

# Prognostic Importance of Physical Examination for Heart Failure in Non–ST-Elevation Acute Coronary Syndromes

## The Enduring Value of Killip Classification

Umesh N. Khot, MD

Gang Jia, MS

David J. Moliterno, MD

A. Michael Lincoff, MD

Monica B. Khot, MD

Robert A. Harrington, MD

Eric J. Topol, MD

INCREASINGLY SOPHISTICATED LABORATORY studies and diagnostic testing have led to diminished attention to the importance of the physical examination of patients. This is evidenced by a decreased emphasis on the physical examination in training programs and also by decreased proficiency among trainees in basic physical examination skills, such as cardiac and pulmonary auscultation.<sup>1,2</sup> An important reason for this diminished interest is that studies have documented limitations of physical examination when compared with more sophisticated methods.<sup>3</sup> These studies have given credence to a widespread belief that information obtained by physical examination is of limited value.<sup>4,6</sup>

Yet increasing evidence suggests that assessment for the presence and severity of heart failure by physical examination provides significant independent prognostic information. For example, in chronic heart failure, the presence of an S<sub>3</sub> gallop, elevated jugular venous pressure, or both has been found to independently predict long-term mortality.<sup>7</sup> In ST-elevation myo-

**Context** In acute myocardial infarction, the presence and severity of heart failure at the time of initial presentation have been formally categorized by the Killip classification. Although well studied in ST-elevation myocardial infarction, the prognostic importance of Killip classification in non–ST-elevation acute coronary syndromes is not well established.

**Objectives** To determine the prognostic importance of physical examination for heart failure analyzed according to Killip classification in non–ST-elevation acute coronary syndromes and to understand its predictive value relative to other variables.

**Design, Setting, and Patients** From April 2001 to September 2003, We analyzed information from 26090 patients with non–ST-elevation acute coronary syndromes enrolled in the GUSTO IIb, PURSUIT, PARAGON A, and PARAGON B trials. Demographic information was categorized by Killip class. Killip classes III and IV were combined into 1 category. Multivariate Cox proportional hazard models were developed to determine the prognostic importance of Killip classification in comparison with other variables.

**Main Outcome Measure** Association between Killip classification and all-cause mortality at 30 days and 6 months.

**Results** Patients in Killip class II (n=2513) and III/IV (n=390) were older than those in Killip class I (n=23 187), with higher rates of diabetes, prior myocardial infarction, ST depression, and elevated cardiac enzymes (all  $P<.001$ ). Higher Killip class was associated with higher mortality at 30 days (2.8% in Killip class I vs 8.8% in class II vs 14.4% in class III/IV;  $P<.001$ ) and 6 months (5.0% vs 14.7% vs 23.0%, respectively;  $P<.001$ ). Patients with Killip class II, III, or IV constituted 11% of the overall population but accounted for approximately 30% of the deaths at both time points. In multivariate analysis, Killip class III/IV was the most powerful predictor of mortality at 30 days (hazard ratio [HR], 2.35; 95% confidence interval [CI], 1.69-3.26;  $P<.001$ ) and 6 months (HR, 2.12; 95% CI, 1.63-2.75;  $P<.001$ ). Killip class II was predictive of mortality at 30 days (HR, 1.73; 95% CI, 1.44-2.09;  $P<.001$ ) and 6 months (HR, 1.52; 95% CI, 1.31-1.76;  $P<.001$ ). Five factors—age, Killip classification, heart rate, systolic blood pressure, and ST depression—provided more than 70% of the prognostic information for 30-day and 6-month mortality.

**Conclusions** Killip classification is a powerful independent predictor of all-cause mortality in patients with non–ST-elevation acute coronary syndromes. Age, Killip classification, heart rate, systolic blood pressure, and ST depression should receive particular attention in the initial assessment of these patients.

JAMA. 2003;290:2174-2181

www.jama.com

**Author Affiliations:** Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio (Drs U. Khot, Moliterno, Lincoff, M. Khot, and Topol and Mr Jia); and Duke Clinical Research Institute, Durham, NC (Dr Harrington). Drs U. Khot and M. Khot are

now with the Indiana Heart Physicians, Indianapolis. **Corresponding Author and Reprints:** Umesh N. Khot, MD, Indiana Heart Physicians, 112 N 17th Ave, Suite 300, Beech Grove, IN 46107 (e-mail: khot@cvresearch.net).

cardial infarction, the presence and severity of heart failure at the time of presentation have been formally categorized by use of the well-known Killip classification.<sup>8</sup> Originally described among 250 patients in 1967 in the pre-thrombolytic therapy era,<sup>8</sup> this classification has been subsequently validated to predict mortality in patients treated with thrombolytic agents and those treated with primary percutaneous coronary intervention.<sup>9,10</sup> However, the relevance of Killip classification among patients with non-ST-elevation acute coronary syndromes is not well established. We therefore sought to determine the prognostic importance of the presence and severity of heart failure analyzed according to Killip classification in patients with non-ST-elevation acute coronary syndromes and to understand the predictive value of Killip classification compared with other common prognostic variables.

## METHODS

From April 2001 to September 2003, we analyzed information from 4 large clinical trials of patients with acute coronary syndromes without ST elevation in which prospectively recorded data regarding Killip classification were available. These trials included GUSTO IIB,<sup>11</sup> PURSUIT,<sup>12</sup> PARAGON A,<sup>13</sup> and PARAGON B.<sup>14</sup> In brief, GUSTO IIB compared hirudin and heparin in 12 142 patients with both acute ST-elevation myocardial infarction and non-ST-elevation acute coronary syndromes; for our investigation, the 4131 patients with ST-elevation myocardial infarction were excluded. PURSUIT compared eptifibatid with placebo in 10948 patients with chest pain and electrocardiographic evidence of myocardial ischemia or positive cardiac enzymes. PARAGON A compared lamifiban with placebo in 2282 patients with chest pain and electrocardiographic evidence of myocardial ischemia. PARAGON B compared lamifiban with placebo in 5225 patients with chest pain and electrocardiographic evidence of myocardial ischemia or positive cardiac enzymes. All

trials had independent source documentation, prespecified independent data monitoring, and clinical events committees for end-point adjudication.

### Determination of Killip Classification

In 3 trials (GUSTO IIB, PARAGON A, and PARAGON B), Killip classification was determined by the treating cardiologist and recorded prospectively at the time of entry into the clinical trial. In the fourth trial (PURSUIT), Killip classification was determined by recoding prospectively recorded information regarding severity of heart failure (rales) and systolic blood pressure at randomization. Specifically, Killip class I patients had no evidence of heart failure; Killip class II patients had mild heart failure with rales involving one third or less of the posterior lung fields and systolic blood pressure of 90 mm Hg or higher; Killip class III patients had pulmonary edema with rales involving more than one third of the posterior lung fields and systolic blood pressure of 90 mm Hg or more; and Killip class IV patients had cardiogenic shock with any rales and systolic blood pressure of less than 90 mm Hg. For all 4 trials, Killip classes III and IV were combined for the purpose of this analysis because very few enrolled patients were classified as having Killip class IV heart failure (overall  $n=90$  [0.3%]).

### Statistical Analysis

Demographic information is reported as either mean (SD) or number (percentage). Categorical variables were analyzed with the Pearson  $\chi^2$  test. Continuous variables were tested for normality. If normality could be assumed,  $t$  tests were used; otherwise, Wilcoxon rank sum tests were used.

The primary end points of this study were 30-day and 6-month all-cause mortality. Data from the 4 individual trials were combined to determine the overall impact of Killip classification on mortality. Killip class was modeled as 2 dummy variables, class II and class III/IV, with class I as the reference group. A Kaplan-Meier curve was constructed

for the end points of 30-day and 6-month all-cause mortality according to Killip classification. Log-rank tests were used to compare the Kaplan-Meier estimates of event rates between Killip classification groups. Multivariate Cox proportional hazard models were developed by stepwise variable selection from either variables determined to be of prognostic importance in previous studies or variables easily obtainable at initial presentation. Patients with missing data were excluded from the final analyses. However, missing patterns were checked and determined not to create bias, and analyses with imputed data showed no meaningful differences (data not shown).

The specific variables studied in addition to Killip classification were age, heart rate, and systolic blood pressure, studied as linear predictors, and body mass index, transformed using linear splines. Creatine kinase MB fraction (CK-MB) was studied as a dichotomous variable with the upper limit of normal as a cut point. If CK-MB was unavailable, total creatine kinase was used with the upper limit of normal as a cut point.<sup>15</sup> Sex, ST depression, and medical history (prior angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, congestive heart failure, diabetes, hypertension, peripheral vascular disease, stroke, severe chronic obstructive pulmonary disease, family history of coronary heart disease, chronic renal insufficiency, hypercholesterolemia, and smoking) were treated as dichotomous variables. Elements of medical history were identified through physician interview and by patient self-report. Allocation to placebo or active control vs treatment was not included in the multivariable analyses since treatment with the various study drugs in all 4 studies had shown no impact on all-cause mortality.<sup>11-14</sup> The predictive performance of the model was measured using the  $c$  statistic. In addition, the Breslow-Day test for homogeneity of odds ratios was performed to test for heterogeneity across studies. All analyses were performed with SAS version

**Table 1.** Characteristics of Patients According to Killip Classification\*

Characteristics	Killip Class			P Value	
	I (n = 23 187)	II (n = 2513)	III/IV (n = 390)	Class I vs II	Class I vs III/IV
<b>Demographics</b>					
Age, mean (SD), y	63 (11)	69 (10)	69 (11)	<.001	<.001
Female	7804 (33.7)	992 (39.5)	171 (43.9)	<.001	<.001
<b>Race</b>					
White	21 049 (90.9)	2250 (89.5)	343 (88.2)	.03	.16
Black	833 (3.6)	115 (4.6)	20 (5.1)		
Other	1283 (5.5)	148 (5.9)	26 (6.7)		
Body mass index, mean (SD)†	27 (4.7)	28 (5)	28 (5.5)	.19	.12
<b>Risk factors</b>					
Current smoking	7193 (34.9)	641 (29.5)	93 (27.7)	<.001	.006
Diabetes	4589 (19.8)	746 (29.7)	150 (38.6)	<.001	<.001
Hypercholesterolemia	10 023 (43.5)	997 (39.9)	165 (43.1)	.001	.89
Hypertension	12 032 (51.9)	1457 (58.0)	253 (64.9)	<.001	<.001
Family history of CHD	8894 (38.8)	862 (35.0)	132 (34.8)	<.001	.12
<b>Other history</b>					
Previous MI	7125 (30.8)	1064 (42.4)	159 (40.8)	<.001	<.001
Previous angina	17 557 (75.9)	2017 (80.5)	300 (76.9)	<.001	.62
Previous CHF	1632 (7.0)	723 (28.8)	142 (36.5)	<.001	<.001
Previous CABG	2725 (11.8)	352 (14.0)	53 (13.6)	.001	.27
Previous PCI	2828 (12.2)	298 (11.9)	40 (10.3)	.62	.25
Previous CVA	542 (2.3)	94 (3.8)	19 (4.9)	<.001	.001
Previous PVD	1758 (7.6)	357 (14.2)	59 (15.2)	<.001	<.001
Chronic renal insufficiency	155 (0.7)	58 (2.3)	13 (3.3)	<.001	<.001
Severe COPD	656 (2.8)	211 (8.4)	32 (8.2)	<.001	<.001
<b>Presenting characteristics</b>					
Systolic BP, mean (SD), mm Hg	134 (21)	133 (22)	131 (24)	.005	.001
Diastolic BP, mean (SD), mm Hg	77 (13)	75 (14)	74 (14)	<.001	<.001
Heart rate, mean (SD), beats/min	73 (15)	79 (18)	86 (19)	<.001	<.001
ST-segment depression (>0.5 mm)	10 424 (45.8)	1442 (59.0)	234 (60.9)	<.001	<.001
Elevated CK-MB	6559 (31.4)	930 (39.9)	150 (41.4)	<.001	<.001

Abbreviations: BP, blood pressure; CABG, coronary artery bypass graft surgery; CHD, coronary heart disease; CHF, congestive heart failure; CK-MB, creatine kinase MB fraction; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

\*Data are expressed as No. (%) unless otherwise noted.

†Body mass index is calculated as weight in kilograms divided by the square of height in meters.

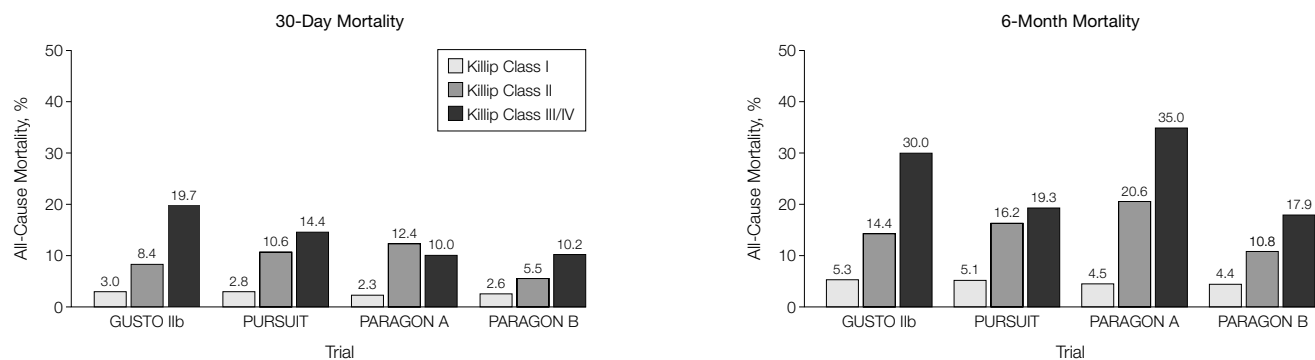
8 software (SAS Institute Inc, Cary, NC).  $P < .05$  indicates statistical significance for all comparisons.

**RESULTS**

A total of 26 466 patients were enrolled in the 4 studies; information regarding Killip classification was available for 26 090 (98.6%). Patients in Killip class II, III, or IV were generally older and had significantly more comorbidities, including higher rates of diabetes, prior myocardial infarction, prior congestive heart failure, severe lung disease, chronic renal insufficiency, prior stroke, and peripheral vascular disease (all  $P \leq .001$ ) (TABLE 1). They were more likely to have ST depression and elevated cardiac enzymes on admission (both  $P < .001$ ), and they had higher heart rates ( $P < .001$ ) and lower systolic blood pressures ( $P \leq .005$ ) and diastolic blood pressures ( $P < .001$ ).

Higher Killip class was a powerful predictor of all-cause mortality in all 4 trials studied (FIGURE 1). In the combined analysis, Killip class II was associated with a more than 3-fold increase in 30-day mortality compared with Killip class I (8.8% vs 2.8%;  $P < .001$ ). Killip class III/IV was associated with a more than 5-fold increase in 30-day mortality compared with Killip class I (14.4% vs 2.8%;  $P < .001$ ). The increase in mortality was evident early after trial entry; in addition, the absolute mortality differences between Killip classes increased with

**Figure 1.** All-Cause Mortality According to Killip Classification in Each Trial at 30 Days and 6 Months



All comparisons of Killip class I vs II and Killip class I vs III/IV are statistically significant at  $P < .001$  except Killip class I vs III/IV at 30 days in PARAGON A ( $P = .03$ ).

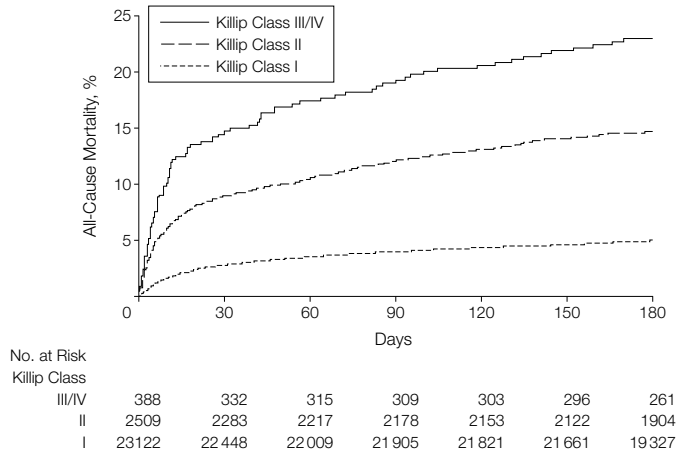
time (FIGURE 2). At 6 months, the step-wise increase in all-cause mortality with increasing Killip class was significant (5.0% for class I vs 14.7% for class II vs 23.0% for class III/IV;  $P < .001$ ). Patients with Killip class II, III, or IV constituted only 11% of the overall population but accounted for approximately 30% of the deaths at both time points.

The relationship between increasing Killip class and mortality was evident for both unstable angina (30 days: 2.4% for class I vs 6.4% for class II vs 11.8% for class III/IV;  $P < .001$ ; 6 months: 4.6% vs 11.9% vs 21.4%, respectively;  $P < .001$ ) and non-ST-elevation myocardial infarction (CK-MB higher than the upper limit of normal) (30 days: 3.4% vs 11.9% vs 18%, respectively;  $P < .001$ ; 6 months: 5.5% vs 18.0% vs 26.0%, respectively;  $P < .001$ ). The incidence of end-point myocardial infarction was also increased at both 30 days (9.5% vs 13.7% vs 15.0%, respectively,  $P < .001$ ) and 6 months (11.0% vs 16.0% vs 20.2%, respectively;  $P < .001$ ), although the magnitude of increased risk was considerably less prominent than that observed for mortality.

Complete data for multivariate analysis were available for 21 171 patients at 30 days and for 21 045 patients at 6 months. In multivariable analysis, Killip class III/IV was the most powerful predictor of mortality at both 30 days (hazard ratio [HR], 2.35; 95% confidence interval [CI], 1.69-3.26;  $P < .001$ ) and 6 months (HR, 2.12; 95% CI, 1.63-2.75;  $P < .001$ ) and was superior to age, ST depression, elevated CK-MB, heart rate, systolic blood pressure, and common aspects of medical history (FIGURE 3). Killip class II was an important predictor of mortality at both 30 days (HR, 1.73; 95% CI, 1.44-2.09;  $P < .001$ ) and 6 months (HR, 1.52; 95% CI, 1.31-1.76;  $P < .001$ ) (Figure 3).

A total of 18 variables at 30 days and 21 variables at 6 months provided statistically significant prognostic information (Figure 3). Five of these variables—age, Killip classification, heart rate, systolic blood pressure, and ST depression—provided more than 70% of the

**Figure 2.** Kaplan-Meier Curve of All-Cause Mortality in Combined Analysis of 26090 Patients With Non-ST-Elevation Acute Coronary Syndromes According to Killip Classification



$P < .001$  for comparison of Killip class I vs class II vs class III/IV.

prognostic information for the end points of 30-day and 6-month all-cause mortality (TABLE 2). The overall  $c$  statistic of the models at both 30 days and 6 months was 0.789. The Breslow-Day test comparing odds ratios for Killip class III/IV vs Killip class I/II across studies showed that the effect of Killip classification on mortality was not heterogeneous at 30 days ( $P = .47$ ) or at 6 months ( $P = .17$ ).

## COMMENT

This study of more than 26 000 patients with non-ST-elevation acute coronary syndromes indicates that assessment for the presence and severity of heart failure through Killip classification provides powerful independent prognostic information regarding both short-term (30-day) and long-term (6-month) all-cause mortality. Furthermore, Killip class III/IV is the most powerful predictor of short-term and long-term mortality in non-ST-elevation acute coronary syndromes. Thus, the physical examination should be viewed as an evidence-based aspect of the assessment of these patients, similar to interpretation of an electrocardiogram or measurement of serum cardiac markers. In fact, Killip class appears to be of greater prognostic importance than the results of these widely accepted studies.

Previous research of Killip classification in non-ST-elevation acute coronary syndromes has been limited to 2 studies to date. In 1 study, elevated Killip class was found to be a significant predictor of 1-year mortality, although the inclusion of in-hospital events such as recurrent ischemia and revascularization procedures in the multivariate analysis may have underestimated the prognostic strength of Killip class at the time of initial presentation.<sup>16</sup> In the other study, Killip class II or higher was a significant predictor of 90-day cardiovascular mortality.<sup>17</sup>

In contrast with Killip classification, the presence of heart failure on initial assessment has long been considered a risk factor for adverse outcomes.<sup>18</sup> However, there have been conflicting reports regarding the magnitude of risk associated with this finding, and its presence as an adverse factor has been notably absent in many risk-stratification studies.<sup>19-23</sup> This absence often simply is due to lack of information regarding physical examination findings at the time of presentation.<sup>19-21</sup> In other cases, the number of patients with heart failure is very small, making it difficult to achieve adequate statistical power.<sup>22,23</sup> Furthermore, our finding that higher Killip class is more strongly related to

risk of mortality than to that of myocardial infarction has important implications. In studies focusing on composite end points, heart failure and Killip class would be less impressive, if not insignificant, risk factors since their ability to predict common end points other than death is modest. Yet, in studies focusing solely on mortality, heart failure is often a powerful risk factor for death.<sup>24</sup>

Killip classification has been extensively studied in patients with ST-elevation myocardial infarction, in which it has been associated with high-risk characteristics, including increasing age, diabetes, prior myocardial infarction, and prior congestive heart failure.<sup>10,25,26</sup> In addition, these patients have more severe angiographic coronary artery disease, a higher incidence of depressed ventricular function, and larger myocardial infarctions.<sup>26</sup> In our study, patients with higher Killip class had similar high-

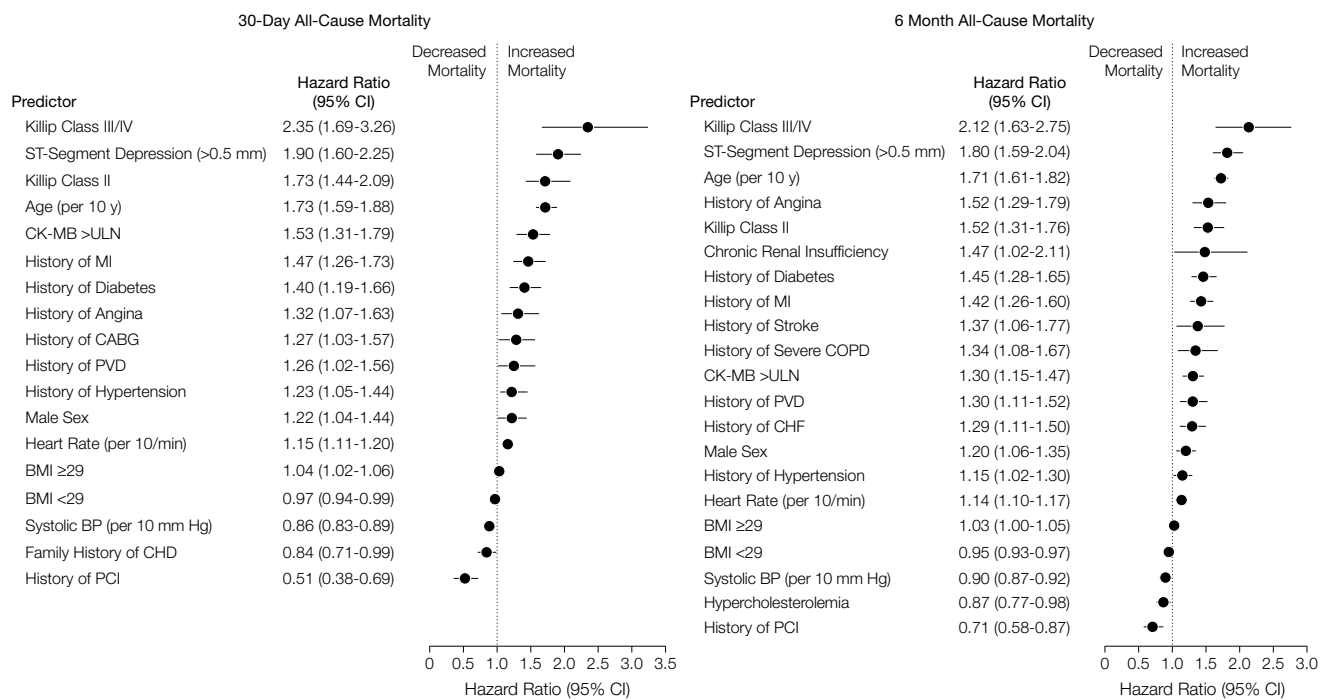
risk characteristics and were more likely to have ST depression, a marker for severe coronary disease,<sup>27</sup> and elevated cardiac enzymes consistent with myocardial infarction (Table 1). Thus, the demographic and clinical findings in non-ST-elevation acute coronary syndromes with higher Killip class parallel those found in ST-elevation myocardial infarction.

However, it is critically important to appreciate that elevated Killip class is not simply a surrogate marker for either these high-risk findings or ventricular dysfunction. Instead, it uniquely provides independent prognostic information that is unavailable by other means. In the GUSTO I trial, Killip class remained one of the most powerful predictors of mortality, despite controlling for more than 20 other baseline characteristics.<sup>9</sup> Similarly, the risk associated with elevated Killip class is independent of ventricular function and adds prognostic value in patients with

depressed ventricular function and those with normal ventricles.<sup>28-31</sup> The mechanism behind the increased risk associated with Killip class is unknown, although recent studies suggest that diastolic dysfunction<sup>32</sup> and a propensity to develop delayed left ventricular dilatation may play a role.<sup>26</sup>

Killip class IV or cardiogenic shock was a rare finding in our study, occurring in only 0.3% of patients. This finding may reflect considerable selection bias because higher-risk patients are less likely to be enrolled in clinical trials.<sup>33</sup> Yet our finding is in accordance with those of other studies indicating that cardiogenic shock at the time of initial presentation is far less common in patients with non-ST-elevation acute coronary syndromes than in those with ST-elevation myocardial infarction.<sup>34</sup> Instead, cardiogenic shock tends to develop during hospitalization, often secondary to recurrent ischemia or infarction.<sup>34</sup> Once it develops, it is asso-

**Figure 3.** Hazard Ratios for Significant Predictors of 30-Day and 6-Month All-Cause Mortality



CK-MB indicates creatine kinase MB fraction; ULN, upper limit of normal; MI, myocardial infarction; CABG, coronary artery bypass graft surgery; PVD, peripheral vascular disease; BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; PCI, percutaneous coronary intervention; CI, confidence interval; COPD, chronic obstructive pulmonary disease; and CHF, congestive heart failure.

ciated with an extremely high mortality rate, similar to that of cardiogenic shock complicating ST-elevation myocardial infarction.<sup>34</sup> The delay in presentation of cardiogenic shock in non-ST-elevation acute coronary syndromes creates a fortuitous window, during which early revascularization may prevent cardiogenic shock among those at greatest risk.

Our multivariable model underscores the importance of 5 factors—age, Killip class, heart rate, systolic blood pressure, and ST depression on electrocardiogram—which provide more than 70% of the prognostic information for both 30-day and 6-month mortality in non-ST-elevation acute coronary syndromes. These findings are analogous to those for ST-elevation myocardial infarction, in which these 5 factors—substituting infarction location for ST depression—provided more than 90% of the prognostic information for 30-day mortality.<sup>9</sup> The less-pronounced impact on mortality by these 5 factors in non-ST-elevation acute coronary may represent the more sudden and acute nature of complete coronary artery thrombosis in ST-elevation myocardial infarction, which makes immediate hemodynamic factors such as systolic blood pressure, heart rate, and Killip class of greater importance in determining prognosis. In addition, patients with non-ST-elevation acute coronary syndromes are more heterogeneous than those with ST elevation since they often include a minority who do not have significant coronary artery disease.<sup>27,35</sup> The prognosis of these low-risk patients is markedly different, making it more difficult to predict outcomes accurately in non-ST-elevation acute coronary syndromes. Nevertheless, these 5 factors should receive particular attention in the initial assessment of all patients with acute coronary syndromes, regardless of the presence or absence of ST elevation.

Guidelines for management of unstable angina and non-ST-elevation myocardial infarction, issued originally by the Agency for Health Care Policy and Research<sup>36</sup> and subse-

quently by the American College of Cardiology and the American Heart Association,<sup>18</sup> list a number of features associated with high risk of early death or nonfatal myocardial infarction. Our results confirm the appropriateness of many of these factors in predicting mortality, including age, tachycardia, hypotension, ST depression, elevated car-

diac enzymes, and heart failure (or, more specifically, Killip class). Additionally, our data support the high-risk nature of prior myocardial infarction, which is currently noted as an intermediate-risk finding, and diabetes mellitus, which is currently not listed. However, the 30-day mortality of patients with unstable angina classified as high risk by these

**Table 2.** Proportional Importance of Significant Predictors of All-Cause Mortality at 30 Days and 6 Months

Predictors	%	$\chi^2$	P Value
<b>30-Day All-Cause Mortality</b>			
Age	31.1	164.6	<.001
Systolic blood pressure	12.5	66.3	<.001
Killip class	11.4	60.1	<.001
ST-segment depression	10.4	54.9	<.001
Heart rate	8.4	44.4	<.001
CK-MB >upper limit of normal	5.4	28.4	<.001
History of myocardial infarction	4.3	22.6	<.001
History of PCI	3.6	19.3	<.001
History of diabetes	3.0	15.9	<.001
BMI $\geq 29$	2.6	13.6	<.001
History of angina	1.2	6.6	.01
History of hypertension	1.2	6.6	.01
BMI <29	1.1	5.8	.02
Male sex	1.1	5.8	.02
History of CABG	0.9	4.9	.03
History of PVD	0.9	4.6	.03
Family history of CHD	0.8	4.3	.04
<b>6-Month All-Cause Mortality</b>			
Age	37.2	279.1	<.001
ST-segment depression	11.1	83.1	<.001
Killip class	8.4	62.9	<.001
Systolic blood pressure	8.1	60.5	<.001
Heart rate	7.8	58.7	<.001
History of diabetes	4.6	34.4	<.001
History of myocardial infarction	4.4	32.7	<.001
History of angina	3.2	24.3	<.001
BMI <29	2.8	21.1	<.001
CK-MB >upper limit of normal	2.4	18.3	<.001
History of PCI	1.5	11.3	.001
History of CHF	1.5	11.3	.001
History of PVD	1.4	10.8	.001
Male	1.1	8.1	.004
History of severe COPD	0.9	7.1	.008
History of stroke	0.8	5.8	.02
BMI $\geq 29$	0.7	5.5	.02
Hypercholesterolemia	0.7	5.5	.02
History of hypertension	0.7	5.4	.02
Chronic renal insufficiency	0.6	4.3	.04

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CABG, coronary artery bypass graft surgery; CHD, coronary heart disease; CHF, congestive heart failure; CK-MB, creatine kinase MB fraction; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

guidelines was only 1.7% when prospectively studied.<sup>37</sup> This finding points to the need to develop more sophisticated algorithms of these risk factors to accurately predict a particular patient's risk of mortality.

Our analysis has several limitations. Our determination of Killip class was not standardized or adjudicated, although we believe it reflects typical clinical practice. In addition, there have been no prior studies on the accuracy, interrater reliability, and intrarater reliability of physicians' determinations of Killip classification. However, inaccurate assignment of patients due to these factors would have supported the null hypothesis, showing no relationship between Killip classification and mortality. Patients with underlying severe lung disease may have physical examination findings that mimic heart failure, confounding accurate determination of Killip classification. However, the relationship between Killip classification and mortality remained, even when controlling for this factor. In addition, the comparative value of Killip classification vs other risk stratification tests, such as nuclear and echocardiographic stress testing<sup>38,39</sup> or serum brain natriuretic peptide and C-reactive protein, is not known.<sup>40</sup> However, because these particular tests involve varying needs for sophisticated medical equipment, technical expertise, and patient stability, as well as considerable expense, we believe that there will be a continued prominent role for simple physical examination in early risk stratification of these patients. Our study predates the widespread adoption of serum troponin measurements; thus, its contemporary relevance may be questioned. However, CK-MB measurements remain widely used and are a well-validated predictor of mortality.<sup>15,41</sup> Furthermore, it is likely that higher Killip class represents a different risk process than that of elevated troponin level, particularly since it was completely independent of CK-MB. Finally, we studied patients enrolled in clinical trials, who may not fully reflect the broader community of

patients with non-ST-elevation acute coronary syndromes.

Our study underscores the independent prognostic importance of physical examination, particularly Killip classification, during the initial assessment of patients with non-ST-elevation acute coronary syndromes. In addition, 5 factors—age, Killip class, heart rate, systolic blood pressure, and electrocardiogram—provide important prognostic information for patients with acute coronary syndromes, regardless of ST elevation. Further studies are needed to better understand the pathophysiologic mechanisms behind Killip classification in non-ST-elevation acute coronary syndromes and to determine its potential role in risk-stratification algorithms.

**Author Contributions:** The authors designed and performed this study, had full access to the data, prepared the final manuscript, and controlled the decision to publish independently of the sponsors.

**Study concept and design:** U. Khot, Topol.

**Acquisition of data:** U. Khot, Jia, Moliterno, Lincoff, M. Khot, Harrington, Topol.

**Analysis and interpretation of data:** U. Khot, Jia, Moliterno, Lincoff, M. Khot, Harrington, Topol.

**Drafting of the manuscript:** U. Khot.

**Critical revision of the manuscript for important intellectual content:** U. Khot, Jia, Moliterno, Lincoff, M. Khot, Harrington, Topol.

**Statistical expertise:** U. Khot, Jia.

**Obtained funding:** Topol.

**Administrative, technical, or material support:** U. Khot, Moliterno, Lincoff, M. Khot, Harrington, Topol.

**Study supervision:** U. Khot, Topol.

**Funding/Support:** Various sponsors originally sponsored each individual study in this analysis: GUSTO IIb: Ciba-Geigy, Summit, NJ, Boehringer Mannheim, Indianapolis, Ind, and Guidant, Redwood City, Calif; PARAGON A: Hoffman La Roche, Basel, Switzerland; PARAGON B, Hoffman-La Roche; PURSUIT: Cor Therapeutics, South San Francisco, Calif, and Schering-Plough Research Institute, Kenilworth, NJ.

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The first idea that the child must acquire, in order to be actively disciplined, is that of the difference between good and evil, and the task of the educator lies in seeing that the child does not confound good with immobility, and evil with activity.

—Maria Montessori (1870-1952)