White Blood Cell Count and Major Adverse Cardiovascular Events After Percutaneous Coronary Intervention in the Contemporary Era: Insights from the PARIS Study

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Background: Elevated white blood cell count (WBC) is associated with increased major adverse cardiovascular events (MACE) in the setting of acute coronary syndrome (ACS). The aim of this study was to evaluate whether similar associations persist in an all-comers population of patients undergoing percutaneous coronary intervention (PCI) in the contemporary era.

Methods and Results: In the multicenter prospective observational patterns of non-adherence to anti-platelet regimens in stented patients (PARIS) study, 4222 patients who underwent PCI in the USA and Europe between July 1, 2009 and December 2, 2010 were evaluated. The association between baseline WBC and MACE (composite of cardiac death, stent thrombosis, spontaneous myocardial infarction, or target lesion revascularization) at 24 months follow-up were analyzed using multivariable Cox regression. Patients with higher WBC were more often younger, smokers, and with less comorbid risk factors compared to those with lower WBC. After adjustment for baseline and procedural characteristics, WBC remained independently associated with MACE (hazard ratio (HR) per 10^3 cells/uL increase 1.05 [95% confidence intervals (CI) 1.02-1.09], p=0.001), cardiac death (HR 1.10 [1.05-1.17], p<0.001, and clinically indicated target revascularization (HR 1.04 [1.00-1.09], p=0.03), but not stent thrombosis (HR 1.07 [0.99-1.16], p=0.10) or spontaneous myocardial infarction (HR 1.03 [0.97-1.09] p=0.29). The association between WBC and MACE was consistent in ACS and non-ACS presentations (interaction p=0.15).

Conclusions: Increased WBC is an independent predictor of MACE after PCI in a contemporary all-comer cohort. Further studies to delineate the underlying pathophysiologic role of elevated WBC across a spectrum of coronary artery disease presentations are warranted.

Keywords: white blood cell, major adverse cardiovascular events, percutaneous intervention

Introduction

Inflammation is increasingly recognized as a key player in the development of major adverse cardiovascular events (MACE) (1-2). In addition, much has been hypothesized about the role of inflammation on the initiation and propagation of atherothrombosis, and current data highlight the importance of the inflammatory thrombosis interface (3-4). White blood cell count (WBC) is considered a marker of inflammation measured on routine hemograms, and earlier studies demonstrated an association between WBC and MACE in patients with acute coronary syndrome (ACS) (5-6). However, as medical therapy has evolved, a greater proportion of patients are on dual antiplatelet and statin therapies, which have been shown to attenuate systemic inflammatory markers and the inflammatory-thrombosis interface (7-10). Although recent data do demonstrate a persistent association between WBC and MACE in contemporary patients with ACS undergoing percutaneous coronary intervention (PCI), whether or not this association is present in a contemporary all-comers population undergoing PCI remains uncertain (11).

In this analysis of the multicenter, international, prospective, observational patterns of non-adherence to anti-platelet regimens in stented patients (PARIS) study with adjudicated clinical events, we sought to determine the association between WBC and MACE in an all-comers population in the current era of optimal medical therapy and PCI technique.

Methods

Study design and cohort

The prospective observational PARIS registry was designed to evaluate different dual anti-platelet therapy cessation methods and cardiovascular risk after PCI. Details of the registry have

been previously described (12). Of the 5031 patients who underwent successful PCI and were enrolled in the PARIS registry from 15 sites across the United States and Europe between July 1, 2009 and December 2, 2010, 809 (16%) were excluded due to missing WBC. A total of 4222 (84%) patients comprised the currently studied final cohort. Participation in the registry was voluntary and requires written informed consent.

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Variables of interest

Baseline demographic characteristics and medical co-morbidities were self-reported, while body mass index was measured by clinical personnel at each site. The definitions of dyslipidemia, hypertension, and diabetes mellitus required the use of lipid-lowering, anti-hypertensive, and glucose-lowering agents, respectively. Prior coronary artery disease was defined as prior PCI, coronary artery bypass graft surgery, or myocardial infarction (MI). Tobacco use was defined as use within 30 days. Aspirin and thienopyridine use is defined as use on admission.

Baseline WBC was measured at the time of the PCI by site-specific clinical laboratories. Tertiles of WBC were defined as follows: 1st tertile 2.1-7.1 x 10^3 cells/uL (n=1469), 2nd tertile 7.11-9.1 x 10^3 cells/uL (n=1353), and 3rd tertile 9.11-29.0 x 10^3 cells/uL (n=1400).

Outcomes

The primary outcome of interest was MACE defined as a composite of cardiac death, definite or probable stent thrombosis, spontaneous MI, or target lesion revascularization at 24-month follow-up. Secondary outcomes of interest included individual components of MACE. Definite and probable stent thrombosis were defined according to the academic research consortium criteria, and spontaneous MI was defined according the Universal Definition (13-14). Clinically indicated target lesion revascularization was defined as any repeat percutaneous intervention of the index lesion (within 5 mm of the previously placed stent) or surgical bypass of the index vessel. All outcomes were site reported and adjudicated by an independent clinical events committee.

Statistical analyses

Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables are presented as proportions. Co-variates and outcomes were compared across WBC tertiles using a test of trend. MACE over 24 months follow-up were compared across WBC tertiles using the Kaplan-Meier method. The unadjusted and adjusted associations between a per 10^3 cells/uL increase in WBC and outcomes were determined using a multivariable Cox regression model and presented as hazard ratio (HR) [95% confidence interval (CI)]. The following variables were included in the adjusted models: age, sex, body mass index, dyslipidemia, hypertension, diabetes mellitus, prior coronary artery disease, tobacco use, admission aspirin use, admission thienopyridine use, Gp IIb/IIIa use, ACS presentation, presence of thrombotic lesion, stent type, and stent length. The adjusted model also included mode of dual antiplatelet therapy cessation (recommended discontinuation, interruption, disruption), which was introduced as a time

dependent covariate as previously described (12). All statistical analyses were performed using STATA version 11.2 (StataCorp LP, College Station, Texas). All p-values are two-sided, with $p<0.05$ considered statistically significant.

Results

Baseline characteristics

Baseline clinical and procedural characteristics across baseline WBC tertiles are shown in Tables 1 and 2. Overall, a higher baseline WBC count was noted in younger patients with a lower proportion of medical comorbidities such as dyslipidemia, hypertension, diabetes mellitus, and prior coronary artery disease, but a higher proportion of tobacco use. Consistent with the lower rate of coronary artery disease, aspirin or thienopyridine use on admission was less frequent in patients with a higher baseline WBC count. Finally, patients with a higher baseline WBC count were more likely to present with an ACS, have a thrombotic lesion, and to be treated with Gp IIb/IIIa inhibitors and long bare metal stents.

The proportion of patients with any dual antiplatelet therapy cessation was not significantly different across baseline WBC tertiles at 30 days (tertile 1: 3.2% [95% confidence interval 2.4-4.3], tertile 2: 3.3% [2.4-4.4], tertile 3: 3.8% [2.9-5.0]; p=0.39) or 12 months (tertile 1: 23.2% [21.1-25.5], tertile 2: 24.6% [22.3-27.0], tertile 3: 25.0% [22.8-27.4]; p=0.33). However, at 24 months there was a significant increase in any dual antiplatelet therapy cessation with increasing baseline WBC tertiles (tertile 1: 55.1% [52.5-57.8], tertile 2: 54.8% [52.1-57.6], tertile 3: 59.7% [57.1-62.4]; p=0.02).

Outcomes

Outcomes stratified by baseline WBC tertiles are shown in Table 3 and Figure 1. The proportion of patients with the primary composite outcome of MACE was significantly higher in patients with a higher baseline WBC count at 30 days, 12 months, and 24 months follow-up, as were the individual components of cardiac death, definite/probable stent thrombosis, and clinically indicated target vessel revascularization. The proportion of patients with spontaneous MI, however, was not significantly different across baseline WBC tertiles. Results were consistent when outcomes were stratified by baseline WBC quartiles (Supplemental Table, Supplemental Figure).

Unadjusted and adjusted associations between a per 10^3 cells/uL increase in WBC and and outcomes at 24-month follow-up are shown in Table 4. After adjustment for age, sex, body mass index, dyslipidemia, hypertension, diabetes mellitus, prior coronary artery disease, tobacco use, admission aspirin use, admission thienopyridine use, Gp IIb/IIIa use, ACS presentation, presence of thrombotic lesion, stent type, stent length, and mode of dual antiplatelet therapy cessation, there remained a significant association between WBC and MACE, cardiac death, and clinically indicated target lesion revascularization, but not definite or probable stent thrombosis or spontaneous MI. The association between WBC and MACE was consistent in ACS and non-ACS presentations (interaction p=0.15).

Other factors associated with an increase in long-term MACE were presence of diabetes mellitus, prior coronary artery disease, total stent length of $\geq$40 mm, and disruption of dual antiplatelet

therapy, while use of drug-eluting stent and recommended discontinuation of dual antiplatelet therapy was associated with lower long-term MACE.

Discussion

This large, prospective, multicenter, international, registry demonstrated a significant independent association between baseline WBC and independently adjudicated long-term MACE in an all-comers population of patients undergoing PCI. This association is independent of the presence of ACS, thereby raising a potential role for inflammation on clinical outcomes in patients across a spectrum of coronary artery disease presentations even in the current era of medical and device therapy. The significant independent association between baseline WBC and target lesion revascularization highlights the need to explore a potential role of inflammation and/or the inflammatory/thrombosis interface in the setting of PCI. Whether or not these associations would be attenuated with targeted anti-inflammatory therapy, however, remains uncertain.

Earlier reports demonstrated an association between WBC and short-term outcomes in patients presenting with ACS. A substudy of the Thrombolysis in Myocardial Infarction (TIMI) 10A and 10B trials evaluated 975 patients who underwent thrombolytic therapy for ST-segment elevation MI (5). A higher WBC count was noted in patients with a closed infarct artery and worse TIMI myocardial perfusion grades, which translated to a higher rate of 30-day mortality, new congestive heart failure, or shock. Another analysis from the 2208 patients in the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS)-TIMI 18 study also demonstrated a significant association between higher WBC

counts and lower TIMI flow grades, lower perfusion grades, and higher rate of 6-month mortality (6).

Medical therapy, however, has evolved significantly since these previous reports and current data support the anti-inflammatory effects of dual antiplatelet and statin therapy. Platelet P2Y12 receptor inhibitors have been shown to significantly reduce the formation of aggregates between platelets and WBC subtypes, as well as cytokine release, in both experimental human models and patients with ACS (7-8). These platelet-WBC aggregates have been shown to be elevated across the spectrum of cardiovascular disease and associated with adverse cardiovascular outcomes (15-18). Statin therapy has also been shown to significantly lower platelet-WBC aggregates and cellular adhesion molecules associated with the endothelial inflammatory response in the setting of ACS and stable coronary artery disease (9-10). These reductions parallel the significant reductions in MACE observed in patients on high dose statin therapy-undergoing PCI (19-21). In the current analysis, the patients with higher baseline WBC were younger and with less co-morbidities, but with a significantly higher rate of tobacco use. Data on the impact of tobacco use on long-term outcomes has been mixed. Smokers have been shown to have lower mortality after an acute MI, termed the "smoker's paradox", and possibly due to their younger age and fewer co-morbidities (22). However, a recent study of the Global Registry of Acute Coronary Events further stratified by the type of acute MI presentations and demonstrated that over the years from 1999 to 2007, smokers presenting with ST-segment elevation MI did not have a reduction in 30-day mortality, while those with non-ST-segment ACS did demonstrate this reduction. Nonetheless, the association between baseline WBC in the current analysis remains independent of age, co-morbidities, ACS presentation, and tobacco use (23).

Device technology has also advanced over time to potentially decrease the inflammatory milieu induced by mechanical injury during PCI. Inflammatory responses to drug-eluting stent polymers were thought to play a large role in the underlying pathophysiology of in-stent restenosis and stent thrombosis. In earlier pre-clinical models, leukocytes were seen to be recruited soon after vascular injury. Rogers et al demonstrated that an antibody to the WBC adhesion integrin, Mac-1 (CD11/CD18), led to a significant decrease in neointimal growth at the site of balloon denudation and stent-induced injury in animal models (24). Similar results were seen in rodent models that lacked the Mac-1 gene (25). In the bare metal stent era, a significant increase in CD11b and CD18 after PCI correlated with subsequent restenosis, while a single nucleotide polymorphism in the CD18 gene was shown to be associated with a significantly lower rate of restenosis at 1-year follow-up (26-27). Second generation drug-eluting stents were designed to reduce the inflammatory response with thinner strut designs and more biocompatible polymers, resulting in significantly lower rates of stent-related adverse events compared with earlier generation stents (28). In the current analysis, there was a significantly greater rate of thrombotic lesions with higher WBC tertiles. However, WBC remained an independent predictor of MACE and clinically indicated target lesion revascularization even after adjustment for presence of thrombotic lesion, anti-platelet therapy use, stent type, and stent length.

The significance of an elevated WBC in ACS remains despite the improvements in medical therapy. A single-center retrospective observational study of 2833 patients presenting with ACS between December 1998 and October 2004 demonstrated a significant association between WBC subtypes and in-hospital and 6-month mortality (29). An analysis of 363 patients randomized in

the Evaluation of MCC-135 for Left Ventricular Salvage in Acute Myocardial Infarction (EVOLVE) study between May 2003 and November 2004 demonstrated that higher WBC and WBC subtypes independently predicted larger myocardial infarct size, lower left ventricular ejection fraction, and a higher rate of adverse clinical events in patients presenting with ST-segment elevation MI and undergoing PCI (30). Although the clinical outcome was a not traditionally used composite of death, reinfarction, new or worsening congestive heart failure during index rehospitalization, all cardiac rehospitalizations, life-threatening ventricular arrhythmias, and new cardiogenic shock, the outcomes were adjudicated by an independent clinical events committee. In the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, WBC was an independent predictor of 1-year mortality in the 13,678 patients with moderate- or high-risk non-ST-segment elevation MI undergoing PCI between August 2003 and December 2005 (31). More recently, WBC was associated with increased 1-year mortality in 3193 patients who underwent PCI for ST-segment elevation MI between March 2005 and May 2007 in the Harmonizing Outcome with Revascularization and Stent in Acute Myocardial Infarction (HORIZONS-AMI) trial (11).

In the setting of ACS, it remains uncertain if an elevated WBC is a marker of inflammation or a result of demargination in the setting of acute stress. The proposed pathophysiology of elevated WBC in the setting of stable coronary artery disease is even less clear. Very little data exists regarding a relationship of WBC and MACE in an all-comers population. One large multicenter prospective cohort study of 72,242 post-menopausal women enrolled in the Women's Health Initiative Observational Study reported WBC to be an independent predictor of cardiovascular events, defined as fatal coronary heart disease, nonfatal MI, stroke and total mortality (32). The

multicenter, randomized A Coronary disease Trial Investigating Outcome with Nifedipine gastrointestinal therapeutic system (ACTION) trial also demonstrated a significant association between WBC and the composite of long-term death, MI, or stroke in 7311 patients with stable angina (33). However, both of these studies were conducted more than a decade ago, prior to the contemporary era of optimal medical therapy. More recently, a single-center registry of 3005 consecutive patients referred for coronary angiography in Israel demonstrated a higher rate of MACE over a mean follow-up period of 486 days in patients with elevated neutrophil lymphocyte ratio (34).

Despite the improvement in mortality related to coronary artery disease, there remains room for improvement, and an anti-inflammatory agent in addition to the current treatment algorithms may provide additional benefit in this patient population. A recent study by Nidorf et al demonstrated a significant reduction on the primary composite outcome of ACS, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke in patients with stable coronary artery disease on anti-platelet and statin therapy randomized to receive the anti-inflammatory agent colchicine versus no colchicine (35). This is likely due to the effect of colchicine on the endothelial inflammatory response, as well as the inflammatory-thrombosis axis (36-37). Our results combined with previously published data lend support to ongoing studies targeting the inflammatory pathway across the spectrum of cardiovascular disease (NCT01594333, NCT02594111, NCT02551094).

Limitations

There are several limitations to the current study. First, this secondary analysis of the PARIS registry was not pre-specified, and no causal relationships may be inferred from the associations observed in this prospective registry. Second, data on race, the use of statin therapy, and data on case urgency (with the exception of ACS presentation), such as left ventricular ejection fraction and presence of cardiogenic shock, were not collected. Third, 16% of the study population were excluded due to lack of WBC data and may represent a potential source of selection bias. Nonetheless, this remains the most current observation regarding the association between baseline inflammatory status and adjudicated clinical outcomes in a large, multicenter, international, prospective all-comers population.

Conclusions

Baseline WBC independently predicts MACE in a contemporary all-comers population undergoing PCI. In the setting of ACS, elevated WBC may represent a marker of inflammation or result from demargination in the setting of acute stress. Studies to determine the underlying pathophysiological role of elevated WBC in the setting of stable coronary artery disease are warranted. Trials evaluating the role of anti-inflammatory therapy in coronary artery disease are on-going.

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Disclosures

The authors report no relevant disclosures.

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Figure 1. Kaplan-Meier Curves of Major Adverse Cardiovascular Events Through 24 Months Stratified by Tertiles of Baseline White Blood Cell Count

Table 1. Baseline characteristics of patients discharged on dual anti-platelet therapy after percutaneous coronary intervention compared across baseline white blood cell count (WBC) tertiles

	WBC tertile 1 (2.1-7.1 x 10^3 cells/uL) (n=1469)	WBC tertile 2 (7.11-9.1 x 10^3 cells/uL) (n=1353)	WBC tertile 3 (9.11-29.0 x 10^3 cells/uL) (n=1400)	p_{trend}
Age (years)	65.4 ± 10.6	64.1 ± 11.0	61.8 ± 11.9	<0.001
Male sex (%)	73.8	74.4	75.6	0.28
Body mass index (kg/m^2)	29.0 ± 5.4	29.6 ± 5.7	29.2 ± 5.9	0.27
Medical history (%)				
Dyslipidemia	80.0	78.1	68.1	<0.001
Hypertension	84.8	81.7	75.1	<0.001
Diabetes mellitus	35.3	34.7	30.6	0.01
Prior coronary artery disease (MI, PCI or CABG)	54.7	49.8	38.8	<0.001
Stroke	3.2	3.3	3.3	0.90
Peripheral vascular disease	6.5	7.2	7.5	0.28
Tobacco use (%)	11.4	17.7	31.0	<0.001
Medications (%)				
Aspirin	78.4	73.5	58.6	<0.001
Thienopyridine	50.6	41.9	32.0	<0.001
Gp IIb/IIIa inhibitor use	11.1	14.5	19.9	<0.001
Cardiac status at admission (%)				
Acute coronary syndrome	32.6	38.7	56.9	<0.001

CABG = coronary artery bypass graft, Gp = glycoprotein, MI = myocardial infarction, PCI = percutaneous coronary intervention with stent placement

Continuous data presented as mean ± standard deviation

Table 2. Procedural characteristics of patients discharged on dual anti-platelet therapy after percutaneous coronary intervention compared across baseline white blood cell count (WBC) tertiles

	WBC tertile 1 (2.1-7.1 x 10^3 cells/uL) (n=1469)	WBC tertile 2 (7.11-9.1 x 10^3 cells/uL) (n=1353)	WBC tertile 3 (9.11-29.0 x 10^3 cells/uL) (n=1400)	p_{trend}
Coronary artery treated (%)				
Left main	2.9	2.7	2.8	0.90
Left anterior descending	46.6	47.5	44.4	0.26
Circumflex	30.4	30.9	30.6	0.93
Right coronary artery	33.6	32.2	37.6	0.03
Number of arteries treated (%)				
One	87.3	87.6	85.2	0.09
Two	11.9	11.6	14.2	0.07
Three	0.8	0.8	0.6	0.58
Bifurcation lesion (%)	11.0	12.1	11.2	0.82
Chronic total occlusion (%)	2.7	3.7	4.0	0.048
Thrombotic lesion (%)	3.9	6.7	17.1	<0.001
Stent type (%)				
Bare metal	13.6	14.4	22.6	<0.001
1st generation drug-eluting stent	17.0	12.1	10.4	<0.001
2nd generation drug-eluting stent	69.4	73.5	66.9	0.16
Total stent length (%)				
<20 mm	41.5	35.5	32.6	<0.001
20 mm – 39 mm	35.1	36.7	35.5	0.83
≥40 mm	23.4	27.9	31.9	<0.001

Table 3. Outcomes of patients discharged on dual anti-platelet therapy after percutaneous coronary intervention compared across baseline white blood cell count (WBC) tertiles

		WBC tertile 1 (2.1-7.1 x 10^3 cells/uL) (n=1469)	WBC tertile 2 (7.11-9.1 x 10^3 cells/uL) (n=1353)	WBC tertile 3 (9.11-29.0 x 10^3 cells/uL) (n=1400)	p_{trend}
Major adverse cardiovascular event (composite of cardiac death, definite or probable stent thrombosis, spontaneous myocardial infarction, or target lesion revascularization) (%)	30 days	0.4 [0.2-0.9]	0.5 [0.3-1.1]	2.1 [1.5-3.0]	<0.0001
	12 months	6.2 [5.1-7.6]	6.7 [5.5-8.2]	9.7 [8.3-11.4]	0.0002
	24 months	10.0 [8.6-11.7]	11.2 [9.6-13.0]	14.1 [12.4-16.1]	0.0004
Cardiac death (%)	30 days	0.1 [0.0-0.5]	0.2 [0.1-0.7]	0.6 [0.3-1.1]	0.01
	12 months	1.3 [0.8-2.0]	1.8 [1.2-2.7]	2.4 [1.7-3.4]	0.02
	24 months	2.4 [1.7-3.3]	3.6 [2.7-4.7]	3.9 [3.0-5.1]	0.02
Definite/probable stent thrombosis (%)	30 days	0.1 [0.0-0.6]	0.4 [0.2-1.0]	1.1 [0.7-1.8]	0.0007
	12 months	0.7 [0.4-1.3]	0.8 [0.5-1.5]	1.9 [1.3-2.8]	0.003
	24 months	0.9 [0.5-1.6]	1.3 [0.8-2.1]	2.3 [1.6-3.2]	0.003
Spontaneous myocardial infarction (%)	30 days	0.3 [0.1-0.8]	0.3 [0.1-0.8]	0.7 [0.4-1.3]	0.14
	12 months	2.1 [1.5-3.0]	1.7 [1.1-2.5]	2.8 [2.0-3.8]	0.20
	24 months	3.4 [2.5-4.5]	3.3 [2.4-4.4]	4.6 [3.6-5.9]	0.09
Clinically indicated target lesion revascularization (%)	30 days	0	0.4 [0.2-0.9]	1.2 [0.8-2.0]	<0.0001
	12 months	3.9 [3.0-5.0]	4.6 [3.6-5.9]	7.0 [5.8-8.5]	0.0001
	24 months	6.2 [5.0-7.6]	7.0 [5.7-8.5]	9.4 [7.9-11.1]	0.0009

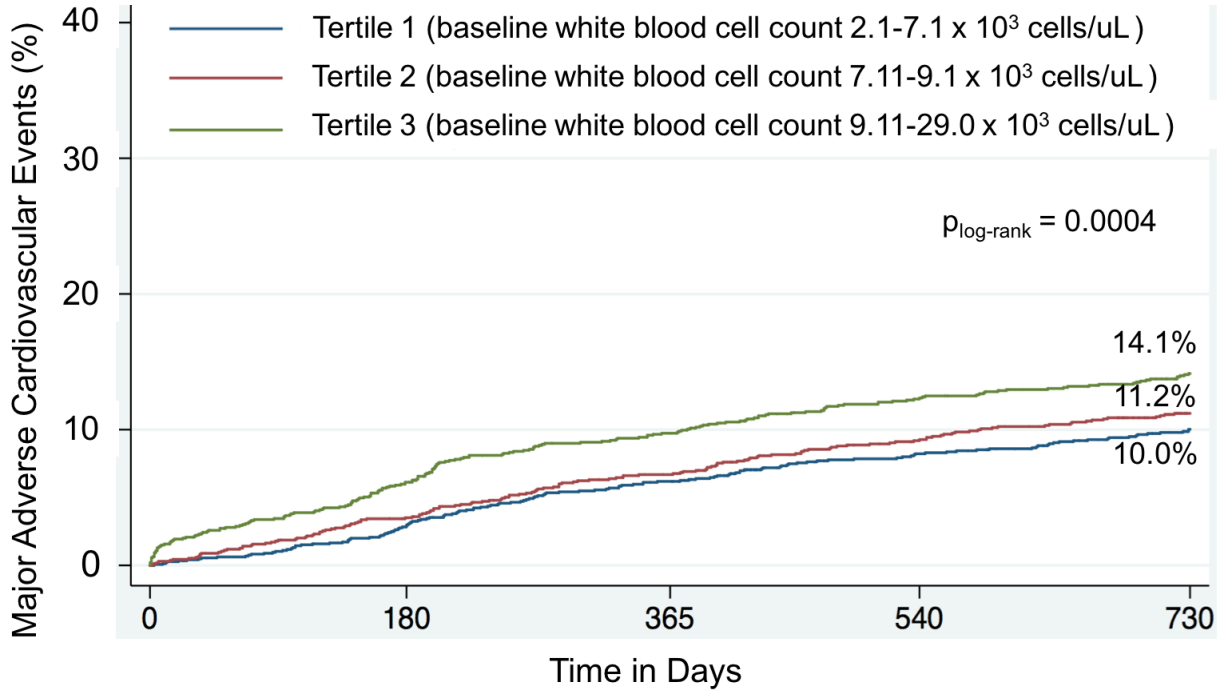
Data are shown as crude estimates [95% confidence intervals]

Table 4. Unadjusted and adjusted associations between a per 10^3 cells/uL increase in baseline white blood cell count and clinical outcomes at 24-month follow-up in patients discharged on dual anti-platelet therapy after percutaneous coronary intervention

	Unadjusted Model		Adjusted Model	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
Major adverse cardiovascular event	1.06 (1.03-1.09)	<0.001	1.05 (1.02-1.09)	0.001
Cardiac death	1.09 (1.03-1.15)	0.001	1.10 (1.05-1.17)	<0.001
Definite/probable stent thrombosis	1.14 (1.06-1.22)	<0.001	1.06 (0.98-1.15)	0.12
Spontaneous myocardial infarction	1.06 (1.00-1.11)	0.04	1.03 (0.97-1.09)	0.35
Clinically indicated target lesion revascularization	1.06 (1.02-1.10)	0.002	1.04 (1.00-1.09)	0.03

Model adjusts for the following variables: age, sex, body mass index, dyslipidemia, hypertension, diabetes mellitus, prior coronary artery disease, tobacco use, admission aspirin use, admission thienopyridine use, glycoprotein IIb/IIIa use, acute coronary syndrome presentation, presence of thrombotic lesion, stent type, stent length, and mode of dual antiplatelet therapy cessation.

Figure 1.


Tertile 1 (baseline white blood cell count 2.1-7.1 x 10³ cells/uL)
Tertile 2 (baseline white blood cell count 7.11-9.1 x 10³ cells/uL)
Tertile 3 (baseline white blood cell count 9.11-29.0 x 10³ cells/uL)
$p_{log\text{-}rank}$ = 0.0004
14.1%
11.2%
10.0%
Major Adverse Cardiovascular Events (%)
0
10
20
30
40
0
180
365
540
730
Time in Days