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Preprocedural white blood cell count as a predictor of death and major adverse cardiac events in patients undergoing percutaneous coronary intervention with drug-eluting stents

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ABSTRACT: Background. Patients with elevated white blood cell (WBC) counts who undergo percutaneous coronary intervention (PCI) are at increased risk for short- and long-term mortality as well as major adverse cardiac events (MACE). We assessed the relationship between elevated WBC counts and clinical events in patients who underwent PCI with drug-eluting stents (DES).

Methods. Our retrospective study includes 878 consecutive patients who underwent both elective and emergent PCI with DES at the UCLA Medical Center. The cohort was divided into tertiles based upon the presenting WBC count: 2.8–6.3 x 10⁹ cells/L (tertile 1 [T1]), 6.4–8.7 x 10⁹ cells/L (tertile 2 [T2]), ≥ 8.8 x 10⁹ cells/L (tertile 3 [T3]). Results. Survival at 1 year was significantly different between all three tertiles, and was poorest in patients with WBC counts in T3 (93.9%-T1, 98.4%-T2, 87.3%-T3; p Conclusion. Both elevated and low WBC counts are associated with increased mortality and MACE at 1 year following PCI with DES. WBC count is an independent predictor of survival in patients who undergo PCI with DES implantation.


Key words: White blood cell count, drug-eluting stents

Inflammation plays a key role in arterial atherogenesis and the development of myocardial infarction (MI).¹ The white blood cell (WBC) count, a standardized, available and inexpensive measure of systemic inflammation, is an independent predictor of cardiovascular disease and all-cause mortality.²⁻⁵ Clinical and epidemiologic studies have shown the leukocyte count to be an independent risk factor for coronary artery disease (CAD), future cardiovascular events in
individuals without CAD and a prognostic indicator of future events in patients with CAD.\textsuperscript{2–5} Moreover, patients with elevated WBC counts are at greater risk for adverse events in the acute setting and have higher short- and long-term mortality rates.\textsuperscript{6–15} A study of ST-elevation myocardial infarction (STEMI) patients reported that the WBC count provided independent and additional predictive value to 30-day mortality risk stratification when added to the thrombolysis in myocardial infarction (TIMI) risk index compared to the TIMI risk index alone.\textsuperscript{8} Proposed mechanisms responsible for this association include leukocyte-mediated no-reflow, a leukocyte-mediated hypercoagulable state and indirect cardiotoxicity mediated through proinflammatory cytokines.\textsuperscript{14,16–20}

While the association between elevated WBC count and worse clinical outcomes has been well demonstrated with fibrinolysis,\textsuperscript{14} primary angioplasty\textsuperscript{8,21} and percutaneous coronary intervention (PCI) with bare-metal stents (BMS),\textsuperscript{8,21} there is a paucity of data demonstrating the association between WBC count and mortality in PCI with drug-eluting stents (DES). The goal of the study was to evaluate the relationship between WBC count and survival in the setting of PCI with DES implantation.

**Methods**

From April 2003 to December 2006, 878 consecutive patients underwent PCI with DES with either the Cypher™ sirolimus-eluting stent (Cordis Corp., Miami Lakes, Florida), or the Taxus® paclitaxel-eluting stent (Boston Scientific Corp., Natick, Massachusetts) at the UCLA Medical Center. Baseline WBC counts were obtained upon admission to the hospital prior to PCI. The cohort was divided by WBC count tertile: 2.8–6.3 × 10^9 cells/L (tertile 1 [T1]), 6.4–8.7 × 10^9 cells/L (tertile 2 [T2]), ≥ 8.8 × 10^9 cells/L (tertile 3 [T3]). The institutional review board approved the use of the database review for this study.

PCI was performed using the standard percutaneous approach via the femoral artery in the vast majority of cases using either a 6 or 8 Fr sheath. The choice of a sirolimus-eluting or paclitaxel-eluting stent, use of intravascular ultrasound and antithrombotic agent was at the discretion of the operator. High-pressure inflations were performed using an initial inflation of 16 atm. Postdilatation with additional balloons was performed for optimal stent apposition to achieve acceptable angiographic results. Glycoprotein (GP) IIb/IIIa antagonists and intra-aortic balloon pumps were used if clinically indicated. All patients received aspirin (325 mg/day) indefinitely and a loading dose of 300 mg of clopidogrel. Clopidogrel was continued for at least 6 months. Cardiac enzymes were not measured routinely unless there was a clinical suspicion of ischemia.

The primary endpoint was survival at 1 year. The secondary endpoint was freedom from major adverse cardiac events (MACE). Death was defined as all causes of mortality. A myocardial infarction (MI) was defined as ischemic symptoms associated with cardiac enzyme elevation ≥ 3 times the upper limit of the normal value. Target vessel revascularization (TVR) was defined as a repeat revascularization to treat a vessel. MACE was defined as a composite of death, MI and TVR.

**Statistics.** Continuous variables are presented as mean ± standard deviation (SD) and were compared by the ANOVA or Kruskal-Wallis test. The chi-square test or Fisher’s exact test was used to determine the significance of differences in categorical variables, as appropriate. Left
ventricular (LV) dysfunction was defined as an ejection fraction (EF) 1.5 mg/dL), hematocrit, presentation with MI, unstable angina or stable angina pectoris, peripheral arterial disease (PAD), prior mitral or aortic valve surgery, need for repeat revascularization and use of GP IIb/IIIa inhibitors. A p-value (SPSS, Inc., Chicago, Illinois).

Results
Baseline demographic, angiographic and procedural characteristics. Of the 878 patients in the analyses, 294 were categorized into T1 (33.5%), 302 into T2 (34.4%) and 282 into T3 (32.1%). Baseline demographic and procedural data are presented in Tables 1 and 2. Statistically significant differences were found between the WBC count tertiles involving multiple variables including age, EF, hematocrit, a history of hypertension, hyperlipidemia and prior revascularization procedures. A greater percentage of patients in T3 were smokers (5.9%-T1 vs. 8.1%-T2 vs. 18.2%-T3; p

One-year survival and MACE. Survival at 1 year was significantly different between all three tertiles, and was poorest in patients in T3 (93.9%-T1 vs. 98.4%-T2 vs. 87.3%-T3; p

Multivariable analyses were performed to identify predictors of survival and MACE at 1 year using the Cox proportional hazards model (Table 3). Age, CRI, chronic obstructive pulmonary disease (COPD), low WBC count in T1, elevated WBC count in T3 and presentation with MI were identified as multivariable predictors for 1-year survival. Age, COPD, CRI, PAD, history of previous PCI, stent length, low WBC count in T1, elevated WBC count in T3 and MI were identified as multivariable predictors of 1-year MACE.

Discussion
In patients undergoing PCI with DES implantation, we report an elevated WBC count to be an independent predictor of death and MACE at 1 year. This is consistent with a large body of clinical data demonstrating a higher WBC count to be an independent predictor of increased morbidity and mortality following fibrinolysis, balloon angioplasty and BMS implantation.6–15 Additionally, our data demonstrate a low WBC count to be a strong predictor of death and MACE at 1 year.

The TIMI-10 and -18 substudies evaluated epicardial blood flow, myocardial perfusion grade and clinical outcomes in the setting of STEMI and unstable angina/non-STEMI, respectively.6,14 These trials showed an elevated WBC count to be associated with reduced epicardial blood flow and myocardial perfusion grade,6,14 while Smit et al demonstrated a decrease in WBC count with successful reperfusion (TIMI 3 flow, myocardial blush grade 3) following STEMI.22 These findings, dubbed the “no-reflow” phenomenon, are seen in increasing severity in patients with high WBC counts undergoing PCI, which is an important mechanism that may contribute to the increased mortality seen in this at-risk population.

Numerous animal experiments have shown that the interaction between neutrophils and monocytes with the microvasculature limits reperfusion in acute MI.23–27 Additionally, Neumann et al described an increase in platelet-leukocyte interaction in patients with acute MI.28 The leukocyte beta2-integrin Mac-1 plays a key role. In this interaction, platelets attach to myeloid leukocytes by tethering of the platelet’s P-selectin to P-selectin glycoprotein ligand-1 (PSGL-1)
on leukocytes. This heterotypic interaction is stabilized by binding Mac-1 to an unknown counter-receptor on the platelet. This binding, coupled with numerous other molecular interactions with the vascular endothelial wall, leads to expression of proinflammatory cytokines, oxidative burst and increased surface expression of Mac-1 causing microvascular plugging, and is thought to be a major factor in the “no-reflow” phenomenon seen during the acute setting.29 Therapeutically, the addition of GP IIb/IIIa inhibitors has been shown to decrease Mac-1 surface expression and platelet-leukocyte interactions.30 However, the use of GP IIb/IIIa inhibitors was not a predictor of survival or decreased MACE in our study. The TIMI-10 and -18 substudies demonstrated poor myocardial reperfusion following fibrinolysis and higher mortality rate in patients with higher WBC counts, thus implicating the “no-reflow” phenomenon as a primary culprit. On the contrary, the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial showed no significant difference in myocardial perfusion grade across all WBC count ranges following mechanical revascularization.11 Nonetheless, it did show increased mortality in patients with higher WBC counts, independent of post-procedure myocardial perfusion grade. Moreover, patients with a high baseline WBC count had higher peak serum creatine-kinase levels. This suggests an inflammatory milieu, which may promote greater myocardial necrosis and dysfunction after PCI despite equivalent reperfusion success. In fact, several studies report an association between higher WBC counts and development of congestive heart failure following acute MI.14,30 In our study, patients in the T3 tertile had a higher incidence of LV dysfunction upon presentation and a lower baseline mean EF. Local or systemic inflammation may promote myocyte injury, thus affecting survival, as seen in T3.

Our study population included not only acute coronary syndromes, but also patients undergoing elective PCI with stable CAD. In a pooled analysis of three randomized, controlled trials that included patients undergoing elective PCI, there was an increase in 3-year mortality associated with an elevated WBC count.21 In the absence of MI, PCI alone has been associated with leukocyte activation, increased expression of adhesion molecules and the development of platelet-leukocyte complexes.31–33 Additionally, numerous epidemiologic studies support an elevated WBC count as an independent predictor of mortality in patients with stable CAD.2–4,34 Unexpectedly, our data showed a lower WBC count to also be an independent predictor of mortality following PCI, suggesting the existence of a J-shaped survival curve. This has been described once before by Gurm et al who found that those with the lowest WBC count had an almost two-fold excess mortality rate after adjusting for multiple predictors of outcome after PCI,7 while our study shows a four-and-a-half-fold increase in mortality associated with T1. Patients in T1 were more likely to have hypertension, hyperlipidemia, have undergone revascularization, and were presenting more often for repeat PCI after initially failed procedures. This population is sicker at baseline, which normally may be excluded from clinical trials, emphasizes the real-world nature of database analysis. Moreover, low WBC count may be a marker of poor overall health in certain patients.

**Study limitations.** Our study was a single-center, retrospective, nonrandomized registry with a relatively small number of patients. Follow-up angiography was not available for all patients. Although all efforts were made to obtain complete follow up, including contacting referring physicians and institutions, because of the retrospective nature of the study, all clinical events
may not have been captured. The Social Security Death Index, which lists more than 90% of people who die, was used to determine patient survival if hospital source documentation was not available. However, it does not state the cause of death, therefore, we were unable to determine whether patients died from cardiovascular or noncardiovascular causes.

WBC count is a simple, readily available and inexpensive inflammatory marker that was measured once, preprocedurally, in this study. However, other important inflammatory markers that have been implicated in increased cardiovascular risk, such as C-reactive protein and interleukin 6, were not measured. Our study does not account for the additive and/or independent risk of these markers. Additionally, for future study, it may be of great utility to evaluate the association between outcome and change in WBC count immediately and late after PCI. Of note, our study shows an association between lower and higher WBC counts and increased mortality, but does not demonstrate a direct causal relationship.

**Conclusion**

Our study provides evidence that both elevated and low WBC counts are associated with increased all-cause mortality and MACE at 1 year following PCI with DES. Because of its low cost and availability, the WBC count can be of great utility as a prognostic marker to risk-stratify patients when preprocedural PCI laboratory values are obtained. However, further studies are needed to evaluate WBC count trends post PCI to examine its close relationship with death and MACE in order to incorporate the data into the clinical decision-making process.

**References**

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