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STATE OF THE ART REVIEW
Heart failure and cardiomyopathies

The emerging role of clonal haematopoiesis in the pathogenesis of dilated cardiomyopathy

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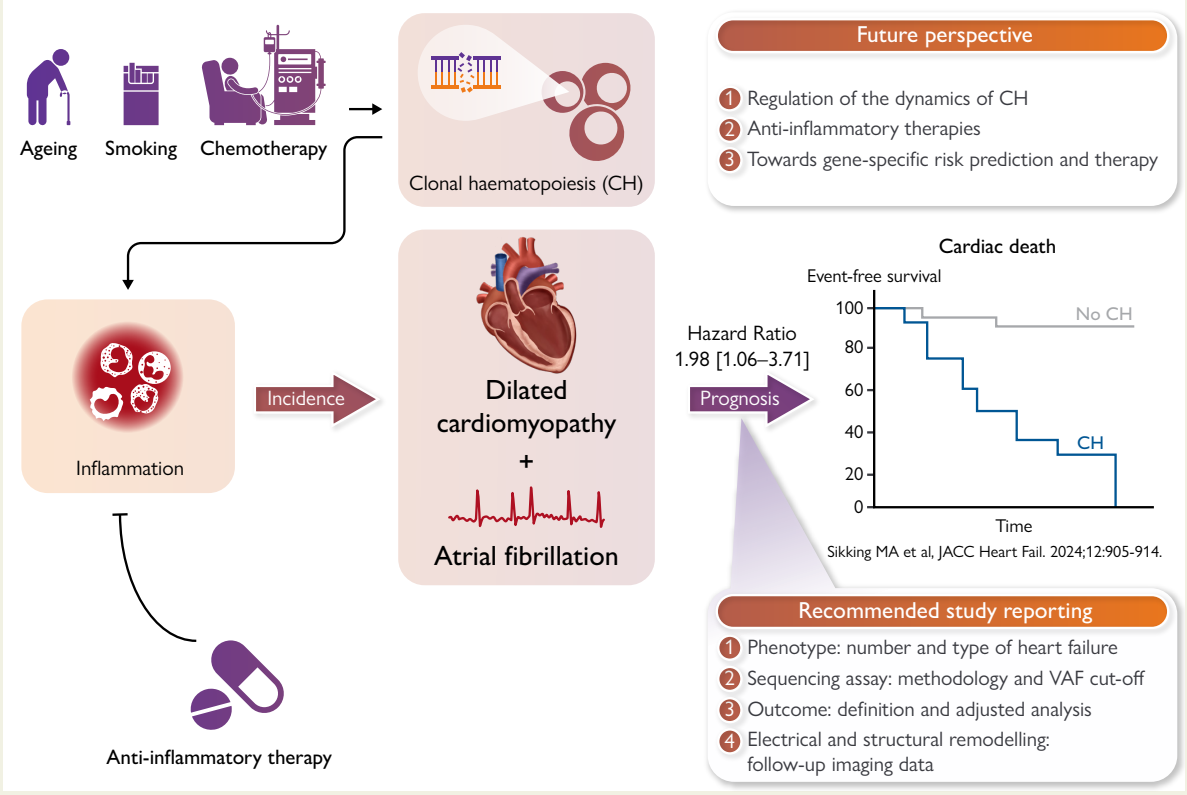
Graphical Abstract



Clonal haematopoiesis in the pathogenesis of dilated cardiomyopathy. CH, clonal haematopoiesis; VAF, variant allele frequency.

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Abstract

The increased sensitivity of novel DNA sequencing techniques has made it possible to identify somatic mutations in small circulating clones of haematopoietic stem cells. When the mutation affects a 'driver' gene, the mutant clone gains a competitive advantage and has the potential to expand over time, a phenomenon referred to as clonal haematopoiesis (CH), which is emerging as a new risk factor for various non-haematological conditions, most notably cardiovascular disease (e.g. heart failure). Dilated cardiomyopathy (DCM) is a form of non-ischaemic heart failure that is characterized by a heterogeneous aetiology. The first evidence is arising that CH plays an important role in the disease course in patients with DCM, and a strong association of CH with multiple aetiologies of DCM has been described (e.g. inflammation, chemotherapy, and atrial fibrillation). The myocardial inflammation induced by CH may be an important trigger for DCM development for an already susceptible heart, e.g. in the presence of genetic variants, environmental triggers, and comorbidities. Studies investigating the role of CH in the pathogenesis of DCM are expected to increase rapidly. To move the field forward, it will be important to report the methodology and results in a standardized manner, so results can be combined and compared. The accurate measurement of CH in patients with DCM can provide guidance of specific (anti-inflammatory) therapies, as mutations in the CH driver genes prime the inflammasome pathway.

Keywords Dilated cardiomyopathy • Clonal haematopoiesis • Heart failure • Sequencing • Somatic mutations • CHIP

Introduction

Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular dilatation and systolic dysfunction unexplained solely by abnormal loading conditions or coronary artery disease.[1] The causes of DCM are heterogeneous, including both genetic and environmental factors, also determining the disease progression and outcome.[2,3] Chronic myocardial inflammation is often present in patients with DCM, and can be either the cause or consequence of disease progression.[4] A broad and aggressive immunosuppressive therapy may be beneficial in DCM patients with increased myocardial inflammation,[5,6] but more targeted immunomodulation strategies are lacking.[7] Given the connection between clonal haematopoiesis (CH) and inflammation, CH may be a marker and target for immunomodulatory therapy in patients with DCM.[8] Recent studies indicate an age-independent effect of CH on the prognosis of DCM, suggesting that CH may also be involved in its pathogenesis. The current review elaborates on (i) the current evidence of CH involvement in DCM, (ii) the knowledge gaps in the road towards clinical impact, and (iii) the future prospects (Graphical Abstract).

General background on clonal haematopoiesis

The advent of next-generation DNA sequencing methodologies and their increasing utilization in large human cohorts have led to a new era in human genetics and genomics for clinical and research purposes. Within the specific setting of cardiovascular disease (CVD), investigations into the influence of human genetics have predominantly concentrated on germline variants, which are heritable and therefore present uniformly across all cells within an organism. Numerous inherited genetic variants clearly contribute to a diverse set of different cardiovascular pathologies.[9–12] However, research during the last decade has exposed a similarly important role of certain somatic variants. These variants are non-inherited and accumulate in a mosaic manner within an individual from conception onwards as a result of DNA damage or random errors in DNA replication and repair.[13] The clinical implications of this somatic genome mosaicism are particularly relevant in the haematopoietic system. Haematopoietic stem cells (HSCs) accumulate random mutations continuously as an individual grows older.[14–16] While most of these mutations are deemed neutral 'passenger' mutations, a select subset will affect a 'driver' gene, providing a competitive advantage to the mutant hematopoietic stem cells (HSC) by promoting its proliferation, survival or self-renewal. Consequently, these mutations drive the progressive expansion of the mutant cell population over time, a phenomenon commonly referred to as somatic mutation-driven CH (*Figure 1*).[17,18]

Clonal haematopoiesis-driving mutations are typically detected through next-generation DNA sequencing of blood samples, which allows the detection of expanded somatic mutations by calculating variant allele frequency (VAF), representing the proportion of reads that support a mutant allele out of the total sequencing reads (*Figure 1*). Such sequencing analyses have unveiled a diverse array of mutations detectable in blood, including base substitutions [known as single-nucleotide variants (SNVs)], small insertions and deletions (indels), cytogenetic aneuploidies, and structural chromosomal variants. Consequently, it is possible to define different forms of CH based on the detected mutation type. In this context, the type of CH that is gaining more clinical relevance, particularly in the cardiology and haematology fields, is a condition referred to as CH of indeterminate potential (CHIP). CHIP is defined as the presence in blood or bone marrow of an expanded SNV or indel in a known gene associated with haematological malignancies, typically myeloid-biased, with a VAF of at least 2%, and in the absence of overt haematological abnormalities.[19] Although a diverse range of cancer-related genes have been identified as potential drivers of CHIP, most mutations occur in a limited subset of genes, most frequently in those encoding the epigenetic regulators *DNMT3A*, *TET2*, and *ASXL1*. Additionally, other frequently mutated CHIP genes encode for DNA damage response (DDR) proteins (e.g. TP53 and PPM1D), splicing factors (e.g. *SF3B1*, *SRSF2*, and *U2AF1*) and signalling mediators (e.g. *JAK2*).

CHIP is strongly associated with aging[20–23] and with age-related diseases.[24–38] Unsurprisingly, CHIP mutations increase the risk of incident haematological malignancy.[20,22,39] However, CHIP is also emerging as a new risk factor for various non-haematological conditions, most notably CVD.[13,24,28,29,31,34,36,37] First, a robust correlation between

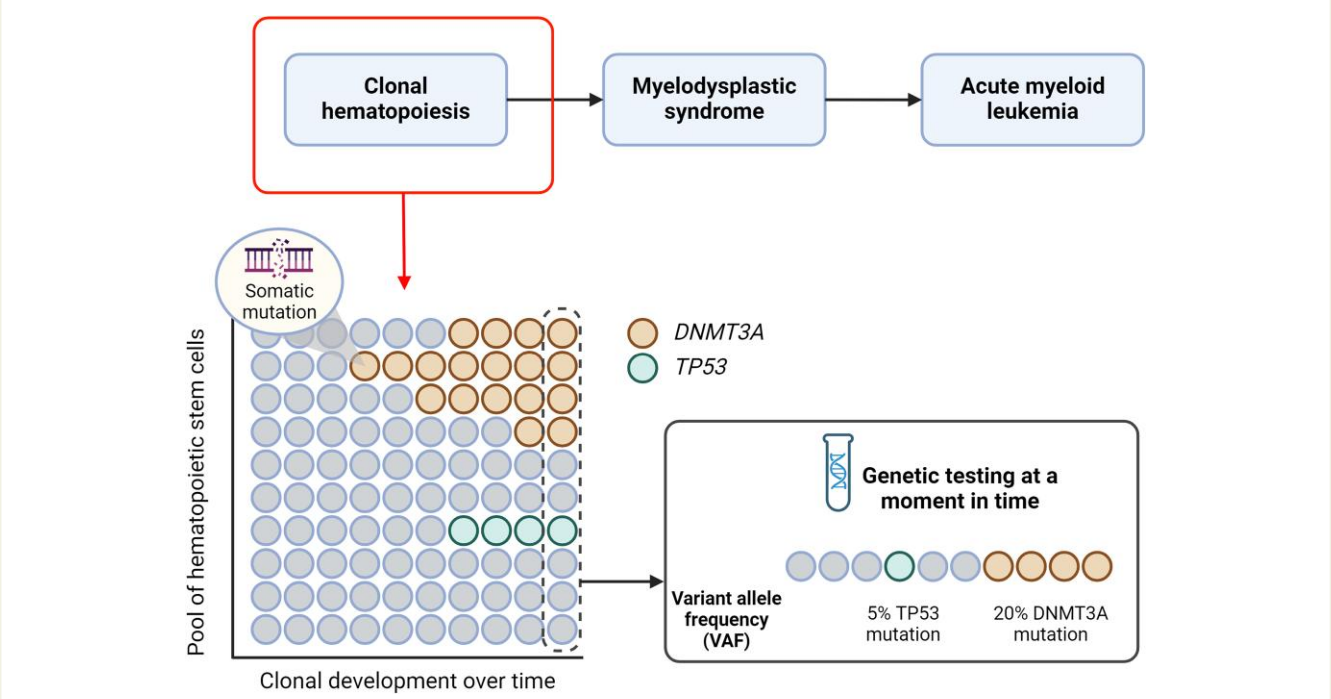

Figure 1 Clonal haematopoiesis in relation to secondary haematological diseases and genetic testing of clonal expansion. When clonal haematopoiesis is followed by cytopenia and dysplasia it results in myelodysplastic syndrome that can lead to acute myeloid leukaemia. Clonal haematopoiesis is characterized by expansion of a clone that gained a selective advantage due to a somatic mutation (in this example in the *DNMT3A* and *TP53* gene). Genetic testing at a certain time point will detect the variant allele frequency (VAF): the percentage of sequencing read with the specific mutation, reflecting a somatic mosaicism which is different from germline mutations. Clonal haematopoiesis is defined as the presence of a clone with a mutation in a known gene associated with haematological malignancies and a VAF of at least 2%

CHIP mutations and an increased risk of developing atherosclerotic conditions, such as coronary artery disease and peripheral artery disease, independent of age, sex, or traditional cardiovascular risk factors have been described.[24,28,31,34] Furthermore, recent studies suggest that CHIP may also be associated with cardiac dysfunction and disease beyond its effects on coronary arteries, as further discussed below (*Table 1*, *Figure 2*).

From a mechanistic standpoint, it is important to note that the clonal expansion of CHIP mutations primarily occurs among the HSC population in the bone marrow, resulting in a variable proportion of progeny immune cells carrying the CHIP mutation. Consequently, CHIP has the potential to significantly influence inflammatory responses, which play a central role in CVD and heart failure (HF). Experimental studies in animal models in various contexts are elucidating the specific immunomodulatory pathways and mechanisms dysregulated in CHIP.[28,51–54] While some common mechanisms are emerging, the links between CHIP and CVD appear to be dependent on the specific mutated gene, offering avenues for the development of precision medicine approaches to prevent or treat CVD by targeting the pro-inflammatory effects of specific CHIP mutations.

Clonal haematopoiesis in patients with heart failure

The association between CH and various forms of HF have been extensively described,[55] either in relation to the prognosis of patients with HF, or the incidence of HF in the general population (*Figure 3*). The methodology and cohort characteristics (e.g. the number of individuals and types of HF included) significantly differ between studies, which is important to take into account when interpreting the results.

The association of CH with the incidence of HF remains uncertain (*Table 1*),[29,30,40,41] although several predictors and modifiers have been identified. The association is modified by age: CH is mainly associated with new-onset HF in younger individuals (<65 years).[29] The largest study with the longest follow-up showed a significant association of CH with incident HF, but mainly due to mutations in *ASXL1*, *TET2*, and *JAK2* independent of age.[30] Most studies distinguish between HF with preserved (HFpEF) or with reduced ejection fraction (HFrEF), creating the opportunity to compare the effect of CH between these types. Two population studies identified *TET2* mutations associated with incident HFpEF, but not in HFrEF.[40,41] Concluding, CH is predominantly associated with the incidence of HFpEF and not HFrEF, which is mainly attributable to mutations in *TET2*, with the effect being modified by age. However, we require more studies investigating (gene-specific) CH and HF development to draw definite conclusions.

Most studies investigating the association between CH and prognosis were conducted in patients with ischaemic HF, where CH was a predictor of worse outcome, independent of age (defined as cardiac death and HF hospitalization).[43–50,56] As such, the presence of a CH driver mutation is an independent prognostic marker for a worse outcome in patients with an ischaemic form of HF (*Figure 3*).

Table 1 Overview of clinical studies investigating the association of clonal haematopoiesis with the development or prognosis of heart failure

Study	Patient population	Size population cohort	Size cohort	Age (years)[d]	CH	Cut-off VAF (%)	Outcome definition	Association (hazard ratio)	Dominant genes
Incidence									
Shi *et al.*[29]	HFrEF + HFpEF	8592	374 (4.3%)	65 [58–70]	66 (18%)	2	NA	1.2 [0.9–1.7][a]	*DNMT3A, TET2*
Yu *et al.*[30]	HF	56 597	4.694 (8.3%)	NR	414 (9%)	2	NA	1.3 [1.1–1.4]	*ASXL1, TET2, JAK2*
Schuermans *et al.*[40]	HFpEF	8090	459 (5.7%)	NR	NR	2	NA	1.3 [0.9–1.8]	*TET2*[b]
	HFrEF		339 (4.2%)					0.8 [0.5–1.3]	
Reiner *et al.*[41]	HFpEF	5214	301 (5.8%)	NR	NR	2	NA	1.4 [1.1–1.9]	*TET2*
	HFrEF		213 (4.1%)					NR	
Prognosis									
Sikking *et al.*[42]	DCM	NA	520	58 [53–66]	109 (21%)	0.01	Cardiac death	2.0 [1.1–3.7]	*DNMT3A*
Pascual-Figal *et al.*[43]	NICMP	NA	32	74 [69–79]	12 (38%)	2	HF mortality + hospitalization	2.0 [1.1–3.7]	*DNMT3A, TET2*
	IHF		30		12 (40%)				
Wu *et al.*[44]	DCM	NA	52	62 (26–94)	10 (19%)	5	All-cause mortality + hospitalization	1.7 [0.6–4.9]	*DNMT3A, TET2*
	IHF		48	69 (26–94)	6 (13%)			1.4 [0.4–4.7]	*DNMT3A, CUX*
Scolari *et al.*[45]	NICMP[c]	NA	446	55 ± 15	149 (22%)	2	All-cause mortality	2.7 [1.3–5.7]	*TET2, ASXL1*
	IHF[c]		213						
Assmus *et al.*[46]	IHF	NA	404	63 (25–87)	227 (56%)	0.5	All-cause mortality	1.8 [1.1–2.9]	*DNMT3A, TET2*
Dorsheimer *et al.*[47]	IHF	NA	200	65 [56–72]	38 (19%)	2	All-cause mortality + hospitalization	2.1 [1.1–4.0]	*DNMT3A, TET2*
Cochran *et al.*[48]	HFpEF	NA	81	77 ± 7	36 (44%)	0.5	Hospitalization	5.1 [1.1–24.2]	*TET2*
Cremer *et al.*[49]	IHF	NA	419	63	154 (37%)	0.5	All-cause mortality	2.8 [1.5–5.2]	*DNMT3A, TET2*
Amancherla *et al.*[50]	HTx	NA	479	NR	77 (16%)	2	Cardiac allograft vasculopathy	1.4 [0.9–2.3]	*DNMT3A*

CH, clonal haematopoiesis; DCM, dilated cardiomyopathy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HTx, heart transplant; IHF, ischaemic heart failure; NA, not applicable; NR, not reported; NICMP, non-ischaemic cardiomyopathy; VAF, variant allele frequency.

[a]Association was significant in the sub-cohort of patients younger than 65 years: HR 2.1 [1.3–3.3].

[b]Association was significant for TET2: HR 2.4 [1.3–4.1].

[c]Study including patients with cardiogenic shock with different heart failure aetiologies.

[d]The age of included patients with heart failure reported either as mean ± standard deviation, median [inter-quartile range], or median (absolute range).

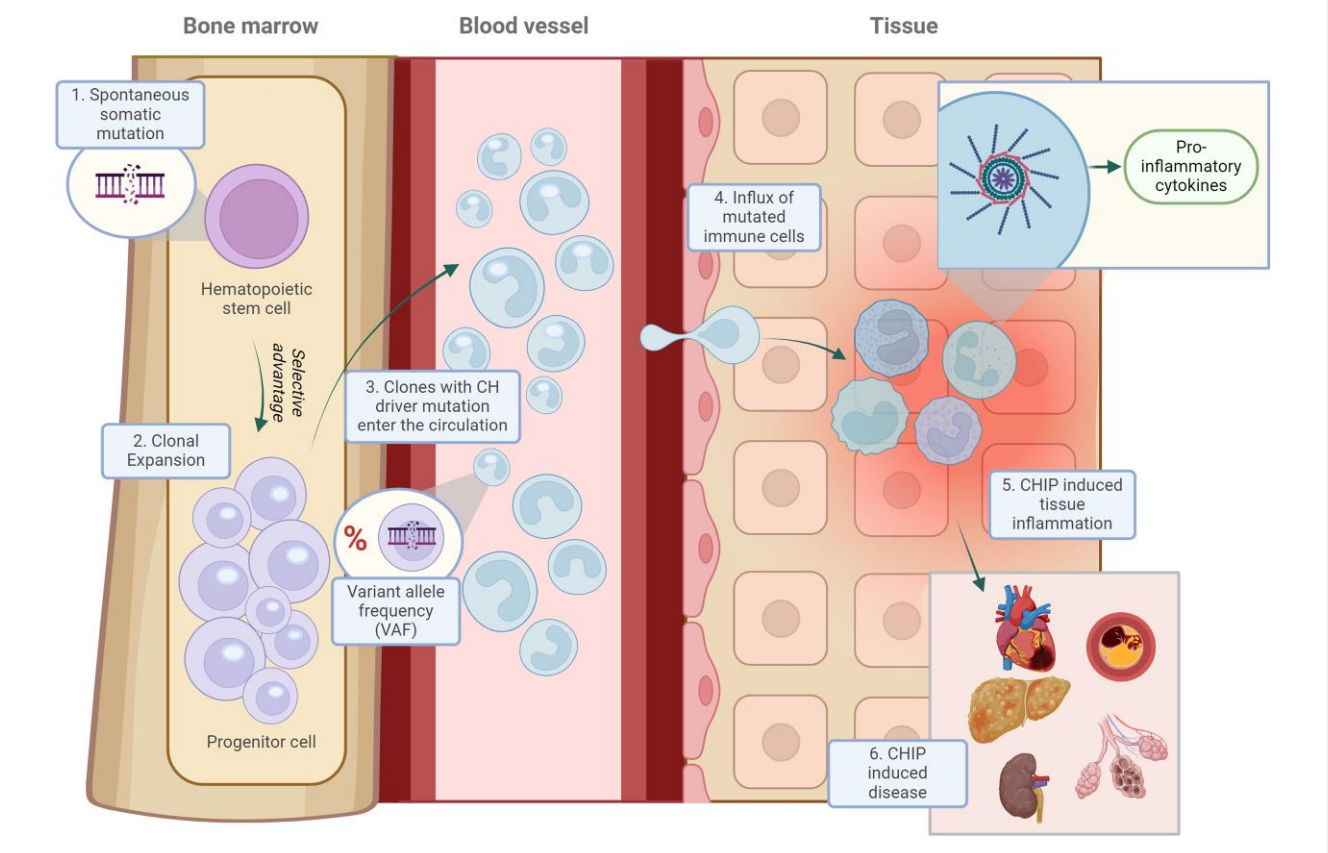

Figure 2 The association between clonal haematopoiesis, inflammation, and disease development. Somatic mutations origin in haematopoietic stem cells in the bone marrow due to environmental triggers or as a result of ageing (1). When the mutation affects a (driver) gene that provides the cell a competitive advantage, that cell can expand, leading to a mutant cell population (2). The size of the clone can be measured by the variant allele frequency (VAF). The mutated cell progeny enter the circulation (3) where they may infiltrate organ tissue (4) resulting in elevated levels inflammation (5) and consequently leading to tissue damage and organ failure (6)

Impact of clonal haematopoiesis in patients with dilated cardiomyopathy

Studies investigating the role of CH in the prognosis of patients with DCM are scarce, and thus far only one dedicated DCM cohort.[42] Two cohorts included a low number of non-ischaemic (and ischaemic) HF patients,[43,44] and one study reported on non-ischaemic HF in patients in cardiogenic shock[45] (*Table 1*). The constitution of the patients with non-ischaemic patients was not further specified in the latter studies, it remains therefore unknown how many patients with DCM were included. The largest cohort including 520 patients with DCM, detected CH in 109 patients (21%) using a VAF of 0.01% to detect small clones.[42] Interestingly, relatively large clones (>2%) were already detected in patients below the age of 30, which is higher compared to that observed in the general population.[57] CH significantly increased the risk of cardiac death (hazard ratio of 1.98) independent of the clone size, where even a VAF threshold of 0.36% predicted worse outcome. Notably, these clone sizes are smaller than the 2% threshold that is used by the DNA sequence technologies in many of the other studies. In another study, 10 out of 52 patients (19%) with DCM had CH using a VAF threshold of 5%, to detect only relatively large clones.[44] The statistical power was too low to draw any conclusions on the prognostic impact of CH. Noteworthy, large CH clones were already detected at a young age in patients with DCM in contrast to the included patients with ischaemic HF. In a cohort of 32 patients with HF of non-ischaemic origin, 12 patients (38%) had CH using a VAF threshold of 2%.[43] In the overall cohort (also including patients with ischaemic HF), CH was associated with HF hospitalization and HF-related death, which was independent of ischaemic or non-ischaemic aetiology. A study investigating the role of CH as predictor of mortality in patients with cardiogenic shock included 686 patients, of which 65% had a non-ischaemic cardiomyopathy.[45] Patients with cardiogenic shock had a higher prevalence of CH mutations compared to ambulatory HF patients, which was also associated with a decreased survival. However, there was no further distinction in aetiology in the analysis.

Overall, there is a large variation in (i) the sensitivity of DNA sequencing methodologies, (ii) cohort sizes providing well-powered studies, (iii) outcomes reported, and (iv) patient selection. With regard to the latter, the definition of the HF aetiology remains often unclear (i.e. non-ischaemic could indicate hypertrophic, dilated, arrhythmogenic, or even valvular cardiomyopathy). Comparing or aggregating study results, therefore, remain difficult to interpret. We propose the following reporting criteria that should be included in future studies investigating

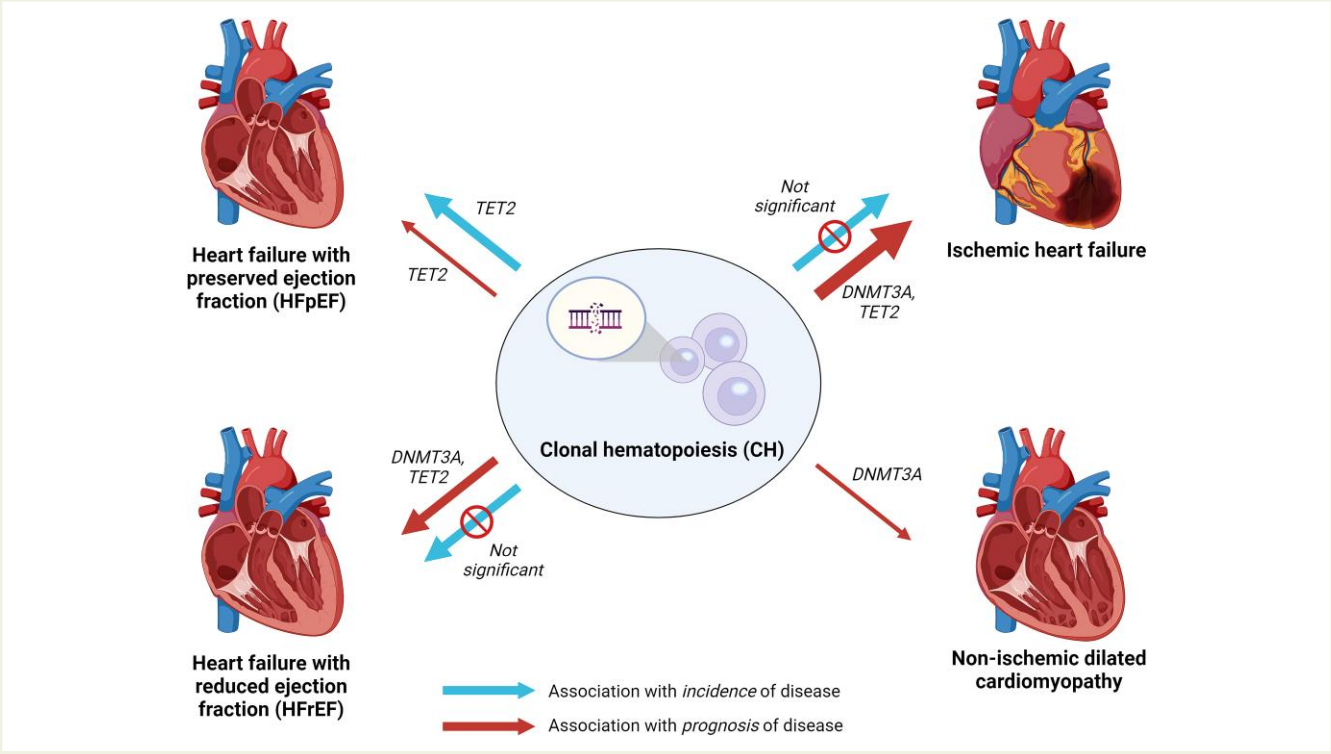

Figure 3 Association between clonal haematopoiesis on the development and prognosis of heart failure. The width of the arrow indicates the number of independent studies that investigated the association. Further details on the studies can be found in *Table 1*

the prognostic impact of CH in patients with DCM (and by extension different cardiac diseases) to better interpret the current evidence and possibilities for future translation:

(1) Definition of HF aetiology (e.g. definition of DCM), and the exact number of patients included with this diagnosis.
(2) Sequencing methodology used, required to interpret the number of genes and their coverage, including the sensitivity of the assay to detect clones.
   (a) If a high sensitivity assay is used (VAF below 2%), still report a separate analysis using a cut-off value of 2% allowing to compare with earlier studies.
(3) Outcome parameters, especially all-cause mortality and further differentiate into cardiac, or HF-related outcome. We would propose to always include all-cause mortality as an outcome, as this information will be available in all cohorts. Adding more details to the cause of death is recommended in subsequent analysis.
(4) Impact on structural, functional, and/or electrical remodelling is to be determined. We appreciate including any data on the association of CH with follow-up information on echocardiography and/or magnetic resonance imaging.

Second hit model in patients with dilated cardiomyopathy

The exact role or relative contribution of CH in the pathogenesis of DCM remains unclear, as current studies are only associative. The fact that large clones are already present at a younger age in DCM patients[44] might suggest a direct role of CH in the development of DCM. Still, the environmental triggers causing DCM, could also be the ones driving CH mutations such as cardiotoxic chemotherapy and inflammation (*Figure 4*). Although these associations are described indirectly, they render the blueprint of the design for future studies.

Cardiac arrhythmias and dilated cardiomyopathy

Arrhythmias such as atrial fibrillation (AF) occur commonly in patients with DCM, but can also be involved in the development of DCM (e.g. tachycardiomyopathy).[4,58,59] The presence of CH is also associated with supraventricular arrhythmias, bradyarrhythmias, and ventricular arrhythmias independent of the presence of HF or coronary artery disease.[36] In this study, the increased risk was mainly observed in carriers of *TET2*, *ASXL1*, *PPM1D*, or *TP53* mutations. In a separate study using an East Asian cohort, CH was independently associated with AF, with carriers of *DNMT3A*, *TET2*, or *ASXL1* being most commonly mutated.[37] CH driver mutations were associated with a more progressive nature of AF (longer AF duration, larger atrial volume, and elevated E/E′) and unfavourable clinical outcomes defined as HF, ischaemic stroke, or death. Overall, CH seems to play a role throughout the disease course of (supra)ventricular arrhythmias, and potentially the evolution towards HF. Therefore, the interplay between arrhythmias, DCM, and CH in disease progression seems interesting, but remains uninvestigated.

Myocardial inflammation as driver of progression of dilated cardiomyopathy

The presence of leucocyte infiltrates and subsequent inflammation in the myocardium is detected in ~20% of patients with DCM, and it is often termed as inflammatory DCM or chronic myocarditis.[59,60] Whether the inflammation is causal or secondary to the disease progress is in a

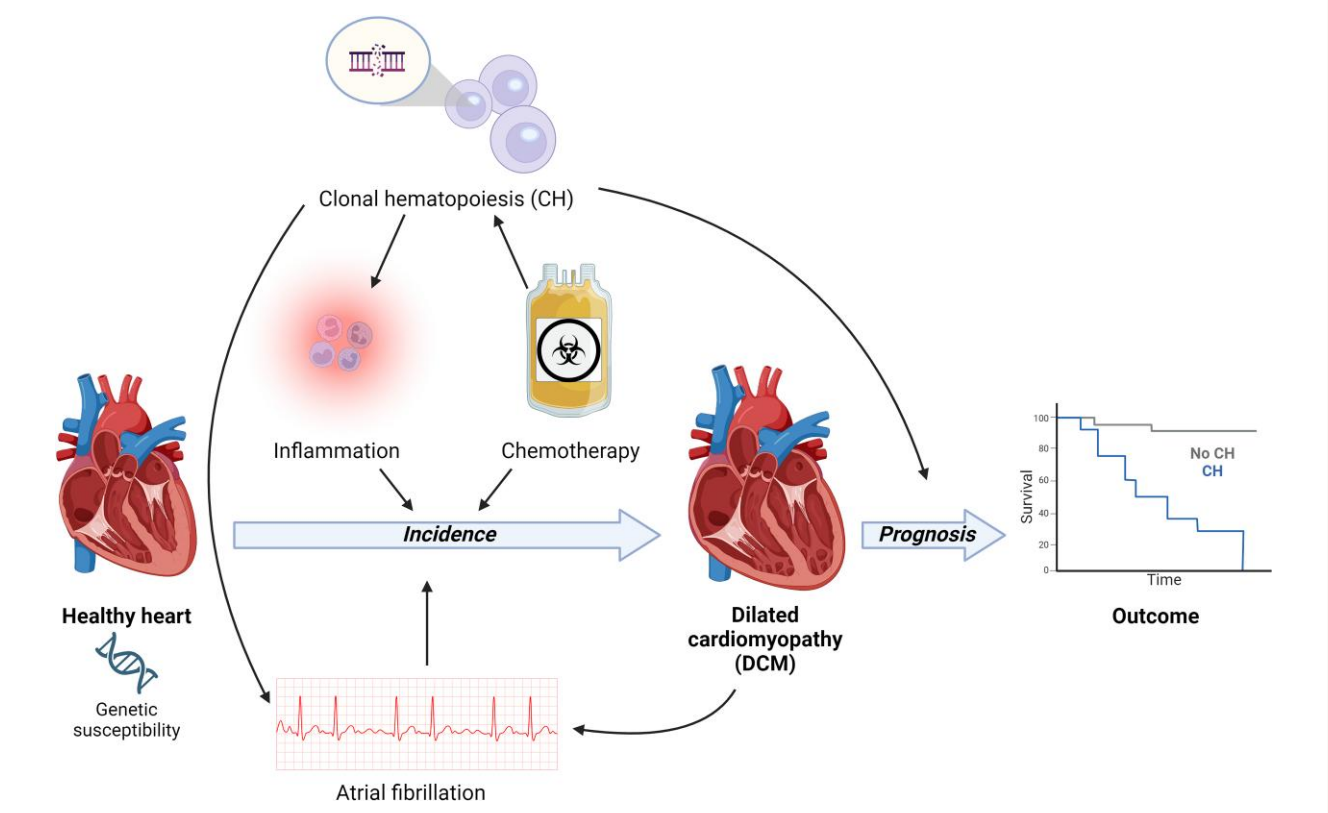

Figure 4 Role of environmental factors in the development of dilated cardiomyopathy, and the association with clonal haematopoiesis. Although there are no studies that have directly investigated the association between clonal haematopoiesis and the incidence of dilated cardiomyopathy, there are associations between drivers of dilated cardiomyopathy development and clonal haematopoiesis. Additionally, clonal haematopoiesis directly impacts the prognosis of patients with dilated cardiomyopathy

chronic situation often unknown, but studies with immunosuppressive therapies have shown beneficial effects in a selection of patients with chronic DCM.[5,6] Additionally, there is ample evidence that CH driver mutations induce inflammation. Loss of function or deletion of *TET2* leads to a higher expression of interleukin (IL)-6 and IL-1β, as well as heightened secretion of IL-1β via the NLRP3-inflammasome in mouse models.[51,61–63] Mutations in *DNMT3A* have been associated with myeloid up-regulation of NLRP3, IL-1, and IL-6,[64] and studies suggest that the inflammatory environment can subsequently be beneficial for clonal expansion of *DNMT3A* clones.[65] It could be worthwhile to determine CH in patients with inflammatory DCM to investigate whether the increased myocardial inflammation could be a consequence of CH driver mutations. Elucidation of the role of CH in the disease progression of (inflammatory) DCM could provide a better patient stratification for novel and specific immunomodulatory treatment regimens. As an example, an ongoing phase II study investigates the beneficial effects of colchicine in patients with CH and ischaemic HFrEF (2021-001508-13 in the European Union Clinical Trials Register). The question remains if colchicine is the medication of choice to go forward, as is it a broad-spectrum anti-inflammatory agent that acts by inhibiting microtubule polymerization. Among many other actions, resulting in partial inhibition of the NLRP3-inflammasome although this might depend on the dosage of colchicine.[66] The primary outcome of this study is endothelial function assessed by flow-mediated dilation after 60 days of treatment, which is not an outcome relevant for patients with DCM. Specific studies and trials to investigate CH-guided immunomodulatory therapy for patients with (inflammatory) DCM are still absent.

Inflammation and (cardiac) fibrosis are intertwined by multiple pathways.[67] Fibrosis in the heart is a well-known risk factor for malignant ventricular arrhythmias and sudden cardiac death in patients with DCM.[68] However, studies including patients with DCM investigating the association of CH with cardiac fibrosis are absent. A recent study identified that monocytes isolated from patients with HF and mutations in *DNMT3A* stimulate the release of heparin-binding epidermal growth factor-like growth factor, thereby facilitating activation of cardiac fibroblasts and subsequent cardiac fibrosis.[69] Large CH clones in patients are associated with increased myocardial fibrosis as measured with cardiac magnetic resonance imaging.[36] Additionally, a murine model of HFpEF, *Tet2*-mediated CH led to greater cardiac fibrosis.[63] Thus, CH might also prime cardiac fibrosis, independent of the association with inflammation.

Chemotherapy-induced cardiomyopathy

Cardiomyopathies can arise from patient exposure to anthracyclines and other cytotoxic therapies. Some cytotoxic therapies promote the formation of a distinct form of CH that results from mutations in the DDR pathway genes that include TP53, PPM1D, CHK1, CHK2, and ATM.[70–73] This type of CH has been referred to as therapy-related CH (t-CH). Unlike the driver genes that give rise to age-related CH by promoting the proliferation and self-renewal of HSCs (e.g. DNMT3A, TET2, and ASXL1), t-CH driver genes confer a selective advantage to HSC by promoting their survival under conditions of genotoxic stress,[73,74] which has been previously reviewed.[75] This form of CH is

of potential interest because patients with cancer and cancer survivors exhibit an increased risk of CVD.[75,76] While cytotoxic agents can directly damage the heart by acting on cells of the myocardium, it has been proposed that the cardiac toxicity associated with long latency periods could be due in part to the effects of t-CH that develops in this patient population.[77] Of particular interest is the t-CH found in childhood cancer survivors, as it would be assumed that, due to their youth, they would be largely void of age-associated CH and hence exhibit a simplified mutational landscape compared to elderly cancer survivors. Notably, childhood cancer survivors display accelerated biological aging[78,79] and a markedly increased risk of CVD.[80,81] Although conflicting data on the prevalence of CH among the survivors of childhood cancer has been presented,[82,83] Novetsky Friedman *et al.*[84] recently reported that there is a nearly two-fold increase in the frequency of CH in childhood cancer survivors compared to healthy controls when they were assessed by ultradeep, error-corrected DNA sequencing. As expected, childhood cancer survivors showed a significant enrichment of DDR gene-mutant clones compared with clonal mutations in DNMT3A, TET2, or ASXL1 genes. Furthermore, the enrichment of CH in the survivor cohort was also observed relative to a treatment-naïve cohort with solid tumours suggesting that the overrepresentation of CH in the childhood cancer survivors resulted from exposure to some cancer therapies.

Could t-CH be contributing to this increased risk of DCM in this patient population? Recent experimental studies have shown that Trp53 and Ppm1d driver genes can contribute to HF and/or atherosclerotic CVD.[28,85,86] An experimental study examined the effects of t-CH on cardiac function by transplanting mice with Trp53 heterozygous-knockout bone marrow cells or bone marrow cells harbouring a common TP53 missense mutation, Trp53R270H.[86] To establish a model of t-CH, mice were treated with a course of the chemotherapeutic agent doxorubicin. Doxorubicin accelerated the expansion of haematopoietic Trp53-mutant cells, and these mice displayed worse doxorubicin-induced cardiotoxicity compared with mice transplanted with wild-type bone marrow. Mechanistic studies revealed that doxorubicin promoted greater Trp53-mutant neutrophil infiltration of the myocardium, leading to greater reactive oxygen species production and greater inflammatory cytokine production.[86] While these experimental findings suggest that t-CH can contribute to the development of DCM in cancer survivors, clinical evidence in support of this hypothesis is lacking and could potentially be addressed by examining the associations between CH and CVD outcomes in cancer survivors. If validated by further studies, these data would suggest that t-CH is predictive of DCM in cancer survivors and that this subset of patients could have heightened therapeutic responses to anti-inflammatory medications.

Future perspectives

Regulation of the dynamics of clonal haematopoiesis

As our understanding of the mechanisms linking CH to CVD deepens, it becomes essential to also identify the factors regulating mutant cell expansion. Highly sensitive DNA sequencing suggests that very low levels of blood cells carrying CH-related mutations can be found in virtually every middle-aged individual.[73,87] However, only a fraction of individuals develop a marked clonal expansion of those mutant cells. Since such expansion is likely a prerequisite for the pathophysiological effects of CH, it is of high clinical value to identify the factors determining whether a mutant HSC remains quiescent and indolent or instead expands to a substantial clone size. To date, our understanding of the regulation of the dynamics of mutant cell expansion is limited, as most previous CH studies were based on cross-sectional sequencing analysis at a single timepoint. An important advancement in this context is the development of a mathematical approach for inferring the fitness advantage conferred by a given somatic mutation based on a single whole genome sequencing time point.[88] Applying this tool to a large sequencing dataset led to the identification of inherited genetic variance in the *TCL1A* gene as an important modulator of the fitness advantage of several commonly mutated driver genes in CH.[88] Similar analyses in other large sequencing datasets could deepen our understanding of the biology of CH. Additionally, an increasing number of human cohorts with serially sampled blood over years are allowing for longitudinal sequencing analyses of the dynamics of CH.[72,89–93] The data available to date lead to two major conclusions. First, the expansion rates of mutant haematopoietic clones is substantially different among different driver genes. Although further research is needed, available evidence suggest that mutations in epigenetic regulatory genes expand slower than those in genes encoding splicing regulators or involved in the DDR.[89–91] Second, even when considering the same mutated gene or the same hotspot mutation, the expansion rates of mutant clones vary considerably between individuals, suggesting that the dynamics of CH are markedly influenced by non-mutational factors that remain to be determined. The clinical implications of identifying the factors or mechanisms controlling clonal outgrowth are manifold. For example, it may aid the development of interventions to slow down or even reverse the expansion of mutant clones, blunting their adverse effects on health. Furthermore, it may lead to new algorithms that enhance the predictive and prognostic value of CH in the setting of CVD, as a small mutant clone identified at a given timepoint may have a substantial long-term impact on health if it undergoes rapid expansion.

Anti-inflammatory therapies

Therapeutic targeting of CH in HF is an emerging area of research with several potential approaches. Understanding the mechanistic link between CH and HF may lead to new drug targets that can specifically modulate the detrimental effects of mutated blood cells on the heart. One can inhibit the enhanced activation of inflammatory pathways related to CH, including IL-1β, IL-6, TNF, NLRP3, or the JAK pathway,[64] helping to reduce the inflammatory burden caused by CH. Whereas this approach is not specific for CH itself, it opens the way for tailored medicine in HF and DCM patients. In murine models of HF, CH associated with TET2 loss-of-function leads to worsened cardiac remodelling and function, through an IL-1β-mediated mechanism.[62] Thus, individuals with TET2-mediated CH might respond better to IL-1β-NLRP3-inflammasome inhibition, an example of personalized medicine. An illustration of this is the finding that the IL-1β neutralizing antibody, canakinumab, reduced the relative risk of major adverse cardiovascular events by 62% in high-risk CVD patients with TET2 mutations compared with 7% in those without CH.[8] Furthermore, it is conceivable that DNA methyltransferase inhibitors could potentially be used to prevent the hypomethylation related to DNMT3A mutations, but these can still have widespread effects on healthy cells. Moreover, histone deacetylase inhibitors, which could alter chromatin structure to activate the transcription of genes that are silenced in the presence of DNMT3A mutations, may potentially counteract some of the negative effects on gene expression.

Eliminating the mutated blood cells themselves by selectively killing these cells is another therapeutic option. The precise identification of

cell surface antigens specific to CH cells is crucial in this regard. Chimeric antigen receptor T-cell therapy, which would work by modifying a patient's T-cells to recognize and attack CH cells expressing specific antigens, is one approach to eliminate these cells.[94] Another approach is bispecific T-cell engagers, which are engineered proteins that can simultaneously bind to a T-cell and a target cell. These T-cell engagers would bring T-cells and CH cells into close proximity leading to the destruction of CH cells.[95] Since the mutations driving CH predominantly occur in genes that regulate DNA methylation, histone modification, and chromatin organization (e.g. DNMT3A, TET2, and ASXL1), rather than genes that encode cell surface proteins, identifying specific antigens remains a major challenge. However, another more invasive approach in severe cases could include gene editing with CRISPR–Cas9 to correct the mutations in HSCs responsible for CH.[96] This approach would involve collecting HSCs from the patient, correcting the mutation *ex vivo*, and then re-infusing the corrected cells back into the patient, a quite challenging but potentially impactful therapeutic approach in HF patients.

In summary, targeting CH in cardiomyopathies could involve a multifaceted approach, including targeting CH specific inflammatory, metabolic and methylation pathways, developing therapies to eliminate mutated cells, and even considering stem cell transplantation in severe cases. Developing therapies that effectively target mutated cells without harming healthy cells is a significant challenge, and it will require more research to identify CH specific cell surface antigens and CH mediated intracellular pathways that can be therapeutically exploited.

Conclusion

The increased sensitivity of novel DNA sequencing techniques has significantly increased the accessibility of CH sequencing. CH might be the consequence of aetiologies of DCM (e.g. chemotherapy) but can also lead to triggers that subsequently contribute to DCM development and progression (e.g. inflammation, AF). The tissue inflammation triggered by CH provides a specific treatment target. The exact involved inflammatory pathways differ per mutated CH driver gene, thus the benefit of immunomodulatory therapy might differ per individual patient with DCM and CH. However, the number of studies that are currently investigating the role of CH in DCM are low, and the individual studies strongly differ in their set-up and definitions. It will be important for future studies to systematically report on the specification of the DNA sequencing technique, accurate phenotyping of the cohort, and the statistical analysis in order to compare the results of different studies towards developing clinical trials investigating CH-based treatment stratification.

Supplementary data

Supplementary data are not available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

No data were generated or analysed for or in support of this article.

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