Editorial

Neutrophil counts and their potential prognostic value in cardiovascular diseases

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The recently published article of Shah and colleagues (1) focuses on the association of neutrophil counts and presentation of distinct major cardiovascular diseases.

Indeed, neutrophils play a role in the formation of atherosclerotic. Different studies independently corroborated an important contribution of neutrophils during the different phases of atherosclerosis. Neutrophils are one of the most important cells in innate immunity and provide a first line defense against bacterial challenges and are thereby important for pathogen clearance. In order to use these characteristics diagnostically, neutrophil counts serve as an indicator for inflammation. Although the pathophysiological role of inflammation and its association to cardiovascular diseases has been investigated intensively and extensive understanding could be achieved already, the current study of Shah provides new evidence for the role of neutrophils as an underrated prognostic biomarker.

The researchers examined the association of neutrophil counts in more than 775,000 individuals from the CALIBER (Clinical Research Using Linked Bespoke Studies and Electronic Health Records) registry and the initial presentation of more than twelve distinct cardiovascular diseases. Individuals with former cardiovascular diseases as well as pregnancy within a time frame of six months before the start of the study were excluded. The CALIBER registry includes approximately 4% of the population of England and thereby shows a substantial strength in size. Importantly, the study registry was shown to be representative with regard to age, sex, ethnicity and mortality and its enormous size made it possible to study even less common CVDs like abdominal aortic aneurysm or intracerebral hemorrhage (2,3).

Neutrophil counts of the individuals were grouped into below ($<2\times10^9$/L), within (2×10^9–7×10^9/L), and above normal limits ($>7\times10^9$/L). Based on the size of the cohort they could record more than 55,000 cardiovascular events during the study period of roughly 4 years.

The occurrence of higher neutrophil counts was associated with comorbidities such as diabetes, asthma, chronic obstructive pulmonary disease, connective tissue diseases, and inflammatory bowel disease. As a matter of fact, affected patients more often were smokers and lived in socioeconomically deprived areas.

Comprehensively, comparing neutrophil counts of individuals at the lower limit of the normal range and individuals with neutrophil counts close to (and above) the upper limit of the standard range revealed strong correlation with heart failure, peripheral arterial disease, unheralded coronary death, abdominal aortic aneurysm and nonfatal myocardial infarction (MI). Importantly, these associations have been confirmed by multivariable survival models. Weaker associations were seen for ventricular arrhythmia, transient ischemic attack and ischemic stroke. However, no associations could be demonstrated with stable and unstable angina, hemorrhagic stroke or subarachnoid hemorrhage (1).

The observed associations were linear and demonstrated an increased hazard already among individuals with high normal versus low normal neutrophil counts ($3–4\times10^9$ *vs.* $<3\times10^9$/L). Interestingly, neutrophil counts displayed a similar puissance of correlation with CVD as systolic blood pressure, without cusp effect for higher neutrophil

counts. The data confirm that neutrophils are convoluted in the genesis of atherosclerosis, but suggest that they may also foster the danger of arterial thrombosis. Putative processes that drive these phenomena may be interactions of neutrophils with the endothelium, and platelets, and macrophages and smooth muscle cells as well as overactivity of neutrophil-dependent proinflammation. First neutrophils will be caught, then pore the endothelium where they discern cytokines and chemokines and convey the activation of cell adhesion molecules especially selectins and integrins to enable a firm contact of the cell.

Albeit the presented data shed new light on the usefulness of a routinely determined laboratory analyte, these data also raise several questions. Due to the observational character of the study, no causal relationships may be inferred. Therefore, neutrophils may act as a causative factor or conversely may be just simple markers of cardiovascular disease. Moreover, it is possible that important and not recorded confounders (e.g., adipositas, diabetes, smoking, chronic kidney disease) may explain the findings better than neutrophil counts thus limiting the conclusions of the study. Additionally, the presented classification of the neutrophil count is not uniform and thus differs depending on the laboratory.

Irrespective of the major study limitations the presented study suggests that the importance of neutrophil counts and its impact on cardiovascular diseases might be underestimated, particularly if neutrophils are within the normal range. This point of view is supported by previous smaller studies, in which neutrophils were positively associated with incident heart failure and stroke (4,5). Since the CALIBER registry is valid for a representative population this unexpected observation is highlighted. Conversely, we also have to consider possible underestimation of effects as a result of the heterogeneity of the applied analytical methods and further heterogeneity among the study population itself that might have biased the results.

To better classify the results, it is worth to acknowledge the pathophysiological role of neutrophils in cardiovascular diseases more deeply. Neutrophils mirror the patient's condition of infection and inflammation, and consequently is associated to cardiovascular risk. They are rapidly recruited to the sites of inflammation, where their main function is to fight effectively against pathogens by phagocytosis, release of granzymes and perforins as well as by the production of reactive oxygen species. These features are clearly beneficial in order to ensure clearance of the pathogens. However, these destructive abilities accompany the potential to damage healthy tissues (6).

Nevertheless, in terms of cardiovascular events neutrophils are not only associated with bad outcome. For neutrophils, it has been recognized that they not only orchestrate the onset of inflammation but may also control the resolution of inflammation and the return to tissue functionality (7). Interestingly, both clinical data and recent experimental evidence derived from mice suggest that neutrophils also seem to have beneficial effects during healing after MI (8). This would emphasize the importance of neutrophils in terms of its risk for cardiovascular events but also their role in tissue recovery.

Not only neutrophils, but also several established markers like C-reactive protein and proinflammatory cytokines are upregulated in cardiac insufficiency and congestive heart failure (4,9,10). Consistently with the data herein discussed, in population-based studies the above-mentioned inflammatory markers proved to be predictive for an elevated hazard of future heart failure (11-14). Taking into account that leukocytes are one of the predominant sources of cytokines, brings us back to the current study: if the neutrophil count of each patient can be regarded representative for the status of (chronic) inflammation, then neutrophil counts would provide us with an inexpensive but helpful commonly available marker that supplies important prognostic information for distinct cardiovascular diseases with an extremely good cost-efficacy-ratio.

Finally, these considerations propose a critical re-thinking of the normal range of neutrophil counts and their possible clinical impact. To scrutiny regular neutrophil counts as potentially hazardous automatically brings up the question of treatment and surveillance of patient cohorts to reduce hazard and incidence of cardiovascular diseases.

From a more practical point of view, significant scientific effort will be dedicated to the evaluation of potential pathophysiological mechanisms and the development of potentially diagnostic and therapeutic tools (e.g., GRACE or Framingham Risk score) (15,16). Clearly, most of these will not have direct clinical impact or immediate availability. Therefore, studies like that of Shah and colleagues punctuate the importance of simple and inexpensive but commonly used diagnostic tools that provide important prognostic risk assessment besides their clinical implication.

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