ELSEVIER

Blood 142 (2023) 568–569

The 65th ASH Annual Meeting Abstracts

# ORAL ABSTRACTS

## 332.THROMBOSIS AND ANTICOAGULATION: CLINICAL AND EPIDEMIOLOGICAL

### Clonal Hematopoiesis and Venous Thromboembolism in the UK Biobank

*Becky Zon, MD[1], Aswin Sekar, MDPhD[1], Katharine Clapham, MD[2], Abhishek Niroula, PhD[1,3], Alexander G. Bick, MD PhD[4], Christopher James Gibson, MD[5], Gabriel K. Griffin, MD[6], Md Mesbah Uddin, PhDMS[7], Pradeep Natarajan, MDMMSc[8,9,10], Benjamin L. Ebert, MD PhD[11,12,13,14]*

[1] Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA
[2] Department of Medicine, Division of Cardiology, University of Utah School of Medicine, Salt Lake City, UT
[3] Institute of Biomedicine, University of Gothenburg, Gothenburg, Sweden
[4] Department of Medicine, Vanderbilt University Medical Center, Nashville, TN
[5] Dana Farber Cancer Institute, Boston, MA
[6] Department of Pathology, Dana-Farber Cancer Institute, Boston, MA
[7] Massachusetts General Hospital, Cambridge, MA
[8] Cardiovascular Research Center and Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA
[9] Harvard Medical School, Boston, MA
[10] Broad Institute, Boston, MA
[11] Broad Institute of MIT and Harvard University, Cambridge, MA
[12] Howard Hughes Medical Institute, Boston, MA
[13] Department of Medicine, Harvard Medical School, Boston, MA
[14] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background: Patients with myeloid malignancies have an increased risk of thrombosis, but less is known about the risk of thrombosis in clonal hematopoiesis of indeterminate potential (CHIP). We evaluated genotype-specific associations between CHIP and both prevalent and incident venous thromboembolism (VTE) in the largest such analysis to date of the UK Biobank.
Methods: We examined 425,573 individuals without a prevalent hematologic malignancy diagnosis from the UK Biobank. Whole exome sequencing and single nucleotide polymorphism array data were analyzed to identify individuals with CHIP and/or mosaic chromosomal alterations (mCA), respectively. Prevalent and incident VTE cases were ascertained with respect to the time of DNA sampling. VTE events were identified based on ICD10 codes, including but not limited to, pulmonary embolism, phlebitis/thrombophlebitis of deep veins of lower veins, portal vein thrombosis, and Budd Chiari syndrome. Median follow-up time for incident VTE was 11.8 years. Associations of CHIP and VTE were assessed using logistic regression for prevalent analyses and Cox proportional hazards for incident analyses. The association analyses were adjusted for age at the time of DNA sampling, sex, Caucasian ancestry, genetic principal components, ever smoked status, and body mass index (BMI) as covariates.
Results:
Prevalent VTE and CHIP:
While CHIP overall was not associated with an increased risk of prevalent VTE (odds ratio (OR) 1.06; 95% CI 0.87-1.28, *P*= 0.56) (Figure 1), *JAK2*-mutant CHIP and *JAK2* CHIP with loss of heterozygosity at the *JAK2* locus (LOH 9p) were powerfully associated with increased risk of thrombosis, OR = 7.49 (95% CI 3.02-18.56, *P*=1.41e-05) and 6.74 (95% CI 1.62-28.08; *P*=8.71e-03). Having both CHIP and autosomal mCA was associated with a nominally increased risk of VTE (OR 1.76; 95% CI 1.02-3.06, *P*= 0.04). Otherwise, non- *JAK2* CHIP , *ASXL1* CHIP , *TET2* CHIP , *DNMT3A* CHIP were not associated with increased prevalent VTE, regardless of clone size.
Incident VTE and CHIP:
CHIP was modestly associated with incident VTE with a hazard ratio of 1.15 (1.03-1.28; *P*=0.01), and CHIP with a larger clone size (VAF > 10%) was associated with a hazard ratio of 1.22 (95% CI 1.08-1.39; *P*= 0.001) (Figure 2). Consistent with our analysis of prevalent VTE, *JAK2*-CHIP and *JAK2*-CHIP with LOH 9p were strongly associated with incident VTE with hazard ratios of 3.76 (95% CI 1.79-7.9, *P*= 0.0004) and 4.89 (95% CI 1.84-13.04; *P*=0.0015). Other associations, including overall CHIP, CHIP

with VAF >10%, CHIP together with autosomal mCA, autosomal mCA, non- *JAK2* CHIP, *TET2* CHIP with VAF >10%, showed modest increased hazard ratios between 1 and 2.
Conclusions: In this study of risk of thrombosis in the UK Biobank, CHIP was not significantly associated with prevalent VTE and was modestly associated incident VTE. Among CHIP genotypes analyzed, only *JAK2* mutations were significantly associated with both prevalent and incident VTE risk (OR 7.49 and HR 3.76, respectively). *JAK2*-mutant CHIP may be an undetected contributor to cases of VTE and may have therapeutic implications.

**Disclosures Zon:** *Amagma Therapeutics:* Consultancy, Current equity holder in private company. **Sekar:** *Vertex Pharmaceuticals:* Other: Stock . **Clapham:** *United Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Tectonic Therapeutics:* Other: Speaker. **Bick:** *TenSixteen Bio:* Membership on an entity's Board of Directors or advisory committees. **Natarajan:** *Allelica:* Other: Personal Fees, Research Funding; *Apple:* Other: Personal Fees, Research Funding; *Amgen:* Research Funding; *Boston Scientific:* Research Funding; *Genentech/Roche:* Other: Personal Fees, Research Funding; *Novartis:* Research Funding; *AstraZeneca:* Other: Personal Fees; *Blackstone Life Sciences:* Other: Personal Fees; *Foresite Labs:* Other: Personal Fees; *GV:* Other: Personal Fees; *HeartFlow:* Other: Personal Fees; *Magnet Biomedicine:* Other: Personal Fees; *Esperion Therapeutics:* Membership on an entity's Board of Directors or advisory committees; *Preciseli:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *TenSixteen Bio:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees, Other: Co-Founder; *MyOme:* Current equity holder in private company; *Vertex Pharmaceuticals:* Other: Spousal employment. **Ebert:** *Novartis:* Research Funding; *Abbvie:* Consultancy; *Neomorph Inc.:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *TenSixteen Bio:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Skyhawk Therapeutics:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Exo Therapeutics:* Current equity holder in private company, Membership on an entity's Board of Directors or advisory committees; *Calico:* Research Funding.

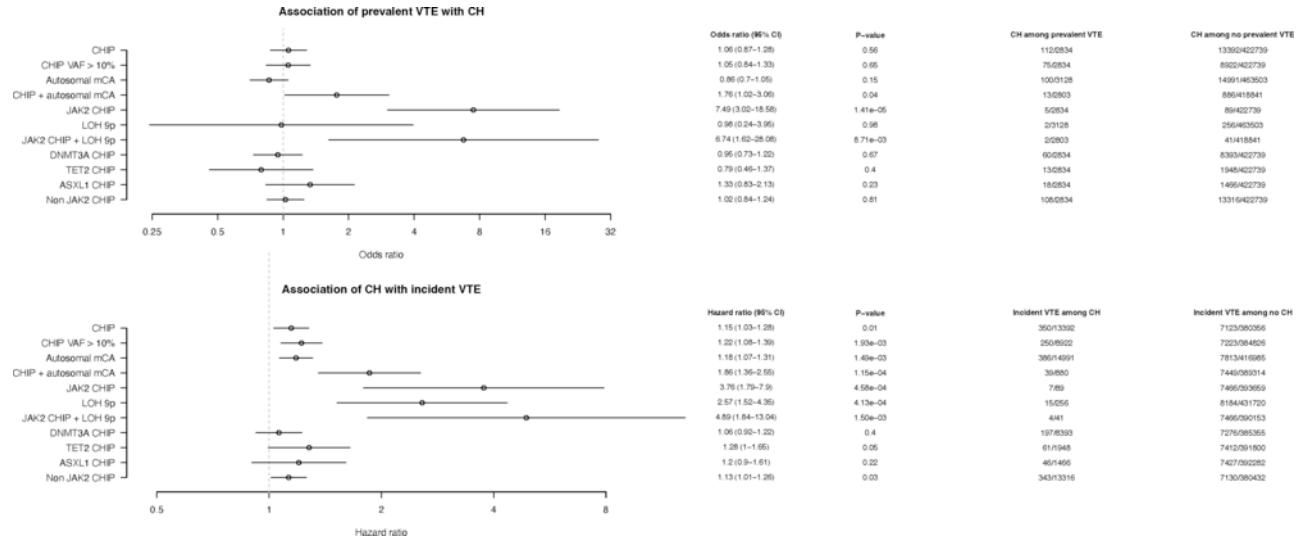


**Figure 1**

https://doi.org/10.1182/blood-2023-180764