

Clonal Hematopoiesis and Cardiovascular Events in Patients with ESKD on Hemodialysis Results from the VIVALDI Study

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Key Points

- The prevalence of clonal hematopoiesis in patients with ESKD on hemodialysis was 7%.
- Clonal hematopoiesis was not associated with stroke, myocardial infarction, or venous thromboembolism.
- Clonal hematopoiesis was associated with vascular access thrombosis.

Abstract

Background Patients with ESKD on hemodialysis are at high risk for cardiovascular complications. Clonal hematopoiesis (CH), defined as clonal expansion of hematopoietic stem cells due to acquired mutations, was shown to be associated with cardiovascular events, but this association was not yet assessed in patients with impaired kidney function.

Methods Our aim was to investigate the CH-associated mutation prevalence in patients with ESKD on hemodialysis included in the population-based prospective observational Vienna InVestigation of Atrial Fibrillation and thromboembolism in hemoDialysis (VIVALDI) study and to assess an association between CH and cardiovascular outcomes. Peripheral blood DNA samples collected at study inclusion were screened for CH-associated mutations.

Results Five hundred seventy patients were analyzed (median age, 66 years [interquartile range [IQR], 55–75]; 37.1% female). The median follow-up time was 39 months (IQR, 35–41). We detected 44 CH-associated variants in 40 patients (7%), most commonly in the gene *DNMT3A* (43%), *TET2* (18%), and *TP53* (18%). Patients with CH were older (75 [IQR, 68–80] versus 65 [IQR, 54–74] years, $P < 0.001$) and had longer cumulative dialysis time (4 [IQR, 1.0–4.0] versus 2 [IQR, 1.9–5.5] years, $P = 0.02$). CH was not associated with stroke (subdistribution hazard ratio [SHR], 0.25; 95% confidence interval [CI], 0.04 to 1.84), myocardial infarction (SHR, 0.90; 95% CI, 0.20 to 4.13), three-point major adverse cardiovascular events (SHR, 0.65; 95% CI, 0.33 to 1.28), or venous thromboembolism (SHR, 1.68; 95% CI, 0.35 to 8.12) risk. Patients with CH exhibited a higher risk of vascular access thrombosis (SHR, 2.47; 95% CI, 1.34 to 4.56) and patients with non-*DNMT3A* CH present with a higher all-cause mortality risk (hazard ratio, 1.71; 95% CI, 1.03 to 2.85).

Conclusions Seven percent of patients with ESKD on hemodialysis presented with CH. There was no association between CH and stroke, myocardial infarction, or venous thromboembolism. CH was associated with vascular access thrombosis.

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Introduction

Patients with ESKD are at high-risk for cardiovascular complications.^{1,2} Particularly those undergoing hemodialysis frequently suffer from cardiovascular disease, with

cardiovascular events and associated cardiovascular mortality being the leading cause of death in this population.^{3,4}

Patients with ESKD not only face a significantly higher risk of cardiovascular events in the arterial system but

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also the risk of venous thromboembolism (VTE) rises as kidney function declines,^{5,6} with the highest risk observed in patients on hemodialysis.⁷ The clinical management of patients with ESKD is particularly difficult, as their bleeding risk is also elevated.⁸ Furthermore, common comorbidities such as atrial fibrillation (AF) require anticoagulation for stroke prevention, complicating the clinical management, as anticoagulation increases the risk of bleeding.⁹ Therefore, a well-planned strategy is necessary to balance both risks to ensure clinical benefit.¹⁰ Currently, there is a lack of validated risk assessment tools, for both thromboembolic/ischemic and hemorrhagic complications, in patients with ESKD. Therefore, improved knowledge of risk factors for cardiovascular outcomes, especially thromboembolic complications, is desired to improve clinical decision making regarding optimal patient selection for preventive strategies.

Clonal hematopoiesis (CH) is defined as clonal expansion of a subset of hematopoietic stem cells due to acquired somatic mutations—most commonly in the genes *DNMT3A*, *TET2*, and *ASXL1*—providing them with a survival benefit or proliferative advantage.¹¹ CH was reported to be prevalent in the general aging population and was shown to be associated with higher risk of all-cause mortality.¹² Previous research indicates that CH is not only associated with cardiovascular diseases, such as myocardial infarction, coronary artery disease, peripheral artery disease, stroke, or VTE, but also with impaired kidney function.^{13–16} Moreover, it was reported that CH is associated with AKI and GFR decline in patients with CKD.^{17–19} Data from a mouse models further indicate a causal link between CH and kidney injury.¹⁹ However, studies investigating CH-associated mutations in patients with ESKD on hemodialysis are lacking so far, and potential associations with cardiovascular events such as myocardial infarction, stroke, or VTE are unknown in this patient population.

Therefore, we aimed at assessing the prevalence of CH in a population-based cohort study of patients with ESKD on hemodialysis, in which detailed follow-up information on cardiovascular outcomes is available. Furthermore, we aimed at investigating a possible association between CH and arterial cardiovascular events, particularly major adverse cardiovascular events (MACE), VTE, and all-cause mortality. Moreover, we analyzed whether routine laboratory and hemostatic parameters, and biomarkers of biologic aging differ according to CH carrier status.

Methods

Patient Cohort

This project was performed within the framework of the Vienna InVestigation of Atrial Fibrillation and thromboembolism in hemoDialysis study, a prospective multicenter population-based cohort study. Patients with ESKD on hemodialysis were recruited in a cross-sectional fashion between April 2014 and July 2015 at seven dialysis centers in Vienna, Austria. Details about the cohort have been published previously.^{7,9} In brief, all adult patients with ESKD receiving hemodialysis in Vienna, except patients who were pregnant, lactating, currently hospitalized, or serving a prison term, were eligible for inclusion. At study

inclusion, a trained study investigator performed personal, structured interviews, and verified findings with medical documentation of the participating dialysis centers and in consensus with the treating nephrologists. After enrollment, patients were prospectively followed during routine hemodialysis visits for a maximum of 1350 days and the occurrence of outcomes was assessed with one interim and one final personal interview and review of medical documentation at the dialysis centers.⁹ Patients undergoing kidney transplantation were censored at this time point ($N=106$) and one patient was lost to follow-up.

The Vienna InVestigation of Atrial Fibrillation and thromboembolism in hemoDialysis study was approved by the local ethics committees (EC Number: 1146/2014), was conducted in accordance with the Declaration of Helsinki, and all participants provided written informed consent. We analyzed 602 patients with available whole blood samples from study inclusion, of which 32 had to be excluded from analyses due to insufficient read coverage in the sequencing analysis.

Outcomes of Interest

For the current analysis, the primary outcomes of interest were cardiovascular events including ischemic stroke, myocardial infarction, three-point MACE (comprising myocardial infarction, ischemic stroke, and cardiovascular death), and VTE (comprising deep vein thrombosis of the lower and upper extremity [also when catheter-associated] and pulmonary embolism). Secondary outcomes of interest included vascular access thrombosis (thrombosis of the arteriovenous fistula or graft), cardiovascular death, *de novo* AF, and all-cause mortality. All outcomes were adjudicated by independent experts from the respective fields, including neurology, cardiology, vascular medicine, and hematology.

Targeted Resequencing

DNA was isolated from patients' peripheral blood samples using the Maxwell RSC Blood DNA Kit on a Maxwell RSC Instrument (all Promega, Vienna, Austria). Laboratory parameter and biomarker measurements are described in detail in the supplement.

Library preparation for targeted resequencing of selected genomic regions including hotspots for CH-associated mutations (*DNMT3A*, *TET2*, *ASXL1*, *JAK2*) was performed, as previously described,²⁰ and expanded to include screening of selected DNA damage repair genes (*PPM1D*, *CHEK2*, and *TP53*).²¹ A more detailed description is available in the supplement.

Variant Annotation and Filtering

For variant annotation, RefSeq was selected. Variants were filtered, as previously described.²⁰ In brief, the following inclusion criteria were used: variant site depth >100, variant reported as somatic in the catalogue of somatic mutations in cancer,²² population allele frequency <0.1% in gnomAD databases,²³ protein coding, nonsynonymous, variant allele frequency between 2% to 40% and 60% to 90% (except for *JAK2*^{V617F} mutations, where all VAF $\geq 2\%$ was accepted). For variants passing filters applied on the screening run, samples were rerun to confirm validity at adjusted filter settings

(inclusion criteria for validation run: variant site depth ≥ 200 , VAF $\geq 1\%$). While variants not passing the validation criteria were removed, variant call characteristics including VAFs for validated variants were exported from the screening run.

Statistical Analysis

All statistical analysis was performed using SPSS (version 28.0, IBM SPSS Statistics, Chicago, IL) and R Studio (version 4.2.3, Vienna, Austria). Standard statistical summary modes were used to depict patient characteristics (absolute and relative frequencies, median, interquartile range [IQR]). The α level was set at 0.05. Follow-up time was calculated with the reverse Kaplan-Meier method.

Between-group differences were assessed with a Mann-Whitney *U* test or a chi-square test as appropriate. All-cause mortality was assessed with a Kaplan-Meier analysis and compared using a log-rank test. Furthermore, Cox regression analysis was performed to assess the association between CH and death. This analysis was additionally adjusted to age, sex, AF, cancer, coronary heart and peripheral artery disease, and cumulative time on dialysis based on previous data.

Owing to the high mortality rate in our cohort, cardiovascular and thrombotic outcomes were assessed in a competing risk framework with all-cause mortality as competing event of interest. Furthermore, cardiovascular mortality was assessed in a competing risk framework as well, with death due to any other cause being the competing event of interest. Moreover, a proportional subhazard regression model according to Fine and Gray was conducted. The analysis assessing the association between CH and VTE/vascular access thrombosis was adjusted for age, sex, body mass index (BMI), AF, history of VTE, cancer, and cumulative time on dialysis. The analysis evaluating the association between CH and *de novo* AF was adjusted to age, sex, BMI, coronary heart disease, peripheral artery disease, cancer, and cumulative time on dialysis. The analyses for stroke, myocardial infarction, three-point MACE, and cardiovascular death were additionally adjusted to AF. Selection of confounders was based on previous data and domain knowledge.

For the exploratory biomarker analysis, a Mann-Whitney *U* test was performed. Sensitivity analyses were also conducted, focusing solely on non-*DNMT3A* driven CH to assess its association with clinical outcomes of interest and excluding patients with a history of chronic lymphocytic leukemia (CLL).

Results

Patient Characteristics

Overall, we included 570 patients with a median age of 66 years (IQR, 55–75), of which 212 (37%) were female. Most patients (96%) were of White race, and the most common reasons for ESKD were diabetic nephropathy (25%), vascular nephropathy (19%), and glomerular sclerosis/nephritis (14%). Detailed patient characteristics at study inclusion are summarized in [Table 1](#).

Detection of CH-Associated Mutations

We detected 44 CH variants in 40 patients (7%), with two patients carrying two mutations and one patient

carrying three mutations. The median variant allele frequency of the 44 variants was 6% (IQR, 2.9–14.1), and the most commonly mutated genes were *DNMT3A* (43%), *TET2* (18%), and *TP53* (18%). Most variants were single-nucleotide variants (96%) and missense mutations (73%, [Figure 1](#)). Of note, no mutation in the *ASXL1* gene was detected ([Supplemental Table 1](#)).

Patients with CH were older than patients without CH (75 [IQR, 68–80] versus 65 [IQR, 54–74] years; $P < 0.001$). In addition, individuals with CH had a longer median time on dialysis than those without CH (4 [IQR, 1.0–4.0] versus 2 [IQR, 1.9–5.5] years; $P = 0.02$; [Table 1](#)). Furthermore, they were borderline significantly more likely female and to suffer from AF at study inclusion ([Table 1](#)). Patients with CH were equally likely to be current smokers or have a history of cancer or active cancer ([Table 1](#)). Of the nine patients with a history of or active cancer with CH, five carried a *DNMT3A*, two a *PPM1D*, and one each a *TET2* or *TP53* mutation. The etiology of ESKD did not differ according to CH carrier status, and patients with a history of kidney transplantation or intake of immunosuppressive agents at study inclusion were equally likely to be CH carriers ([Table 1](#)).

CH and Its Association with Primary Outcomes of Interest

Over a median follow-up time of 39 months (IQR, 35–41), we observed 39 (7%) strokes, 34 (6%) myocardial infarctions, 22 (4%) VTE events, and MACE in 142 (25%) patients. This translated into a 12- and 24-month cumulative incidence of stroke of 2.6% (95% confidence interval [CI], 1.2 to 3.9) and 5.0% (95% CI, 3.1 to 6.8), myocardial infarction of 2.7% (95% CI, 1.4 to 4.1) and 4.7% (95% CI, 2.9 to 6.5), three-point MACE of 11.5% (95% CI, 8.8 to 14.1) and 18.6% (95% CI, 15.3 to 21.9), and VTE of 1.6% (95% CI, 0.6 to 2.7) and 2.5% (95% CI, 1.1 to 3.8).

CH was neither associated with risk of stroke (adjusted subdistribution hazard ratio [SHR], 0.25; 95% CI, 0.04 to 1.84), risk of myocardial infarction (adjusted SHR, 0.90; 95% CI, 0.20 to 4.13), three-point MACE (adjusted SHR, 0.65; 95% CI, 0.33 to 1.28), nor VTE (adjusted SHR, 1.68; 95% CI, 0.35 to 8.12). Correspondingly, the cumulative incidence of these outcomes did not differ between patients with CH carrier and noncarrier status ([Figure 2](#) and [Supplemental Table 2](#)). The multivariable models, progressively adjusted for potential confounders, are summarized in [Supplemental Figure 1](#).

The sensitivity analysis including only non-*DNMT3A* driven CH and the analysis excluding patients with history of CLL revealed very similar results, which are summarized in the [Supplemental Tables 3 and 4](#).

CH and Its Association with Secondary Outcomes of Interest

Furthermore, we observed 95 (17%) vascular access thrombosis events. This translated into a 12- and 24-month cumulative of vascular access thrombosis incidence of 8.2% (95% CI, 5.9 to 10.4) and 13.1% (95% CI, 10.2 to 16.0). *De novo* AF was observed in 66 (12%) patients during follow-up, with a 12- and 24-month cumulative incidence of 4.7% (95% CI, 3.0 to 6.5) and 8.9% (95% CI, 6.5 to 11.2).

CH was not associated with risk of *de novo* AF (adjusted SHR, 0.77; 95% CI, 0.32 to 1.88) and the 24-month

Table 1. Patient characteristics at study inclusion overall and stratified according to their clonal hematopoiesis carrier status

Patient Characteristics	<i>n</i> of Available Data	Overall (<i>n</i> =570)	No CH (<i>n</i> =530)	CH (<i>n</i> =40)
Female	570	212 (37)	192 (36)	20 (50)
Age (yr)	570	66 (55–75)	65 (54–74)	75 (68–80)
BMI (kg/m ²)	570	25.5 (22.3–29.4)	22.4 (25.6–29.4)	25.3 (21.7–30.8)
Ethnicity	570			
African, African American, or African Caribbean		10 (2)	10 (2)	0
Asian or pacific islander		13 (2)	13 (3)	0
Caucasian		547 (96)	507 (96)	40 (100)
Median follow-up time (mo)		39 (35–41)	39 (35–41)	40 (33–42)
Etiology of ESKD	570			
Diabetic nephropathy		145 (25)	133 (25)	12 (30)
Vascular nephropathy		109 (19)	101 (19)	8 (20)
Glomerular sclerosis/nephritis		78 (14)	75 (14)	3 (8)
Other		56 (10)	52 (10)	4 (10)
Atrophic nephropathy		50 (9)	43 (8)	7 (18)
Cystic nonhereditary nephropathy		35 (6)	34 (6)	1 (3)
Toxic nephropathy		27 (5)	26 (5)	1 (3)
Hereditary nephropathy		26 (5)	24 (5)	2 (5)
Nephrectomy		19 (3)	18 (3)	1 (3)
Interstitial nephropathy		16 (3)	15 (3)	1 (3)
Unknown		9 (2)	9 (2)	0
Time on dialysis (yr)	570	2 (1–4)	2 (1.0–4.0)	4 (1.9–5.5)
Comorbidities				
Atrial fibrillation	570	151 (26)	137 (26)	16 (40)
Arterial hypertension	570	524 (92)	486 (92)	38 (95)
History of kidney transplantation	570	84 (15)	81 (15)	3 (8)
History of or active cancer ^a	570	137 (24)	128 (24)	9 (23)
History of stroke or TIA	570	114 (20)	103 (19)	11 (28)
History of MI	570	92 (16)	88 (17)	4 (10)
History of coronary heart disease	570	213 (37)	201 (38)	12 (30)
History of VTE	570	56 (10)	50 (9)	6 (15)
Peripheral artery disease	570	179 (31)	162 (31)	17 (43)
Liver disease	570	132 (23)	124 (23)	8 (20)
Diabetes mellitus	570	217 (38)	199 (38)	18 (45)
Current smoking	561	281 (49)	265 (50)	16 (40)
Use of immunosuppressive agent	567	41 (7)	39 (7)	2 (5)

Values are presented as absolute numbers (percentages) or median (interquartile range). Percentages are calculated per column. BMI, body mass index; CH, clonal hematopoiesis; MI, myocardial infarction; TIA, transient ischemic attack; VTE, venous thromboembolism.

^aProstate (*n*=23), skin (*n*=19), kidney (*n*=18), bladder and urothelial (*n*=14), breast (*n*=12), colorectal (*n*=10), thyroid and parathyroid (*n*=5), gynecologic (*n*=5), multiple myeloma (*n*=5), gastroesophageal (*n*=4), lung (*n*=4), brain (*n*=4), lymphoma (*n*=3), chronic lymphocytic leukemia (*n*=3), head and neck (*n*=2), hepatobiliary (*n*=2), adrenal gland (*n*=2), pancreatic (*n*=1), and testicular (*n*=1) cancer.

cumulative incidence did not differ between patients with and without CH (10.3% versus 8.8%, *P* = 0.72; [Figure 3A](#)).

Remarkably, CH carrier status was significantly associated with risk of vascular access thrombosis (SHR, 2.12; 95% CI, 1.16 to 3.88), also when adjusting for age, sex, BMI, AF, history of VTE, cancer, and cumulative time on dialysis (adjusted SHR, 2.47; 95% CI, 1.34 to 4.56) and patients with CH showed a higher 24-month cumulative vascular access thrombosis incidence (23.4% versus 12.3%; *P* = 0.01, [Figure 3B](#) and [Supplemental Table 2](#)). [Supplemental Figure 2](#) summarizes the multivariable models with stepwise adjustments for potential confounders.

The sensitivity analyses including only non-DNMT3A driven CH or excluding patients with history of CLL are summarized in [Supplemental Tables 3 and 4](#).

CH and Its Association with Survival

During the observation period, 231 (41%) patients died, of which 94 (17%) died due to a cardiovascular reason.

The corresponding 12- and 24-month overall survival was 85.1% (95% CI, 82.1 to 88.1) and 72.0% (95% CI, 68.2 to 75.9), and the 12- and 24-month cumulative incidence of cardiovascular death was 6.9% (95% CI, 4.8 to 9.0) and 11.9% (95% CI, 9.2 to 14.6).

There was a tendency that patients with CH exhibited an impaired overall-survival compared to those without CH (12- and 24-month survival: 79.3% versus 85.5% and 63.2% versus 72.7%, respectively, *P* = 0.09; [Figure 4A](#)). There was no significant association between CH and risk of all-cause mortality (HR, 1.49; 95% CI, 0.95 to 2.34), especially after adjusting for patient characteristics and time on dialysis (adjusted HR, 1.12; 95% CI, 0.71 to 1.77). Furthermore, the incidence of cardiovascular death did not differ between individuals with and without CH carrier status (12-month and 24-month cumulative incidence: 2.6% versus 7.2% and 10.4% versus 12.0%, respectively, *P* = 0.39, [Figure 4B](#)). CH was not associated with risk of cardiovascular death in multivariable

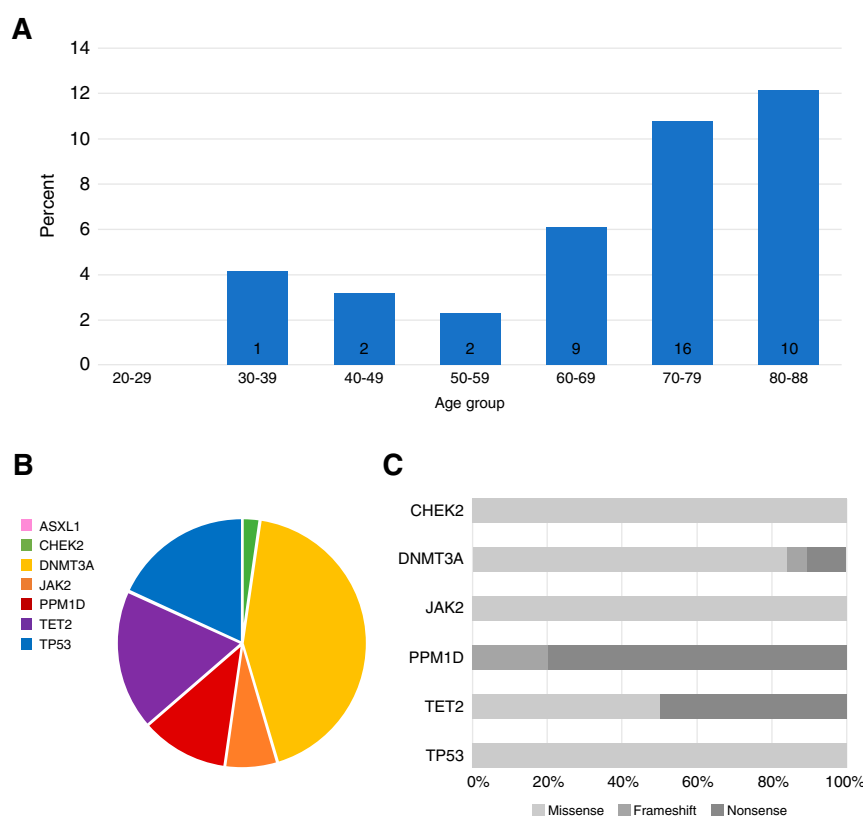


Figure 1. Characteristics of CH mutations detected in the VIVALDI study. (A) Percent of patients with CH carrier status stratified according to age groups. Numbers in the bars indicate absolute number of patients with CH mutation. (B) Frequency distribution of genes affected by a CH mutation. (C) Types of mutations detected in individual genes. CH, clonal hematopoiesis; VIVALDI, Vienna Investigation of Atrial Fibrillation and thromboembolism in hemoDialysis. Figure 1 can be viewed in color online at www.cjasn.org.

analysis (adjusted SHR, 1.06; 95% CI, 0.53 to 2.10, Supplemental Table 5). Supplemental Figure 3 presents the multivariable models with sequential adjustments for potential confounders.

Although excluding patients with a history of CLL revealed comparable results, a significant association between non-*DNMT3A* CH and all-cause mortality was revealed (Supplemental Tables 6 and 7).

CH and Its Association with Laboratory Parameters and Biomarkers of Hemostasis, Inflammation, and Aging

First, we analyzed differences of blood count parameters in individuals with CH compared with those without CH. Hemoglobin, red cell distribution width, platelet, leukocyte counts, albumin, and LDL-cholesterol levels did not differ according to the presence of CH carrier status (Table 2). C-reactive protein (CRP) levels were similar in patients with and without CH. When assessing hemostatic biomarkers according to CH carrier status, we did not observe a difference in fibrinogen, D-dimer, and soluble P-selectin (sP-selectin) levels (Table 2). Finally, we investigated whether markers of biologic aging were associated with CH. However, both telomere length and mtDNA levels were not significantly different in patients with and without CH (Table 2).

Discussion

In our cohort study, CH was found in 7% of patients with ESKD on hemodialysis. There was a trend that individuals with CH exhibited a poor overall-survival and patients with CH had a higher risk of vascular access thrombosis. By contrast, the presence of CH was not associated with risk of stroke, myocardial infarction, *de novo* AF, MACE, VTE, or cardiovascular death.

The rationale of our investigation is based on the fact that CH was shown to be associated not only with cardiovascular events but also with declining kidney function.^{13–15,17–19} Early studies investigating CH noted that patients with CH presented with lower GFR and more commonly CKD.^{24–26} More recently, it was reported that CH is associated with AKI and a decline in GFR in patients with CKD.^{17–19} A causal link between kidney injury and CH emerged from studies using *TET2* and *DNMT3A*-deficient mouse models,^{13,27} demonstrating enhanced foam-cell accumulation and glomerulosclerosis in the kidney, along with enhanced kidney fibrosis after angiotensin II infusions, respectively.^{13,27} In addition, a mouse model with acute ischemic kidney injury exhibited a more severely impaired kidney function, higher markers of tubular injury, elevated inflammation markers including IL-1 β , and subsequently more fibrosis development in the

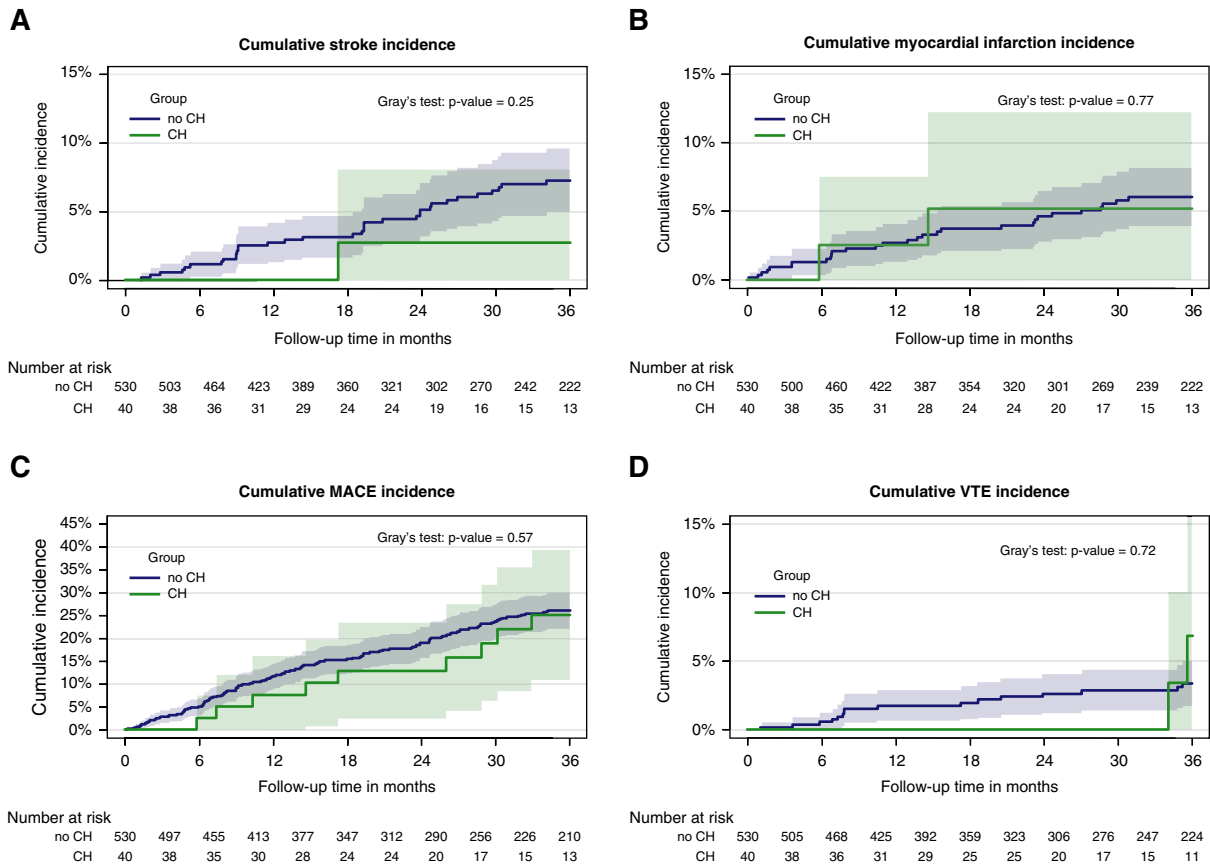


Figure 2. Clonal hematopoiesis and its association with primary outcomes of interest. Cumulative stroke (A), myocardial infarction (B), major adverse cardiovascular event (C), and VTE (D) incidence stratified according to CH carrier status. Patients were divided into two groups according to CH carrier status, and the two groups were compared within a Fine and Gray subdistribution hazard model. AF, atrial fibrillation; MACE, major adverse cardiac event; VTE, venous thromboembolism. Figure 2 can be viewed in color online at www.cjasn.org.

presence of *TET2*-driven CH.¹⁹ As patients with impaired kidney function face a high cardiovascular risk,^{1,2} we aimed to investigate whether CH has an influence on this elevated risk, especially as no CH studies in patients with ESKD on hemodialysis were conducted so far.

We observed a CH prevalence of 7% in our study of patients with ESKD on maintenance hemodialysis. In general, a CH frequency of around 2%–7% was observed in individuals in their 60s, while it was about 10% in those 70 years or older.²⁸ Interestingly, previous data indicated that patients with CKD have a higher prevalence of CH compared with those without, across different age groups with, *e.g.*, a frequency of nearly 11% seen in those aged 65–74 years.²⁹ Similar to previous reports, patients with CH were older than those without^{30–32} and had a longer prior cumulative time on dialysis in our cohort. One reason for this observation could be that age and cumulative time on dialysis are associated. Another reason could be that longer exposure to uremic toxins might lead to a proinflammatory environment that facilitates the expansion of clones in the bone marrow. This hypothesis is supported by studies showing that an inflammatory environment might promote *TET2* and *DNMT3A* clone expansion.^{33,34} In fact, *DNMT3A* and *TET2* were the most prevalent CH-associated mutations in our study. Furthermore, previous

data showed that chronic inflammation associates with higher risk of disease progression and mortality in patients with CKD.^{35–37} Only patients with non-*DNMT3A* driven CH had a poor overall survival, which is in contrast to previous studies reporting an elevated mortality risk with CH, regardless of mutation.^{12,38} Given our medium-sized cohort with diverse ESKD etiologies, larger studies are needed to further explore the association between CH and mortality in hemodialysis patients, including potential interactions with different CKD etiologies.

One of our major findings is that CH was not associated with cardiovascular events including stroke, myocardial infarction, or MACE, in patients with ESKD on hemodialysis, which is in contrast to studies in the general population.^{12,13} This may be due to the already high cardiovascular risk in ESKD, driven by prevalent traditional risk factors such as diabetes, hypertension, and smoking in our cohort. Patients with ESKD on hemodialysis suffer from accelerated atherosclerosis³⁹ and exhibit chronic inflammation that further enhances their risk of cardiovascular diseases.^{40,41} Furthermore, the high AF prevalence in our cohort predisposes patients to cardiovascular events, *e.g.*, stroke.⁴² Synoptically, in this population, stronger risk factors may overshadow a potential milder influence of CH, and the high competing risk of all-cause mortality must also be considered.

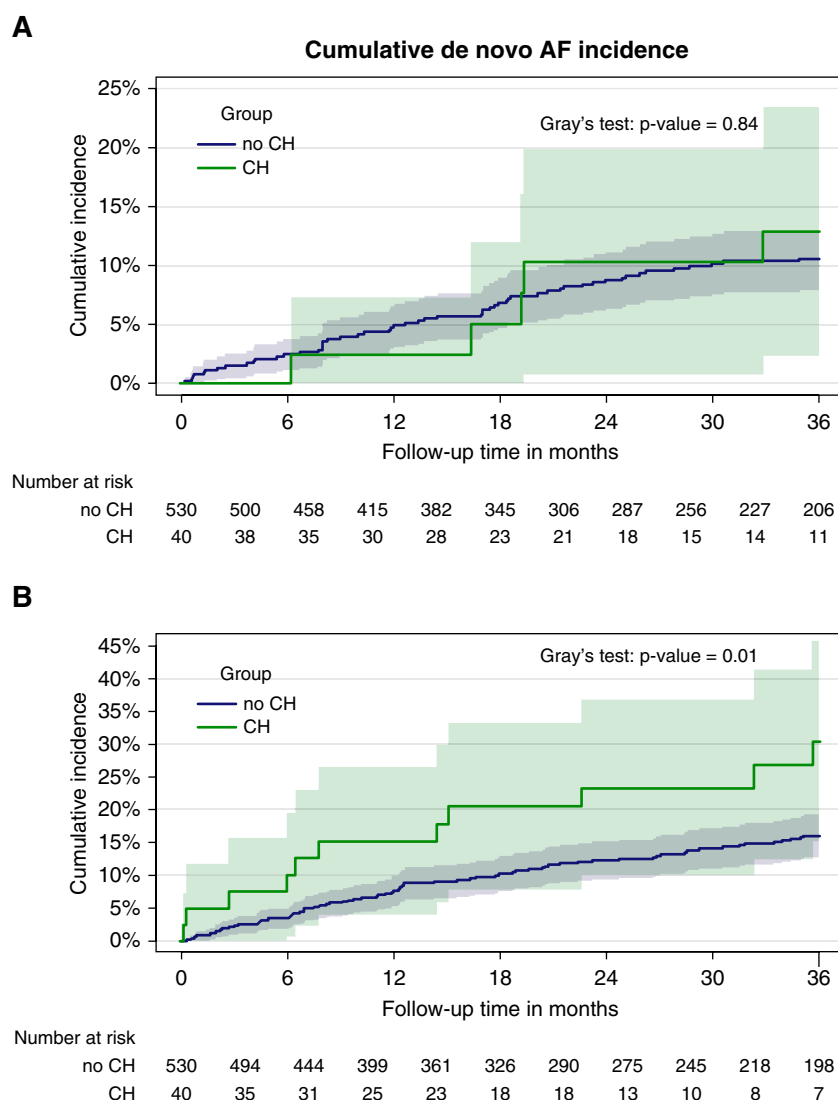


Figure 3. Clonal hematopoiesis and its association with secondary outcomes of interest. Cumulative incidence of *de novo* AF (A) and vascular access thrombosis (B) stratified according to the presence of CH. Patients were divided according to CH presence into two group and those were compared within a Fine and Gray subdistribution hazard model. Figure 3 can be viewed in color online at www.cjasn.org.

Studies investigating the link between CH and venous thrombosis are limited. CH was not associated with VTE in our cohort of patients with ESKD on hemodialysis. However, there was a significant association between presence of CH and vascular access thrombosis, which is one of the most frequent and challenging complications in patients on chronic hemodialysis. In a previous analyses, vascular access complications were one of the most common reasons for hospitalization.⁴³ Generally, it is thought that mainly anatomical reasons and/or surgical techniques are the main drivers of vascular access thrombosis and other risk factors were rarely reported so far. In a previous study, we observed that toxic nephropathy is associated with a higher risk of vascular access thrombosis.⁷ In our present analysis, we found an association between CH and vascular access thrombosis that was independent of other risk factors. Unfortunately, we are unable to offer insight into the underlying mechanism(s), but we hypothesize that CH-associated

mutations may also directly affect endothelial cells.⁴⁴ Previously, higher expression of P-selectin was observed in a *TET2* CH mouse model,⁴⁵ indicating the presence of activated and prothrombotic endothelial cells. This could subsequently lead to thrombus formation at sites where activation of the endothelium and hemostatic system already exists, such as at foreign surfaces of vascular access devices or native shunts. Thus, this observation needs to be further investigated and validated in independent studies in the future.

In our study, CH was not clearly associated with AF. However, prior research suggests an association between CH and AF,^{46–48} potentially mediated by a CH-related proinflammatory state, which may lead to cardiac remodeling,⁴⁷ and arrhythmogenic mechanism, as seen in *TET2*-deficient mice.⁴⁸ The elevated risk of AF in patients with ESKD is attributed to inflammation, electrolyte abnormalities, anemia, uremia, diastolic dysfunction, and postcapillary

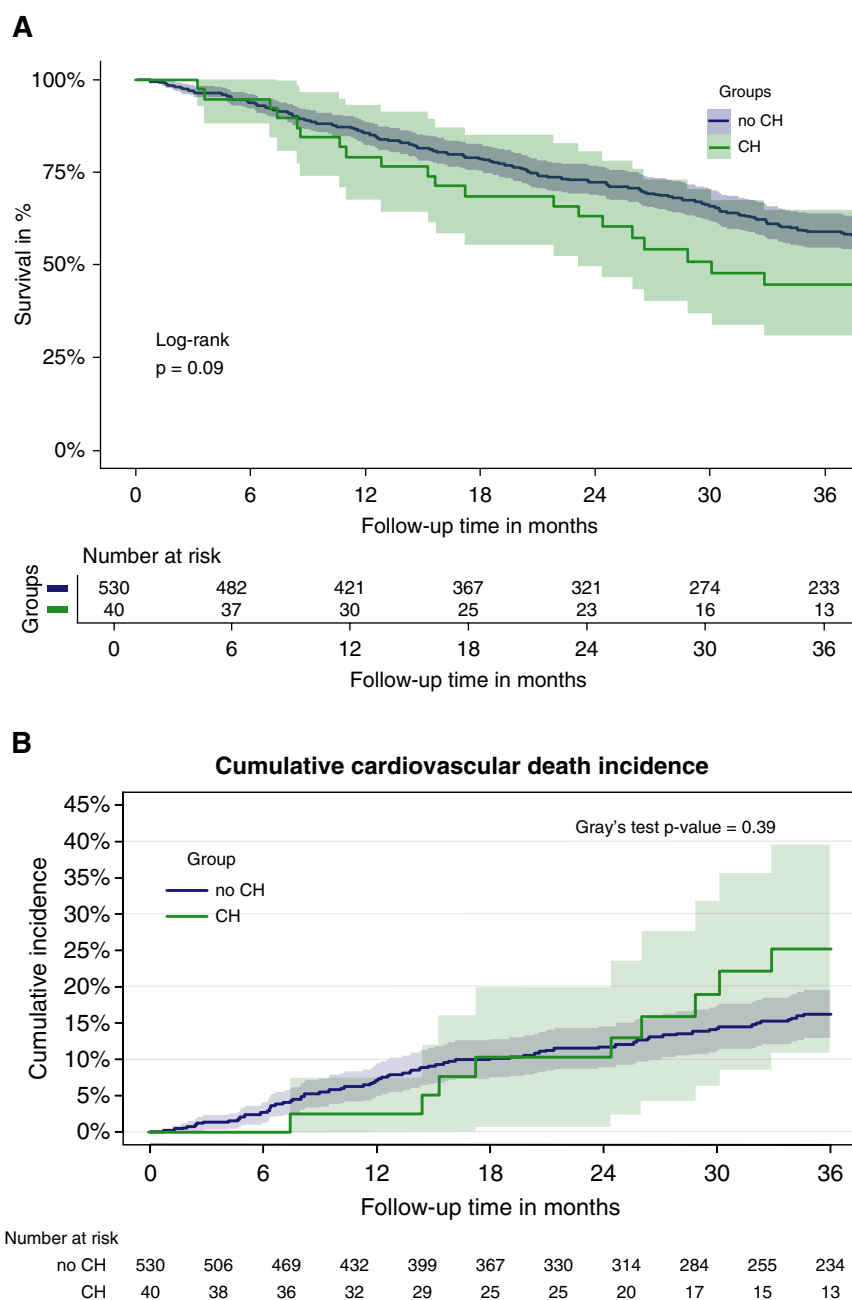


Figure 4. Clonal hematopoiesis and its association with all-cause and cardiovascular mortality. Overall survival (A) in patients with and without CH and cumulative cardiovascular death (B) incidence according to CH carrier status. Patients were divided according to their CH carrier status and the overall survival was compared within a Kaplan-Meier analysis using a log-rank test, while cardiovascular death incidence was compared with a Fine and Gray subdistribution hazard model. Figure 4 can be viewed in color online at www.cjasn.org.

hypertension⁴⁹; factors that partly overlap with CH suggested pathomechanisms. This overlap may have masked the effect of CH on AF risk in our study, highlighting the need for further investigations into shared mechanisms.

Laboratory parameters (*e.g.*, hemoglobin, blood counts) did not differ according to CH carrier status in our study, in contrast to previous reports.²⁵ Similarly, hemostatic biomarker (D-dimer, fibrinogen, sP-selectin) and CRP levels were comparable between groups, despite prior findings of elevated CRP levels in CH carriers.^{25,50} Given the presence

of chronic inflammation in patients with ESKD,^{40,41} this may have masked any effect of CH on CRP levels. In addition, we explored a potential link between and biologic aging markers (mtDNA levels, telomere length⁵¹) due to reports of an association between telomere attrition and CKD risk⁵²; we were interested to further analyze a potential linkage to CH in our present study but found no difference.

We would like to highlight some limitations of our study. First, we screened a medium-sized cohort; thus,

Table 2. Laboratory values, inflammatory, hemostatic, and biologic aging biomarker levels in patients with and without clonal hematopoiesis

Laboratory Value/Biomarker	Overall (n=570)	No CH (n=530)	CH (n=40)
Hemoglobin (g/dl)	10.9 (10–11.7)	10.9 (10–11.7)	10.9 (10.2–12.2)
RDW (%)	15.9 (14.6–18.0)	15.9 (14.6–18.0)	14.8 (14.1–18.0)
Platelets (10 ⁹ /L)	210 (169–258)	212 (169–258)	195 (166–257)
Leucocytes (10 ⁹ /L)	6.4 (5.2–8.0)	6.4 (5.2–8.0)	6.4 (5.2–8.8)
Albumin (mg/dl)	39.0 (36.0–41.8)	39.0 (36.0–41.7)	38.6 (35.7–42.2)
LDL-cholesterol (mg/dl)	77.2 (58.4–104.4)	77.7 (59.0–105.1)	72.4 (54.6–97.0)
CRP (mg/dl)	0.51 (0.20–1.30)	0.49 (0.21–1.27)	0.74 (0.20–1.65)
Fibrinogen (mg/dl)	383 (322–456)	382 (321–458)	388 (330–440)
D-dimer (μg/ml)	0.88 (0.50–1.69)	0.86 (0.5–1.64)	1.29 (0.56–2.41)
sP-selectin (ng/ml)	36.95 (28.36–48.38)	36.95 (28.33–48.54)	37.18 (29.5–43.1)
Telomere length (kb)	2.54 (0.95–36.46)	2.65 (0.95–40.13)	1.43 (0.93–8.57)
mtDNA (per diploid cell)	413.79 (46.22–1476.87)	401.77 (46.25–1412.49)	816.93 (61.14–1726.32)

Data presented as median (interquartile range). CH, clonal hematopoiesis; CRP, C-reactive protein; RDW, red cell distribution width.

we were restricted in our ability to analyze the association between outcomes of interest and individual CH mutations in more detail. Nevertheless, a major strength of our study is the prospective design, and to the best of our knowledge, this is the first study that assessed the association between CH and cardiovascular risk in patients with ESKD on hemodialysis. However, further studies with a higher sample size are needed to support our findings, as the power of our study might have been too low to draw definite conclusions. Owing to a lack of availability, we could not confirm our results in a second independent cohort. Second, to investigate an association between CH and inflammation, only CRP levels were available, and we could not include specific proinflammatory markers such as IL-6 or IL-1 β in our analysis. Third, our analyses were restricted to mutational hotspots within selected genes, potentially resulting in an underestimation of CH frequencies. Nevertheless, the genomic regions included in our screening assay comprise most mutations described in previous pivotal studies of CH.¹² Our observed CH prevalence may have been lower than expected; however, direct comparisons between different methodologic approaches are challenging. Furthermore, given the high mortality risk in patients with CKD, survivorship bias may have influenced the CH prevalence observed in our study.

In summary, as expected, CH was prevalent in our cohort of patients with ESKD on hemodialysis. Although CH was not associated with cardiovascular events, such as stroke, myocardial infarction, VTE, or cardiovascular endpoints (MACE), it was independently associated with risk of vascular access thrombosis. Future research to investigate a causal link between CH and clinical outcomes, especially vascular access thrombosis, in patients with ESKD on hemodialysis is needed.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at <http://links.lww.com/CJN/C397>.

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Data Availability Statements

Original data generated for the study will be made available on reasonable request to the corresponding author. Data Type: Observational Data. Reason for Restricted Access: Requests to share data require a formal approval from the corresponding authors institution. Decline color.

Supplemental Material

This article contains the following supplemental material online at <http://links.lww.com/CJN/C398>.

Supplemental Table 1. Overview of detected variants.

Supplemental Table 2. Association between CH ($n=40$) and clinical outcomes of interest.

Supplemental Table 3. Association between non-DNMT3A CH ($n=23$) and clinical outcomes of interest.

Supplemental Table 4. Association between CH ($n=39$) and clinical outcomes of interest excluding patients with CLL.

Supplemental Table 5. Association between CH ($n=40$) and all-cause mortality and cardiovascular mortality.

Supplemental Table 6. Association between non-DNMT3A CH ($n=23$) and all-cause mortality and cardiovascular mortality.

Supplemental Table 7. Association between CH ($n=39$) and all-cause mortality and cardiovascular mortality excluding patients with CLL.

Supplemental Figure 1. Multivariable models assessing the association between CH and stroke (A), myocardial infarction (B), MACE (C), and VTE (D).

Supplemental Figure 2. Multivariable models assessing the association between CH and *de novo* AF (A) and vascular access thrombosis (B).

Supplemental Figure 3. Multivariable models assessing the association between CH and all-cause mortality (A) and cardiovascular mortality (B).

References

- Seliger SL, Gillen DL, Longstreth WT Jr., Kestenbaum B, Stehman-Breen CO. Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int.* 2003;64(2):603–609. doi:10.1046/j.1523-1755.2003.00101.x
- Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351(13):1296–1305. doi:10.1056/NEJMoa041031
- Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol.* 2006;17(7):2034–2047. doi:10.1681/ASN.2005101085
- de Jager DJ, Grootendorst DC, Jager KJ, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA.* 2009;302(16):1782–1789. doi:10.1001/jama.2009.1488
- Ocak G, Lijfering WM, Verduijn M, et al. Risk of venous thrombosis in patients with chronic kidney disease: identification of high-risk groups. *J Thromb Haemost.* 2013;11(4):627–633. doi:10.1111/jth.12141
- Wattanakit K, Cushman M, Stehman-Breen C, Heckbert SR, Folsom AR. Chronic kidney disease increases risk for venous thromboembolism. *J Am Soc Nephrol.* 2008;19(1):135–140. doi:10.1681/ASN.2007030308
- Königsbrügge O, Lorenz M, Auinger M, et al. Venous thromboembolism and vascular access thrombosis in patients with end-stage renal disease on maintenance hemodialysis: cross-sectional results of the Vienna Investigation of Atrial Fibrillation and thromboembolism in patients on hemodialysis (VIVALDI). *Thromb Res.* 2017;158:59–64. doi:10.1016/j.thromres.2017.08.011
- Molnar AO, Bota SE, Garg AX, et al. The risk of major hemorrhage with CKD. *J Am Soc Nephrol.* 2016;27(9):2825–2832. doi:10.1681/ASN.2015050535
- Königsbrügge O, Posch F, Antlanger M, et al. Prevalence of atrial fibrillation and antithrombotic therapy in hemodialysis patients: cross-sectional results of the Vienna Investigation of Atrial Fibrillation and thromboembolism in patients on Hemodialysis (VIVALDI). *PLoS One.* 2017;12(1):e0169400. doi:10.1371/journal.pone.0169400
- Königsbrügge O, Meisel H, Beyer A, et al. Anticoagulation use and the risk of stroke and major bleeding in patients on hemodialysis: from the VIVALDI, a population-based prospective cohort study. *J Thromb Haemost.* 2021;19(12):2984–2996. doi:10.1111/jth.15508
- Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. *Blood.* 2015;126(1):9–16. doi:10.1182/blood-2015-03-631747
- Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med.* 2014;371(26):2488–2498. doi:10.1056/NEJMoa1408617
- Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N Engl J Med.* 2017;377(2):111–121. doi:10.1056/NEJMoa1701719
- Bhattacharya R, Zekavat SM, Haessler J, et al. Clonal hematopoiesis is associated with higher risk of stroke. *Stroke.* 2022;53(3):788–797. doi:10.1161/strokeaha.121.037388
- Zekavat SM, Viana-Huete V, Matesanz N, et al. TP53-mediated clonal hematopoiesis confers increased risk for incident atherosclerotic disease. *Nat Cardiovasc Res.* 2023;2:144–158. doi:10.1038/s44161-022-00206-6
- Zon RL, Sekar A, Clapham K, et al. JAK2-mutant clonal hematopoiesis is associated with venous thromboembolism. *Blood.* 2024;144(20):2149–2154. doi:10.1182/blood.2024024187
- Vlasschaert C, McNaughton AJM, Chong M, et al. Association of clonal hematopoiesis of indeterminate potential with worse kidney function and anemia in two cohorts of patients with advanced chronic kidney disease. *J Am Soc Nephrol.* 2022;33(5):985–995. doi:10.1681/ASN.2021060774
- Kestenbaum B, Bick AG, Vlasschaert C, et al. Clonal hematopoiesis of indeterminate potential and kidney function decline in the general population. *Am J Kidney Dis.* 2023;81(3):329–335. doi:10.1053/j.ajkd.2022.08.014
- Vlasschaert C, Robinson-Cohen C, Chen J, et al. Clonal hematopoiesis of indeterminate potential is associated with acute kidney injury. *Nat Med.* 2024;30(3):810–817. doi:10.1038/s41591-024-02854-6
- Jäger JG, Hoke M, Mayer FJ, et al. Combined effects of clonal hematopoiesis and carotid stenosis on cardiovascular mortality. *J Am Coll Cardiol.* 2024;83(18):1717–1727. doi:10.1016/j.jacc.2024.02.043
- Englisch C, Vostatek R, Schramm T, et al. Association of clonal haematopoiesis with recurrent venous thromboembolism: a case-control study. *Br J Haematol.* 2025;206(1):263–271. doi:10.1111/bjh.19871
- Tate JR, Bamford S, Jubb HC, et al. COSMIC: the catalogue of somatic mutations in cancer. *Nucleic Acids Res.* 2019;47(D1):D941–d947. doi:10.1093/nar/gky1015
- Chen S, Francioli LC, Goodrich JK, et al. A genomic mutational constraint map using variation in 76,156 human genomes. *Nature.* 2024;625(7993):92–100. doi:10.1038/s41586-023-06045-0
- 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(5):521–528. doi:10.1001/jamacardio.2022.0386
- Arends CM, Liman TG, Strzelecka PM, et al. Associations of clonal hematopoiesis with recurrent vascular events and death in patients with incident ischemic stroke. *Blood.* 2023;141(7):787–799. doi:10.1182/blood.2022076661
- Shannon ML, Heimlich JB, Olson S, et al. Clonal hematopoiesis and inflammation in the vasculature: CHIVE, a prospective, longitudinal clonal hematopoiesis cohort and biorepository. *Blood Adv.* 2024;8(13):3453–3463. doi:10.1182/bloodadvances.2023011510
- Sano S, Oshima K, Wang Y, Katanasaka Y, Sano M, Walsh K. CRISPR-mediated gene editing to assess the roles of Tet2 and Dnmt3a in clonal hematopoiesis and cardiovascular disease. *Circ Res.* 2018;123(3):335–341. doi:10.1161/CIRCRESAHA.118.313225
- Natarajan P, Jaiswal S, Kathiresan S. Clonal hematopoiesis: somatic mutations in blood cells and atherosclerosis. *Circ Genom Precis Med.* 2018;11(7):e001926. doi:10.1161/CIRCGEN.118.001926
- Huang Z, Vlasschaert C, Robinson-Cohen C, et al. Emerging evidence on the role of clonal hematopoiesis of indeterminate

- potential in chronic kidney disease. *Transl Res.* 2023;256:87–94. doi:10.1016/j.trsl.2022.12.009
30. Bolton KL, Ptashkin RN, Gao T, et al. Cancer therapy shapes the fitness landscape of clonal hematopoiesis. *Nat Genet.* 2020; 52(11):1219–1226. doi:10.1038/s41588-020-00710-0
 31. Mayerhofer E, Strecker C, Becker H, et al. Prevalence and therapeutic implications of clonal hematopoiesis of indeterminate potential in young patients with stroke. *Stroke.* 2023;54(4):938–946. doi:10.1161/strokeaha.122.041416
 32. 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(20):1996–2009. doi:10.1016/j.jacc.2023.03.401
 33. 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(6):833–849.e5. doi:10.1016/j.stem.2018.10.013
 34. Hormaechea-Agulla D, Matatall KA, Le DT, et al. Chronic infection drives Dnmt3a-loss-of-function clonal hematopoiesis via IFN γ signaling. *Cell Stem Cell.* 2021;28(8):1428–1442.e6. doi:10.1016/j.stem.2021.03.002
 35. Amdur RL, Feldman HI, Gupta J, et al. Inflammation and progression of CKD: the CRIC study. *Clin J Am Soc Nephrol.* 2016;11(9):1546–1556. doi:10.2215/CJN.13121215
 36. Bash LD, Erlinger TP, Coresh J, Marsh-Manzi J, Folsom AR, Astor BC. Inflammation, hemostasis, and the risk of kidney function decline in the Atherosclerosis Risk in Communities (ARIC) Study. *Am J Kidney Dis.* 2009;53(4):596–605. doi:10.1053/j.ajkd.2008.10.044
 37. Weiner DE, Tighiouart H, Elsayed EF, et al. Inflammation and cardiovascular events in individuals with and without chronic kidney disease. *Kidney Int.* 2008;73(12):1406–1412. doi:10.1038/ki.2008.75
 38. Singh J, Li N, Ashrafi E, et al. Clonal hematopoiesis of indeterminate potential as a prognostic factor: a systematic review and meta-analysis. *Blood Adv.* 2024;8(14):3771–3784. doi:10.1182/bloodadvances.2024013228
 39. Echegu G, Stowe I, Burka S, Basu-Ray I, Kumbala D. Pathophysiological concepts and screening of cardiovascular disease in dialysis patients. *Front Nephrol.* 2023;3:1198560. doi:10.3389/fneph.2023.1198560
 40. Shlipak MG, Fried LF, Crump C, et al. Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation.* 2003;107(1):87–92. doi:10.1161/01.cir.0000042700.48769.59
 41. Cobo G, Lindholm B, Stenvinkel P. Chronic inflammation in end-stage renal disease and dialysis. *Nephrol Dial Transplant.* 2018;33(suppl 3):iii35–iii40. doi:10.1093/ndt/gfy175
 42. Dad T, Weiner DE. Stroke and chronic kidney disease: epidemiology, pathogenesis, and management across kidney disease stages. *Semin Nephrol.* 2015;35(4):311–322. doi:10.1016/j.semnephrol.2015.06.003
 43. Steiner D, Schmaldienst S, Lorenz M, et al. Atrial fibrillation and anticoagulation are associated with hospitalisations in patients with end-stage kidney disease on haemodialysis: a prospective population-based cohort study. *Thromb J.* 2022;20(1):71. doi:10.1186/s12959-022-00434-7
 44. Winter S, Götz KS, Hecker JS, et al. Clonal hematopoiesis and its impact on the aging osteo-hematopoietic niche. *Leukemia.* 2024;38(5):936–946. doi:10.1038/s41375-024-02226-6
 45. Fuster JJ, MacLauchlan S, Zuriaga MA, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice. *Science.* 2017;355(6327):842–847. doi:10.1126/science.aag1381
 46. Schuermans A, Vlasschaert C, Nauffal V, et al. Clonal haematopoiesis of indeterminate potential predicts incident cardiac arrhythmias. *Eur Heart J.* 2024;45(10):791–805. doi:10.1093/eurheartj/ehad670
 47. Saadatagah S, Naderian M, Uddin M, et al. Atrial fibrillation and clonal hematopoiesis in TET2 and ASXL1. *JAMA Cardiol.* 2024; 9(6):497–506. doi:10.1001/jamacardio.2024.0459
 48. Lin AE, Bapat AC, Xiao L, et al. Clonal hematopoiesis of indeterminate potential with loss of Tet2 enhances risk for atrial fibrillation through Nlrp3 inflammasome activation. *Circulation.* 2024;149(18):1419–1434. doi:10.1161/circulationaha.123.065597
 49. Gadde S, Kalluru R, Cherukuri SP, Chikatimala R, Dasaradhan T, Koneti J. Atrial fibrillation in chronic kidney disease: an Overview. *Cureus.* 2022;14(8):e27753. doi:10.7759/cureus.27753
 50. Busque L, Sun M, Buscarlet M, et al. High-sensitivity C-reactive protein is associated with clonal hematopoiesis of indeterminate potential. *Blood Adv.* 2020;4(11):2430–2438. doi:10.1182/bloodadvances.2019000770
 51. Vostatek R, Hohensinner P, Schmaldienst S, et al. Telomere length is associated with increased risk of cardiovascular events in patients with end-stage kidney disease on hemodialysis. *Cardiorenal Med.* 2024;14(1):524–532. doi:10.1159/000541112
 52. Park S, Lee S, Kim Y, et al. A Mendelian randomization study found causal linkage between telomere attrition and chronic kidney disease. *Kidney Int.* 2021;100(5):1063–1070. doi:10.1016/j.kint.2021.06.041