amongst other roles key to health and disease. Emerging evidence suggests somatic mutation may occur in atheroma-associated ECs [4], with one study finding *JAK2*^{V617F} in both peripheral blood mononuclear cells (PBMCs) and ECs from carotid atherosclerotic plaque [69]. Mouse models of endothelial *JAK2*^{V617F} mutation exhibit systemic disease including cardiomyopathy [70], along with increased EC and leukocyte-endothelial adhesion, and a pro-thrombotic and inflammatory state [71].

A murine model of myeloid *JAK2*^{V617F} expression also demonstrated loss of endothelial barrier integrity and EC cell apoptosis [72], illustrating how *JAK2*^{V617F} has both cell autonomous and non-autonomous adverse effects on the endothelium.

TET2, a frequently mutated gene in CHIP, has also been implicated in contributing to endothelial dysfunction. *TET2* regulates autophagy, a process which is critical for cellular homeostasis [73]. Under low shear stress, endothelial cell autophagy was found to be reduced through *TET2* downregulation [74].

Conversely, restoring *TET2* can improve EC function by increasing autophagy [75]. However, it is yet to be determined whether *TET2* somatic mutation occurs in ECs, and overall, the data supporting EC somatic mutation in atherosclerosis should be seen as preliminary.

Vascular Smooth Muscle Cell Somatic Mutation and CVD

Besides blood and ECs, somatic mutation in vascular smooth muscle cells (VSMCs) is becoming recognised as a potential contributor to atherosclerosis, given their key role in plaque biology.

VSMCs can clonally expand, switch phenotypes, and may either stabilise or destabilise plaques [76].

This nature was first suggested by Benditt and Benditt (1973), who proposed their clonality in atherosclerotic plaques related to somatic mutation [77]. Subsequent work has supported this theory [78], with lineage-tracing studies in mice showing that a small subset of VSMCs clonally expand after vascular injury [79]. Likewise, Jacobson *et al*. (2017) showed that specific VSMC clones contribute to different regions within plaque (e.g. fibrous cap) [80].

Wang *et al* used a lineage-tracing model to show that a subset of mature hyper-proliferative VSMCs promote a pro-inflammatory environment through activation of the complement cascade [8].

These clonal, pro-inflammatory cells gained a survival advantage, which the authors showed this was via evasion of phagocytosis by macrophages, which could be reversed by blockade of CD47. Evidently, VSMCs demonstrate great plasticity, and can even differentiate into fibrous-cap-stabilising ACTA2+ cells or trans-differentiate into chondrocyte-like or macrophage-like cells [81]. Somatic mutation could promote clonal plasticity, but other mechanisms such as non-mutant vascular wall-resident progenitors and local environmental conditions may play a role, so this requires further investigation.

TET2 is a regulator of proliferation and phenotypic transformation of VSMCs. VSMC loss of *TET2* in human cell culture and mouse models leads to dedifferentiation, a process in which their contractile state switches to a pro-inflammatory and pro-migratory phenotype, as observed in atherosclerosis. Conversely, *TET2* overexpression promoted their contractile properties [82]. The same work showed diminished *TET2* expression in human atherosclerotic plaque but did not address if this was clonal [82].

A recent study reported that CHIP mutations (including in *TET2* and *DNMT3A*) were detectable in blood, atherosclerotic plaque, arterial collaterals, perivascular fat, and subcutaneous tissue from patients with peripheral arterial disease undergoing vascular surgery [83]. The VAFs in these tissues matched or surpassed those in the blood. However, these data may reflect mutant clones from the blood infiltrating the vascular wall rather than somatic mutation in vascular wall-resident cells, such as VSMC.

More recently, whole exome sequencing of carotid plaques revealed somatic mutation in many genes, with locally expanded clonal populations [84]. Somatic mutations were detected in 12 out of 13 investigated plaques, yet none were detected in 11 non-atherosclerotic arterial tissue samples.

VAFs of 1–30% were observed, with some clones spanning as far as 16mm across both medial and intimal layers.

Functional enrichment analyses of mutated genes highlighted contractile function and showed greatest expression in VSMCs using single-cell transcriptomic data. Six patients had CHIP present in their blood, with the same mutations often found in paired plaques [84].

While these findings are interesting, the cellular origins of these mutants and their functional implications are unknown and requires further research.

Collectively, these findings highlight the complexity of VSMCs, and the potential for somatic mutations to promote their clonal expansion and pathogenic phenotype transitions. However, further studies are needed to determine whether somatic mutation occurs in VSMCs and if this plays a causal role in CVD. Indeed, it is also conceivable that somatic mutations could be adaptive and protect against adverse outcomes in some circumstances.

Crosstalk between Blood and Vascular Somatic Mutations in CVD

As noted earlier, CHIP leukocytes exhibit altered paracrine signalling and direct cell-cell contacts with a range of cell lineages relevant to CVD, which may represent an important element of their pathogenicity and a therapeutic opportunity. For example, *DNMT3A*-deficient monocytes have been shown to activate cardiac fibroblasts, which promotes cardiac fibrosis and heart failure [60]. *JAK2*^{V617F} mutant myeloid cells were similarly found to adversely alter the biology of ECs, contributing to thrombosis [72]. In a murine bone marrow transplant model with 1.5% mutant *JAK2* bone marrow cells and 98.5% wild-type cells, altered signalling between mutant and non-mutant leukocytes were observed.

Increased IL-1β paracrine signalling from mutant myeloid cells were observed, which modulated non-mutant aortic macrophages to promote inflammation, NETosis, and plaque growth [85]. As noted earlier, paracrine activity in *JAK2*^{V617F} also alters the function of non-mutant platelets [33].

Hence, altered paracrine activity arising from CHIP-mutant leukocytes, even at a modest VAF, can have wide-ranging implications for multiple cell lineages relevant to CVD.

There is currently no evidence that paracrine signalling from leukocytes may cause somatic mutations in vascular cell walls, but this inflammatory milieu could induce a selective advantage that permits clonal growth of mutant vascular wall cells. This could explain similar cross-tissue clonal mutation profiles, although other possibilities, such as leukocyte DNA contamination in vascular wall analyses need to be considered.

This paradigm is summarised in *Figure 1*, which illustrates how CHIP may directly and indirectly contribute to CVD through its coordinated effects on multiple cell lineages. *Figure 1* also illustrates how a somatic mutation in non-leukocyte vascular wall cells could contribute to CVD, although the direct evidence for this remains limited and such mutations may not necessarily be in CHIP-associated genes.

Crosstalk between mutant leukocytes, and mutant or non-mutant ECs and VSMCs may re-enforce inflammation, enhance immune cell recruitment, and facilitate lipid infiltration, driving plaque development. Such a paradigm involving mutant and non-mutant circulating and tissue-resident cells could be relevant to other CVDs, for example myocardial diseases like heart failure.

Clinical Implications and Future Directions

Somatic mutation holds significant potential in cardiovascular clinical practice, both in risk stratification and therapeutic targeting. Building on the mechanistic insights from somatic mutations in both blood and vascular tissues, this section explores their translational potential.

Biomarkers for Risk Stratification

There is emerging evidence that somatic mutations could be used as biomarkers for CVD risk. CHIP mutations have already shown potential in predicting cardiovascular events [42,43,55,58,86–88]. In 13,129 UK Biobank participants with established atherosclerotic cardiovascular disease (ASCVD), 5% were CHIP-carriers defined by DNA exome sequencing [89], these had a significantly higher risk of future ASCVD events and all-cause mortality compared to those without CHIP. Larger CHIP clones and multiple large CHIP driver mutations amplified risk.

Somatic mutations in genes such as *TET2*, *SF3B1*, *SRSF2*, and *U2AF1* were especially predictive of adverse CVD outcomes, and interestingly, mutations in genes *PPM1D* and *TP53* were strongly associated with mortality in women [89].

Though most evidence focuses on blood-derived mutations, these same principles of clone size, mutation burden, and gene-specific effects are likely relevant for somatic mutations in vascular tissues. However, the challenges of routinely accessing vascular tissue makes blood biomarkers more practical.

Notably, emerging technologies profiling circulating cell free DNA can infer its cellular origin based on methylation status, suggesting 10% of reads arise from the vascular endothelium [90], although further research is needed to explore the potential of this and other approaches.

Recent advances in artificial intelligence (AI) have also improved the ability to discern clonal haematopoiesis variants from those arising from solid organ tumours using circulating cell-free DNA [91]. This approach could conceivably extend to detection of somatic variants arising from cardiovascular disease. Such findings demonstrate the compelling potential of somatic mutations to be used as biomarkers for early detection and risk stratification.

It is also important to emphasise the need for high sequencing depth (i.e. how many examples of each region of DNA is examined) to gain adequate sensitivity and specificity in clinical use.

Table 2 summarises the current experimental approaches used to detect somatic mutation and clonal haematopoiesis, along with their applications and key limitations.

Personalised Medicine

Personalised medicine advances risk prediction by using this to define people who are more or less likely to benefit from (or be harmed by) an intervention. Somatic mutation profiling holds potential in this regard, with early data supporting the planning of larger trials in people with CHIP. For example, as discussed earlier, patients with atherosclerosis appear to derive larger benefits from the anti-inflammatory therapy canakinumab in the presence of *TET2*-mutant versus non-*TET2*-mutant CHIP.

Furthermore, clonal expansion of somatic mutations reflects local and/or systemic selection pressures that are likely to be relevant to the underlying disease process and be amenable to therapeutic modulation.

While the feasibility of this requires further assessment, data from preclinical models, human *in vitro* and human epidemiological data suggest that metformin can suppress the competitive advantage of *DNMT3A*^{R882H}-mutant CHIP.

Therapeutic Targeting

Inflammation is now recognised as a principal mechanism and emerging therapeutic target in ASCVD. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) showed that inhibiting IL-1β with canakinumab significantly reduced incidence of major cardiovascular events in patients with ASCVD [20]. As noted above, a *post hoc* analysis of CANTOS suggested these benefits are greater in patients with *TET2*-mutant CHIP, although this requires validation.

Colchicine, a low-cost, anti-inflammatory drug, has shown promise in some [92,93], but not all [94], ASCVD clinical trials. In atherosclerosis-prone mice with *TET2*-mutant clonal haematopoiesis, colchicine reduced atherosclerosis and IL-1β expression [28]. In large human cohorts, colchicine use was associated with diminished myocardial infarction rates in people with *TET2*-mutant clonal haematopoiesis [28].

Post hoc analysis of the LoDoCo2 clinical trial that randomised people with ASCVD to colchicine found reduced expansion of *TET2* CHIP clones, versus rates in placebo recipients [95]. These findings suggest that CHIP-driven inflammation represent a therapeutic target in CVD.

Ongoing observational and interventional studies are now underway to assess CHIP-associated cardiovascular risk and to test whether CHIP-informed approaches can guide anti-inflammatory therapies. Table 3 summarises ongoing ClinicalTrials.gov registered studies in this field.

Unanswered Questions

Though current somatic mutation and clonal haematopoiesis research is promising, it remains in its infancy. The clonal expansion of somatic mutations in the blood is well characterised, but there is sparse data surrounding vascular cell somatic mutations.

Large-scale longitudinal studies that compare the blood and vascular tissue are needed to determine how common vascular somatic mutations are, how they develop over time, and their association with CVD. Another key uncertainty is whether somatic mutations are causally associated with CVD (or vice versa), and if so whether they represent adaptive or maladaptive responses. Although this knowledge is not essential to inform risk prediction, it is paramount for successfully guiding therapeutic approaches.

Finally, while therapeutic hypotheses have focused on CHIP-driven inflammation in the blood, it is unclear whether these therapies would address the pathological effects of vascular somatic mutations. Much more fundamental research is needed to define whether such hypotheses are valid regarding the vascular wall and therapies directed there.

Conclusion

CVD is the leading cause of death worldwide, and novel methods of prevention, early detection, and treatment are critical. The recent finding that somatic mutations are prevalent in the blood and vascular wall have opened a promising avenue of translational research.

Somatic mutations accumulate with age and are ubiquitous. Some mutations in HSCs can give rise to CHIP and are an independent risk factor for CVD, possibly via enhanced inflammation. Though originally thought confined to blood, CHIP-associated (and other) mutations are also present in vascular tissue, potentially giving a new perspective on CVD development.

Somatic mutations in vascular cells represent a further layer of disease complexity and an opportunity in translational CVD research. However, many important questions remain about their prevalence and implications.

Understanding these might offer important insights into risk stratification, disease mechanisms, and personalised medicine.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

This study is supported by British Heart Foundation (FS/4yPhD/F/23/34194) awarded to Richard Cubbon.

References

1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. *J Am Coll Cardiol* 2020; 76: 2982–3021.

2. Kessler T, Schunkert H. Coronary Artery Disease Genetics Enlightened by Genome-Wide Association Studies. *JACC Basic Transl Sci* 2021; 6: 610–623.

3. Genovese G, Kähler AK, Handsaker RE, et al. Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence. *N Engl J Med* 2014; 371: 2477.

4. Akhiyat N, Lasho T, Ganji M, et al. Clonal Hematopoiesis of Indeterminate Potential Is Associated with Coronary Microvascular Dysfunction in Early Nonobstructive Coronary Artery Disease. *Arterioscler Thromb Vasc Biol* 2023; 43: 774–783.

5. Cochran JD, Yura Y, Thel MC, et al. Clonal Hematopoiesis in Clinical and Experimental Heart Failure With Preserved Ejection Fraction. *Circulation* 2023; 148: 1165–1178.

6. Zeiher AM, Abplanalp WT, Mas-Peiro S, et al. Association of Clonal Hematopoiesis of Indeterminate Potential With Inflammatory Gene Expression in Patients With Severe Degenerative Aortic Valve Stenosis or Chronic Postischemic Heart Failure. *JAMA Cardiol* 2020; 5: 1170–1175.

7. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk for atherosclerotic cardiovascular disease. *N Engl J Med* 2017; 377: 111–121.

8. Wang Y, Nanda V, Direnzo D, et al. Clonally expanding smooth muscle cells promote atherosclerosis by escaping efferocytosis and activating the complement cascade. *Proc Natl Acad Sci U S A* 2020; 117: 15818–15826.

9. Misra A, Rehan R, Lin A, et al. Emerging Concepts of Vascular Cell Clonal Expansion in Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2022; 42: E74–E84.

10. Dederichs TS, Yerdenova A, Horstmann H, et al. Nonpreferential but Detrimental Accumulation of Macrophages with Clonal Hematopoiesis-Driver Mutations in Cardiovascular Tissues - Brief Report. *Arterioscler Thromb Vasc Biol* 2024; 44: 690–697.

11. Snellings DA, Hong CC, Ren AA, et al. Cerebral Cavernous Malformation: From Mechanism to Therapy. *Circ Res* 2021; 129: 195–215.

12. Zhao B, Wu Q, Ye AY, et al. Somatic LINE-1 retrotransposition in cortical neurons and non-brain tissues of Rett patients and healthy individuals. *PLoS Genet* 2019; 15: e1008043.

13. Luzzatto L. Somatic mutations in cancer development. *Environmental Health* 2011; 10: S12.

14. Martincorena I, Fowler JC, Wabik A, et al. Somatic mutant clones colonize the human esophagus with age. *Science (1979)* 2018; 362: 911–917.

15. Coorens THH, Oh JW, Choi YA, et al. The Somatic Mosaicism across Human Tissues Network. *Nature 2025 643:8070* 2025; 643: 47–59.

16. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 2014; 371: 2488–2498.

17. Xie M, Lu C, Wang J, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. *Nat Med* 2014; 20: 1472–1478.

18. Wikby A, Nilsson BO, Forsey R, et al. The immune risk phenotype is associated with IL-6 in the terminal decline stage: findings from the Swedish NONA immune longitudinal study of very late life functioning. *Mech Ageing Dev* 2006; 127: 695–704.

19. Ferrucci L, Corsi A, Lauretani F, et al. The origins of age-related proinflammatory state. *Blood* 2004; 105: 2294.

20. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *New England Journal of Medicine* 2017; 377: 1119–1131.

21. Haring B, Wissel S, Manson JAE. Somatic Mutations and Clonal Hematopoiesis as Drivers of Age-Related Cardiovascular Risk. *Curr Cardiol Rep* 2022; 24: 1049.

22. Kessler MD, Damask A, O'Keeffe S, et al. Common and rare variant associations with clonal haematopoiesis phenotypes. *Nature 2022 612:7939* 2022; 612: 301–309.

23. Pich O, Reyes-Salazar I, Gonzalez-Perez A, et al. Discovering the drivers of clonal hematopoiesis. *Nat Commun*; 13. Epub ahead of print 1 December 2022. DOI: 10.1038/S41467-022-31878-0.

24. Kim M, Kim JJ, Lee ST, et al. Association Between Aortic Valve Sclerosis and Clonal Hematopoiesis of Indeterminate Potential. *Ann Lab Med* 2024; 44: 279.

25. Bessueille L, Magne D. Inflammation: a culprit for vascular calcification in atherosclerosis and diabetes. *Cell Mol Life Sci* 2015; 72: 2475–2489.

26. Rauch PJ, Gopakumar J, Silver AJ, et al. Loss-of-function mutations in Dnmt3a and Tet2 lead to accelerated atherosclerosis and concordant macrophage phenotypes. *Nature Cardiovascular Research 2023 2:9* 2023; 2: 805–818.

27. Cobo I, Tanaka T, Glass CK, et al. Clonal hematopoiesis driven by DNMT3A and TET2 mutations: role in monocyte and macrophage biology and atherosclerotic cardiovascular disease. *Curr Opin Hematol* 2021; 29: 1.

28. Zuriaga MA, Yu Z, Matesanz N, et al. Colchicine prevents accelerated atherosclerosis in TET2-mutant clonal haematopoiesis. *Eur Heart J* 2024; 45: 4601–4615.

29. Zekavat SM, Viana-Huete V, Matesanz N, et al. TP53-mediated clonal hematopoiesis confers increased risk for incident atherosclerotic disease. *Nature cardiovascular research* 2023; 2: 144.

30. Zon RL, Sekar A, Clapham K, et al. JAK2-mutant clonal hematopoiesis is associated with venous thromboembolism. *Blood* 2024; 144: 2149.

31. Liu W, Pircher J, Schuermans A, et al. Jak2V617F clonal hematopoiesis promotes arterial thrombosis via platelet activation and cross talk. *Blood* 2023; 143: 1539.

32. Gurumurthy G, Gurumurthy S, Somervaille TCP, et al. Bleeding Complications in JAK2-Variant Essential Thrombocythemia: A Revisit in 2025. *EJHaem*; 6. Epub ahead of print August 2025. DOI: 10.1002/jha2.70088.

33. Liu W, Pircher J, Schuermans A, et al. Jak2 V617F clonal hematopoiesis promotes arterial thrombosis via platelet activation and cross talk. *Blood* 2024; 143: 1539–1550.

34. Lo Sardo V, Chubukov P, Ferguson W, et al. Unveiling the Role of the Most Impactful Cardiovascular Risk Locus through Haplotype Editing. *Cell* 2018; 175: 1796.

35. Musunuru K, Post WS, Herzog W, et al. Association of SNPs on Chromosome 9p21.3 with Platelet Reactivity: A Potential Mechanism for Increased Vascular Disease. *Circ Cardiovasc Genet* 2010; 3: 445.

36. Smith-Sørensen B, Hovig' E. CDKN2A (p16INK4A) Somatic and Germline Mutations. *Hum Mutat* 1996; 7: 294403.

37. Quin C, DeJong EN, McNaughton AJM, et al. Chronic TNF in the aging microenvironment exacerbates Tet2 loss-of-function myeloid expansion. *Blood Adv* 2024; 8: 4169–4180.

38. Cai Z, Kotzin JJ, Ramdas B, et al. Inhibition of Inflammatory Signaling in Tet2 Mutant Preleukemic Cells Mitigates Stress-Induced Abnormalities and Clonal Hematopoiesis. *Cell Stem Cell* 2018; 23: 833-849.e5.

39. Challen GA, Goodell MA. Clonal hematopoiesis: mechanisms driving dominance of stem cell clones. *Blood* 2020; 136: 1590–1598.

40. Sano S, Oshima K, Wang Y, et al. Tet2-mediated Clonal Hematopoiesis Accelerates Heart Failure through a Mechanism Involving the IL-1β/NLRP3 Inflammasome. *J Am Coll Cardiol* 2018; 71: 875.

41. Murakami T, Ruengsinpinya L, Nakamura E, et al. Cutting Edge: G Protein Subunit β 1 Negatively Regulates NLRP3 Inflammasome Activation. *The Journal of Immunology* 2019; 202: 1942–1947.

42. Dorsheimer L, Assmus B, Rasper T, et al. Association of Mutations Contributing to Clonal Hematopoiesis With Prognosis in Chronic Ischemic Heart Failure. *JAMA Cardiol* 2019; 4: 25–33.

43. Assmus B, Cremer S, Kirschbaum K, et al. Clonal haematopoiesis in chronic ischaemic heart failure: prognostic role of clone size for DNMT3A- and TET2-driver gene mutations. *Eur Heart J* 2021; 42: 257–265.

44. Sikking MA, Stroeks SLVM, Henkens MTHM, et al. Clonal Hematopoiesis Has Prognostic Value in Dilated Cardiomyopathy Independent of Age and Clone Size. *JACC Heart Fail* 2024; 12: 905–914.

45. Schuermans A, Flynn S, Niroula A, et al. Clonal Hematopoiesis and Risk of New-Onset Myocarditis and Pericarditis. *JAMA Cardiol* 2025; 10: 1147–1156.

46. Heyde A, Rohde D, McAlpine CS, et al. Increased stem cell proliferation in atherosclerosis accelerates clonal hematopoiesis. *Cell* 2021; 184: 1348.

47. Morley AP, Ardissino M, Carter P, et al. Causal relevance of clonal haematopoiesis with cardiac disease and adverse remodelling: a Mendelian randomisation study. *Open Heart* 2025; 12: e003602.

48. Díez-Díez M, Ramos-Neble BL, de la Barrera J, et al. Unidirectional association of clonal hematopoiesis with atherosclerosis development. *Nat Med* 2024; 30: 2857–2866.

49. Busque L, Patel JP, Figueroa ME, et al. Recurrent somatic TET2 mutations in normal elderly individuals with clonal hematopoiesis. *Nat Genet* 2012; 44: 1179–1181.

50. Wang Y, Sano S, Yura Y, et al. Tet2-mediated clonal hematopoiesis in nonconditioned mice accelerates age-associated cardiac dysfunction. *JCI Insight* 2020; 5: e135204.

51. Sano S, Oshima K, Wang Y, et al. CRISPR-Mediated Gene Editing to Assess the Roles of Tet2 and Dnmt3a in Clonal Hematopoiesis and Cardiovascular Disease. *Circ Res* 2018; 123: 335.

52. Fuster JJ, MacLauchlan S, Zuriaga MA, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science (1979)* 2017; 355: 842–847.

53. Svensson EC, Madar A, Campbell CD, et al. TET2-Driven Clonal Hematopoiesis and Response to Canakinumab: An Exploratory Analysis of the CANTOS Randomized Clinical Trial. *JAMA Cardiol* 2022; 7: 521–528.

54. Lassalle F, Duployez N, Vincent F, et al. Negative Impact of TET2 Mutations on Long-Term Survival After Transcatheter Aortic Valve Replacement. *JACC Basic Transl Sci* 2023; 8: 1424–1435.

55. Mas-Peiro S, Hoffmann J, Fichtlscherer S, et al. Clonal haematopoiesis in patients with degenerative aortic valve stenosis undergoing transcatheter aortic valve implantation. *Eur Heart J* 2020; 41: 933–939.

56. Zeng Z, Li F, Gai S, et al. The effect of clonal hematopoiesis on long-term outcomes in patients undergoing coronary artery bypass grafting. *BMC Med* 2025; 23: 322.

57. Buscarlet M, Provost S, Zada YF, et al. DNMT3A and TET2 dominate clonal hematopoiesis and demonstrate benign phenotypes and different genetic predispositions. *Blood* 2017; 130: 753–762.

58. Pascual-Figal DA, Bayes-Genis A, Díez-Díez M, et al. Clonal Hematopoiesis and Risk of Progression of Heart Failure With Reduced Left Ventricular Ejection Fraction. *J Am Coll Cardiol* 2021; 77: 1747–1759.

59. Abplanalp WT, Cremer S, John D, et al. Clonal Hematopoiesis-Driver DNMT3A Mutations Alter Immune Cells in Heart Failure. *Circ Res* 2021; 128: 216–228.

60. Shumliakivska M, Luxán G, Hemmerling I, et al. DNMT3A clonal hematopoiesis-driver mutations induce cardiac fibrosis by paracrine activation of fibroblasts. *Nature Communications 2023 15:1* 2024; 15: 1–20.

61. Min KD, Polizio AH, Kour A, et al. Experimental ASXL1-Mediated Clonal Hematopoiesis Promotes Inflammation and Accelerates Heart Failure. *J Am Heart Assoc* 2022; 11: 26154.

62. Yu B, Roberts MB, Raffield LM, et al. Supplemental Association of Clonal Hematopoiesis With Incident Heart Failure. *J Am Coll Cardiol* 2021; 78: 42–52.

63. Sano S, Wang Y, Yura Y, et al. JAK2V617F-Mediated Clonal Hematopoiesis Accelerates Pathological Remodeling in Murine Heart Failure. *JACC Basic Transl Sci* 2019; 4: 684.

64. Bhattacharya R, Zekavat SM, Haessler J, et al. Clonal Hematopoiesis Is Associated with Higher Risk of Stroke. *Stroke* 2022; 29: 788–797.

65. Salybekov AA, Hassanpour M. Unveiling the Genetic Footprint: Exploring Somatic Mutations in Peripheral Arterial Disease Progression. *Biomedicines 2023, Vol 11, Page 2288* 2023; 11: 2288.

66. Kiefer KC, Cremer S, Pardali E, et al. Full spectrum of clonal haematopoiesis-driver mutations in chronic heart failure and their associations with mortality. *ESC Heart Fail* 2021; 8: 1873–1884.

67. Yokokawa T, Misaka T, Kimishima Y, et al. Clonal Hematopoiesis and JAK2V617F Mutations in Patients With Cardiovascular Disease. *JACC CardioOncol* 2021; 3: 134–136.

68. Perner F, Perner C, Ernst T, et al. Roles of JAK2 in Aging, Inflammation, Hematopoiesis and Malignant Transformation. *Cells* 2019; 8: 854.

69. Diz-Küçükkaya R, İyigün T, Albayrak Ö, et al. JAK2V617F Mutation in Endothelial Cells of Patients with Atherosclerotic Carotid Disease. *Turkish Journal of Hematology* 2024; 41: 167–174.

70. Castiglione M, Jiang YP, Mazzeo C, et al. Endothelial JAK2V617F mutation leads to thrombosis, vasculopathy, and cardiomyopathy in a murine model of

myeloproliferative neoplasm. *Journal of Thrombosis and Haemostasis* 2020; 18: 3359.

71. Guy A, Gourdou-Latyszenok V, Le Lay N, et al. Vascular endothelial cell expression of JAK2V617F is sufficient to promote a pro-thrombotic state due to increased P-selectin expression. *Haematologica* 2018; 104: 70.

72. Molinaro R, Sellar RS, Vromman A, et al. The clonal hematopoiesis mutation Jak2V617F aggravates endothelial injury and thrombosis in arteries with erosion-like intimas. *Int J Cardiol*; 409. Epub ahead of print 15 August 2024. DOI: 10.1016/J.IJCARD.2024.132184.

73. De Meyer GRY, Grootaert MOJ, Michiels CF, et al. Autophagy in vascular disease. *Circ Res* 2015; 116: 468–479.

74. Yang Q, Li X, Li R, et al. Low Shear Stress Inhibited Endothelial Cell Autophagy Through TET2 Downregulation. *Ann Biomed Eng* 2016; 44: 2218–2227.

75. Peng J, Yang Q, Li AF, et al. Tet methylcytosine dioxygenase 2 inhibits atherosclerosis via upregulation of autophagy in ApoE−/− mice. *Oncotarget* 2016; 7: 76423.

76. Bennett MR, Sinha S, Owens GK. Vascular smooth muscle cells in atherosclerosis. *Circ Res* 2016; 118: 692.

77. Benditt EP, Benditt JM. Evidence for a Monoclonal Origin of Human Atherosclerotic Plaques. *Proc Natl Acad Sci U S A* 1973; 70: 1753.

78. Schwartz SM, Murry CE. Proliferation and the monoclonal origins of atherosclerotic lesions. *Annu Rev Med* 1998; 49: 437–460.

79. Chappell J, Harman JL, Narasimhan VM, et al. Extensive Proliferation of a Subset of Differentiated, yet Plastic, Medial Vascular Smooth Muscle Cells Contributes to Neointimal Formation in Mouse Injury and Atherosclerosis Models. *Circ Res* 2016; 119: 1313–1323.

80. Jacobsen K, Lund MB, Shim J, et al. Diverse cellular architecture of atherosclerotic plaque derives from clonal expansion of a few medial SMCs. *JCI Insight*; 2. Epub ahead of print 5 October 2017. DOI: 10.1172/JCI.INSIGHT.95890.

81. Feil S, Fehrenbacher B, Lukowski R, et al. Transdifferentiation of vascular smooth muscle cells to macrophage-like cells during atherogenesis. *Circ Res* 2014; 115: 662–667.

82. Liu R, Jin Y, Tang WH, et al. TET2 is a Master Regulator of Smooth Muscle Cell Plasticity. *Circulation* 2013; 128: 2047.

83. Büttner P, Böttner J, Krohn K, et al. Clonal Hematopoiesis Mutations Are Present in Atherosclerotic Lesions in Peripheral Artery Disease. *Int J Mol Sci* 2023; 24: 3962.

84. Steffensen L, Kavan S, Jensen P, et al. Somatic mutations reveal clonal cell populations in atherosclerotic plaques. *medRxiv* 2023; 2022.05.16.22275001.

85. Liu W, Hardaway BD, Kim E, et al. Inflammatory crosstalk impairs phagocytic receptors and aggravates atherosclerosis in clonal hematopoiesis in mice. *J Clin Invest* 2024; 135: e182939.

86. Wang S, Hu S, Luo X, et al. Prevalence and prognostic significance of DNMT3A- and TET2- clonal haematopoiesis-driver mutations in patients presenting with ST-segment elevation myocardial infarction. *EBioMedicine* 2022; 78: 103964.

87. Scolari FL, Abelson S, Brahmbhatt DH, et al. Clonal haematopoiesis is associated with higher mortality in patients with cardiogenic shock. *Eur J Heart Fail* 2022; 24: 1573–1582.

88. Böhme M, Desch S, Rosolowski M, et al. Impact of Clonal Hematopoiesis in Patients With Cardiogenic Shock Complicating Acute Myocardial Infarction. *J Am Coll Cardiol* 2022; 80: 1545–1556.

89. Gumuser ED, Schuermans A, Cho SMJ, et al. Clonal Hematopoiesis of Indeterminate Potential Predicts Adverse Outcomes in Patients With Atherosclerotic Cardiovascular Disease. *J Am Coll Cardiol* 2023; 81: 1996–2009.

90. Moss J, Magenheim J, Neiman D, et al. Comprehensive human cell-type methylation atlas reveals origins of circulating cell-free DNA in health and disease. *Nature Communications 2018 9:1* 2018; 9: 1–12.

91. Arango-Argoty G, Haghighi M, Sun GJ, et al. An artificial intelligence-based model for prediction of clonal hematopoiesis variants in cell-free DNA samples. *NPJ Precis Oncol* 2025; 9: 1–8.

92. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. *New England Journal of Medicine* 2020; 383: 1838–1847.

93. Tardif J-C, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *New England Journal of Medicine* 2019; 381: 2497–2505.

94. Jolly SS, d'Entremont M-A, Lee SF, et al. Colchicine in Acute Myocardial Infarction. *New England Journal of Medicine* 2025; 392: 633–642.

95. Mohammadnia N, Xue L, Vestjens LTW, et al. Colchicine and Longitudinal Dynamics of Clonal Hematopoiesis: An Exploratory Substudy of the LoDoCo2 Trial. *J Am Coll Cardiol* 2025; 86: 1983–1996.

96. Flynn S, Schuermans A, Uddin M, et al. Clonal Hematopoiesis and Incident Heart Failure. *JAMA Cardiol* 2026; 11: 126–135.

97. Greenfield G, McMullin MF. Splanchnic venous thrombosis in JAK2 V617F mutation positive myeloproliferative neoplasms – long term follow-up of a regional case series. *Thromb J* 2018; 16: 33.

Tables

Table 1: Quantified risks of specific cardiovascular outcomes associated with CHIP.

Mutation	**Type of Mutation**	**Mechanism**	**Cell Type**	**Clinical Phenotype**
DNMT3A	Missense (var R882) + nonsense	Epigenetic dysregulation can lead to altered myeloid differentiation, resulting in increased	Monocytes/macrophages (+ T cell effects reported)	Increased ASCVD risk HR 1.70 (1.1-2.6), p=0.01[7], (cardiac fibrosis, heart failure[5,6,59], stroke; HR 1.44, p=0.03 [64], mortality after TAVR [55])

		expression of pro-inflammatory cytokines		
TET2	Missense + nonsense	Epigenetic dysregulation (reduced methylation), skewing haematopoietic differentiation towards pro-inflammatory myeloid cells	Myeloid cells (monocytes/macrophages	Increased ASCVD risk HR 1.90 (1.0-3.7), p=06 [7]. HF; HR 1.59 (1.18-2.14)[5,58,62,96], aortic stenosis/ mortality after TAVR[55], stroke; HR 1.85, (p=0.004)[64] and differential treatment responses to anti-inflammatory therapies)
ASXL1	Nonsense, loss-of-function	Chromatic regulation disruption	Myeloid cells	Increased ASCVD risk HR 2.0 (1.0-3.9), p=0.05 [7]. HF; HR 1.58 (1.20-2.08) [62,96]. (often weaker than TET2/DNMT3A)
JAK2	Missense (var V617F)	Altered JAK/STAT signalling,	Megakaryocytes/platelets /neutrophils	ASCVD; HR 12 (3.8-38), P<0.0001 [7] , thrombosis (JAK2^{V617F})[30,31],

		platelet/megakaryocyte reprogramming		MI/stroke, VTE (splanchnic vein thrombosis[97]), bleeding/platelet dysfunction, HF; HR 2.50 (1.35-4.64)[62,96]; $JAK2^{V617F}$ specific increased risk of cardiovascular events HR 3.35 (1.22-9.21), p=0.019[67]
TP53	Missense + nonsense	Macrophages	Impaired DNA damage response	Increased risk of; ASCVD, CAD HR 2.31 (1.03-5.16), p=0.042; PAD HR 4.98 (1.23-20.09), p=0.024 [29]. Mechanisms and associations less established.

Table 2: Key experimental techniques used to detect somatic mutation and clonal haematopoiesis

Technique	Use
Whole-exome or whole-genome sequencing (WES/WGS)	Used for variant discovery but less sensitive at detecting variants with a low VAF due to sequencing depth
Targeted NGS (gene panels/amplicon sequencing)	Target next-generation sequencing of CHIP panels with greater depth to detect variants with low VAFs
Droplet digital PCR (ddPCR)	Non-sequencing-based technique to quantify VAF of a known variant. Not used for discovery of new variants

Table 3: Ongoing clinical trials in somatic mutation and CVD

Study (ClinicalTrials.gov ID)	**Study Type**	**Objective**
CHIP/CCUS Natural History Protocol (NCT04102423)	Observational	Verify association of myeloid somatic mutations with atherosclerosis and blood cancers and find new potential clinical associations
Ropeginterferon for High Risk *JAK2* Clonal Hematopoiesis (NCT07249840)	Phase 1 interventional	Test the feasibility and safety of drug Ropeginterferon alfa-2b in the treatment of patients with *JAK2* mutation and high risk features, in the absence of a

		myeloproliferative neoplasm
RICO-HF (NCT06626685)	Observational trial; acute and chronic HF cohorts	Investigate the role of CHIP in inflammation, and study the relevance of inflammatory signalling by immune cells in cardiac dysfunction and HF
CHIVE (NCT06701214)	Observational	Contribute to the understanding of cardiovascular phenotypes and CHIP and better characterise clinical outcomes and co-morbidities in CHIP carriers
CHAPTER (NCT07313059)	Observational	Assess risk of CVD, blood cancers, and personalised care in patients with CHIP

CHIP-RETENTION (NCT04987268)	Observational	Identify association of CHIP and residual cardiovascular risk after smoking cessation.
CLODETTE (NCT05711173)	Interventional	Ascertain the prevalence of CHIP and/or increased NETosis formation in patients with venous thrombosis
TECTONIC (NCT06691217)	Phase 2 interventional	Test the efficacy of drug canakinumab, an inhibitor of IL-1β, on vascular inflammation in individuals with coronary artery disease
Genetic Test Based Risk Prediction of Early Calcific	Observational	Determine the impact of CHIP on the progression of

Aortic Valve Disease in Patients with Bicuspid Aortic Valve (NCT06153407)		early aortic valve calcification in patients with bicuspid aortic valves
Effect of Colchicine on Progression of Coronary Atherosclerosis in Patients with *TET2*-CHIP Variant (NCT07362966)	Phase 4 interventional	Elucidate whether *TET2*-CHIP can be used as a biomarker to guide precision-use of drug colchicine in patients with coronary atherosclerosis, and if *TET2* status is an indicator of response to colchicine
CHiEF (NCT05828888)	Observational	Determine the link between CHIP in endothelial dysfunction and heart failure

Table Legends

[1] Quantified risks of specific cardiovascular outcomes associated with CHIP mutations. Risk estimates reported in studies were defined using HR with a 95% CI or p-value. Abbreviations: HR (hazard ratio), HF (heart failure), MI (myocardial infarction), ASCVD (atherosclerotic cardiovascular disease), CAD (coronary artery disease), PAD (peripheral artery disease), TAVR (transcatheter aortic valve replacement), var (variant)

[2] Experimental approaches summarised by their primary use (broad discovery vs targeted detection vs validation/quantification), and their ability to detect low VAF clones. Whole-exome/genome sequencing enables genome-wide variant discovery but has limited sensitivity at low VAF due to sequencing depth. Targeted deep sequencing increases sensitivity within predefined regions of the genome. Droplet digital PCR provides sensitive quantification of known variants and is used for validation. Abbreviations: VAF (variant allele fraction)

[3] Active studies investigating somatic mutation/clonal haematopoiesis and CVD according to ClinicalTrial.gov. Trials are summarised by their registry ID, design (observational vs interventional, and phase where applicable), and primary objective. Abbreviations: CHIP (clonal haematopoiesis of indeterminate potential), CCUS (clonal cytopenia of undetermined significance), HF (heart failure), NETosis (neutrophil extracellular trap formation), IL-1β (interleukin-1 beta)

Figure Legends

Figure 1: The integrated mechanisms linking somatic mutation in blood and non-blood cells to cardiovascular disease

Somatic mutations may contribute to CVD across multiple cell types. Somatic mutations in HSCs – particularly CHIP-driver genes such as *TET2*, *DNMT3A*, or *JAK2* – can confer a selective advantage and lead to clonal expansion. These mutant clones give rise to pro-inflammatory myeloid cells, which can circulate in the blood and release pro-inflammatory cytokines (e.g. IL-1β, IL-6, and TNFα). There is some evidence that these mutations may be present in ECs and VSMCs, which may contribute to EC dysfunction, or VSMC phenotypic switching. Crosstalk between ECs and immune cells via cytokines has also been suggested. These mechanisms could promote plaque development and progression.

Generated with the assistance of ChatGPT.