

Clonal hematopoiesis of indeterminate potential: A joint risk factor for cancer and atherosclerosis

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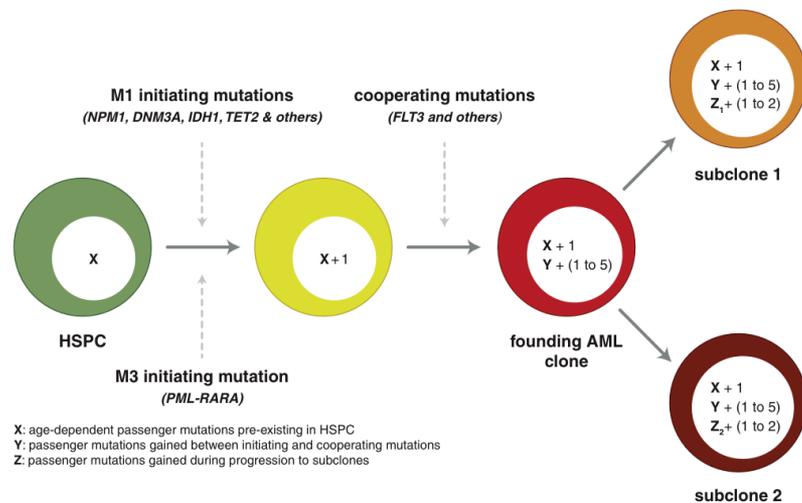


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GENERAL HOSPITAL

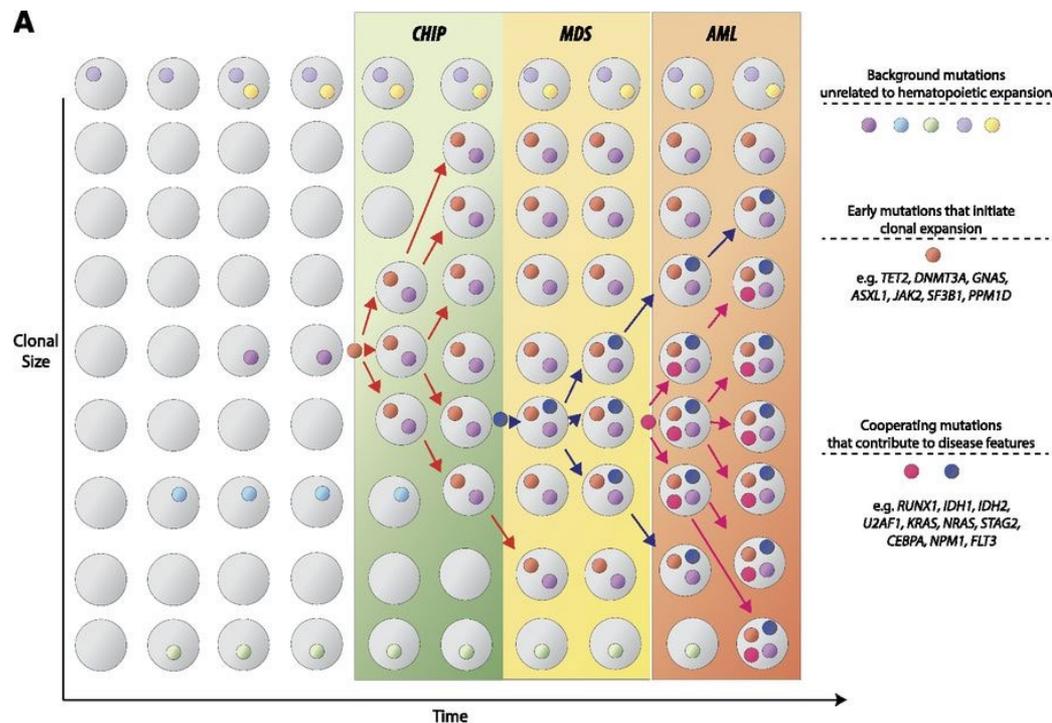
CORRIGAN MINEHAN
HEART CENTER

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 - Spousal employment: Vertex
- Conflicts of interest:
 - None

'Clonal Hematopoiesis of Indeterminate Potential'

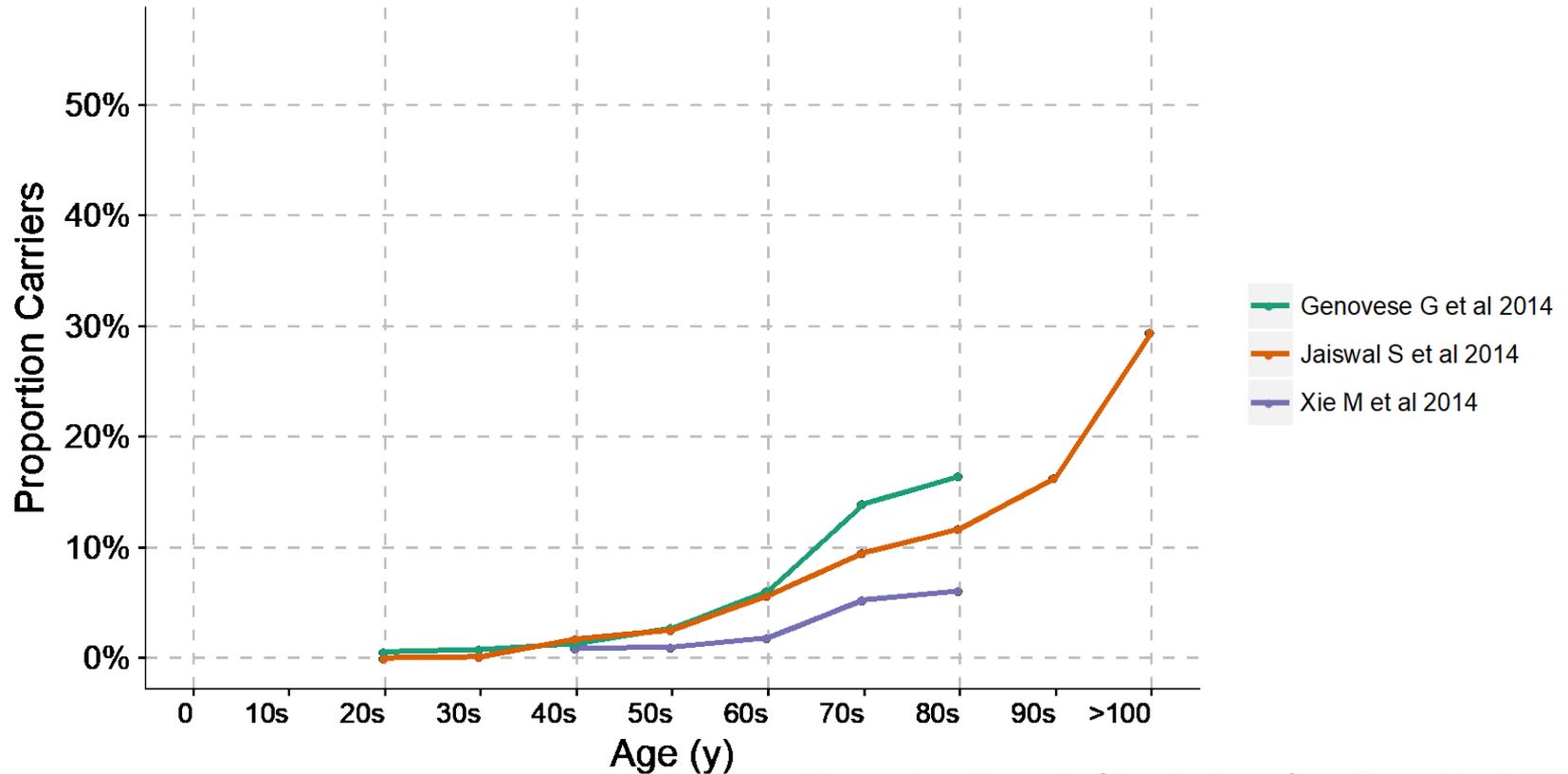


Welch JS et al. *Cell*. 2012



Steensma DP et al. *Blood*. 2015

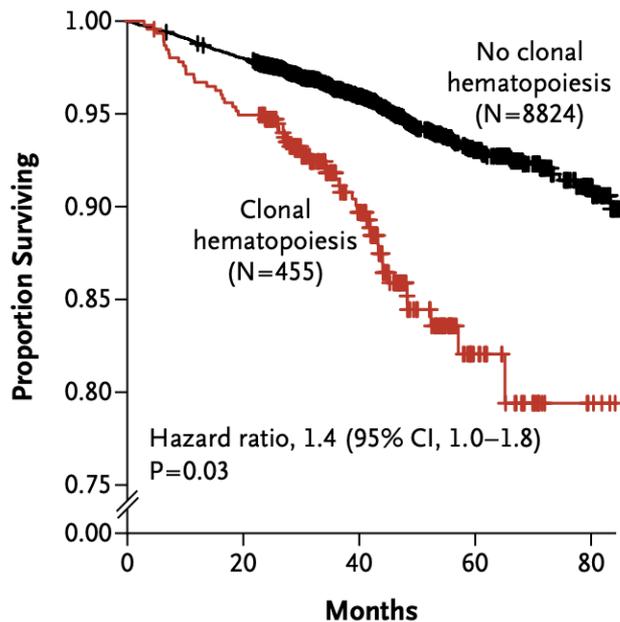
1 in 10 individuals >70 years have CHIP



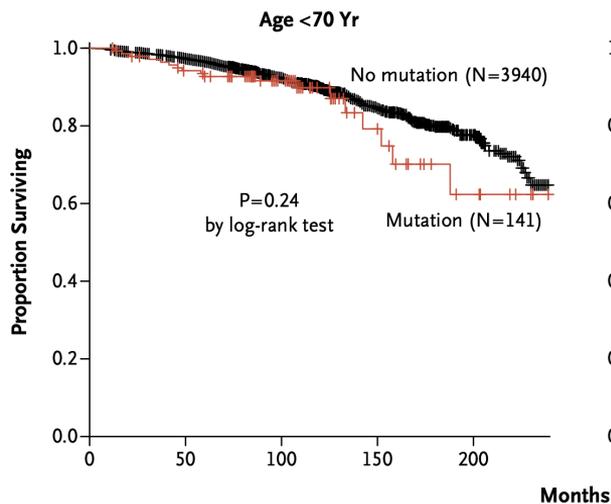
Clinical risk factors of CHIP mirror CVD risk factors

	Beta coefficient	OR(95 CI)	p-value	Variance explained
Age	0.07	1.08(1.07-1.09)	<0.001	0.06
European (referent)				0.003
African-American	0.15	1.16(0.93-1.44)	0.19	
East-Asian	-0.08	0.92(0.71-1.2)	0.56	
Hispanic	-0.37	0.69(0.56-0.85)	<0.001	
South Asian	-0.25	0.78(0.6-1)	0.057	
No T2D (referent)				0.002
Has T2D	0.28	1.32(1.14-1.54)	<0.001	
Male (referent)				0.001
Female	1.01		0.026	
BMI	-0.02	0.98(0.96-0.99)	0.005	0.001
Age:Female	-0.02		0.009	0.001

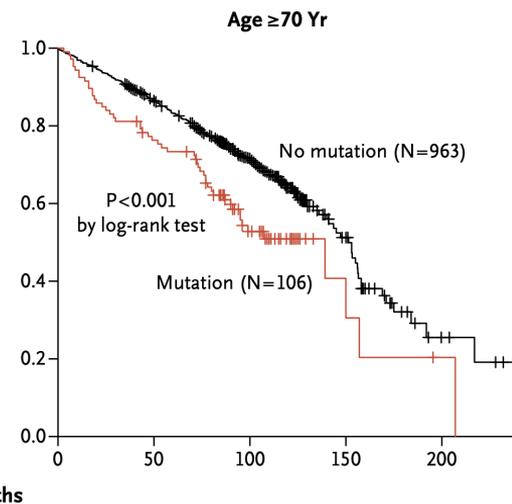
1.4-fold risk for all-cause mortality



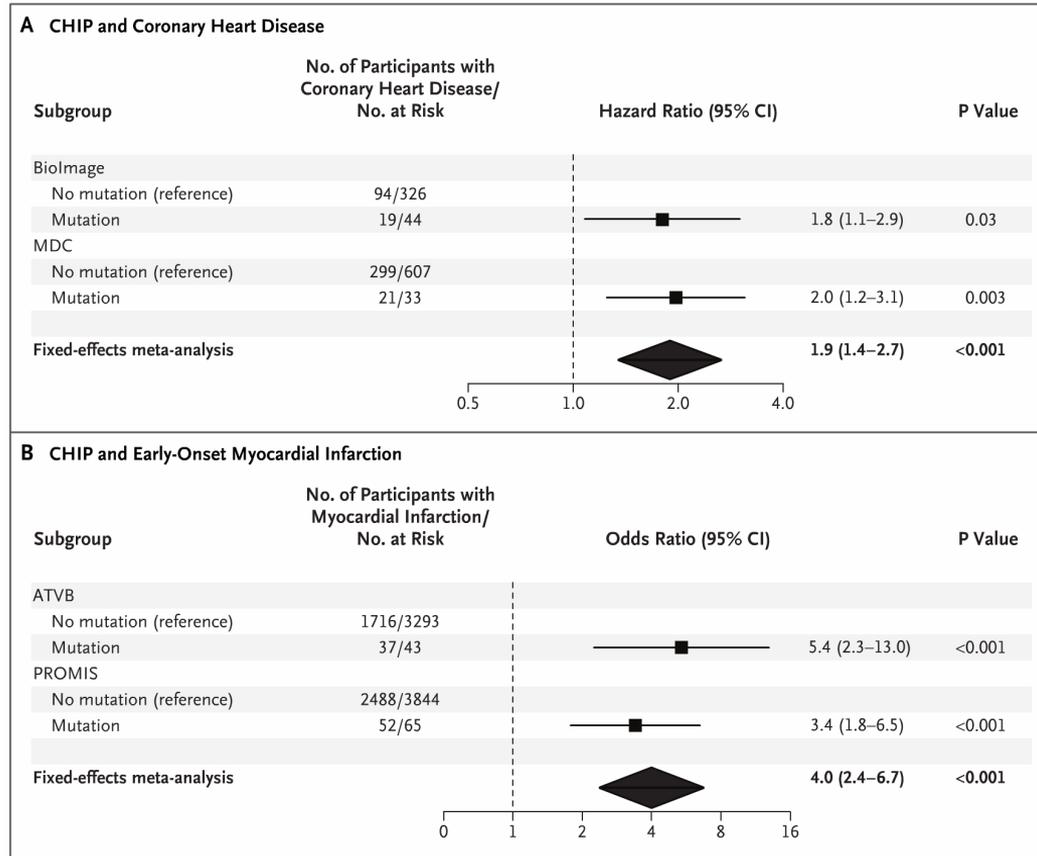
Genovese G et al. *N Eng J Med.* 2014



Jaiswal S et al. *N Eng J Med.* 2014

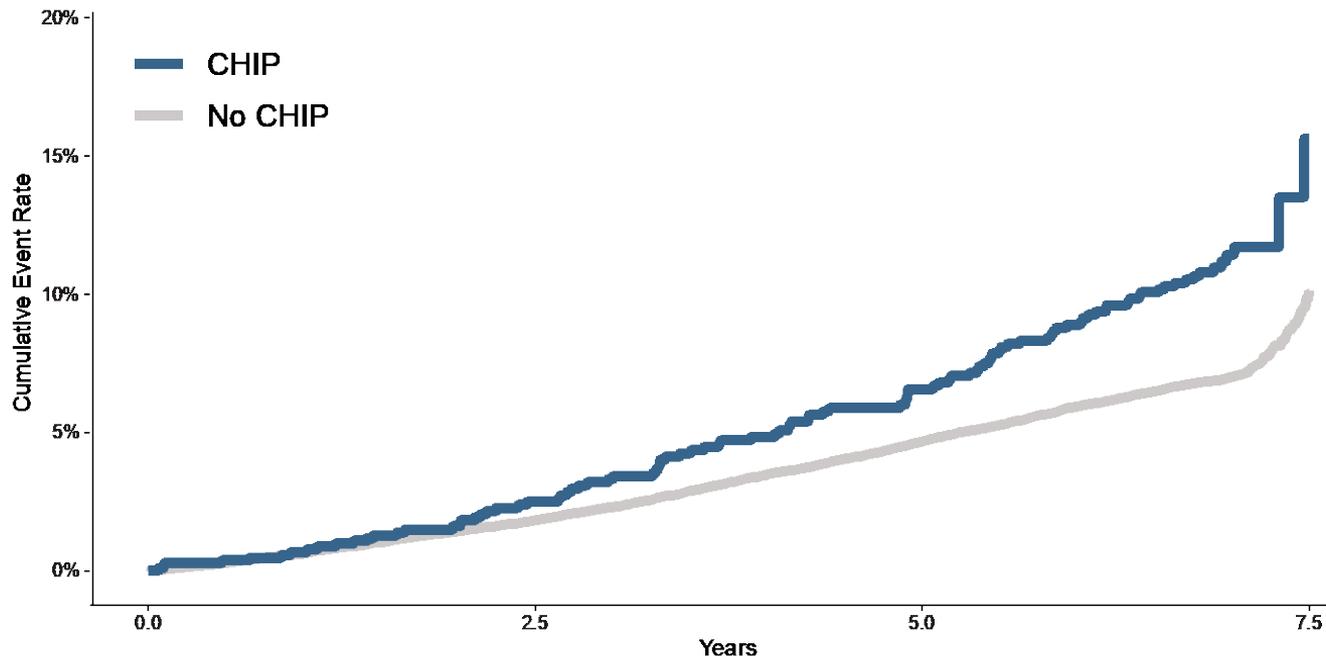


CHIP is associated with increased CAD and early-onset MI risk

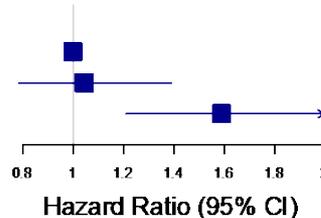


Jaiswal S, Natarajan P et al.
N Eng J Med. 2017

CHIP, particularly 'large CHIP,' is associated with incident CVD risk

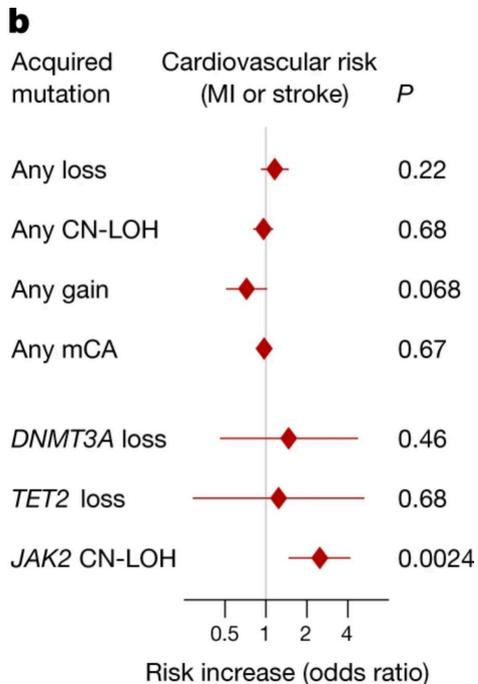


Group	At risk	Incident Events	P-value	HR
Baseline	34337	1951		1
CHIP, VAF ≤ 0.1	647	48	0.7704	1.04
CHIP, VAF > 0.1	432	53	9e-04	1.59

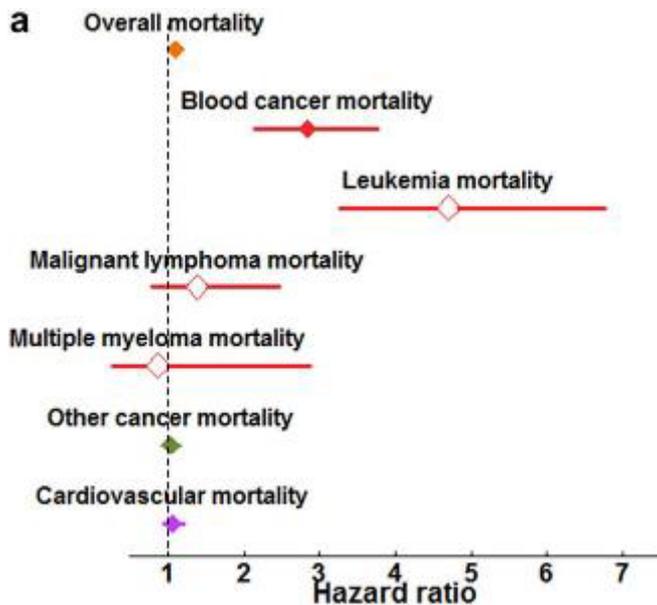


Bick A*, Pirruccello J*,
...Natarajan P.
Circulation. 2020

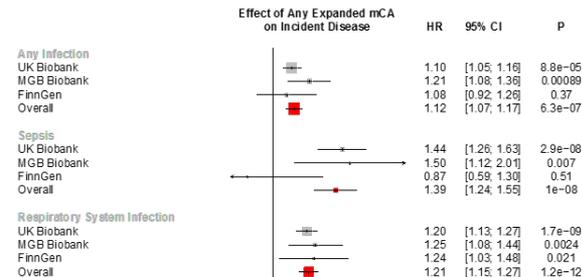
Another form of clonal hematopoiesis is not linked to CAD



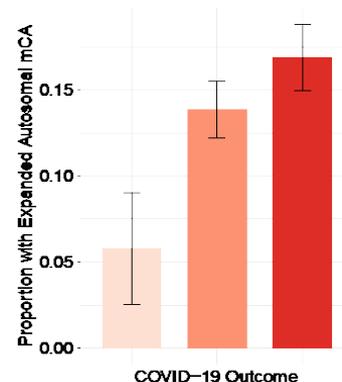
Loh PR, et al. *Nature*. 2020



Terao C, et al. *Nature*. 2020



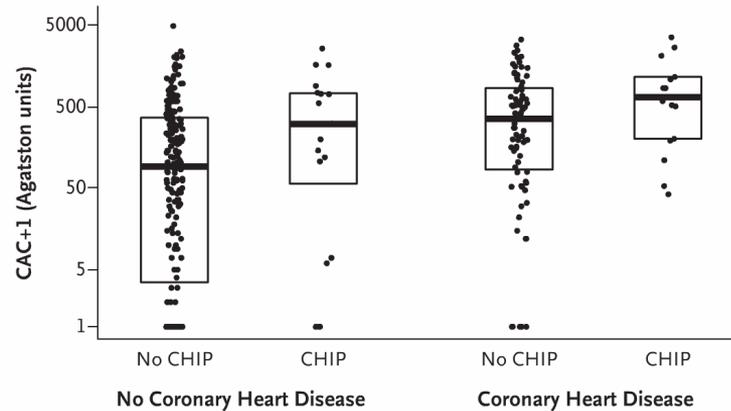
■ Mild (WHO scale 1-3)
■ Moderate (WHO scale 4-6)
■ Severe (WHO scale 7-10)



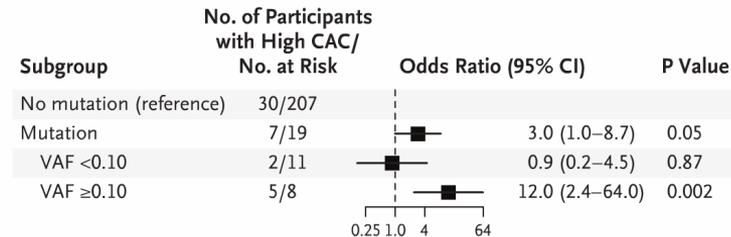
Zekavat SM, ..., Natarajan P.
Nature Medicine. 2021

Humans and mice with CHIP have a greater burden of subclinical atherosclerosis

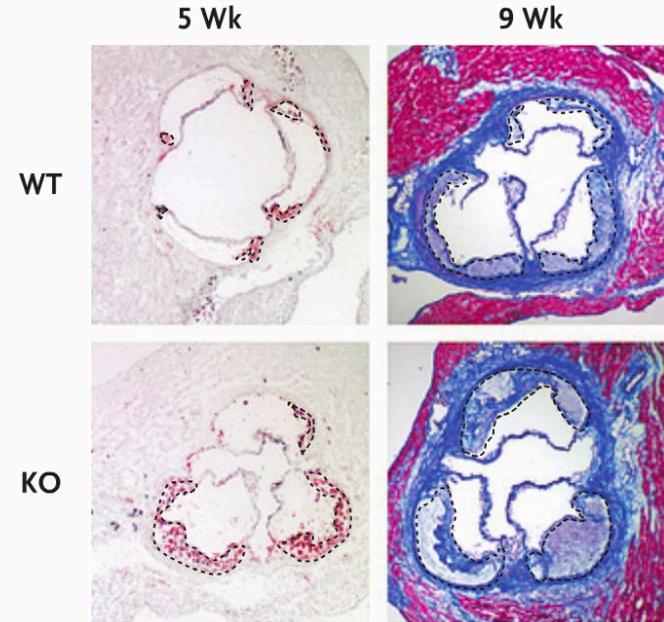
A Coronary-Artery Calcification (CAC) Scores, According to CHIP Status



B CHIP and CAC Score of ≥ 615 Agatston Units, According to Variant Allele Fraction

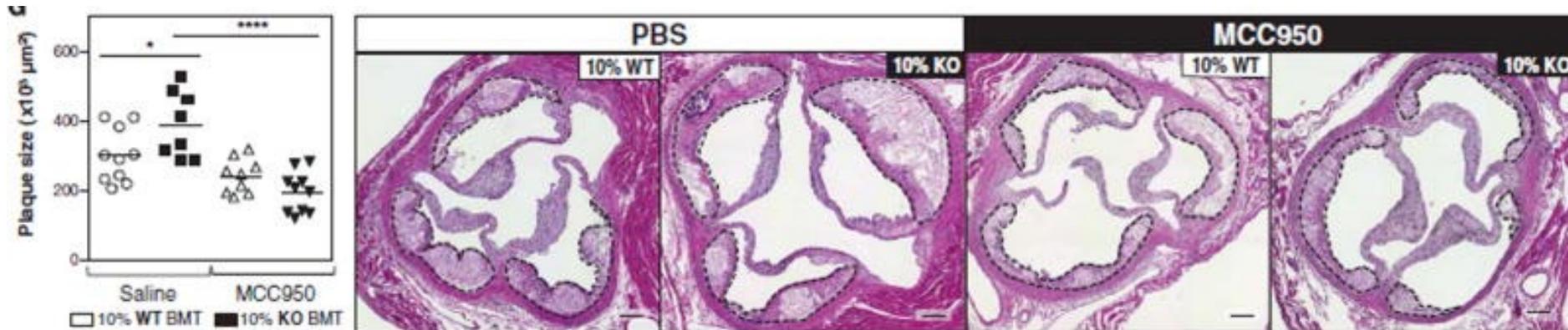


A Aortic-Root Sections, According to *Tet2* Status

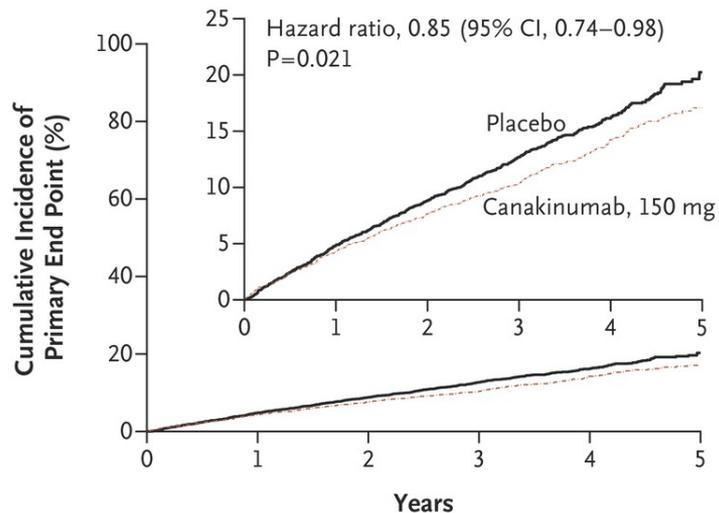


Jaiswal S, Natarajan P et al. *N Eng J Med.* 2017

Inhibition of NLRP3 inflammasome mitigates atherogenesis in murine model



B Primary End Point with Canakinumab, 150 mg, vs. Placebo



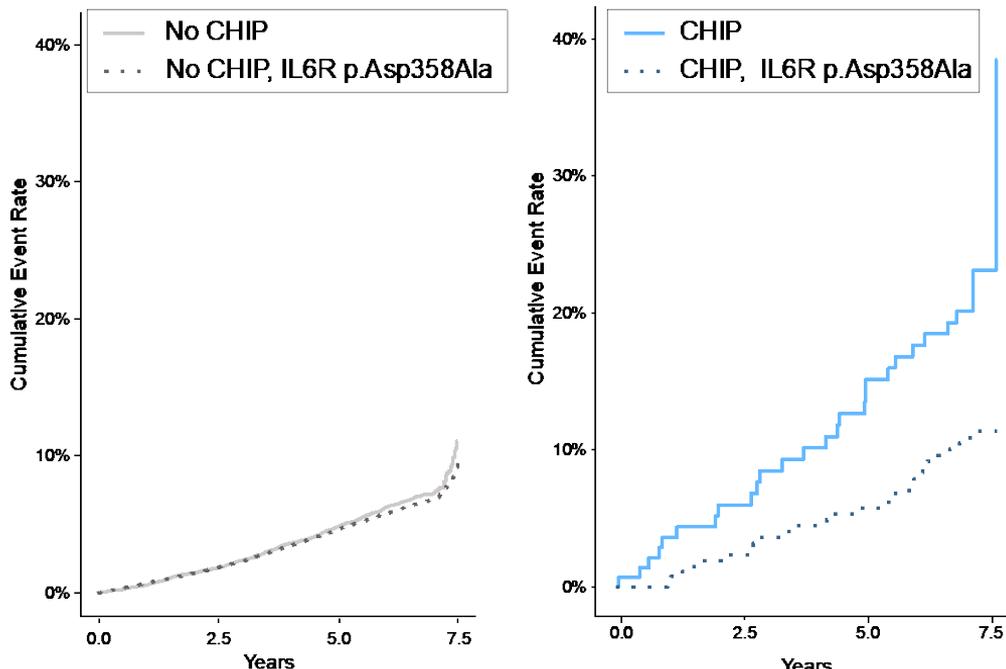
No. at Risk

Placebo	3344	3141	2973	2632	1266	210
Canakinumab	2284	2151	2057	1849	907	207

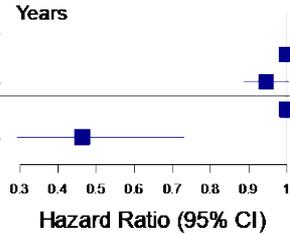
CANTOS: *TET2* CHIP may predict greater CVD relative risk reduction from IL1B inhibition

- Overall trial: HR 0.85 (Ridker P et al. *NEJM* 2017)
- *TET2* CHIP carriers (104 / 3925): HR 0.36 (Svensson EC et al. AHA Abstract 15111. 2018)

CHIP-associated CHD risk is specifically abrogated when *IL6R* p.Asp358Ala is present



Group	At risk	Incident Events	P-value	HR
No CHIP	11874	703		1
No CHIP, <i>IL6R</i> p.Asp358Ala	22463	1248	0.083	0.95
CHIP	143	27		1
CHIP, <i>IL6R</i> p.Asp358Ala	289	26	0.00095	0.46

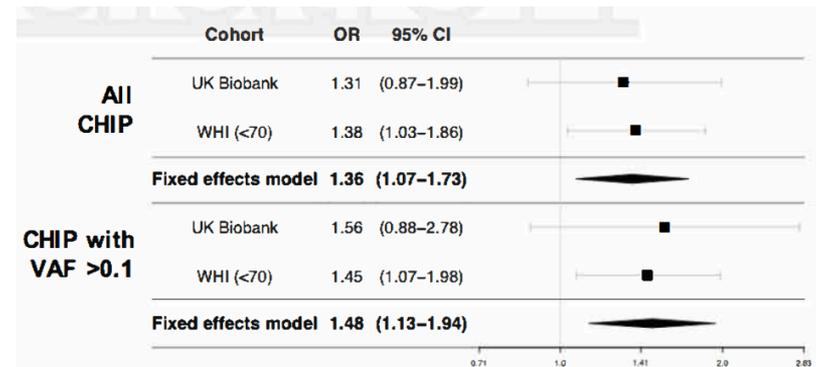
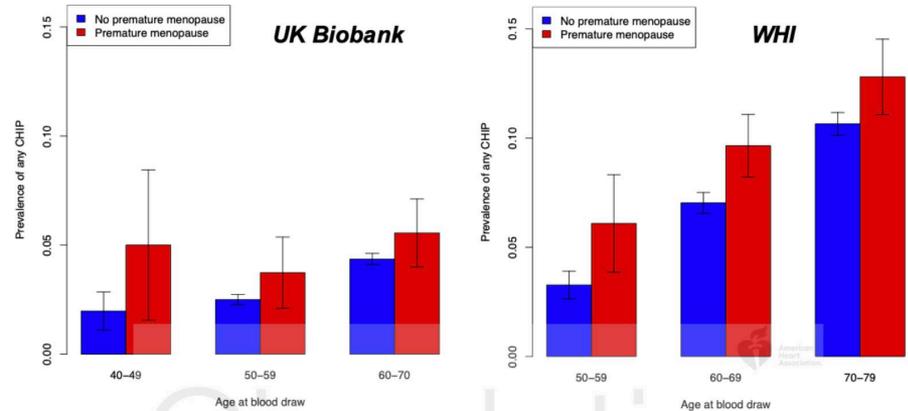


Bick A*, Pirruccello J*,
...Natarajan P. *Circulation*.
2020

Accelerated ovarian aging is correlated with clonal hematopoiesis

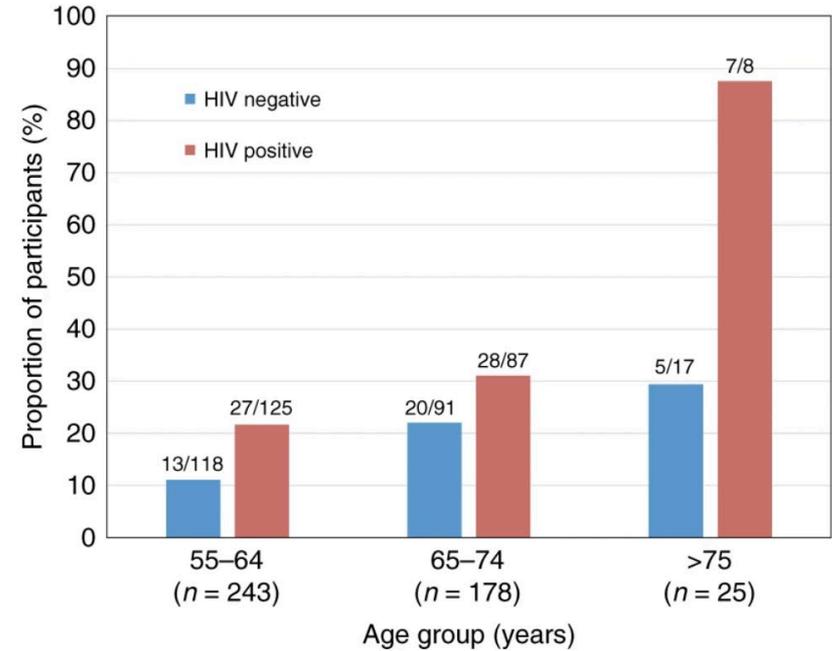
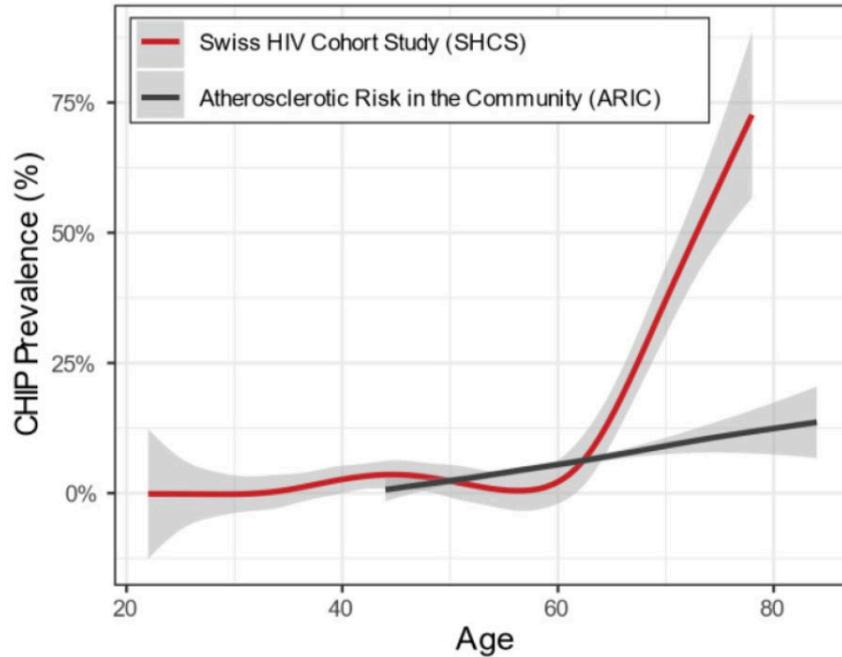
	Surgical Premature Menopause		Natural Premature Menopause		P Value for Heterogeneity ^d
	Hazard Ratio (95% CI)	P Value ^c	Hazard Ratio (95% CI)	P Value ^c	
First cardiovascular disease diagnosis ^a	2.21 (1.66-2.92)	<.001	1.60 (1.42-1.80)	<.001	.04
Coronary artery disease	3.76 (2.42-5.86)	<.001	1.81 (1.44-2.28)	<.001	.004
Heart failure	2.74 (1.42-5.29)	.003	1.56 (1.14-2.16)	.006	.14
Aortic stenosis	3.41 (1.27-9.16)	.02	2.48 (1.62-3.80)	<.001	.56
Mitral regurgitation	3.40 (1.41-8.27)	.007	0.95 (0.52-1.74)	.87	.02
Atrial fibrillation	1.87 (1.14-3.06)	.01	1.44 (1.18-1.77)	<.001	.34
Ischemic stroke	1.18 (0.38-3.66)	.78	1.59 (1.12-2.28)	.01	.62
Peripheral artery disease	2.19 (0.70-6.83)	.18	1.96 (1.27-3.03)	.002	.86
Venous thromboembolism	2.57 (1.41-4.67)	.002	1.68 (1.29-2.20)	<.001	.20

Honigberg M, et al. *JAMA*. 2019



Honigberg M, et al. *Circulation*. 2021

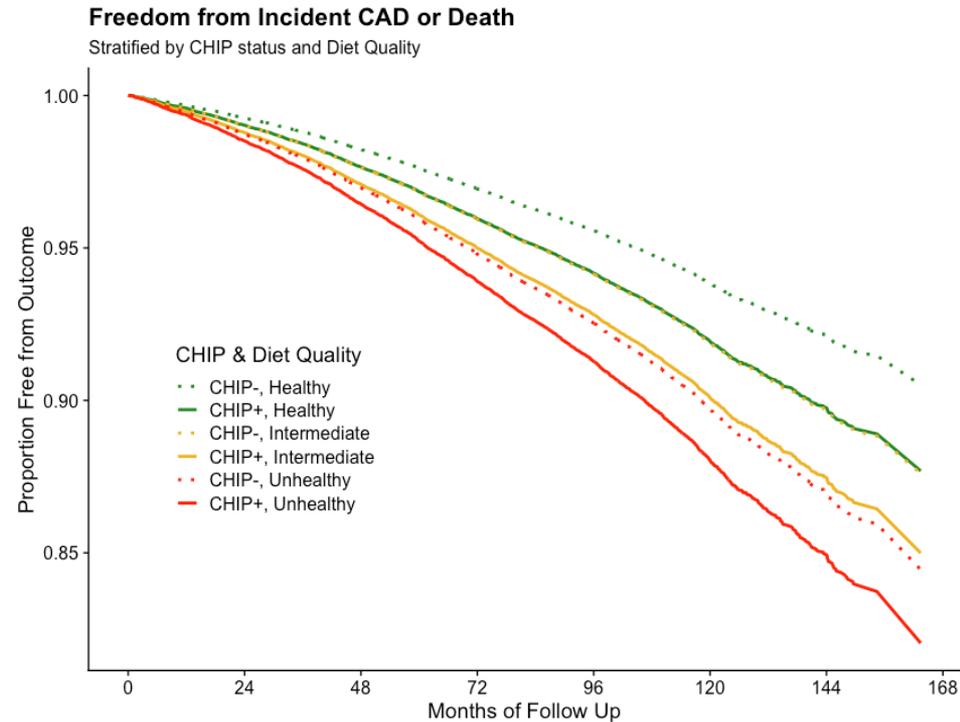
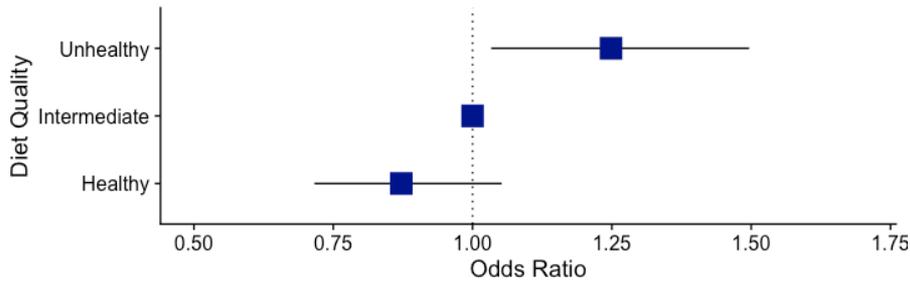
CHIP is more common among people living with HIV



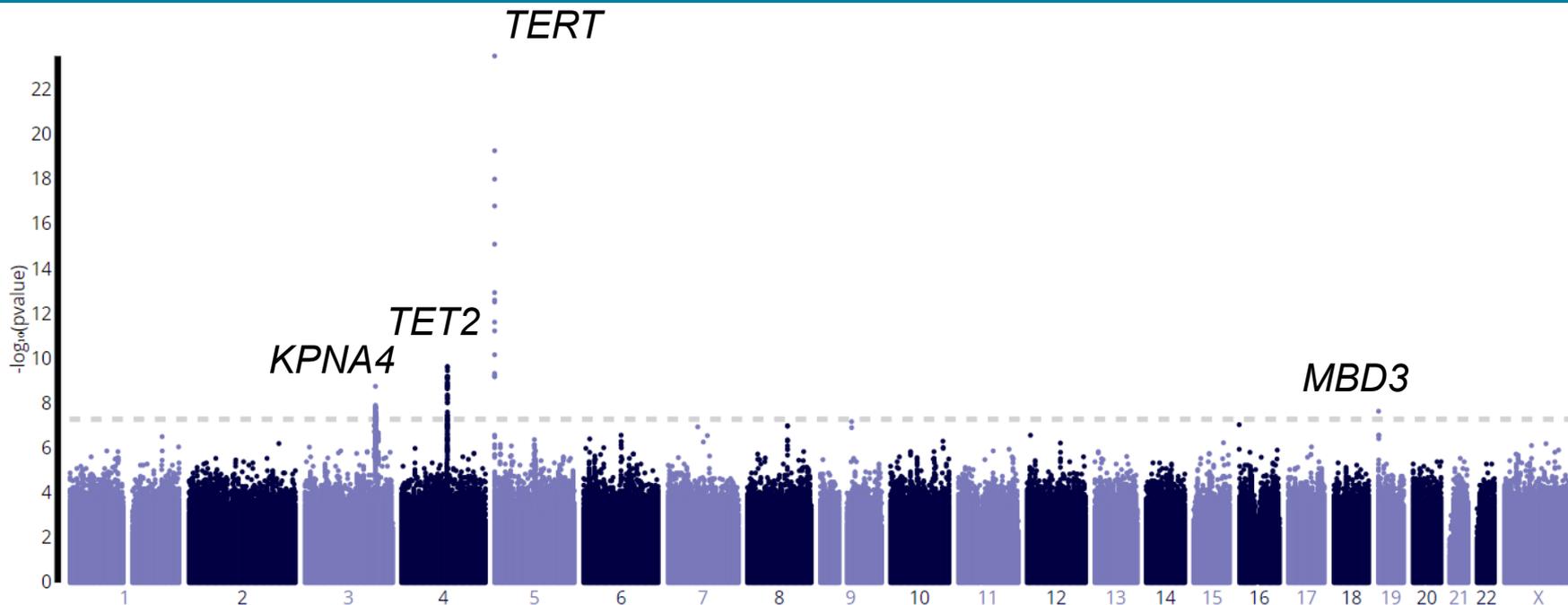
Bick A*, Popadin K*, ..., Natarajan P*,
Fellay J*. *medRxiv*. 2020

Dharan NJ et al. *Nature
Medicine*. 2021

CHIP is enriched for individuals with an unhealthy diet, and stratifies CHIP-associated CAD risk



Germline genetic factors influence CHIP

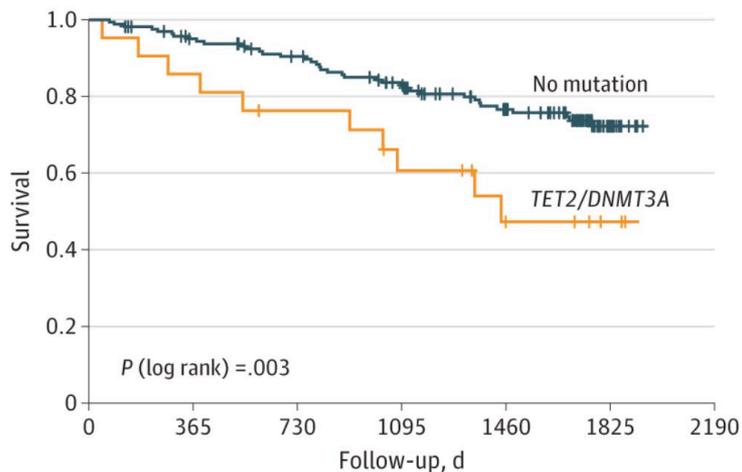


4,431 cases / 85,405 controls

Prognosis is worse in the setting of other cardiovascular conditions

Heart Failure

B Overall survival of patients with *DNMT3A* or *TET2* mutations

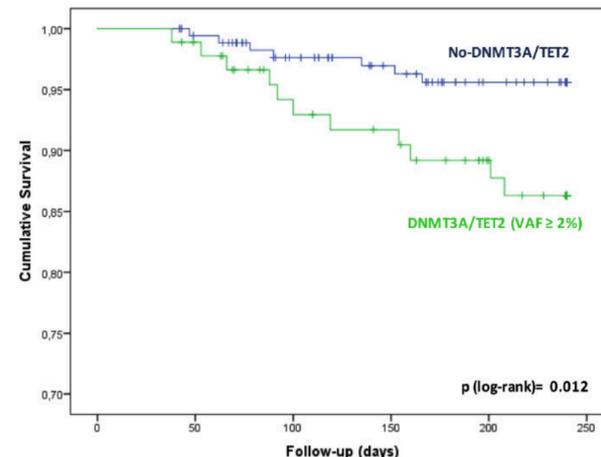


No. at risk

<i>TET2/DNMT3A</i>	21	18	15	11	7	3
No mutation	162	146	134	116	89	33

Dorsheimer L, et al. *JAMA Cardio.* 2019

Aortic Stenosis



No-TET2/DNMT3A	178	176	172	159	148	142	131	125	116
TET2/DNMT3A	91	91	86	78	74	72	68	60	56

Take home figure Overall survival of patients with *DNMT3A*- or *TET2*-CHIP-driver mutations with a variant allele frequency $\geq 2\%$ vs. patients without *DNMT3A* or *TET2* mutations. *Patients with follow-up <30 days have been excluded in order to remove mortality due to peri-procedural complications.

Mas-Peiro S, et al. *Eur Heart J.* 2019

- Clonal hematopoiesis of indeterminate potential (CHIP) represents a new risk factor for ASCVD
- CHIP is not readily identifiable by current clinical assessments
- NLRP3/IL1B/IL6 axis inhibition may be a particularly effective strategy to reduce ASCVD risk conferred by CHIP
- CHIP may be implicated in other age-related cardiovascular condition

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NHLBI R01HL148050 (Natarajan, Ballantyne)
NHLBI R01HL151283 (Natarajan)
NHLBI R01HL127564 (Natarajan, Peloso)

NHLBI R01HL148565 (Reiner, Whitsel)
NHLBI R01HL135242 (Nguyen)
NHLBI R01HL151152 (Koopersberg)
NIDDK R01DK125782 (Kelly)

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