Relation of Characteristics of Metabolic Syndrome to Short-Term Prognosis and Effects of Intensive Statin Therapy After Acute Coronary Syndrome

An analysis of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial

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OBJECTIVE — We examined relations between characteristics of the metabolic syndrome, early cardiovascular risk, and effect of early, intensive statin therapy after acute coronary syndrome.

RESEARCH DESIGN AND METHODS — A total of 3,038 patients in the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial were characterized by the presence or absence of a history of diabetes, a history of hypertension and/or blood pressure ≥130/≥85, BMI >30 kg/m^2, HDL cholesterol <40 mg/dl (men) or <50 mg/dl (women), and triglycerides ≥150 mg/dl. Patients with three or more of these characteristics were categorized as having metabolic syndrome.

RESULTS — A total of 38% of patients (n = 1,161) met criteria for metabolic syndrome as defined in this study and had a 19% incidence of a primary end point event (death, nonfatal myocardial infarction, cardiac arrest, or recurrent unstable myocardial ischemia) during the 16-week trial. Patients with two or fewer characteristics (n = 1,877) were classified as not having metabolic syndrome and had a 14% incidence of a primary end point event. In univariate analysis, the individual characteristics that bore a significant relation to risk were diabetes and low HDL cholesterol. In a multivariable model including age, sex, and randomized treatment assignment, presence of metabolic syndrome was associated with a hazard ratio of 1.49 (95% CI 1.24–1.79, $P < 0.0001$). Relative risk reduction with 80 mg atorvastatin daily compared with placebo was similar in patients with and without metabolic syndrome.

CONCLUSIONS — Metabolic syndrome, as defined in the context of this clinical trial, is a strong predictor of early recurrent ischemic events after acute coronary syndrome.

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Abbreviations: ACS, acute coronary syndrome; IDF, International Diabetes Federation; MIRACL, Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; NCEP, National Cholesterol Education Program; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Clustering of clinical characteristics, including obesity, hypertension, glucose intolerance, and dyslipidemia, define a metabolic syndrome that is characterized by insulin resistance, systemic inflammation, and increased cardiovascular risk (1,2). The prevalence of metabolic syndrome is estimated at 24% of adults and >40% of elderly adults in the U.S. (3). Moreover, the prevalence of metabolic syndrome appears to be increasing rapidly (4), paralleling the increase in obesity and type 2 diabetes in the population.

Acute coronary syndrome (ACS), defined as acute myocardial infarction or unstable angina pectoris, accounts for 1–2 million hospital admissions annually in the U.S. (5). Features of metabolic syndrome are common among patients with ACS. Approximately 20–30% of patients with ACS have type 2 diabetes (6–8), and ~50% of patients meet criteria for hypertension, low HDL cholesterol, and/or high triglycerides as components of metabolic syndrome (9–10).

In patients with stable coronary heart disease, the presence of metabolic syndrome increases the risk of death or major nonfatal cardiovascular events but at the same time increases the absolute benefit achieved from long-term treatment with a statin (11). To date, it has not been determined whether the same paradigm of increased risk but increased benefit of statin treatment applies to patients with ACS and metabolic syndrome. We addressed these questions in an examination of data from the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial.

RESEARCH DESIGN AND METHODS

— The design and results of the MIRACL study have been previously reported (7). The trial was a multicenter study of 3,086 patients admitted to

Table 1—*Baseline characteristics by presence of the metabolic syndrome*

Risk factors	Metabolic syndrome	No metabolic syndrome	*P* value
n	1,161	1,877	
BMI >30 kg/m^2	532 (46)	178 (9)	
History of hypertension or elevated BP	1,045 (90)	1,077 (57)	
Low HDL cholesterol	886 (76)	397 (21)	
History of diabetes	554 (48)	148 (8)	
Triglyceride >150 mg/dl	1,018 (88)	731 (39)	
Age (years)	65 ± 11	65 ± 12	0.1903
Women	518 (45)	545 (29)	<0.0001
Index event = non–Q Wave MI	599 (52)	1,030 (55)	0.0780
Troponin I positive (>0 ng/ml)	927 (80)	1,452 (77)	0.1060
History of MI	337 (29)	420 (22)	<0.0001
Current smoker	287 (25)	559 (30)	0.0002
C-reactive protein (mg/l)	10 (5–33)	10 (4–38)	0.7767
Randomized atorvastatin treatment	568 (49)	948 (51)	0.3965

Data are *n* (%), means ± SD, or median (interquartile range) unless otherwise indicated. BP, blood pressure; MI, myocardial infarction.

the hospital with diagnoses of unstable angina or non–Q wave acute myocardial infarction (index events) and unequivocal objective evidence of acute myocardial ischemia or injury. Exclusion criteria included serum cholesterol >7.0 mmol/l (270 mg/dl), anticipated coronary revascularization, treatment with lipid-lowering drugs other than study medication, and brittle or type 1 diabetes. All patients provided informed consent. The protocol was approved by each local institutional review board.

Between 24 and 96 h after hospital admission, patients were randomly assigned to double-blind treatment with 80 mg/day atorvastatin or matching placebo for 16 weeks. Resting blood pressure and BMI were recorded at randomization. Plasma lipids and high-sensitivity C-reactive protein were measured at randomization and at follow-up visits. Presence or absence of a history of hypertension and/or diabetes was recorded on case report forms by the responsible investigator. The protocol did not specify measurement of fasting blood glucose or waist circumference. The primary efficacy outcome was the time to first occurrence of death from any cause, nonfatal acute myocardial infarction, cardiac arrest with resuscitation, or worsening angina with new objective evidence of ischemia requiring emergency rehospitalization. Secondary efficacy measures included all-cause mortality.

Definitions of diabetes, dyslipidemia, obesity, and hypertension

The analysis was undertaken post hoc after completion of the parent clinical trial. Patients with three or more of the following risk factors were defined as having metabolic syndrome: BMI >30 kg/m^2, triglycerides ≥150 mg/dl, HDL cholesterol <40 mg/dl in men or <50 mg/dl in women, a history of hypertension or baseline blood pressure ≥130/≥85 mmHg, and a history of diabetes. Due to limitations of the data collected in the MIRACL trial, this definition for the metabolic syndrome differs in some respects from the working definitions established by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (12), the World Health Organization (WHO) (13), and the International Diabetes Federation (IDF) (14). Waist circumference was not measured in the MIRACL trial; therefore, we used a criterion of BMI >30 kg/m^2 for obesity, as in the WHO definition. The MIRACL protocol did not specify that the baseline blood sample follow an overnight fast, as indicated in NCEP guidelines. Finally, because measurements of fasting blood glucose were not

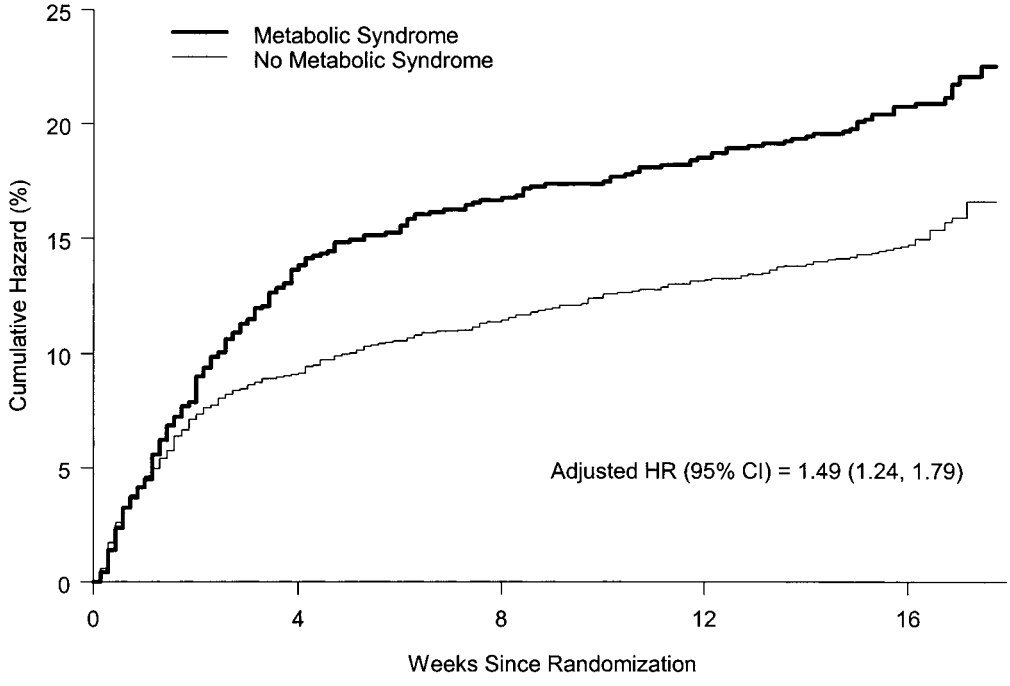

Figure 1—*Cumulative hazard of primary end point by presence of metabolic syndrome.*

Table 2—*Composite primary end point and its components by presence of the metabolic syndrome*

Characteristics	Metabolic syndrome	No metabolic syndrome
n	1,161	1,877
Primary end point	223 (19.2)	268 (14.3)
Death or nonfatal MI	146 (12.6)	174 (9.3)
Death	58 (5.0)	72 (3.8)
Nonfatal MI	100 (8.6)	111 (5.9)
Resuscitated cardiac arrest	8 (0.7)	9 (0.5)
Recurrent ischemia with evidence requiring hospitalization	104 (9.0)	120 (6.4)

Data are number of unique subjects (%).

specified in the MIRACL protocol, the criterion for diabetes was solely based upon a medical history of this condition.

Statistical analysis

Differences in baseline demographics between groups were summarized using Wilcoxon's rank-sum tests for continuous variables and χ^2 tests for categorical data. Prespecified Cox proportional hazards models with stratification for country and index event were used to assess association between baseline variables and the primary efficacy outcome. Separate models assessed association between these variables and the secondary efficacy outcome of all-cause mortality. Multivariable models included the main effects of sex, age, the presence of the metabolic syndrome and atorvastatin treatment. Interactions between metabolic syndrome and each of its components with treatment were also examined.

RESULTS — Analyses were performed on 3,038 of 3,086 randomized patients (98%) who had data recorded for all risk factors. A total of 38% ($n = 1,161$) of the analysis population met the definition for metabolic syndrome. Table 1 summarizes baseline characteristics of patients classified with and without metabolic syndrome. Comparisons between the two groups indicate that patients with metabolic syndrome were more likely to be female and to have a history of prior myocardial infarction and less likely to be current smokers relative to patients without metabolic syndrome. In the setting of an ACS event, C-reactive protein was markedly and similarly elevated in both groups.

The presence of metabolic syndrome was associated with increased risk of the composite primary outcome over the 16-week follow-up period (Fig. 1). The increase in risk was most pronounced between 2 and 6 weeks. By 16 weeks, 19% of the patients with metabolic syndrome and 14% of the patients without metabolic syndrome had experienced a primary end point event (Table 2). In addition, patients with metabolic syndrome were at greater risk of experiencing each of the components of the primary composite end point. The hazard ratio for a primary end point event associated with metabolic syndrome was 1.30 in males and 1.92 in females, with interaction between metabolic syndrome and sex of borderline significance ($P = 0.052$).

Unadjusted and multivariable hazard ratios for the composite primary outcome are listed in Table 3. The univariate effects of individual components of metabolic syndrome on the risk of a primary end point event are shown in Fig. 2. In the unadjusted models, metabolic syndrome and the individual components of diabetes and low HDL were associated with increased risk for the primary outcome. In particular, the combined presence of diabetes and low HDL cholesterol was associated with nearly an 8% increase in absolute risk (Fig. 2). In the multivariable model, metabolic syndrome was associated with a 49% increased risk (95% CI 24–79%, $P < 0.0001$) for the primary outcome. A similar result was observed for all-cause mortality (hazard ratio [HR] [95% CI] 1.49 [1.04–2.14], $P = 0.029$).

In models with the primary composite end point as the outcome, there were no statistically significant interactions between metabolic syndrome or its individual components and treatment assignment (all $P > 0.10$). This indicates that there was no evidence that the relative risk reduction associated with atorvastatin treatment was different among patients who did or did not meet the definition of metabolic syndrome or among those who did or did not have each of the individual component characteristics.

Table 3—*Univariate and multivariable analyses of metabolic syndrome as a predictor of primary end point*

	Primary end point univariate model	*P*	Primary end point multivariable model	*P*
Metabolic syndrome	1.40 (1.16–1.67)	<0.001	1.49 (1.24–1.79)	<0.0001
Component characteristics				
BMI > 30 kg/m^2	0.96 (0.77–1.19)	0.71		
History of hypertension or elevated BP at randomization	1.02 (0.83–1.24)	0.88		
Low HDL cholesterol	1.28 (1.07–1.53)	<0.01		
History of diabetes	1.33 (1.09–1.62)	<0.01		
Triglyceride >150 mg/dl	1.17 (0.97–1.40)	0.10		
Age, 1-year increment	1.03 (1.03–1.04)	<0.0001	1.04 (1.03–1.05)	<0.0001
Female sex	0.94 (0.78–1.14)	0.54	0.77 (0.63–0.93)	<0.01
Atorvastatin treatment			0.84 (0.70–1.00)	0.047

Data are HRs (95% CI) unless otherwise indicated. All models include randomized treatment assignment with country and index event as stratification factors. All interactions of metabolic syndrome and risk factors with treatment yielded *P* values >0.10.

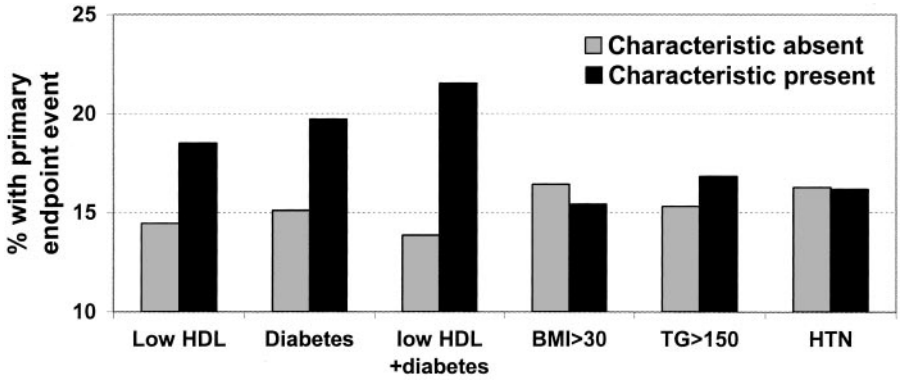

Figure 2—*Univariate effects of individual characteristics of metabolic syndrome on risk of primary end point events.*

To further explore the risk reduction in the primary composite associated with atorvastatin treatment, the HR and absolute risk reduction for treatment was calculated for subgroups defined by the number of metabolic syndrome risk factors (Table 4). Relative and absolute risk reductions were consistent across the subgroups except for the group with three risk factors. Given the absence of significant interaction between metabolic syndrome and treatment and the consistency of treatment effect with atorvastatin in the other five subgroups (20–33% relative risk reduction, 3.5 –6.5% absolute risk reduction), the increased risk observed in patients with three risk factors is most likely a chance finding.

CONCLUSIONS — This study demonstrates that patients with characteristics of metabolic syndrome are at substantially increased risk for recurrent cardiovascular events after an index ACS event. During the 16 weeks following ACS, patients with metabolic syndrome (as defined in this analysis) had unadjusted relative and absolute risks of death, reinfarction, cardiac arrest, or emergency rehospitalization for recurrent myocardial ischemia that were 34 and 5% higher, respectively, than patients without metabolic syndrome. The individual characteristics of metabolic syndrome that accounted for increased risk were diabetes and low HDL cholesterol. Risk was less strongly related to elevated triglycerides and was not related to hypertension or obesity (BMI >30 kg/m^2).

When the MIRACL trial was designed in 1995–96, recognition of the importance of metabolic syndrome was less widespread than at present. Consequently, some of the data needed to classify patients according to NCEP, WHO, or IDF definitions of metabolic syndrome (12–14) were not collected. With respect to the criterion for abnormal glucose metabolism, fasting blood glucose and insulin levels were neither protocol specified nor systematically measured in MIRACL; consequently, this analysis used the simple criterion of a medical history of diabetes. With respect to the criterion for obesity, measurements of waist and hip circumference were neither protocol specified nor systematically made in the MIRACL trial; therefore, the present analysis utilized the WHO criterion of BMI >30 kg/m^2. We used the shared NCEP and IDF definitions of hypertension, low HDL cholesterol, and elevated triglycerides. Although the definitions used in the present analysis most likely define a subset of patients with an insulin resistance syndrome, they do not define precisely the same subset of patients that would have been identified by applying all NCEP, WHO, or IDF criteria for metabolic syndrome. Nonetheless, the classification scheme used in the present analysis is consistent with the broader definition of metabolic syndrome proposed in the American Diabetes Association consensus statement (15). Moreover, because a placebo-controlled trial of a statin in ACS is no longer feasible, it is unlikely that the questions investigated in this study will ever be addressed prospectively.

Our finding of a strong association between diabetes and short-term risk after ACS is concordant with findings in previous studies of patients with ACS. For example, in analyses of the GUSTO-IIB (Global Use of Strategies to Open Occluded Coronary Arteries IIB) and SYMPHONY (Ischemic Heart Events Post-Acute Coronary Syndromes) trials, diabetes increased risk in the 3–6 month period after ACS by 20–65% (16,17). Our finding is also in agreement with that of Stern et al. (18), who concluded that the excess risk associated with metabolic syndrome in patients with stable coronary heart disease was attributable to the diabetic component of this syndrome. Prior analyses have shown that following ACS, nondiabetic patients with impaired glucose tolerance or insulin resistance are at substantially increased risk compared with patients with normal glucose tolerance and insulin sensitivity (19–21). It is likely that many nondiabetic patients with impaired glucose tolerance would have been classified as having metabolic syndrome by NCEP or WHO criteria but were not classified as such in the present analysis. Therefore, our analysis may underestimate the actual difference in risk between patients with and without metabolic syndrome.

Table 4—*Cumulative incidence of composite primary end point by number of risk factors and treatment*

Number of risk factors	Placebo	Atorvastatin	Atorvastatin:placebo	All subjects
n	1,522	1,516		3,038
0	21/123 (17.1)	15/110 (13.6)	0.76 (0.36–1.58)	36/233 (15.5)
1	63/383 (16.4)	46/374 (12.3)	0.80 (0.54–1.17)	109/757 (14.4)
2	67/423 (15.8)	56/464 (12.1)	0.76 (0.53–1.08)	123/887 (13.9)
3	64/345 (18.6)	77/356 (21.6)	1.19 (0.84–1.66)	141/701 (20.1)
4	42/201 (20.9)	24/167 (14.4)	0.67 (0.40–1.11)	66/368 (17.9)
5	9/47 (19.1)	7/45 (15.6)	0.70 (0.23–2.11)	16/92 (17.4)

Data are *n*, *n*/N (%), or HRs (95% CI).

There are surprisingly few data relating lipid and lipoprotein measurements at the time of ACS to short-term risk following ACS. In an analysis of the MIRACL trial that considered lipid and lipoprotein measurements as continuous variables, HDL cholesterol and its associated apolipoprotein A-I were the only ones to bear a significant relation to short-term risk (22).

Obesity, particularly abdominal obesity, has been associated with risk of first and recurrent cardiovascular events (23–25) but has not been well studied in relation to short-term risk following ACS. In the present analysis, the absence of a univariate relation between obesity and short-term risk after ACS may reflect the fact that BMI is a less robust indicator of cardiovascular risk than measures of abdominal obesity (i.e., waist circumference or waist-to-hip ratio). For example, in a study of 8,800 patients with stable cardiovascular disease followed for 4.5 years, BMI was not predictive of cardiovascular mortality, but waist circumference and waist-to-hip ratio were predictive (24). Second, obese patients who present with ACS have been observed to have less severe coronary disease at angiography than nonobese patients (26), a factor that may mitigate prognosis in obese patients. Finally, obesity may not have been a univariate predictor of risk in the present analysis because patients with BMI >30 kg/m^2 were more likely to have other characteristics associated with lower risk: patients with BMI >30 were more often female (44 vs. 33% of patients with BMI ≤30) and younger (mean age 62 vs. 66 years for patients with BMI ≤30).

Hypertension was the most prevalent individual characteristic among patients who met our definition of metabolic syndrome, but we did not find a univariate relation between hypertension and short-term risk after ACS. This is consistent with findings of several prior analyses indicating that a history of hypertension is a nonsignificant or modest predictor of short- and long-term cardiovascular risk after acute myocardial infarction (27–29), particularly when patients are well treated (30).

Importantly, we found no significant interaction between features of the metabolic syndrome and treatment assignment (80 mg atorvastatin or placebo) on short-term risk of ischemic cardiovascular events after ACS. Thus, even though characteristics of diabetes and/or low HDL cholesterol identified patients at increased risk, they did not identify patients who derive greater or less relative benefit from early treatment with 80 mg atorvastatin daily. Nonetheless, patients with these characteristics derive greater absolute benefit from early treatment with 80 mg atorvastatin daily compared with patients without these characteristics. Accordingly, in the entire MIRACL study population, treatment with 80 mg atorvastatin reduced the absolute risk of a primary end point event by 2.6% compared with treatment with placebo. Among patients with diabetes or low HDL cholesterol, treatment with 80 mg atorvastatin reduced absolute risk by 4.4 or 3.7%, respectively.

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