Neutrophilia Predicts Death and Heart Failure After Myocardial Infarction
A Community-Based Study

Adelaide M. Arruda-Olson, MD, PhD; Guy S. Reeder, MD; Malcolm R. Bell, MD; Susan A. Weston, MS; Véronique L. Roger, MD, MPH

Background—The relationship between neutrophils and outcomes post–myocardial infarction (MI) is not completely characterized. We examined the associations of neutrophil count with mortality and post-MI heart failure (HF) and their incremental value for risk discrimination in the community.

Methods and Results—MI was diagnosed with cardiac pain, biomarkers, and Minnesota coding of the ECG. Neutrophil count at presentation, reported as counts $/10^9/L$, was categorized by tertiles (lower tertile, <5.7; middle tertile, 5.7 to 8.5; upper tertile, >8.5). From 1979 to 2002, 2047 incident MIs occurred in Olmsted County, Minn (mean age, 68±14 years; 44% women). Median (25th to 75th percentile) neutrophil count was 7.0 (5.1 to 9.5). Within 3 years post-MI, 577 patients died, and 770 developed HF. Overall survival and survival free of HF decreased with increased neutrophil tertile ($P<0.001$). Compared with the lower tertile, the age and sex adjusted hazard ratio for death was 1.44 (95% CI, 1.14 to 1.81) for the middle tertile and 2.60 (95% CI, 2.10 to 3.22) for the upper tertile ($P<0.001$). Similarly, for HF, the hazard ratio was 1.32 (95% CI, 1.09 to 1.59) for the middle and 2.12 (95% CI, 1.77 to 2.53) for the upper tertile ($P<0.001$). These associations persisted after adjustment for risk factors, comorbidities, Killip class, revascularization, and ejection fraction. Neutrophil count improved risk discrimination as indicated by increases in the area under the receiver operating characteristic curves (all $P<0.05$) and by the integrated discrimination improvement analysis (all $P<0.001$).

Conclusions—In the community, the neutrophil count was strongly and independently associated with death and HF post-MI and improved risk discrimination over traditional predictors. (Circ Cardiovasc Qual Outcomes. 2009;2:656-662.)

Key Words: myocardial infarction ▪ blood cells ▪ mortality ▪ heart failure

Inflammatory biomarkers have been identified as an important tool for risk stratification post–myocardial infarction (MI).1,2 The peripheral leukocyte count provides an assessment of the inflammatory status, and is inexpensive and readily available.3–5 Myocardial infarction promotes inflammation which is frequently characterized by peripheral leukocytosis,6 and in previous studies this has been associated with increased early post-MI mortality7–10 and greater frequency of post-MI heart failure (HF).11

A major component of the post-MI peripheral leukocytosis is attributable to elevation of the peripheral neutrophil count. However, secondary analyses of clinical trials of ST-elevation MI have shown conflicting associations between peripheral neutrophil count and 30-day post-MI outcomes.12,13 Furthermore, little is known about the association between peripheral neutrophil count with late post-MI outcomes in community-based patients who typically have a wider spectrum of the disease which includes both ST-elevation MI and non–ST-elevation MI.

Accordingly, this study was undertaken to address these gaps in knowledge using the strengths of a rigorously ascertained geographically defined MI incidence cohort. The goals of this study were to examine the associations of neutrophil count with mortality and with the development of post-MI HF, and the incremental value of neutrophil count for risk discrimination over traditional predictors.

Methods

MI Ascertainment

The parent study, which enabled the present investigation, consists of a retrospective observational cohort of subjects with MI within the geographically defined population of Olmsted County, Minn, where the Mayo Clinic and Olmsted Medical Center provide medical care for all county residents. These facilities use a unified record linkage system that accumulates comprehensive clinical records. The Rochester Epidemiology Project enables these records to be easily retrieved.14

Received October 23, 2008; accepted July 27, 2009.
Correspondence to Véronique L. Roger, MD, MPH, Cardiovascular Diseases, Mayo Clinic, 200 First St SW, Rochester, MN 55905. E-mail roger.veronique@mayo.edu
© 2009 American Heart Association, Inc.

Circ Cardiovasc Qual Outcomes is available at http://circoutcomes.ahajournals.org DOI: 10.1161/CIRCOUTCOMES.108.831024

656
WHAT IS KNOWN

- Clinical studies have consistently demonstrated intense systemic activation of neutrophils in patients with acute coronary syndromes.
- Studies reporting data from secondary analyses of clinical trials demonstrated conflicting findings regarding the association between peripheral neutrophil count and post–myocardial infarction outcomes.

WHAT THE STUDY ADDS

- In this population-based incidence cohort, the absolute neutrophil count on presentation was strongly and independently associated with death and heart failure post–myocardial infarction in a dose-response relationship.
- The peripheral neutrophil count on presentation provided incremental value in risk discrimination over traditional predictors.

The methodology used to assemble the retrospective cohort has been previously reported. Briefly, subjects discharged from Olmsted County hospitals with diagnoses compatible with an MI were obtained from 2 separate data sources: the Rochester Epidemiology Project Index of Diagnoses and the Hospital Utilization Review Database, an administrative database of hospitalizations maintained by Mayo Clinic. The target International Classification of Diseases, Ninth Revision, codes included 410 (acute MI), 411 (other acute and subacute forms of ischemic heart disease), 412 (old MI), 413 (angina pectoris), and 414 (other forms of ischemic heart disease). All events coded as 410, a 50% random sample of codes 411, and a 10% random sample of codes 412, 413, and 414 were reviewed. The sampling fractions were similar to those used in other studies. Trained nurse abstractors reviewed cases meeting criteria for residency and collected information to classify the MI. Standard criteria were applied to assign a MI diagnosis based on cardiac pain, cardiac biomarkers, and Minnesota coding of the ECG. Information on the reliability of these criteria have been published before.

Data Collection

Clinical data obtained included comorbidities measured by the Charlson index and Killip class. Clinical diagnoses were used to ascertain hypertension, diabetes mellitus, hyperlipidemia, family history of coronary disease (defined as coronary disease in first line male descendants less than 55 years of age and in first line female descendants less than 65 years of age), and smoking status. Body mass index (BMI) was calculated using the presentation height and weight and analyzed as a continuous variable. Clinical diagnosis was used to ascertain metastatic cancer, leukemia, lymphoma, polycythemia vera, chronic pancytopenia, thrombocytopenia, myeloproliferative disorder, and treatment with chemotherapy during the year before the diagnosis of MI. We also abstracted clinical diagnosis infections within 2 weeks before the acute event and results of anti-HIV serology. Reperfusion or revascularization therapy was defined as the use of thrombolytic therapy, percutaneous coronary intervention, or coronary artery bypass surgery within the same hospitalization. All decisions regarding patient management were left to the discretion of the attending cardiologists, the majority of whom were not involved in this study.

Blood samples were obtained at presentation for the MI. Blood draws were also obtained during ambulatory outpatient visits for unrelated problems or for general medical examinations before the MI diagnosis. Peripheral blood leukocyte count was estimated with an automated hematology analyzer. This instrument uses approximately 100,000 cells per differential to produce a differential count.

Left Ventricular Ejection Fraction

Left ventricular ejection fraction (EF) was measured during the hospitalization for the acute MI by previously validated methods, including M-mode or bidimensional echocardiography using the Quinones formula from the parasternal views, by the quantitative bidimensional biplane volumetric Simpson method from 4 and 2 chambers views, and bidimensional estimate method from multiple echocardiographic views. EF values were averaged when multiple measurements were performed.

Outcome Definitions and Ascertainment

Inpatient and outpatient records of all subjects were reviewed by nurse abstractors who collected clinical data and validated the diagnosis of HF post-MI using Framingham criteria. The reliability of ascertaining Framingham HF in our experience is excellent.

Follow-up was completed by passive surveillance of the community medical records. The ascertainment of death incorporated death certificates filed in Olmsted County, autopsy reports, obituary notices, and electronic files of death certificates obtained from the State of Minnesota Department of Vital and Health Statistics. All aspects of the study were approved by the Mayo Clinic and Olmsted Medical Center institutional review boards.

Statistical Analyses

Cell counts were reported as values $\times 10^9/L$. Patients were classified into tertiles according to neutrophil count at presentation. Data are presented as frequencies for categorical variables, mean±SD for continuous variables, or median (25th to 75th percentile) for skewed variables. Trends in baseline characteristics across tertiles were tested with $\chi^2$ tests for categorical variables, $t$ tests for continuous variables, and Kruskal–Wallis tests for skewed variables.

Survival analysis of time to post-MI events, including death or HF, was conducted with the Kaplan–Meier method. Proportional-hazards regression was used to examine the association between baseline characteristics and death or HF post-MI. To allow for detection of a dose-response effect, tertiles of the distribution for neutrophil count were modeled as 2 indicator variables with neutrophil $<5.7 \times 10^9/L$ as the reference level. Univariate associations between neutrophil count and death or HF post-MI were examined. Demographics (age and sex), cardiovascular risk factors (current smoker, hypertension, body mass index, hyperlipidemia, family history of coronary artery disease, and diabetes mellitus), comorbidity index, Killip class, reperfusion or revascularization, and EF were each added to the model separately. Missing values did not exceed 10% for any of the variables included in the models. The proportional hazards assumption was tested using the Schoenfeld residuals and found to be valid for the first 3 years of follow-up, with evidence of disruption thereafter. Therefore, we restricted analyses to 3 years post-MI.

The incremental value of peripheral neutrophil count in risk discrimination for death or HF was examined by the area under the receiver operating characteristic (ROC) curve (AUC) with 3-year mortality or 3-year HF as the end points. Comparisons of the AUC before and after the addition of the peripheral neutrophil count were performed by the method of Hanley and McNeil.

The change in discrimination (a measure of how well a model can separate patients with an outcome at 3 years from those who did not have the outcome) was evaluated using the integrated discrimination improvement (IDI). The IDI measured the change in the difference in the mean predicted probabilities of death between those dead and alive, or the change in the difference in the mean predicted probabilities of HF between those who experienced HF and those who did not, after the inclusion of neutrophil count in each of the models.

In ancillary analyses, we excluded patients with metastatic cancer, leukemia, lymphoma, polycythemia vera, chronic pancytopenia, thrombocytopenia, myeloproliferative disorders, infection, and those undergoing chemotherapy. We also excluded patients with positive anti-HIV serology. After exclusion of those patients, we repeated all the proportional-hazards regression models described above. In a second ancillary analysis we excluded patients with neutrophil count in the upper 5% and those in the lower 5% of the neutrophil count distribution.
After exclusion of those patients, we repeated all the proportional-hazards regression models described above. A probability value of 0.05 was used for the threshold of statistical significance. Analyses were performed using SAS version 8.2 (SAS Institute, Inc).

Results

Baseline Characteristics

Between January 1, 1979, and December 31, 2002, 2732 patients had an incident MI in Olmsted County. Absolute neutrophil count at presentation was obtained for 2047 patients and those composed the study population. The mean age was 68 years, and 44% were women. Echocardiograms were performed within a median interval of 2 days (25th to 75th percentile: 1 day to 3 days) after hospital admission. The median (25th to 75th percentile) neutrophil count on presentation was 7.0 $\times 10^9/L$ (5.1 $\times 10^9/L$ to 9.5 $\times 10^9/L$). Cutoffs for the tertiles were 5.7 $\times 10^9/L$ and 8.5 $\times 10^9/L$.

Associations Between Baseline Characteristics and Neutrophils

Higher neutrophil counts were associated with older age, female sex, systemic hypertension, diabetes mellitus, smoking, higher comorbidity index, Killip class 2, 3, or 4, and lower EF (Table 1). Lower neutrophil counts were associated with higher BMI, hyperlipidemia, familial coronary disease, use of reperfusion or revascularization, use of statins, $\beta$-blockers, and aspirin during hospitalization. Infection within 2 weeks before the MI was associated with neutrophil count with 9%, 13%, and 26% of the patients having recent infection in the lower, middle, and upper neutrophil tertiles, respectively ($P<0.001$).

Outcomes

The median follow-up was 4.9 years (25th to 75th percentile, 1.8 to 6.7 years). Among all patients, 89% were residents in Olmsted County within 3 years post-MI. For the remainder, 110 died and were last seen as Olmsted County resident before their death; 112 were still alive and last seen as Olmsted County resident less than 3 years post-MI.

Overall Survival

Within 3 years post-MI, 577 patients died. There was a dramatic decrease in survival with increasing neutrophil tertile (Figure, A). The 30-day survival estimates were 0.95 (95% CI, 0.93 to 0.96), 0.91 (95% CI, 0.89 to 0.94), and 0.82 (95% CI, 0.79 to 0.85) for the lower, middle, and upper neutrophil tertiles, respectively. The 3-year survival estimates were 0.82 (95% CI, 0.79 to 0.85), 0.74 (95% CI, 0.71 to 0.78), and 0.58 (95% CI, 0.54 to 0.62), for the lower, middle, and upper neutrophil tertiles, respectively.

The associations between neutrophil count and death are presented in Table 2. In the unadjusted model, there was a

Table 1. Characteristics Among 2047 Olmsted County Residents With Incident MI

<table>
<thead>
<tr>
<th>Entire Cohort</th>
<th>Lower Tertile:</th>
<th>Middle Tertile:</th>
<th>Upper Tertile:</th>
<th>P Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=2047)</td>
<td>$&lt;5.7 \times 10^9/L$</td>
<td>$5.7–8.5 \times 10^9/L$</td>
<td>$&gt;8.5 \times 10^9/L$</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>68 (14)</td>
<td>67 (14)</td>
<td>68 (14)</td>
<td>70 (14)</td>
</tr>
<tr>
<td>Women</td>
<td>895 (44)</td>
<td>273 (40)</td>
<td>286 (42)</td>
<td>336 (49)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28 (5.92)</td>
<td>28 (5.73)</td>
<td>28 (5.65)</td>
<td>27 (6.28)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1156 (57)</td>
<td>360 (53)</td>
<td>381 (56)</td>
<td>415 (61)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>745 (37)</td>
<td>277 (41)</td>
<td>250 (37)</td>
<td>218 (32)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>435 (21)</td>
<td>113 (17)</td>
<td>146 (21)</td>
<td>176 (26)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>552 (27)</td>
<td>157 (23)</td>
<td>199 (29)</td>
<td>196 (29)</td>
</tr>
<tr>
<td>Familial coronary disease</td>
<td>401 (21)</td>
<td>144 (22)</td>
<td>157 (24)</td>
<td>100 (16)</td>
</tr>
<tr>
<td>Comorbidity index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>817 (40)</td>
<td>314 (46)</td>
<td>279 (41)</td>
<td>224 (33)</td>
</tr>
<tr>
<td>1–2</td>
<td>727 (36)</td>
<td>224 (33)</td>
<td>254 (37)</td>
<td>249 (36)</td>
</tr>
<tr>
<td>≥3</td>
<td>503 (25)</td>
<td>142 (21)</td>
<td>153 (22)</td>
<td>208 (31)</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior location</td>
<td>681 (37)</td>
<td>218 (36)</td>
<td>221 (36)</td>
<td>242 (40)</td>
</tr>
<tr>
<td>ST-elevation MI</td>
<td>655 (36)</td>
<td>208 (34)</td>
<td>221 (36)</td>
<td>226 (37)</td>
</tr>
<tr>
<td>Killip class 2, 3, or 4</td>
<td>710 (35)</td>
<td>180 (27)</td>
<td>216 (32)</td>
<td>314 (47)</td>
</tr>
<tr>
<td>Reperfusion/revascularization</td>
<td>974 (48)</td>
<td>400 (59)</td>
<td>330 (48)</td>
<td>244 (36)</td>
</tr>
<tr>
<td>Medications during hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>415 (20)</td>
<td>178 (28)</td>
<td>134 (20)</td>
<td>103 (15)</td>
</tr>
<tr>
<td>ACEI or ARB</td>
<td>657 (32)</td>
<td>220 (33)</td>
<td>213 (31)</td>
<td>224 (33)</td>
</tr>
<tr>
<td>$\beta$-Blockers</td>
<td>1489 (73)</td>
<td>534 (79)</td>
<td>524 (77)</td>
<td>431 (64)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1490 (73)</td>
<td>538 (79)</td>
<td>502 (73)</td>
<td>450 (67)</td>
</tr>
<tr>
<td>Left ventricular EF</td>
<td>49 (35–58)</td>
<td>53 (40–60)</td>
<td>49 (38–58)</td>
<td>45 (33–55)</td>
</tr>
</tbody>
</table>

Data are presented as mean (SD), n (%), or median (25th to 75th percentile). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; and BMI, body mass index.
positive graded association between neutrophil count and death. This association persisted after adding demographics, cardiovascular risk factors, comorbidity index, Killip class, use of reperfusion or revascularization, and EF separately to the model. In the ROC analysis, the addition of neutrophil count improved each of the models (Table 3). Similarly, the IDI indicated improvement in each model after the addition of the neutrophil count (Table 3).

Heart Failure
Within 3 years post-MI, 770 patients developed HF. There was a dramatic reduction of survival free of HF with increasing neutrophil tertile (Figure 1B). The 30-day survival estimates were 0.80 (95% CI, 0.77 to 0.83), 0.73 (95% CI, 0.70 to 0.77), and 0.56 (95% CI, 0.53 to 0.60) for the lower, middle, and upper neutrophil tertiles, respectively. The 3-year survival estimates were 0.72 (95% CI, 0.69 to 0.76), 0.64 (95% CI, 0.60 to 0.68), and 0.47 (95% CI, 0.43 to 0.51), for the lower, middle, and upper neutrophil tertiles, respectively.

The associations between HF post-MI and neutrophil count are presented in Table 4. In the unadjusted model, there was a positive graded association between tertiles of the neutrophil count and HF post-MI. This association persisted after adding demographics, cardiovascular risk factors, comorbidity index, Killip class, use of reperfusion or revascularization, and EF separately to the model. In the ROC analysis, the addition of neutrophil count improved each of the models (Table 3). Similarly, the IDI indicated improvement in each model after the addition of the neutrophil count (Table 3).

In ancillary analysis after excluding patients with metastatic cancer, leukemia, lymphoma, polycythemia vera, chronic pan-cytopenia, thrombocytopenia, myeloproliferative disorder, chemotherapy, infection, and positive anti-HIV serology, the results of the proportional-hazards regression models were similar. In the second ancillary analysis, after exclusion of patients with neutrophil count in the upper 5% and those in the lower 5% of the neutrophil count distribution the results of the proportional-hazards regression models remained unchanged. In a third ancillary analysis, adjustment for infection within 2 weeks before the MI in the models predicting death and heart failure did not change the associations between the outcomes and the neutrophil tertiles.

Discussion
In the present population-based MI incidence cohort, the absolute neutrophil count at presentation for acute MI was strongly, positively, and independently associated with both death and HF post-MI and provided incremental value in risk discrimination over traditional risk factors. Moreover, our data are also consistent with a dose-response relationship between the magnitude of neutrophilia and both death and HF at long-term follow-up. Finally, our data also demonstrated that the increased risk for adverse events in patients in the highest neutrophil tertile at presentation with acute MI began immediately after the MI and persisted over the 3-year follow-up period. These associations were independent of age, sex, cardiovascular risk factors, comorbidities, Killip class, reperfusion or revascularization therapies, and EF.

Leukocytosis and Outcomes
Several studies have reported positive associations between elevated leukocyte count and the incidence of coronary disease or cerebrovascular diseases or with mortality from coronary heart disease among previously healthy individuals. A prospective cohort study that included measurement of the differential blood count indicated that in men the main contributor to the excess risk for ischemic heart disease events was the neutrophil count.

In patients with acute coronary artery disease, prior studies have reported an association of the total leukocyte count with short-term outcomes. In clinical trials of ST-elevation MI, there was an association between leukocytosis and increased short-term post-MI mortality. In the Worcester community,
there was an association between leukocytosis and increased adverse outcomes during hospitalization for acute MI. However, these studies did not report on the influence of leukocyte count on longer-term outcomes post-MI and did not address the incremental value of white blood cell count over the traditional clinical predictors of adverse outcomes. The present study directly addresses these gaps in knowledge.

Peripheral Neutrophils and Outcomes

Studies reporting data from secondary analyses of clinical trials which enrolled patients with ST-elevation MI have demonstrated conflicting findings regarding the association between peripheral neutrophil count and 30-day post-MI outcomes. In a large randomized trial of clopidogrel versus placebo in ST-elevation MI patients undergoing fibrinolysis, the neutrophil count in the highest quartile was independently associated with the risk of cardiovascular death and HF at 30 days. However, in another trial of fibrinolysis in ST-elevation MI, there was no significant association between cell counts and clinical outcomes. Our study examined this point in a large cohort of patients with incident MI recruited in the Olmsted County community with long-term follow-up information.

In prior studies, participants were recruited in multiple centers or were recruited in an intensive coronary care unit. By contrast, we recruited individuals with a wide spectrum of disease severity, and included patients with

Table 3. ROC and IDI Analysis for Death and HF Within 3 Years After MI

<table>
<thead>
<tr>
<th>Models</th>
<th>ROC Analysis</th>
<th>IDI Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC*</td>
<td>Average Predicted Probability of Event</td>
</tr>
<tr>
<td></td>
<td>Model Without Neutrophil Count</td>
<td>Model With Neutrophil Count</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>0.77</td>
<td>0.80</td>
</tr>
<tr>
<td>Risk factors†‡</td>
<td>0.79</td>
<td>0.81</td>
</tr>
<tr>
<td>Comorbidity index†</td>
<td>0.80</td>
<td>0.82</td>
</tr>
<tr>
<td>Killip class†</td>
<td>0.79</td>
<td>0.81</td>
</tr>
<tr>
<td>Reperfusion or revascularization†</td>
<td>0.80</td>
<td>0.82</td>
</tr>
<tr>
<td>EF†</td>
<td>0.76</td>
<td>0.79</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>0.75</td>
<td>0.78</td>
</tr>
<tr>
<td>Risk factors†‡</td>
<td>0.77</td>
<td>0.80</td>
</tr>
<tr>
<td>Comorbidity index†</td>
<td>0.78</td>
<td>0.80</td>
</tr>
<tr>
<td>Killip class†</td>
<td>0.82</td>
<td>0.84</td>
</tr>
<tr>
<td>Reperfusion or revascularization†</td>
<td>0.77</td>
<td>0.79</td>
</tr>
<tr>
<td>EF†</td>
<td>0.79</td>
<td>0.80</td>
</tr>
</tbody>
</table>

AUC indicates area under the curve.
*All P values comparing models with neutrophil to models without neutrophil are less than 0.05.
†Age and sex.
‡Risk factors included current smoking, systemic hypertension, body mass index, hyperlipidemia, family history of coronary artery disease, and diabetes mellitus.
ST-elevation MI and those with non-ST-elevation MIs, and thus extended the findings of prior studies which included only patients with ST-elevation MI.12,13

An elevated neutrophil to lymphocyte ratio has been previously associated with adverse outcomes in patients with suspected coronary disease,35 chronic coronary disease,36 and ST-elevation MI.37 In a study by Nunez et al37 only patients with ST-elevation MI admitted to a tertiary center were recruited. Conversely, we recruited patients with either ST-elevation or non–ST-elevation MI in a geographically defined population, which enhances the generalizability of our findings. Given the role of neutrophils in the inflammatory response after MI, the present study focused on the ability of the absolute neutrophil count to predict outcomes and indicated that absolute neutrophil count was associated with death and HF within 3 years post-MI.

Potential Mechanisms
Clinical studies have consistently demonstrated intense systemic activation of neutrophils in patients with acute coronary syndromes.38–41 Neutrophils are the first leukocytes to infiltrate the infarcted myocardium.42,43 Activated neutrophils release a variety of proteolytic enzymes including elastase38 and myeloperoxidase,40,41 with potential for tissue destruction.44 The inflammatory response fosters cytokine release,45 which may promote demargination of intravascular neutrophils and acceleration of the release of neutrophils by the bone marrow.46,47 In addition, there is evidence for prolongation of the lifespan of neutrophils in unstable plaques.48

The absolute peripheral neutrophil count may be a marker of the severity of myocardial inflammation attributable to ischemic injury49 or of the severity of the inflammation of the coronary arterial tree.41 Increased neutrophil count may also, in part, be explained by a lower probability of successful reperfusion12,13 or impaired microvascular perfusion.12 It is conceivable that the neutrophil count may represent combinations of the aforementioned potential mechanisms.

Limitations and Strengths
Although these results provide insight into the association between neutrophilia and the outcome of acute MI, some limitations should be kept in mind. Changes in neutrophil count may be related to infections, malignancies, or blood disorders. In ancillary analysis, when patients with those conditions were excluded from the analyses, the associations between neutrophilia and post-MI outcomes were similar in both the unadjusted and adjusted models. In further analyses we excluded patients with the neutrophil count in the top or bottom 5% of the neutrophil distribution, and the association between the neutrophil count with post-MI outcomes remained unchanged. This reinforces the robustness of our findings. The relationship of neutrophil count to the time from symptom onset or time of reperfusion could not be analyzed because data on the time of the neutrophil count was not available. As the IDI is a relatively new approach to risk prediction, there is no uniformly accepted threshold for clinically meaningful effect size.50

The racial and ethnic composition of Olmsted County may limit the generalizability of these data to groups under-represented in the population. Although no single community can represent the nation, studies of chronic diseases in Olmsted County indicate that results from the county can be extrapolated to a large part of the population.14 Nonetheless, the present study will need replication in other racial and ethnic groups.

Notable strengths of this study include the evaluation of the peripheral neutrophil count among a population-based cohort, which represents the comprehensive experience of a community. As all MI cases were incident cases, these results are not affected by incidence prevalence bias.

In the clinical practice of most centers in the United States, neutrophil counts are routinely obtained during hospitalization for an acute coronary event. In the present study, this single measurement of neutrophil count was a strong predictor for outcomes, which highlights a potential application of this inexpensive and readily available inflammatory marker for risk stratification post-MI.

Conclusions
In this population-based incidence cohort, the absolute neutrophil count at presentation was strongly and independently associated with death and HF post-MI in a dose-response relationship. Moreover, the peripheral neutrophil count at presentation provided incremental value in risk discrimination over traditional predictors. As it is an inexpensive readily available prognostic marker, it should be incorporated in the clinical practice for risk stratification after MI.

Acknowledgments
We thank Ellen Koepsell, RN, for study management, Kay Traverse, RN, and Susan Stotz, RN, for their assistance with data collection, Ruoxiang Jiang for assistance with statistical analysis, and Kristie Shorter for secretarial support.

Sources of Funding
This study was supported by a Clinician Investigator Fellowship Award from the Mayo Clinic and grants from the Public Health Service and the National Institutes of Health (AR30582, R01 HL 59205, and R01 HL 72435). Dr Roger is an Established Investigator of the American Heart Association. The other authors report no disclosures.

Disclosure
None.

References


Neutrophilia Predicts Death and Heart Failure After Myocardial Infarction: A Community-Based Study
Adelaide M. Arruda-Olson, Guy S. Reeder, Malcolm R. Bell, Susan A. Weston and Véronique L. Roger

Circ Cardiovasc Qual Outcomes. 2009;2:656-662; originally published online September 1, 2009;
doi: 10.1161/CIRCOUTCOMES.108.831024
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/2/6/656

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Quality and Outcomes can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Quality and Outcomes is online at:
http://circoutcomes.ahajournals.org//subscriptions/