



HAL
open science

Total leukocyte count but not C-reactive protein predicts one-year mortality in patients with acute coronary syndromes treated with percutaneous coronary intervention

Gjin Ndrepepa, Siegmund Braun, Raisuke Iijima, Dritan Keta, Robert A. Byrne, Stefanie Schulz, Julinda Mehilli, Albert Schömig, Adnan Kastrati

► **To cite this version:**

Gjin Ndrepepa, Siegmund Braun, Raisuke Iijima, Dritan Keta, Robert A. Byrne, et al.. Total leukocyte count but not C-reactive protein predicts one-year mortality in patients with acute coronary syndromes treated with percutaneous coronary intervention. *Clinical Science*, 2009, 116 (8), pp.651-658. <10.1042/CS20080298>. <hal-00479443>

HAL Id: hal-00479443

<https://hal.science/hal-00479443v1>

Submitted on 30 Apr 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Total Leukocyte Count but not C-reactive Protein Predicts One-Year Mortality in Patients with Acute Coronary Syndromes Treated with Percutaneous Coronary Intervention

Running Title: Leukocyte Count and Mortality

**Gjin Ndrepepa^{*}, Siegmund Braun^{*}, Raisuke Iijima^{*}, Dritan Keta^{*}, Robert A. Byrne^{*},
Stefanie Schulz^{*}, Julinda Mehilli^{*}, Albert Schömig^{*†}, Adnan Kastrati^{*}**

From: ^{*}Deutsches Herzzentrum, Technische Universität, Munich, Germany and [†]1.

Medizinische Klinik rechts der Isar, Technische Universität, Munich, Germany

Address for correspondence:

Gjin Ndrepepa, MD
Deutsches Herzzentrum
Lazarettstrasse 36
80636 München
GERMANY
Phone: +49-89-12184016
Fax: +49-89-12184053
e-mail: ndrepepa@dhm.mhn.de

Accepted Manuscript

Abstract

Although an association between elevated white blood cells (WBC) count and mortality in patients with acute coronary syndromes (ACS) has been established, the independence of this association from coronary risk factors and C-reactive protein has been inadequately studied. This prospective registry included 4329 patients with ACS treated with percutaneous coronary intervention (PCI): 1059 patients with ST-segment elevation acute myocardial infarction, 1753 patients with non-ST-segment elevation acute myocardial infarction and 1517 patients with unstable angina. Blood samples were obtained before angiography for WBC count and C-reactive protein measurements. The primary outcome was 1-year mortality. At one year, 345 patients (8%) died: 45 patients in the 1st tertile, 93 patients in the 2nd tertile and 207 patients in the 3rd tertile of WBC count (Kaplan-Meier estimates of mortality, 3.2%, 6.4% and 14.1% with an odds ratio [OR]=2.42, 95% confidence interval [1.78-3.12], $P<0.001$ for tertile 3 vs tertile 2 and an OR of 1.99, [1.77-2.25], $P<0.001$ for tertile 2 vs tertile 1). The Cox proportional hazards model adjusting for coronary risk factors, ASC presentation, extent of coronary artery disease, C-reactive protein and other covariates identified WBC count with a hazard ratio [HR]=1.05 (95% confidence interval [CI] 1.02-1.07; $P<0.001$ for 1000 cells/mm³ increase) but not C-reactive protein (HR=1.13, 95% CI 0.95-1.34; $P=0.15$ for 1 tertile increase) as an independent correlate of 1-year mortality. We conclude that elevated WBC count but not C-reactive protein predicts one-year mortality independent of cardiovascular risk factors across the entire spectrum of patients with ACS treated with PCI.

Key words: Acute coronary syndrome, mortality, myocardial infarction, statins, unstable angina, white blood cells

Accepted Manuscript

Considerable evidence exists that elevated white blood cell (WBC) count - a nonspecific marker of inflammation - is a risk factor for future cardiovascular events in individuals apparently free of cardiovascular disease [1,2] and a prognostic marker for patients with already cardiovascular disease.[3,4] In patients with acute coronary syndromes (ACS), an elevated baseline WBC count predicts mortality in those with ST-segment elevation acute myocardial infarction[5-7], non-ST-segment elevation acute myocardial infarction[8,9], and unstable angina.[8,10] However, several aspects of the association between elevated WBC and cardiovascular disease require further investigation. First, although an association between elevated WBC count and mortality was almost uniformly confirmed by various studies, the independence of association, i.e., whether elevated WBC count retains its prognostic power after full adjustment for other cardiovascular risk factors has been inadequately studied[11] or is controversial.[12-13] Second, a comparative assessment of prognostic value of elevated WBC and C-reactive protein has not been performed. Third, it is not known whether WBC retains its prognostic potential (capacity) in patients under treatment with statin therapy.

The aim of the present study was three-fold: first, to test the association between WBC count and one-year mortality across the entire spectrum of patients with ACS after adjustment for traditional cardiovascular risk factors; to investigate the relationship between WBC count and C-reactive protein and compare their prognostic discriminatory power in patients with ACS; and third to assess the influence of statin therapy on the relationship between elevated WBC and one-year mortality in patients with ACS.

Methods

Patients

This prospective registry included 4329 patients with ACS who underwent diagnostic coronary angiography and percutaneous coronary intervention (PCI) in the Deutsches Herzzentrum München between September 1997 and December 2006: 1059 patients with ST-segment elevation acute myocardial infarction, 1753 patients with non-ST-segment elevation acute myocardial infarction and 1517 patients with unstable angina. Patients with acute inflammatory states, known malignancies and advanced kidney disease were not included in the present study. The diagnosis of ST-segment elevation acute myocardial infarction was based on the presence of chest pain lasting ≥ 20 min associated with typical changes on surface ECG (ST-segment elevation of ≥ 0.1 mV in ≥ 2 limb leads or ≥ 0.2 mV in ≥ 2 contiguous precordial leads, pathological Q waves, or complete left bundle branch block of new onset). Unstable angina was diagnosed when characteristic chest pain (with an accelerating pattern or prolonged [>20 minutes] or recurrent episodes at rest or with minimal effort) was associated with either ST segment depression of ≥ 0.1 mV and/or T-wave inversion in two continuous leads in the electrocardiogram and with documentation of significant coronary artery disease in the coronary angiography. Diagnosis of non-ST-segment elevation acute myocardial infarction required clinical and electrocardiographic criteria similar to those of unstable angina plus elevated troponin T (troponin T level >0.03 $\mu\text{g/L}$) or creatine kinase or creatine kinase-myocardial band (CK-MB). Arterial hypertension was defined in the presence of active treatment with antihypertensive medications or documentation of a systolic blood pressure of ≥ 140 mmHg and/or diastolic blood pressure of ≥ 90 mmHg in at least two separate occasions. Hypercholesterolemia was defined as a documented total cholesterol concentration of ≥ 240 mg/dl. Current smokers were defined as those currently smoking tobacco. Diabetes mellitus was defined if patients were under active treatment with insulin or oral hypoglycemic agents. For those on diet alone, documentation of an abnormal fasting blood glucose or glucose tolerance test was required. The study has been carried out in accordance with the Declaration of Helsinki and has been approved by the institutional ethics committee.

WBC Count AND C-Reactive Protein Measurement

Blood samples were obtained at the time of admission (before angiographic examination) for WBC count, high-sensitivity C-reactive protein, and other biochemical parameters. For patients with ST-segment elevation and non-ST-segment elevation acute myocardial infarction, time interval (median [25th-75th percentiles]) from the pain onset to admission was 7.8 [3.0-19.0] hours. Total WBC count was counted in EDTA-anticoagulated whole blood specimens using the Sysmex XE 2100 automated haematology analyser. Measurement of WBC count was performed by flow cytometry using a semiconductor laser to detect forward- and side-scattered light information after red cell lysis. The plasma concentrations of high-sensitivity C-reactive protein were measured with a fully automated latex-enhanced immunoturbidometric assay on a Cobas Integra (Roche Diagnostics, Mannheim, Germany). The C-reactive protein assay has an analytical sensitivity of 0.085 mg/L and a measuring range up to 160 mg/L. The upper limit of the reference range of CRP in healthy adults is 5 mg/L. Other biochemical parameters were measured using routine tests. Laboratory personnel were unaware of the results of clinical diagnosis or other study details.

Angiographic Evaluation and Stent Implantation

Coronary angiography was performed according to standard criteria. Angiographic data were analyzed using the same Quantitative Angiographic Core Laboratory. Coronary artery disease was confirmed by the presence of coronary stenoses $\geq 50\%$ lumen obstruction in at least one of the three main coronary arteries. A culprit lesion was described in the presence of an acute occlusion, intraluminal filling defects (or thrombus), ulcerated plaques with contrast-filled pocket protruding into plaque with or without delayed contrast wash-out, extraluminal contrast, dissection or intraluminal flaps.[14] Offline analysis of digital angiograms was performed in the core laboratory using an automated edge detection system (CMS; Medis Medical Imaging Systems, Neuen, the Netherlands). The initial and post-procedural blood flow in the artery owning the culprit lesion was quantified using the Thrombolysis in Myocardial Infarction (TIMI) grading system.[15] Global left ventricular ejection fraction was determined in left ventricular angiograms by using the area-length method.

Stent implantation and periprocedural care were performed according to standard criteria. Bare metal stents were mostly used. Postinterventional antiplatelet therapy consisted of ticlopidine (500 mg/day) or clopidogrel (300 mg or 600 mg as a loading dose followed by 75 mg/day for at least 4 weeks to 6 months) and aspirin (200 mg/day administered orally and continued indefinitely).

Endpoint and Follow-up

The primary outcome of this analysis was 1-year mortality. Occurrence of myocardial infarction, major bleeding and stroke was also assessed. The follow-up protocol after discharge consisted of a phone interview at one month after the procedure, a visit at six months and a phone interview at 12 months. Information about death was obtained from hospital records, death certificates, or phone contact with relatives of the patient or attending physician. The diagnosis of myocardial infarction, major bleeding and stroke was made according to the TIMI criteria.[15]

Patients were advised to present to the outpatient clinic or their referring physicians if they developed chest pain or other cardiac symptoms. In case of symptoms, at least one clinical, laboratory and electrocardiographic check-up was performed.

Statistical Analysis

Data are presented as median (with 25th and 75th percentiles) or counts and proportions (percentages). The distribution of the data was analyzed with one-sample Kolmogorov-Smirnov test. Categorical data were compared with chi-square test. Continuous data were compared with Kruskal-Wallis rank sum test. One-year mortality was estimated by applying the Kaplan-Meier method and log rank test which allowed the calculation of odds ratios (95% confidence intervals and respective P values) associated with being in various tertiles of the

WBC count. Heterogeneity in risk prediction by WBC count in various subgroups was assessed by using the Breslow-Day test. Receiver operating characteristic (ROC) curves were constructed to assess the accuracy of WBC count and C-reactive protein to predict one-year mortality. Differences between the areas under curve were assessed for statistical significance according to the method by DeLong et al.[16] The Cox proportional hazards model was used to assess the association WBC count and one-year mortality while adjusting for potential confounders: age, sex, diabetes, arterial hypertension smoking, hypercholesterolemia, prior myocardial infarction, prior coronary artery bypass surgery, ACS type, cardiogenic shock, serum creatinine, C-reactive protein, left ventricular ejection fraction, multivessel disease, baseline TIMI flow grade, post-PCI TIMI flow grade and WBC count. Analyses were performed using S-plus statistical package (S-PLUS, Insightful Corp, Seattle, Washington). A *P* value < 0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics

Patients were divided into 3 groups according to tertiles of WBC count: first tertile (WBC count <6800 cells/mm³, n=1392 patients), second tertile (WBC count 6800-9400 cells/mm³, n=1466 patients) and third tertile (WBC count >9400 cells/mm³, n=1471 patients). Baseline demographic and clinical characteristics are shown in Table 1. Patients in the 3rd tertile of WBC count were younger, had a higher proportion of women and of current smokers and had less often arterial hypertension, hypercholesterolemia, prior myocardial infarction and prior coronary artery bypass surgery than patients in lower tertiles. They presented more often with acute myocardial infarction and cardiogenic shock and had higher levels of troponin and creatine kinase. Angiographic characteristics are shown in Table 2. Patients in the 3rd tertile of WBC count had lower left ventricular ejection fraction and a lower proportion of patients with multivessel disease than patients in other 2 tertiles (see atable 1 and table 2 for the remaining characteristics).

WBC Count and Clinical Outcome

Thirty-day clinical outcome is shown in Table 3. With the increase in the tertiles of WBC count from 1 to 3 there was a significant increase in the death rate, major bleeding and stroke.

At one year, 345 patients (8%) died: 45 patients in the 1st tertile, 93 patients in the 2nd tertile and 207 patients in the 3rd tertile of WBC count (Kaplan-Meier estimates of mortality, 3.2%, 6.4% and 14.1%, respectively; odds ratio [OR] =2.42, 95% confidence interval [CI] 1.78-3.12, *P*<0.001 for tertile 3 vs tertile 2 and OR=1.99, 95% CI 1.77-2.25, *P*<0.001 for tertile 2 vs tertile 1; Figure 1). WBC count was 10800 [7900-14900] cells/mm³ in patients who died versus 7800 [6200-10100] cells/mm³ in those who survived one-year follow-up (*P*<0.001). There were no significant differences in the one-year occurrence of myocardial infarction according to WBC count tertiles: Kaplan-Meier estimates of 2.5% in the 1st tertile (n=34), 3.9% in the 2nd tertile (n=57) and 3.3% in the 3rd tertile of WBC count (n=48).

Subgroup analyses of relationship between WBC count and one-year mortality are shown in Figure 2. As seen, WBC count predicted mortality across all the analyzed subgroups with the exception of patients with cardiogenic shock. Of note, WBC count predicted one-year mortality in patients with ST-segment elevation acute myocardial infarction OR=4.22, 95% CI 1.52-11.73; *P*<0.001), non-ST-segment elevation acute myocardial infarction (OR=3.65, 95% CI 2.31-5.79); *P*<0.001) and unstable angina (OR=2.71 [1.21-6.08]; *P*=0.01). There was no interaction between WBC count and any analyzed subgroups regarding one-year mortality.

ROC curves were constructed to assess the accuracy of WBC and C-reactive protein regarding one-year mortality. Area under ROC curve [95% confidence interval] was 0.69 [95% CI 0.65-0.72], *P*<0.001 for WBC count and 0.65 [95% CI 0.62- 0.69], *P*<0.001 for C-reactive protein (*P*=0.09; Figure 3).

Results of Multivariable Analysis

The Cox proportional hazards model was applied to the independence of association between WBC count and one-year mortality while adjusting for potential confounders (see methods for variables entered into the model). The model showed that WBC count was an independent correlate of one-year mortality with an increase of 5% of the adjusted risk for every 1000 cell/mm³ increase in WBC count. C-reactive protein was not independently associated with one-year mortality (hazard ratio [HR]=1.09, 95% confidence interval [CI] 0.92-1.36; P=0.20). Significant correlates of one-year mortality are shown in Table 4. We repeated the Cox proportional hazards model with WBC count and C-reactive protein entered as tertiles. Again WBC count was independently associated with one-year mortality with a HR of 1.33, 95% CI 1.09-1.63; P=0.006 for 1 tertile increase in the WBC count; conversely, C-reactive protein was not independently associated with the one-year mortality (HR=1.13, 95% CI 0.95-1.34; P=0.15 for 1 tertile increase in the CRP level).

WBC Count and One-Year Mortality in Patients With and Without Statins

Statin therapy was prescribed in 3898 patients (90%): 1301 patients in the 1st tertile, 1338 in the 2nd tertile and 1259 patients in the 3rd tertile of WBC count. At one year there were 29 deaths among patients of the 1st tertile (2.2%), 56 deaths among patients of 2nd tertile (4.2%) and 71 deaths (5.6%) among patients of the 3rd tertile of WBC count (OR=1.91, 95% CI 1.21-3.02; P=0.004 for tertile 2 vs tertile 1 and OR=2.62, 95% CI 1.69-4.07; P<0.001 for tertile 3 vs tertile 1). In 431 patients statins were not prescribed: 91 patients in the first WBC count tertile, 128 patients in the second WBC count tertile and 212 patients in the third WBC count tertile. Since in patients dying early after acute event (mostly due to cardiogenic shock), statins were not prescribed we analyzed association between WBC count and one-year mortality in patients who survived the first 30 day after acute event. In patients who survived the first 30 days after acute event one year mortality was 9.6% (8 of 83 patients) among patients in the first WBC count tertile, 9.9% (10 of 101 patients) among patients in the second WBC count tertile and 20.8% (20 of 96 patients) among patients in the third WBC tertile (OR=2.46, 95% CI 1.02-5.94; P=0.04 for third vs. first WBC count tertile).

Discussion

In this study, we investigated the association between WBC count and one year-mortality using data of a large prospective registry of patients with ACS treated with PCI. The main findings of this study are as follows: 1) In patients with ACS treated with PCI (mostly coronary stenting) elevated WBC is associated with increased risk of one-year mortality. This association is independent of cardiovascular risk factors including other markers of inflammatory status (C-reactive protein). We found that for every 1000 cells/mm³ increase in the WBC count adjusted one-year mortality was increased by 5%. Moreover, elevated WBC count was associated with higher rates of 30-day mortality, major bleeding and stroke. 2) Comparative analysis of WBC and C-reactive protein in the multivariable model (the Cox proportional hazards model) showed that WBC count but not C-reactive protein was an independent correlate of one-year mortality. 3) WBC count was an independent predictor of one-year mortality in patients with ACS receiving statin therapy.

Multiple studies have demonstrated an association between elevated WBC count and extent of coronary artery disease[8,17] or increased short-term or long-term risk of death in patients with various presentations of coronary artery disease.[5-10] A host of mechanisms through which elevated WBC count may impact coronary artery disease progression and mortality has been proposed and recently reviewed by Madjid et al.[11] In the Global Registry of Acute Coronary Events (GRACE), association between elevated WBC and hospital death or development of congestive heart failure was consistent across the entire spectrum of ACS.[18] Although an association between elevated WBC and mortality is undisputed, the independence of association from other potential confounders remains

controversial.[12,13] In a study by Lloyd-Jones et al.[12] association between elevated WBC and one-year mortality in patients with unstable angina was markedly diminished after adjustment for other covariates. In the same line, a recent study of patients with existing coronary artery disease showed that adjustment for coronary risk factors totally eliminated association between WBC count and cardiac mortality.[13] Other studies assumed that the impact of WBC on mortality may be mediated by smoking[19] or diabetes.[20] Of note, in the majority of reported studies no adjustment for C-reactive protein has been performed. Thus as recently emphasized by Madjid et al.[11] there is a need to determine the degree to which WBC count is independent to other risk factors.

In the present study of patients with ACS, we performed an adjustment for traditional coronary risk factors, clinical presentation of ACS, extent of coronary artery disease, baseline and post-procedural TIMI flow grade and C-reactive protein. We found that in patients with ACS treated with PCI elevated WBC count predicted one-year mortality independent of all above-mentioned coronary risk factors and clinical covariates. Furthermore, the association between WBC count and one-year mortality was consistent in patients with unstable angina, non-ST-segment elevation or ST-segment elevation acute myocardial infarction. In this aspect our data dovetail with those of GRACE study[18] in reporting a consistent ability of WBC count to predict mortality across the entire spectrum of ACS. Of interest is the finding that elevated WBC was associated with a higher incidence of major bleeding and stroke within the first 30 days following PCI which may imply that elevated WBC count may be involved in the genesis of these serious adverse events in patients with ACS undergoing coronary intervention. In the present study, an association between elevated WBC count and occurrence of myocardial infarction could not be demonstrated. With regard to the lack of association between WBC count and future occurrence of myocardial infarction, our study is in agreement with a recent study Mueller et al.[9] in patients with non-ST-segment elevation ACS. In fact, inability of WBC to predict cardiac mortality has been reported [13] and the current finding may be, at least, one of the putative explanations. Of particular interest was the finding that after adjustment in the multivariable model, WBC count but not C-reactive protein was an independent correlate of one-year mortality. Recent studies have also shown that WBC count outperformed the C-reactive protein in predicting severity of coronary artery disease[20] and a list of other inflammatory markers such as serum amyloid A, fibrinogen and interleukin-6 in predicting 5-year mortality in patients with ACS.[21] These data clearly demonstrate that WBC count, a universally available test, is one of the best markers to assess the inflammatory status and its impact on mortality across the entire spectrum of patients with coronary artery disease.

The impact of statin therapy on the association between WBC count and mortality is largely unknown. In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, WBC count predicted cardiac mortality in patients randomized to placebo, but not in those who received pravastatin.[22] In the present study 90% of patients with ACS received statins within the first year following PCI. A separate analysis in these patients demonstrated that WBC predicted one-year mortality in patients receiving statins with odds ratios quite similar to those in the whole group of patients. Reasons for these discrepancies regarding impact of statin therapy on the power of WBC count to predict mortality remain unknown.

The present study does not provide information on WBC count differential. It has recently been reported that neutrophil-to-lymphocyte ratio may be superior to total WBC count in predicting subsequent mortality.[23,24] However, other studies have shown that total WBC was a better correlate of long-term outcome (mortality) than individual subtypes of WBC count.[25]

In conclusion, the present study demonstrated that elevated WBC count but not C-reactive protein predicts one-year mortality independent of risk factors for coronary artery

disease across the entire spectrum of ACS. Statin therapy did not abolish the association between WBC count and one-year mortality in these patients.

Accepted Manuscript

References

1. Friedman GD, Klatsky AL, Siegelau AB. (1974) The leukocyte count as a predictor of myocardial infarction. *N Engl J Med.* **290**, 1275-1278.
2. Mänttari M, Manninen V, Koskinen P, Huttunen JK, Oksanen E, Tenkanen L, Heinonen OP, Frick MH. (1992) Leukocytes as a coronary risk factor in a dyslipidemic male population. *Am Heart J.* **123(4 Pt 1)**, 873-877.
3. Schlant RC, Forman S, Stamler J, Canner PL. (1982) The natural history of coronary heart disease: prognostic factors after recovery from myocardial infarction in 2789 men. The 5-year findings of the coronary drug project. *Circulation.* **66**, 401-414.
4. Lowe GD, Machado SG, Krol WF, Barton BA, Forbes CD. (1985) White blood cell count and haematocrit as predictors of coronary recurrence after myocardial infarction. *Thromb Haemost.* **54**, 700-703.
5. Hajj-Ali R, Zareba W, Ezzeddine R, Moss AJ. (2001) Relation of the leukocyte count to recurrent cardiac events in stable patients after acute myocardial infarction. *Am J Cardiol.* **88**, 1221-1224.
6. Furman MI, Becker RC, Yarzebski J, Savegeau J, Gore JM, Goldberg RJ. (1996) Effect of elevated leukocyte count on in-hospital mortality following acute myocardial infarction. *Am J Cardiol.* **78**, 945-948.
7. Barron HV, Harr SD, Radford MJ, Wang Y, Krumholz HM. (2001) The association between white blood cell count and acute myocardial infarction mortality in patients ≥ 65 years of age: findings from the cooperative cardiovascular project. *J Am Coll Cardiol.* **38**, 1654-1661.
8. Sabatine MS, Morrow DA, Cannon CP, Murphy SA, Demopoulos LA, DiBattiste PM, McCabe CH, Braunwald E, Gibson CM. (2002) Relationship between baseline white blood cell count and degree of coronary artery disease and mortality in patients with acute coronary syndromes: a TACTICS-TIMI 18 (Treat Angina with Aggrastat and determine Cost of Therapy with an Invasive or Conservative Strategy- Thrombolysis in Myocardial Infarction 18 trial) substudy. *J Am Coll Cardiol.* **40**, 1761-1768.
9. Mueller C, Neumann FJ, Perruchoud AP, Buettner HJ. (2003) White blood cell count and long term mortality after non-ST elevation acute coronary syndrome treated with very early revascularisation. *Heart.* **89**, 389-392.
10. Cannon CP, McCabe CH, Wilcox RG, Bentley JH, Braunwald E. (2001) Association of white blood cell count with increased mortality in acute myocardial infarction and unstable angina pectoris. OPUS-TIMI 16 Investigators. *Am J Cardiol.* **87**, 636-639.
11. Madjid M, Awan I, Willerson JT, Casscells SW. (2004) Leukocyte count and coronary heart disease: implications for risk assessment. *J Am Coll Cardiol.* **44**, 1945-1956.
12. Lloyd-Jones DM, Camargo CA Jr, Giugliano RP, O'Donnell CJ. (2000) Effect of leukocytosis at initial examination on prognosis in patients with primary unstable angina. *Am Heart J.* **139**, 867-873.
13. Haim M, Boyko V, Goldbourt U, Battler A, Behar S. (2004) Predictive value of elevated white blood cell count in patients with pre-existing coronary heart disease: the Bezafibrate Infarction Prevention Study. *Arch Intern Med.* **164**, 433-439.
14. Kerensky RA, Wade M, Deedwania P, Boden WE, Pepine CJ; Veterans Affairs Non-Q-Wave Infarction Strategies in-Hospital (VANQWISH) Trial Investigators. (2002) Revisiting the culprit lesion in non-Q-wave myocardial infarction. Results from the VANQWISH trial angiographic core laboratory. *J Am Coll Cardiol.* **39**, 1456-1463.
15. TIMI Study Group. Definitions used in TIMI trials. Available at: <http://www.timi.org>, accessed May 4th, 2007.
16. DeLong ER, DeLong DM, Clarke-Pearson DL. (1988) Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* **44**, 837-845.

17. Amaro A, Gonzalez-Juanatey JR, Iglesias C, Martinez-Sande L, Trillo R, García-Acuña J, Gil de la Peña M. (1993) Leukocyte count as a predictor of the severity ischaemic heart disease as evaluated by coronary angiography. *Rev Port Cardiol.* **12**, 913-917.
18. Furman MI, Gore JM, Anderson FA, Budaj A, Goodman SG, Avezum A, López-Sendón J, Klein W, Mukherjee D, Eagle KA, Dabbous OH, Goldberg RJ; GRACE Investigators. (2004) Elevated leukocyte count and adverse hospital events in patients with acute coronary syndromes: findings from the Global Registry of Acute Coronary Events (GRACE). *Am Heart J.* **147**, 42-48.
19. Kostis JB, Turkevich D, Sharp J. (1984) Association between leukocyte count and the presence and extent of coronary atherosclerosis as determined by coronary arteriography. *Am J Cardiol.* **53**, 997-999.
20. Rasouli M, Kiasari AM, Bagheri B. (2007) Total and differential leukocytes counts, but not hsCRP, ESR, and five fractioned serum proteins have significant potency to predict stable coronary artery disease. *Clin Chim Acta.* **377**, 127-132.
21. Zairis MN, Adamopoulou EN, Manousakis SJ, Lyras AG, Bibis GP, Ampartzidou OS, Apostolatos CS, Anastassiadis FA, Hatzisavvas JJ, Argyrakis SK, Foussas SG; Biomarkers of Inflammation and Outcome in Acute Coronary Syndromes (BIAS) Investigators. (2007) The impact of hs C-reactive protein and other inflammatory biomarkers on long-term cardiovascular mortality in patients with acute coronary syndromes. *Atherosclerosis.* **194**, 397-402.
22. Stewart RA, White HD, Kirby AC, Heritier SR, Simes RJ, Nestel PJ, West MJ, Colquhoun DM, Tonkin AM; Long-Term Intervention With Pravastatin in Ischemic Disease (LIPID) Study Investigators. (2005) White blood cell count predicts reduction in coronary heart disease mortality with pravastatin. *Circulation.* **111**, 1756-1762.
23. Horne BD, Anderson JL, John JM, Weaver A, Bair TL, Jensen KR, Renlund DG, Muhlestein JB; Intermountain Heart Collaborative Study Group. (2005) Which white blood cell subtypes predict increased cardiovascular risk? *J Am Coll Cardiol.* **45**, 1638-1643.
24. Núñez J, Núñez E, Bodí V, Sanchis J, Miñana G, Mainar L, Santas E, Merlos P, Rumiz E, Darmofal H, Heatta AM, Llàcer A. (2008) Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. *Am J Cardiol.* **101**, 747-752.
25. Gurm HS, Bhatt DL, Lincoff AM, Tchong JE, Kereiakes DJ, Kleiman NS, Jia G, Topol EJ. (2003) Impact of preprocedural white blood cell count on long term mortality after percutaneous coronary intervention: insights from the EPIC, EPILOG, and EPISTENT trials. *Heart.* **89**, 1200-1204.

THIS IS NOT THE VERSION OF RECORD - see doi:10.1042/CS20080298

Table 1. Baseline Characteristics According to Tertiles of White Blood Cell Count

Characteristic	Tertile 1 (n = 1392)	Tertile 2 (n = 1466)	Tertile 3 (n = 1471)	P value
Age (years)	68.2 [61.1; 75.6]	67.1 [58.6; 75.6]	65.0 [55.5; 74.1]	<0.001
Women	363 (26.1)	343 (23.4)	412 (28.0)	0.016
Diabetes mellitus	345 (24.8)	403 (27.5)	418 (28.4)	0.076
Body mass index (kg/m ²)	26.3 [24.2; 29.0]	26.6 [24.5; 29.0]	26.4 [24.4; 29.3]	0.005
Arterial hypertension	1182 (84.9)	1185 (80.8)	1060 (72.1)	<0.001
Total cholesterol ≥ 240 mg/dl	1047 (75.2)	1030 (70.3)	897 (61.0)	<0.001
Current smoker	157 (11.3)	315 (21.5)	540 (36.7)	<0.001
Previous myocardial infarction	424 (30.5)	418 (28.5)	293 (19.9)	<0.001
Previous coronary artery bypass surgery	240 (17.2)	211 (14.4)	128 (8.7)	<0.001
Acute coronary syndrome presentation				<0.001
Unstable angina	758 (54.4)	578 (39.4)	181 (12.3)	
Non-ST-segment elevation acute myocardial infarction	537 (38.6)	622 (42.4)	594 (40.4)	
ST-segment elevation acute myocardial infarction	97 (7.0)	266 (18.2)	696 (47.3)	
Cardiogenic shock	7 (0.5)	28 (1.9)	188 (12.8)	<0.001
Systolic blood pressure (mmHg)	150.0 [130.0; 170.0]	145.0 [122.0; 168.0]	130.0 [110.0; 150.0]	<0.001
Heart rate (beats/min)	69 [61; 77]	70 [63; 80]	78 [69; 90]	<0.001
Creatine kinase - myocardial band (U/L)	14.5 [11.0; 19.6]	16.8 [12.0; 29.4]	41.7 [18.0; 105.0]	<0.001
Troponin T (µg/L)	0.01 [0.01; 0.07]	0.03 [0.01; 0.36]	0.34 [0.05; 1.37]	<0.001
Serum creatinine (mg/dl)	1.0 [0.8; 1.2]	1.0 [0.9; 1.2]	1.0 [0.9; 1.3]	<0.001
C-reactive protein (mg/L)	3.2 [1.0; 10.6]	6.1 [1.7; 16.0]	9.5 [2.8; 27.6]	<0.001
White blood cell count (cells/mm ³)	5800 [5000; 6200]	7900 [7300; 8600]	11800 [10400; 14200]	<0.001

Data are median [25th, 75th percentiles] or number of patients (%).

THIS IS NOT THE VERSION OF RECORD - doi:10.1042/CS20080298

Table 2. Angiographic Characteristics According to Tertiles of White Blood Cell Count

Characteristic	Tertile 1 (n = 1392)	Tertile 2 (n = 1466)	Tertile 3 (n = 1471)	P value
Left ventricular ejection fraction (%)	58.0 [48.0; 65.0]	54.0 [44.0; 60.0]	48.0 [37.0; 57.0]	<0.001
Treated coronary artery				0.017
Left main	33 (2.4)	33 (2.2)	41 (2.8)	
Left anterior descending	567 (40.7)	615 (42.0)	620 (42.1)	
Left circumflex	333 (23.9)	337 (23.0)	331 (22.5)	
Right coronary artery	359 (25.8)	394 (26.9)	422 (28.7)	
Bypass graft	100 (7.2)	87 (5.9)	57 (3.9)	
Number of affected coronary arteries				<0.001
1	284 (20.4)	306 (20.9)	387 (26.3)	
2	388 (27.9)	395 (26.9)	412 (28.0)	
3	720 (51.7)	865 (52.2)	672 (45.7)	
Multivessel disease	1108 (79.6)	1160 (79.1)	1084 (73.7)	<0.001
Baseline TIMI flow grade				<0.001
0	152 (10.9)	269 (18.3)	589 (40.0)	
1	85 (6.1)	84 (5.7)	107 (7.3)	
2	275 (19.8)	334 (22.8)	272 (18.5)	
3	880 (63.2)	779 (53.2)	503 (34.2)	
Post-intervention TIMI flow grade				<0.001
0	29 (2.1)	44 (3.0)	67 (4.5)	
1	7 (0.5)	17 (1.2)	30 (2.0)	
2	31 (2.2)	43 (2.9)	92 (6.3)	
3	1325 (95.2)	1362 (92.9)	1282 (87.2)	

Data are median [25th, 75th percentiles] or number of patients (%).

Table 3. Thirty-day Outcome According to Tertiles of White Blood Cell Count

Outcome	Tertile 1 (n = 1392)	Tertile 2 (n = 1466)	Tertile 3 (n = 1471)	P value
Death	10 (0.7)	41 (2.8)	131 (8.9)	0.001
Death or myocardial infarction	44 (3.2)	79 (5.4)	160 (10.9)	<0.001
Major bleeding	33 (2.4)	23 (1.6)	62 (4.2)	<0.001
Stroke	1 (0.001)	8 (0.5)	16 (1.1)	0.002

Data are number of patients (%).

Accepted Manuscript

Table Table 4. Correlates of One-year Mortality and Hazard Ratios Calculated by Cox Proportional Regression Analysis

Variable	HR [95% CI]	P value
Cardiogenic shock	4.41 [3.06 – 6.36]	<0.001
Age (for 10 year increase in age)	1.61 [1.41 – 1.84]	<0.001
Multivessel disease	1.84 [1.21 – 2.80]	0.004
Diabetes	1.30 [1.00 – 1.71]	0.05
Left ventricular ejection fraction (for 10 % decrease)	1.37 [1.24 – 1.52]	<0.001
Post-intervention TIMI flow grade (for 1 grade increase)	0.61 [0.50 – 0.74]	<0.001
Serum creatinine (for 1 mg increase in concentration)	1.45 [1.19 – 1.78]	<0.001
Acute coronary syndrome presentation		0.03
STEMI vs Unstable angina	1.73 [1.07 – 2.78]	
NSTEMI vs Unstable angina	1.74 [1.14 – 2.65]	
WBC count (for 1000 cells/mm ³ increase)	1.05 [1.02 – 1.07]	<0.001

Abbreviations: NSTEMI Non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction; WBC = White blood cell.

Accepted Manuscript

THIS IS NOT THE VERSION OF RECORD - see doi:10.1042/CS20080298

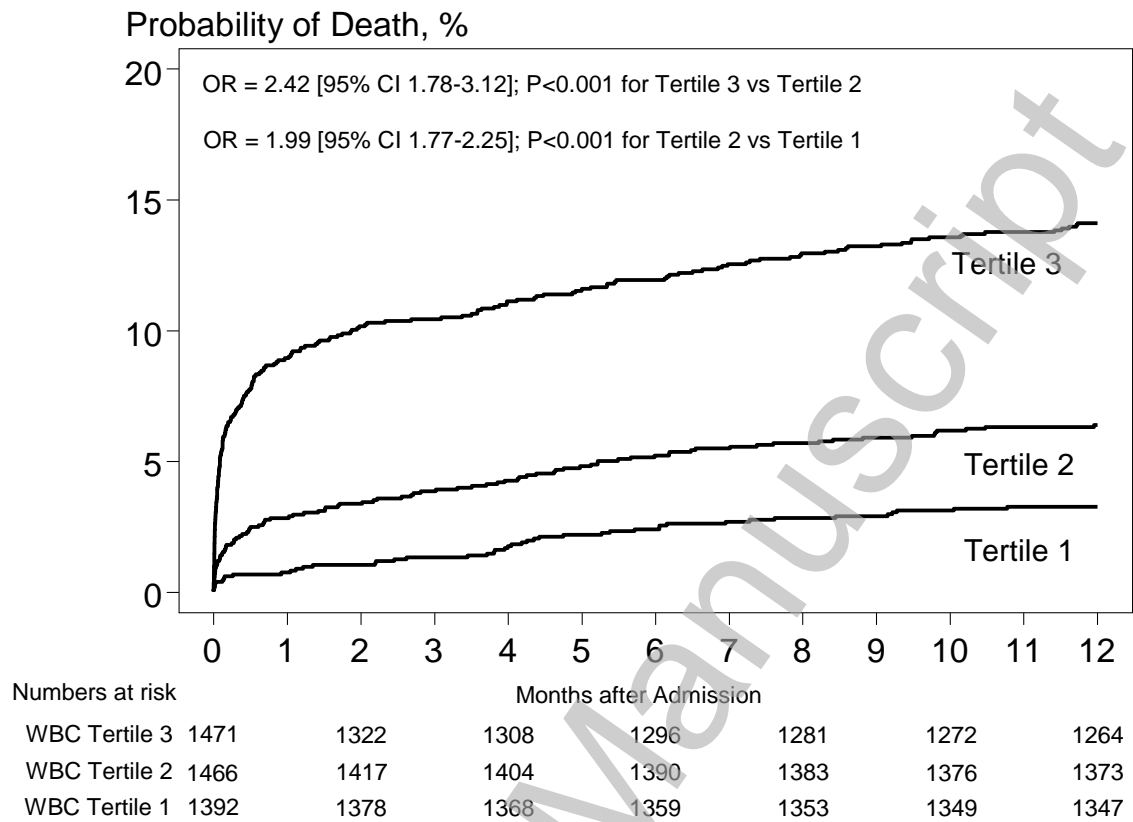


Figure 1. Kaplan-Meier Curves of One-year Mortality According to Tertiles of WBC Count

THIS IS NOT THE VERSION OF RECORD - see doi:10.1042/CS20080298

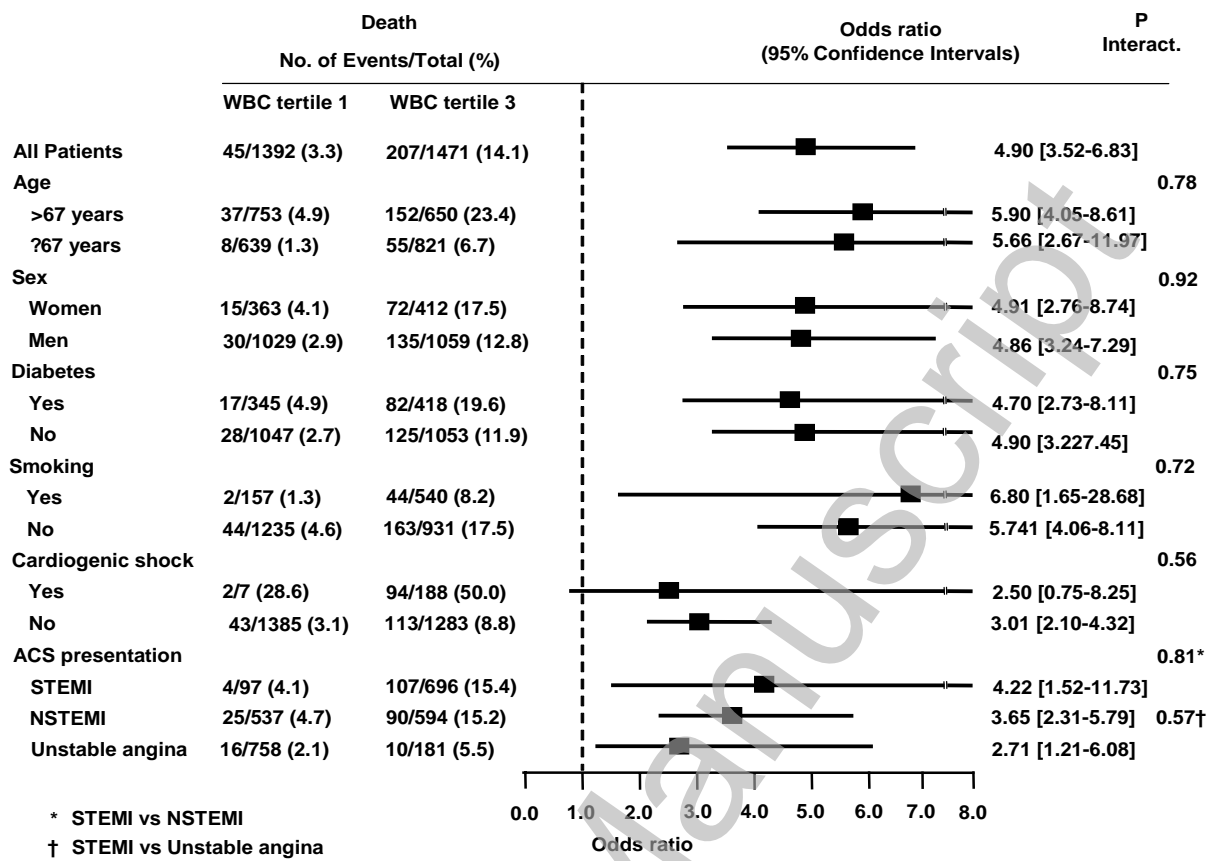


Figure 2. Relative Risk for One-Year Mortality in Various subgroups

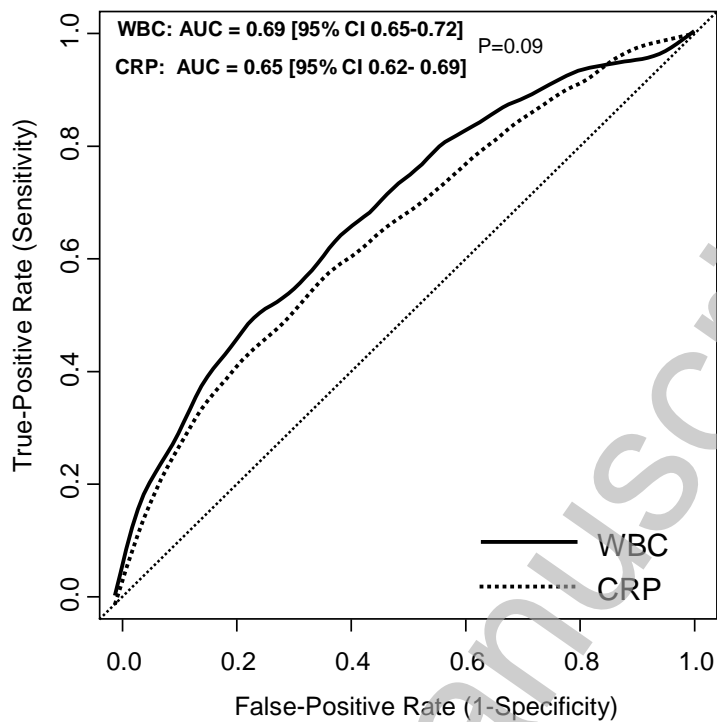


Figure 3. Receiver Operating Characteristic (ROC) Curves Showing Discriminatory Power of White Blood Cells (WBC) and C-reactive Protein (CRP) Regarding One-Year Mortality