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Neutrophil Counts and Initial Presentation of 12 Cardiovascular Diseases

A CALIBER Cohort Study

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ABSTRACT

BACKGROUND Neutrophil counts are a ubiquitous measure of inflammation, but previous studies on their association with cardiovascular disease (CVD) were limited by small numbers of patients or a narrow range of endpoints.

OBJECTIVES This study investigated associations of clinically recorded neutrophil counts with initial presentation for a range of CVDs.

METHODS We used linked primary care, hospitalization, disease registry, and mortality data in England. We included people 30 years or older with complete blood counts performed in usual clinical care and no history of CVD. We used Cox models to estimate cause-specific hazard ratios (HRs) for 12 CVDs, adjusted for cardiovascular risk factors and acute conditions affecting neutrophil counts (such as infections and cancer).

RESULTS Among 775,231 individuals in the cohort, 154,179 had complete blood counts performed under acute conditions and 621,052 when they were stable. Over a median 3.8 years of follow-up, 55,004 individuals developed CVD. Adjusted HRs comparing neutrophil counts 6 to 7 versus 2 to 3 $\times 10^9$/l (both within the 'normal' range) showed strong associations with heart failure (HR: 2.04; 95% confidence interval [CI]: 1.82 to 2.29), peripheral arterial disease (HR: 1.95; 95% CI: 1.72 to 2.21), unheralded coronary death (HR: 1.78; 95% CI: 1.51 to 2.10), abdominal aortic aneurysm (HR: 1.72; 95% CI: 1.34 to 2.21), and nonfatal myocardial infarction (HR: 1.58; 95% CI: 1.42 to 1.76). These associations were linear, with greater risk even among individuals with neutrophil counts of 3 to 4 versus 2 to 3 $\times 10^9$/l. There was a weak association with ischemic stroke (HR: 1.36; 95% CI: 1.17 to 1.57), but no association with stable angina or intracerebral hemorrhage.

CONCLUSIONS Neutrophil counts were strongly associated with the incidence of some CVDs, but not others, even within the normal range, consistent with underlying disease mechanisms differing across CVDs. (White Blood Cell Counts and Onset of Cardiovascular Diseases: a CALIBER Study [CALIBER]; NCT02014610) (J Am Coll Cardiol 2017;69:1160–9)

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The most numerous type of white blood cell, neutrophils, play a major role in inflammation. Neutrophil count is used routinely as a biomarker of acute infection and inflammation, but not in cardiology. Chronic inflammation contributes to atherosclerosis and cardiovascular diseases (CVD) (1,2) but, compared with other inflammatory biomarkers such as C-reactive protein (3) and interleukin-6 (4), neutrophil counts have been little studied in relation to long-term CVD risk, even though they are available at scale in clinically collected electronic health record data.

Previous studies have shown that high neutrophil counts are associated with an higher incidence of coronary disease (5), heart failure (HF) (6), and stroke (7) (Online Table 1). However, these studies were too small to examine thresholds or shape of the association. No study used a clinically recorded measure of neutrophil count, which is important to understand the relevance of findings to usual practice, or studied associations with peripheral vascular diseases.

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This study investigated the association of neutrophil counts with initial presentation of 12 CVDs in a large, population-based cohort from a linked electronic health record database: the CALIBER program (Clinical Research Using Linked Bespoke Studies and Electronic Health Records) (8). CALIBER has been extensively validated, replicating known prospective associations of CVDs with sex (9), smoking (10), blood pressure (11), socioeconomic deprivation (12), and type 2 diabetes (13).

METHODS

We used the same study cohort as our study on the association of eosinophil and lymphocyte counts with incidence of CVD (14). The study population was drawn from the CALIBER program (8), which links 4 sources of electronic health data in England: primary care health records (coded diagnoses, clinical measurements, and prescriptions) from 244 general practices contributing to the Clinical Practice Research Datalink; coded hospital discharges (Hospital Episode Statistics); the Myocardial Ischemia National Audit Project (MINAP); and death registrations (Online Appendix). CALIBER includes about 4% of the population of England (15) and is representative in terms of age, sex, ethnicity, and mortality (8).

The study period was January 1998 to March 2010, and individuals were eligible for inclusion when they were at least 30 years of age and had been registered for at least 1 year in a practice that met research data recording standards. The study start date (index date) for each participant was the date of the first complete blood count recorded in the primary care record while the participant was eligible. Persons with a prior history of CVD and women with a pregnancy record within 6 months of the start of the study were excluded.

Approval was granted by the Independent Scientific Advisory Committee of the Medicines and Healthcare Products Regulatory Agency (protocol 12_153R) and the MINAP Academic Group.

The main exposure was the neutrophil count (part of the complete blood count) as recorded in primary care. We investigated the neutrophil count initially as a categorical variable to avoid assuming a particular shape for association with CVD. We wished to specifically look at associations with 'normal' as well as extreme neutrophil counts; there is no consensus definition for the normal range, but many laboratories quote the range of 2 to 7 $\times$ 10^9/l (16). This lent itself to convenient 5-level categorization within the 'normal' range. All category intervals were closed at the lower bound and open at the upper bound (i.e., '2 to 3' includes 2 but not 3).

White cell counts can be affected by infections, autoimmune diseases, medication, and hematologic conditions. We classified the patient state at the time of the blood test as acute or stable. An acute clinical state was defined as any of the following conditions: in hospital on the date of blood test; vaccination in the previous 7 days; anemia diagnosis within the previous 30 days; symptoms or diagnosis of infection within the previous 30 days; prior diagnosis of myelodysplastic syndrome; hemoglobinopathy, cancer chemotherapy, or injection of granulocyte colony-stimulating factor within the previous 6 months; or the use of drugs affecting the immune system, such as methotrexate or steroids, within the previous 3 months. Patients were considered stable if they did not fulfill the criteria for an acute clinical state. Patients on dialysis, those with human immunodeficiency virus infection, or a history of splenectomy were excluded from this study, because their neutrophil counts may be difficult to interpret. These criteria were based on those proposed by the eMERGE (Electronic Medical Records and Genomics) consortium for studying the genetic determinants of white cell counts (17) (further details in the Online Appendix).

In secondary analyses, we explored associations between onset of CVD and the mean of the first 2 stable measurements of neutrophil count taken since the start of eligibility. We extracted demographic

ABBREVIATIONS AND ACRONYMS

CI = confidence interval
CVD = cardiovascular disease
HF = heart failure
HR = hazard ratio
IQR = interquartile range
MI = myocardial infarction
PAD = peripheral arterial disease