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Clonal Hematopoiesis and Thrombosis

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ABSTRACT

Clonal hematopoiesis (CH) has been the focus of many research efforts in the last years and has emerged as a risk modifier for cardiovascular disease morbidity and mortality. While substantial evidence has accumulated regarding its impact on arterial system diseases, the connection with venous thrombosis has only recently been explored. Both clinical and preclinical evidence suggest that the magnitude and mechanism underlying the association of CH with cardiovascular events vary depending on the specific mutated gene involved, indicating a causal link between CH and thrombosis development, not only in the arterial system, particularly in the context of atherosclerosis, but also in venous thrombosis. Although this growing body of knowledge has driven translational research and provided insights for improving clinical management, several questions remain unanswered. This review aims to summarize the available evidence on the link between CH and thrombosis, while highlighting the gaps that need to be addressed in future research.

1 | Introduction

Clonal hematopoiesis (CH) occurs when hematopoietic stem cells acquire a somatic mutation providing them with a proliferative advantage or survival benefit, resulting in the clonal expansion of these mutated cells [1]. While the presence of CH is rare in individuals younger than 40 years, the prevalence increases with age and clonal expansion becomes nearly universal in those older than 70 years, even in the absence of driver gene mutations [2–6]. A more precise definition was implemented in the last years to clearly differentiate between clonal hematopoiesis of indeterminate potential (CHIP) and hematologic malignancies that arise from hematopoietic clones. CHIP is defined as the presence of a somatic mutation with a variant allele frequency (VAF) of at least 2%. Furthermore, the presence of blasts and dysplasia in the bone marrow as well as differential diagnoses have to be excluded [1]. The most commonly mutated genes are *DNMT3A*, *TET2*, and *ASXL1*, while other common ones include *JAK2*, *TP53*, *PPM1D*, and *SF3B1* (Table 1) [2, 7]. The prevalence of CHIP is also increasing with age and about 10% of people aged 70 years or older are affected [2, 3].

Not surprisingly, CH is associated with the risk of hematological cancer, but the progression rate per year is rather low [8]. A strong association between CH and all-cause mortality led to in-depth research efforts to explain this observation. Overall, data aggregated in the last years suggest that CH is associated with various diseases, including (but not being limited to) coronary heart disease, stroke, peripheral artery disease, diabetes, acute and chronic kidney injury, liver disease, some types of solid cancer, and rheumatologic diseases [2, 7, 9–16]. Given the strong association between CH and cardiovascular diseases, this relationship was further explored in preclinical studies to determine whether a causal link exists, which could in turn lead to the identification of new therapeutic targets and the development of novel treatment approaches.

Cardiovascular diseases, particularly thromboembolic events, have a high incidence and rank among the leading health issues and are increasingly problematic in developing countries [17]. Not only are classic arterial thromboembolic events (ATE), such as myocardial infarction or stroke a leading cause of mortality

TABLE 1 | Summary of most-commonly mutated CHIP-associated genes.

Abbreviation	Gene name	Location	Function	Function of encoded protein
ASXL1	Additional sex combs-like 1	Chromosome 20	Epigenetic regulator	Involved in chromatin remodeling, regulates the expression of many HOX genes
DNMT3A	DNA methyltransferase 3a	Chromosome 2	Epigenetic regulator	Facilitates DNA methylation
JAK2	Janus kinase 2	Chromosome 9	Tyrosine kinase	Non-receptor tyrosine kinase involved in cellular growth and proliferation, regulates growth inhibition and stress induced apoptosis
PPM1D	Protein phosphatase magnesium dependent 1	Chromosome 17	DNA damage repair	Acts as a negative regulator of the p53 pathway
SF3B1	Splicing factor 3b	Chromosome 2	Splicing	Facilitates the splicing recognition of exons
TET2	TET methylcytosine dioxygenase 2	Chromosome 4	Epigenetic regulator	Involved in DNA methylation by oxidizing methylcystosine
TP53	Tumor protein p53	Chromosome 17	DNA damage repair, cell cycle arrest	Regulates cell division and cell death

and morbidity, but also venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism (PE), has a relevant burden of disease and impact on the healthcare system [18]. Approximately 40% of VTE events are considered unprovoked due to an unknown underlying cause, highlighting the need to identify new risk factors to better understand the etiology and develop further preventive strategies.

This review aims to give an overview and summarize data on the association of CH with thrombosis on a clinical, preclinical, as well as translational level. Furthermore, the different mechanisms proposed to causally link CH and thrombosis will be discussed.

2 | Clinical Evidence

2.1 | Coronary Artery Disease

One of the earliest observations was that CH is associated with a higher risk of coronary artery disease, a connection that has been demonstrated across various cohorts [2, 7, 19–21]. In the first landmark study by Jaiswal et al. [2] individuals selected regardless of their history of hematologic disease were screened for CHIP. The authors observed that individuals with CH had a 2-fold higher risk for being diagnosed with coronary artery disease compared to those without CH [2]. Similarly, following studies reported hazard ratios (HR) of around 2 for incident coronary artery disease and 4-times higher odds of having an early-onset myocardial infarction in younger people (age < 50 years) with CH [7]. Additionally, a more recent study described a link between DNA damage repair gene (i.e., *TP53* and *PPM1D*) driven CH and coronary artery disease as well [10]. This is important knowledge, as the magnitude of risk seems to depend on the underlying gene mutated. While mutated *DNMT3A*, *TET2*, or *ASXL1* led to an about 1.7–2-fold increased risk, the presence of a *JAK2* mutation amplified the risk of coronary artery disease 12-fold in another recent study [7]. This difference was also observed when a composite outcome of myocardial infarction, coronary artery disease, or revascularization, stroke, or death was assessed. While *DNMT3A* and *TET2* were associated with a mild risk (1.06–1.11 fold), *ASXL1*, *TP53*, and *PPM1D* conferred a moderate (about 1.4 fold) and *JAK2* conferred a high risk (2.8-fold) [22].

Consequently, in a following study by Jaiswal et al. [7] a potential underlying cause was observed. Namely, it was reported that individuals with CH were 3-fold more likely to have a high coronary artery calcification score [7]. Furthermore, in patients with known atherosclerotic cardiovascular diseases, CH is associated with increased risk for recurrent atherosclerotic cardiovascular disease events in the coronary, cerebral, or peripheral arterial system [23]. Also, patients with myocardial infarction and *DNMT3A* or *TET2*-driven CH were reported to have an increased risk for major adverse cardiovascular events [24]. However, in total contrast to these two studies, a recent study including patients from 5 randomized controlled trials (majority of participants had known atherosclerotic cardiovascular diseases) found no clear association between CH and risk of the composite outcome (cardiovascular death, myocardial infarction, ischemic stroke or coronary revascularization). In this analysis, CH was associated with first but not with recurrent myocardial infarction [25].

2.2 | Stroke

Another cardiovascular event with a high incidence is stroke. The landmark paper from Jaiswal et al. [2] reported that the presence of CH is associated with an increased risk (2.6-fold) of ischemic stroke. In another large study, including eight prospective cohorts or biobanks, CH was associated with a 1.14-fold

increase in stroke risk [9]. In particular, CH was associated with small vessel ischemic stroke. When stratifying the analysis according to the underlying gene mutated, only *TET2*-driven CH was linked to an increased risk of ischemic stroke [9]. CH seems to be more prevalent in younger persons with stroke (age below 60 years), as reported by Mayerhofer et al. [26]. The stroke patients included in that study were aged between 18 and 60 years and exhibited a CH prevalence that was 3-fold higher when compared to the general population [26]. In contrast, the authors observed CH more often in individuals with large-artery stroke [26]. A higher frequency of CH in patients with stroke and large-artery atherosclerosis was also found in another study [27]. That study also reported a high prevalence of CH in patients with a first stroke and a higher risk for the composite endpoint of interest, which compromised stroke, myocardial infarction, and death. This association was most pronounced with *TET2* and *PPM1D*-driven CH [27]. The association between CH and stroke was confirmed in a recent meta-analysis including 88 studies reporting a HR of 1.16 [28].

2.3 | Peripheral Artery Disease

The role of CH was also investigated in other atherosclerotic diseases such as peripheral artery disease. A recent study indicates that CH is associated with "pan-arteriosclerosis", with a risk increase of 31% [10]. This is in agreement with previous studies reporting a high presence of atherosclerotic disease in stroke patients with CH [26].

A large biobank-based study recently reported that CH increased the risk of incident peripheral artery disease about 1.7-fold [10]. In this study, especially mutations in *TP53* and *PPM1D* were linked to peripheral artery disease [10]. Important to note is that while patients with hematological malignancy were excluded, information on the history or presence of solid tumors was not reported in that study. CH and mutations in tumor tissue may confound results, as patients with cancer have an increased baseline risk of arterial thromboembolic events such as myocardial infarction, stroke, and acute peripheral artery embolism [29]. In another recent study, the presence of CH was linked to de novo femoral atherosclerosis [30]. Lastly, a contemporary study described an association between CH and cardiovascular mortality in patients with asymptomatic carotid atherosclerosis [31].

2.4 | Venous Thromboembolism

Only recently, the association between VTE and CH was investigated in more detail. Two small studies screened for CH in patients with unprovoked VTE or PE. In both cohorts, a relatively high prevalence of CH was reported (9%–10%) [32, 33]. The authors suggested that this prevalence is higher than would have been expected in the general population with a similar age distribution, but no matched controls were included in both studies. Similarly, in patients with non-cirrhotic or idiopathic splanchnic vein thrombosis, a high frequency of CH mutations was detected [34, 35]. In contrast, one study, including patients older than 50 years with unprovoked proximal or provoked distal VTE, found a similar CH prevalence as in healthy controls; however, no further details about the included patients were reported [36]. Only one study so far has specifically assessed the role of CH in the risk of cancer-associated VTE and did not find an association with increased risk [37]. In contrast, a biobank analysis revealed an association between CHIP and pulmonary embolism (PE) in both the subgroup of patients with cancer and in those without [38].

More data is available for a specific mutation, namely *JAK2*. Individuals without overt myeloproliferative neoplasm (MPN) and *JAK2* mutation were shown to have increased odds of being diagnosed with VTE [39]. Furthermore, it was discovered that 25% of individuals with *JAK2* mutation in the absence of MPN had a history of VTE [40]. A very recent paper confirmed the association between mutated *JAK2* without overt MPN and VTE in a large biobank-based study and found a 6-fold increased VTE risk [41]. In contrast, when the authors assessed the association between VTE and CH, irrespective of affected gene, only a weak link with incident VTE, with a risk increase of 17%, was observed [41]. Similar findings were also reported from a biobank analysis focusing on the risk of PE. While patients with *JAK2* had a significantly higher risk, *TET2* was associated with a lower risk increase, and other mutations showed no association with PE risk [38].

The studies described in this section are summarized in Table 2.

3 | Experimental Evidence

The clinical observations have subsequently prompted investigations to uncover a potential causal relationship. In the following section, the role of each of the most common CH-defining genes linked with cardiovascular disease and thrombosis is discussed.

3.1 | *TET2*

CH-associated *TET2* mutations most commonly have a loss-of-function as a consequence. Thus, frequently *TET2* knockout models were used to assess the consequences of *TET2* CH. Subsequently, it was reported that *TET2* knockout in hematopoietic stem cells led to an increase in atherosclerotic plaque size in atherosclerosis-prone mice [7]. As normally humans with CH do not have a complete loss of function of *TET2* in all hematopoietic stem cells, a more comparable approach was to transplant mice with only a small proportion of deficient cells. Again, it was demonstrated that those with partly deficient stem cells had increased atherosclerotic lesions [42]. Both models exhibited an increase in pro-inflammatory cytokines in the plaque lesions, especially interleukin (IL)-1ß, which were proposed to originate from *TET2* deficient macrophages [7, 42]. Consequently, it was tested whether having only a fraction of macrophages with *TET2* knockout would lead to a similar phenotype. Supporting the hypothesis of macrophages being a key player, that this was sufficient to reconstitute the previously observed phenotype with bigger atherosclerotic plaques [42]. The enhanced secretion of inflammatory cytokines from macrophages with *TET2* mutation was also confirmed in other studies [43] and in a macaque model of *TET2* CH [44]. Overall, the most commonly reported cytokine to be elevated was interleukin (IL) 1-ß [42].

TABLE 2 | Summary of studies reporting the association between clonal hematopoiesis and thrombotic outcomes in the clinical setting. (a) Studies reporting the association between clonal hematopoiesis and coronary artery disease. (b) Studies reporting the association between clonal hematopoiesis and stroke. (c) Studies reporting the association between clonal hematopoiesis and peripheral artery disease. (d) Studies reporting the association between clonal hematopoiesis and venous thromboembolism.

Study	Design and study population	Number of patients	Observation period	Outcomes of interest	Results
(a)					
Jaiswal et al. 2014 [2]	22 population-based cohorts Individuals were selected without regard to hematologic characteristics	17 182	Median follow-up period: 95 months	Hematologic diseases, survival, and cardiovascular events	HR for all-cause mortality: 1.4 (95% CI: 1.1–1.8) HR for incident coronary heart disease: 2.0 (95% CI: 1.2–3.4)
Jaiswal et al. 2017 [7]	2 prospective cohorts for coronary heart disease, 2 retrospective case–control studies for early-onset myocardial infarction Patients with and without myocardial infarction or coronary revascularization procedures after DNA collection	4 794 cases and 3 537 controls	Median follow-up time: 2.6–17.7 years	Coronary heart disease	HR for incident coronary heart disease: 1.9 (95% CI: 1.4–2.7) OR for early-onset myocardial infarction: 4.0 (95% CI: 2.4–6.7) Coronary artery calcification 3.3-fold increased
Bick et al. 2020 [20]	Electronic health record-based biobank Unrelated participants with European ancestry included in the UK Biobank	35 416	Median follow-up: 6.9 years	CVD events: myocardial infarction, coronary revascularization, stroke, or death	HR for incident CVD events: 1.27 (95% CI: 1.04–1.56)
Rossi et al. 2021 [19]	Prospective study Individuals of Italian ancestry ≥ 80 years old	1 059	Follow-up to 15 years	Myeloid neoplasm, survival, cytopenia, and coronary heart disease	HR for coronary heart disease: 1.61 (95% CI: 1.28–3.21)
Wang et al. 2022 [24]	Post hoc analysis of a prospective cohort study Patients with ST-elevation myocardial infarction	485	Median follow-up: 3 years	MACE: death, myocardial infarction, stroke, or hospitalization due to heart failure	HR for major adverse cardiac events with *DNMT3A/TET2* CH: 1.83 (95% CI: 1.15–2.91) HR for all-cause mortality with *DNMT3A/TET2* CH: 1.97 (95% CI: 1.10–3.51)
Zekavat et al. 2023 [10]	2 electronic health record-based biobanks Unrelated individuals without history of hematologic malignancy	50 122	Median follow-up: 3 and 10 years, respectively	Peripheral artery disease and atherosclerosis	HR for coronary artery disease with general CH: 1.40 (95% CI: 1.20–1.63) HR for coronary artery disease with *TP53/PPM1D* CH: 2.51 (95% CI:1.52–4.13)

(Continues)

TABLE 2 | (Continued)

Study	Design and study population	Number of patients	Observation period	Outcomes of interest	Results
Gumuser et al. 2023 [23]	Electronic health record-based biobank Individuals aged 40–70 years with atherosclerotic cardiovascular diseases enrolled in the UK Biobank	13 129	Median follow-up: 10.8 years	CVD events: coronary artery disease events, acute ischemic cerebrovascular events, peripheral artery disease diagnoses and events All-cause mortality	HR for composite of CVD events and all-cause mortality: 1.23 (95% CI: 1.10–1.38) HR for CVD events: 1.24 (95% CI: 1.08–1.43) HR for all-cause mortality: 1.28 (95% CI:1.09–1.51)
Yu et al. 2023 [22]	Electronic health record-based biobank Unrelated individuals without history of hematologic cancer and cardiovascular diseases enrolled in the UK Biobank	424 651	Median follow-up: 11 years	CVD event: myocardial infarction, coronary artery revascularization, stroke, or death	HR for CVD event: 1.18 (95% CI: 1.14–1.22)
Liu et al. 2024 [21]	Meta-analysis of 3 electronic health record-based biobanks	541 995	Not reported	Coronary artery disease events	HR for coronary artery disease with non-*JAK2* CH: 1.09 HR for coronary artery disease with *JAK2* CH: 2.38 (95% CI: 1.63–3.48)
Marston et al. 2024 [25]	5 randomized TIMI trials Clinical trial participants 74% of included patients with known atherosclerotic cardiovascular diseases	63 700	Median follow-up: 2.5 years	Major CV events: CV death, myocardial infarction, ischemic stroke or coronary revascularization	No association with composite outcome HR for first MI: 1.31 (95% CI: 1.05–1.64) No association with recurrent MI or first/recurrent stroke or coronary revascularization
Singh et al. 2024 [28]	Systematic review and meta-analysis (88 studies)	460045	Not reported	Clinical outcomes: any disease entity and mortality	HR for coronary artery disease: 1.76 (95% CI: 1.27–2.44)
(b)					
Jaiswal et al. 2014 [2]	22 population-based cohorts Individuals were selected without regard to hematologic characteristics	17 182	Median follow-up period: 95 months	Hematologic diseases, survival, and cardiovascular events	HR for ischemic stroke: 2.6 (95% CI: 1.4–4.8)

(Continues)

TABLE 2 | (Continued)

Study	Design and study population	Number of patients	Observation period	Outcomes of interest	Results
Bhattacharya et al. 2022 [9]	6 prospective cohort studies and 2 electronic health record-based biobanks Patients without history of stroke, hematologic malignancy and/or other non-neoplastic clonal disease	7 426 cases and 78 752 controls	Median follow-up: 3.0–20.4 years	Any stroke, ischemic stroke, and hemorrhagic stroke	HR for stroke: 1.14 (95% CI: 1.03–1.27) HR for hemorrhagic stroke: 1.24 (95% CI: 1.01–1.51) HR for small vessel stroke: 1.55
Mayerhofer et al. 2023 [26]	Prospective cohort Patients between 18 and 60 years with stroke or TIA	248 patients 103 282 age-matched controls	Not applicable	CH frequency	51 patients CH (21%), 3-fold higher than frequency in age-matched healthy controls Highest fraction of CH in patients with large-artery stroke
Arends et al. 2023 [27]	Prospective observational cohort Patients with first-ever stroke	581	Follow-up of 3 years	Recurrent stroke, myocardial infarction, and all-cause mortality	HR for composite end point: 1.55 (95% CI: 1.04–2.31)
Singh et al. 2024 [28]	Systematic review and meta-analysis (88 studies)	247 461	Not reported	Clinical outcomes: any disease entity and mortality	HR for stroke: 1.16 (95% CI:1.05–1.28)
(c)					
Zekavat et al. 2023 [10]	2 electronic health record-based biobanks Unrelated individuals without history of hematologic malignancy	50 122	Median follow-up: 3 and 10 years, respectively	Peripheral artery disease and atherosclerosis	HR for peripheral artery disease with CH: 1.66 (95% CI: 1.31–2.11) HR for pan-arterial atherosclerosis with CH: 1.31 (95% CI:1.14–1.49) HR for peripheral artery disease for *TP53* or *PPM1D* CH: 2.72 (95% CI: 1.28–5.76)
Jäger et al. 2024 [31]	Prospective cohort Patients with asymptomatic carotid atherosclerosis	968	Median follow-up: 11.8 years	Cardiovascular or all-cause death	HR for cardiovascular death: 1.50 (95% CI: 1.12–2.00) HR for all-cause mortality: 1.42 (95% CI: 1.11–1.81)
Diez-Diez et al. 2024 [30]	Ongoing observational prospective cohort study Healthy middle-aged individuals followed for progression of early subclinical atherosclerosis	3 692	Follow-up visit after 6 years	Atherosclerosis	OR for de-novo femoral atherosclerosis: 1.56 (95% CI: 1.13–2.13)
(d)					

(Continues)

TABLE 2 | (Continued)

Study	Design and study population	Number of patients	Observation period	Outcomes of interest	Results
Wolach et al. 2018 [40]	Case–control cohort Schizophrenic patients and controls with or without history of VTE without diagnosis of myeloid blood disorder	10 893	Not applicable	CH frequency	25% of patients with *JAK2* CH had VTE
Fidalgo-Fernandez et al. 2020 [Abstract] [32]	Registry Patients < 70 years with unprovoked VTE	66	Not applicable	CH frequency	High CH frequency of 9%
Cordua et al. 2021 [39]	Cross sectional population-based study Individuals with written informed consent	19 958	Not applicable	*JAK2* mutation frequency	OR for prevalent VTE with *JAK2* CH: 2.8 (95% CI: 1.1–7.0)
Dunbar et al. 2021 [37]	Electronic health record-based biobank (MSK-IMPACT) Patients with solid tumors	11 695	Follow-up after 1 year	Cancer-associated thrombosis	No association with cancer-associated thrombosis
Magaz et al. 2021 [34]	Prospective study Patients with non-cirrhotic splanchnic vein thrombosis	74	Not applicable	CH frequency	28 of 74 patents (37.8%) high-molecular-risk variant present
Soudet et al. 2021 [33]	Retrospective pilot study Patients between 18 and 65 years with unprovoked PE	61	Not applicable	CH frequency	High CH frequency of 10%
Carra et al. 2023 [35]	Prospective study Patients with idiopathic splanchnic vein thrombosis	15	Not applicable	CH frequency	In 7 of 15 (46.7%) CH present
Guillotin et al. 2023 [36]	Case–control study Individuals > 50 years with DVT and healthy individuals	94 cases 46 controls	Not applicable	CH frequency	In 7 of 94 (7.5%) VTE cases CH present In 4 of 46 (8.7%) controls CH present
Zon et al. 2024 [41]	Electronic health record-based biobank Individuals without prevalent diagnosis of a hematologic malignancy prior to DNA sampling or within 6 months after enrolment in the UK Biobank	425 399	Median follow-up: 11.8 years	Incident and prevalent VTE	HR for incident VTE with general CH: 1.17 (95% CI: 1.09–1.30) HR for incident VTE with *JAK2* CH: 4.20 (95% CI: 2.18–8.08) OR for prevalent VTE with *JAK2* CH: 6.58 (95% CI: 2.65–16.29)

Abbreviations: CH, clonal hematopoiesis; CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; HR, hazard ratio; MACE, major adverse cardiac events; OR, odds ratio; PE, pulmonary embolism; VTE, venous thromboembolism.

Potential treatment targets were investigated in preclinical models as well. The inhibition of the NLRP3 inflammasome, which plays a key role in IL-1ß secretion, was found to reverse the observed phenotype of increased atherosclerotic lesions [42]. Moreover, treating mice with partly *TET2*-deficient bone marrow with an IL-6 antibody also reversed the increased atherosclerotic lesion size. Furthermore, this led to normalization of acute phase reactants, aortic monocyte and macrophage content, and increased the fibrous cap of lesions, indicating a greater stability [45]. Only recently, it was shown that colchicine, which is known for its general anti-inflammatory properties, could significantly decrease not only IL-1ß levels in *TET2* CH mice but also the plaque size. In contrast, this clear improvement with colchicine treatment was not observed in wild type atherosclerosis-prone mice [46]. Lastly, P-selectin was also suggested to be involved in the pathomechanism of enhanced atherosclerotic plaques, as the expression on endothelial cells was higher in the aorta of mice with partly *TET2*-deficient bone marrow [42].

3.2 | *DNMT3A*

Similar to *TET2* CH models, models with atherosclerosis-prone mice transplanted with a fraction of *DNMT3A* knockout hematopoietic stem cells were assessed. These mice exhibited an increase in lesion size of about 50% compared to those transplanted with wild-type cells [47]. In a detailed analysis of the plaque macrophages, a high expression of several inflammatory mediators was present [47]. Similarly, experiments with isolated *DNMT3A* knockout cells reported that, once stimulated, these cells secreted higher levels of inflammatory cytokines, including IL-6 (but not IL-1ß) compared to wild-type cells [43].

3.3 | *ASXL1*

In contrast to mice with partly *TET2* or *DNMT3A*-deficient bone marrow, atherosclerosis-prone mice with partly *ASXL1* knockout bone marrow had no increased lesions in the aortic root [22]. This might be explainable by the low mutation burden observed in those mice, which could indicate that a longer follow-up might be needed to study the growth of lesions. In bone-marrow-derived isolated *ASXL1* mutated macrophages, an increase in AIM2 inflammasome activation and a subsequent increase in IL-1ß and IL-6 secretion were reported [22].

3.4 | *TP53*

To assess the influence of *TP53* on atherosclerosis, *TP53*-deficient hematopoietic stem cells were transplanted into atherosclerosis-prone mice [10]. Consequently, these mice exhibited an increase in plaque size in the aortic root and a rise of plaque macrophages that were predominantly *TP53*-deficient. This finding indicates that there is a selective expansion advantage present in *TP53*-deficient macrophages [10]. In contrast to other CH mouse models, mice transplanted with *TP53* knockout hematopoietic stem cells did not present with an elevated expression of pro-inflammatory cytokines in the atherosclerotic lesions [10].

3.5 | *JAK2*

In mouse models with pan *JAK2* mutation, complete or partially *JAK2* mutated hematopoietic stem cells, a quicker and more pronounced thrombosis development was observed, utilizing different arterial and venous thrombosis models [21, 40, 48]. Furthermore, an increased thrombus formation was seen in a mouse model with *JAK2* mutation only in the endothelial cells [49]. Mice with partially *JAK2* mutated bone marrow exhibited a larger (up to 2-fold) atherosclerotic lesion size with bigger necrotic areas in the aortic root of atherosclerosis-prone mice [50, 51]. Furthermore, a similar mouse model revealed that partially *JAK2-mutated* bone marrow mice showed a higher incidence of thrombosis in a superficial erosion model [52].

Proposed mechanisms underlying this phenotype are multifactorial and include different components of the hemostatic, vascular, and immune system. In addition to an increased neutrophil-extracellular-trap (NET) formation [40, 52], enhanced binding of *JAK2* cells on surface molecules (such as VCAM, ICAM) [53] is present, as the integrins are in a high-affinity open position on granulocytes with *JAK2* mutation [48]. Also, platelets and endothelial cells could play an important role. Platelets with *JAK2* mutation exhibited enhanced integrin activation and P-selectin exposure, and an increased activity level due to more COX1 and COX2 expression, and elevated ROS, NOX2, and TXA2 production [21]. Endothelial cells also expressed more P-selectin, and levels of soluble P-selectin (sP-selectin) were increased in general in that mouse model [49]. They also presented with impaired endothelial barrier function and higher apoptotic content when challenged in a superficial erosion model [52]. Moreover, *JAK2* mutated macrophages secreted higher levels of IL-6 and IL-1ß. Additionally, they migrated more often into atherosclerotic lesions where they exhibited enhanced proliferation [50, 51].

Consequently, it was investigated whether the observed phenotypical changes in *JAK2* CH mouse models could be reversed as well. So far, the application of JAK–STAT inhibitors could decrease NET formation and thrombosis rates [40, 52]. Additionally, both an integrin receptor-blocking agent [48] and a P-selectin blocking agent [49] could reverse the accelerated thrombus formation. Lastly, an IL-1 receptor antagonist [51] reduced the necrotic core area in plaque lesions in another mouse study, which enhanced the stability of the plaques.

Figure 1 provides a summary of proposed mechanisms causally linking CH to thrombotic outcomes.

4 | Clinical Implications

There is accumulating clinical evidence that CHIP might also be causally linked to thromboembolic events in humans, with most of it suggesting that CHIP-induced inflammation could be the driver. Individuals with CH were reported to have higher levels of high sensitivity (hs)-CRP compared to the general population without CH [23, 54]. Moreover, study participants with CH exhibited elevated levels of IL-6 and IL-8 as well. More specifically, individuals with *TET2* CH were reported to have higher levels

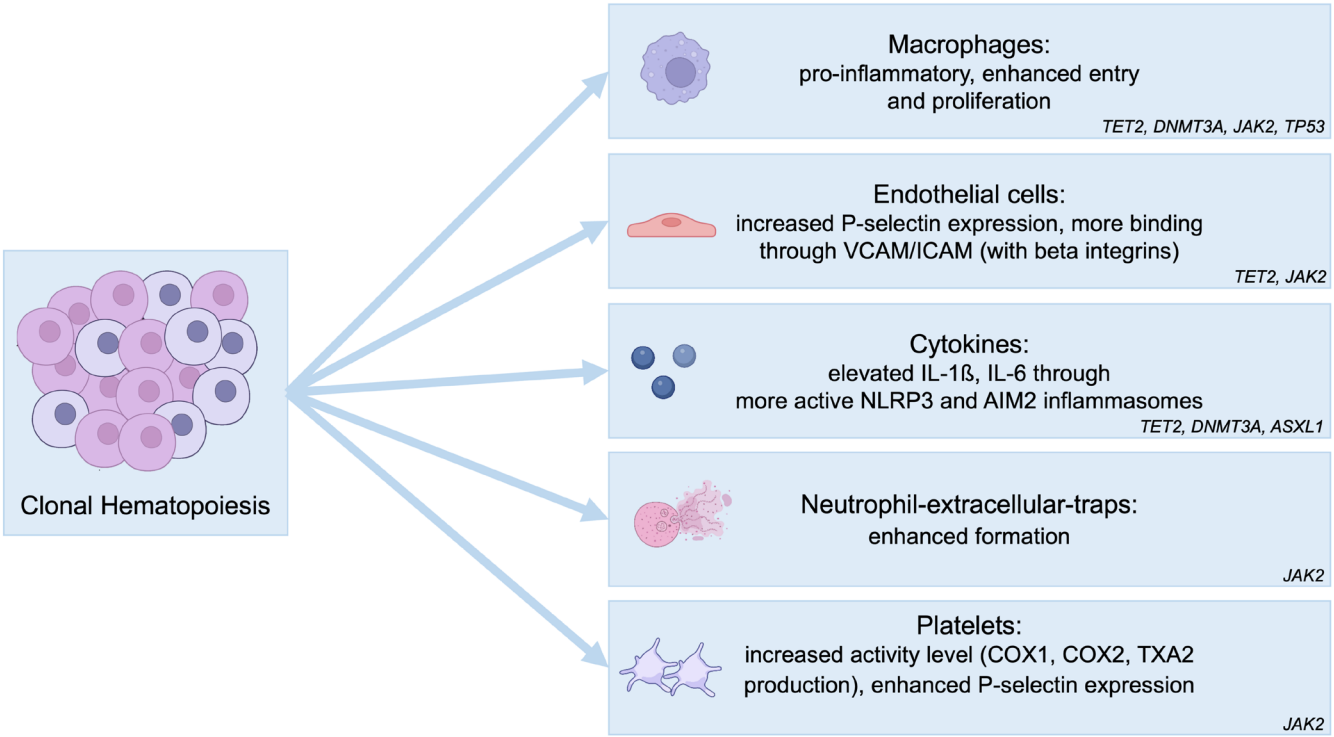

FIGURE 1 | Summary of proposed mechanisms linking CH to cardiovascular and thrombotic outcomes. [Color figure can be viewed at wileyonlinelibrary.com]

of IL-1ß, while those with *JAK2*-mutated CH were observed to have elevated IL-18 levels [7, 27, 55–57].

Furthermore, in a post hoc analysis of the CANTOS trial, participants were screened for CH, and the effect of inhibition of inflammation on cardiovascular risk was assessed. The CANTOS trial was a randomized controlled trial that aimed to investigate canakinumab, an IL-1ß antibody, for secondary prevention in patients with prior myocardial infarction and elevated hs-CRP levels [58]. The highest dose of canakinumab reduced the risk of experiencing a major adverse cardiovascular event [58]. In the post hoc analysis, included patients were screened for CH, with mutations in the *TET2* gene being the most commonly detected. This could indicate a selection bias in patients with prior myocardial infarction and elevated hs-CRP levels, as normally CH-associated mutations are more frequently found in the *DNMT3A* gene. Moreover, only patients with *TET2* mutation had a lower cardiovascular risk when receiving canakinumab (in any dose) compared to those receiving placebo, while the risk reduction was not seen in those without CH or with non-*TET2* CH [55]. However, canakinumab is not yet approved for clinical use. Another approach targeting inflammation that might offer a more straightforward path to clinical use is colchicine, a widely used drug with anti-inflammatory properties. It is important to mention that previous trials reported conflicting results about the effect of colchicine on cardiovascular risk reduction. While in patients with chronic coronary disease colchicine reduced the risk of cardiovascular events [59], it had no influence on future events in patients with recent myocardial infarction [60]. Post hoc analyses of trial populations assessing the influence of CH have not been conducted so far. Nevertheless, a biobank-based analysis found a reduction in myocardial infarction risk in patients with CH receiving colchicine, but only in those carrying *TET2* mutations, and not in those with *DNMT3A* or *ASXL1* mutations [46]. A similar effect was observed in the presence of an IL-6 receptor coding mutation. This mutation was associated with reduced risk for cardiovascular disease in patients with CH; however, not in individuals without a CH mutation [20, 61].

5 | Discussion

In summary, CH has been extensively studied in recent years and is now recognized as a risk factor for cardiovascular diseases. The strongest evidence supporting a causal link between CH and thrombotic events is found in the arterial system, though interest in its role in the venous system is growing.

Data on arterial thromboembolic events and their association with CH was gathered in great number in both clinical and preclinical studies. While this association has been consistently reported so far [2, 7, 9, 10, 28], the underlying mechanisms seem to be multifactorial, with the majority of evidence pointing towards an aggravation of atherosclerosis due to enhanced inflammatory responses of mainly macrophages [7, 42, 43]. Furthermore, platelet and endothelial cell activation are also suggested to be involved; for example, *TET2* knockout mice had increased P-selectin expression on endothelial cells and sP-selectin levels [42]. In in-vivo experimental studies, there were differences between mouse models with different mutated genes, which indicates that more granular research to investigate the impact of CH on cardiovascular risk is needed in the clinical setting as well. Post hoc clinical trial data, as well as evidence from large-scale biobank analyses, indicated that CH could help define patients that would benefit from new interventions, such as targeting the inflammatory system

with, for example, canakinumab [55]. Thus, first attempts to test specific strategies in patients with CH to reduce their cardiovascular risk are currently underway and being conducted. This further points to the importance of considering specific CH-associated mutations in more granularity and distinct from one another. Furthermore, allele location may influence risk, particularly when mutations that alter or reduce enzyme function are present, compared to loss-of-function mutations. Still, open questions remain, for example, whether the knowledge gained from mouse models can be extrapolated to humans and CH in general. Additionally, it remains incompletely understood whether CH interacts with other established risk factors, such as hypertension.

While clinical evidence for the association of CH with VTE is accumulating [32, 33, 41], less is known about underlying mechanisms. Most likely, the mechanisms of a thrombotic phenotype are multifactorial, as indicated for *JAK2* CH, where in addition to macrophages and platelets also neutrophils and endothelial cells also play an important role [21, 40, 48]. However, the impact of other CH mutations on venous thrombosis has not yet been investigated, and there remains a gap in knowledge regarding the connection and interplay between CH and thrombophilia or other established risk factors.

6 | Conclusion

CH is an important modifying factor influencing the thrombotic risk. While the influence on cardiovascular diseases affecting the arterial system is well assessed, evidence indicating an association of CH with VTE is still limited. The proposed underlying pathomechanisms also suggest a causal link between CH and venous thrombosis. Future studies will bring more insight into specific mutations to stimulate further investigations of potential new preventive strategies. The most promising targets are currently the immune system and inflammation, but other strategies such as targeting components of the hemostatic system (e.g., P-selectin) might be promising as well.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

C.E. declares no conflicts of interest. C.A. received personal fees for lectures and/or participation in advisory boards from Bayer, BMS, Pfizer, Daiichi-Sankyo and Sanofi.

Data Availability Statement

The authors have nothing to report.

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