

Impact of Combination Evidence-Based Medical Therapy on Mortality in Patients With Acute Coronary Syndromes

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Background—Several individual pharmacological agents, such as antiplatelet drugs, β -blockers, ACE inhibitors, and lipid-lowering agents, have proven efficacy in reducing mortality in patients with acute coronary syndromes. However, the impact of the combination of these agents on clinical outcomes has not been studied before.

Methods and Results—A total of 1358 consecutive patients presenting with acute coronary syndromes between January 1999 and March 2002 were identified, and data on baseline demographics, comorbidities, and in-hospital management were collected. On the basis of discharge use of evidence-based therapies, we created a composite appropriateness score depending on the number of the drugs used divided by the number of the drugs potentially indicated for each patient. The impact of the composite score on 6-month mortality was analyzed using a risk-adjusted logistic regression model. The odds ratio for death for all indicated medications used (appropriateness level IV) versus none of the indicated medications used (appropriateness level 0) was 0.10 (95% CI, 0.03 to 0.42; $P<0.0001$); similarly, odds ratio for appropriateness level III versus level 0 was 0.17 (95% CI, 0.04 to 0.75; $P=0.0018$), odds ratio for appropriateness level II versus level 0 was 0.18 (95% CI, 0.04 to 0.77; $P=0.01$), and odds ratio for appropriateness level I versus level 0 was 0.36 (95% CI, 0.08 to 1.75; $P=0.20$).

Conclusions—Use of combination evidence-based medical therapies was independently and strongly associated with lower 6-month mortality in patients with acute coronary syndromes. Such therapies, most of which are generic and inexpensive today, seem to offer a marked survival advantage compared with patients in whom such therapies are omitted. (*Circulation*. 2004;109:745-749.)

Key Words: coronary disease ■ mortality ■ survival ■ myocardial infarction

The term *acute coronary syndrome* (ACS) refers to a spectrum of acute severe cardiac disorders that include unstable angina, non-ST-segment elevation myocardial infarction, and ST-segment elevation myocardial infarction. These disorders are characterized by myocardial oxygen demand and supply mismatch, most often caused by atherosclerotic coronary artery disease. Patients presenting with ACS represent a major health problem, accounting for 2.5 million hospitalizations and 500 000 deaths annually in the United States alone. Of these, 1.5 million have a final diagnosis of unstable angina, and myocardial infarction (ST-segment and non-ST-segment elevation) accounts for the remaining 1 million.¹

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We systematically assessed the discharge use of evidence-based medical therapy in consecutive patients admitted with ACS at our institution. Applying a point each to discharge use of antiplatelet agents, β -blockers, ACE inhibitors, and lipid-lowering agents, we then created a composite appropriateness score. The impact of the composite score on 6-month mor-

tality rate was ascertained by using a risk-adjusted logistic regression model.

Methods

Patients

There were 1358 consecutive patients who were admitted to or discharged from inpatient services at the University of Michigan Medical Center from January 1, 1999, to March 11, 2002, with a diagnosis of unstable angina or acute myocardial infarction. All patients were identified by admission or discharge diagnoses; then, the charts were reviewed to screen for entry criteria. Inclusion in the study required 1 or more of the following: symptoms consistent with acute coronary insufficiency, electrocardiographic changes suggestive of ischemia, or elevation of cardiac biomarkers. A final diagnosis of myocardial infarction required elevation of creatine kinase-MB or troponin, as described in the American College of Cardiology (ACC) guidelines.² Ninety-four patients had documented contraindications to β -blocker or ACE inhibitor and were excluded from the analysis. The study cohort included the remaining 1264 patients. The institutional review board at the University of Michigan approved the study protocol, and all patients gave informed consent to participate.

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TABLE 1. Composite Appropriateness Score Based on Use of Evidence-Based Medications

Appropriateness of Evidence-Based Therapy*	Score	Level
None of the indicated medications used	0	0
1 Medication used if 3 or 4 medications indicated	25 or 33.3	I
2 Medications used if 3 or 4 medications indicated or 1 medication used if 2 medications indicated	50 or 66.7	II
3 Medications used if 4 medications indicated	75	III
All indicated medications used	100	IV

*Evidence-based therapy included antiplatelet agents, β -blockers, ACE inhibitors, and lipid-lowering therapy.

Data Collected

Clinical, demographic, treatment, and outcome data were abstracted from medical charts by trained abstractors (cardiology fellows and cardiology research nurses). Definitions were based on those recommended by the ACC data standards committee.³ Demographic variables included age and gender. Comorbidities included smoking, diabetes, hyperlipidemia, hypertension, obesity, and prior history of heart disease (angina, heart failure, myocardial infarction, coronary artery bypass grafting, and percutaneous coronary intervention). ECG changes and initial laboratory data were recorded. Data describing patient management included use of β -blockers, aspirin, ACE inhibitors or angiotensin receptor blockers, lipid-lowering agents, and percutaneous coronary interventions or coronary artery bypass grafting. Discharge medications, hospital length of stay, and number of days spent in the coronary care unit were recorded. Mortality data at 6-month follow-up were obtained for 100% of the patients from health system record review or phone call interview.

Appropriateness Algorithm

An appropriateness algorithm for the use of each of the various secondary pharmacological prevention strategies was created using evidence-based clinical practice guidelines from the ACC and the American Heart Association (AHA).^{4–7} Class I recommendations from ACC/AHA guidelines were used to develop the appropriateness algorithm. On the basis of this information, patients were considered candidates for lipid-lowering therapy if they had known hyperlipidemia. Hyperlipidemia was defined as meeting any of the following criteria: total cholesterol ≥ 200 mg/dL, LDL ≥ 100 mg/dL, triglycerides ≥ 200 mg/dL, or past/present use of lipid-lowering agents.⁸ ACE inhibitors were judged indicated for patients with any of the following conditions: hypertension, heart failure, diabetes, or a documented ejection fraction (EF) $< 40\%$. All patients with ACS were considered candidates for antiplatelet therapy, β -blockers, dietary modification, exercise training, and complete cessation from smoking. Patients with known contraindications to any of these agents, such as ACE inhibitors (intractable cough or angioedema) or β -blockers (severe heart failure or worsening bronchospasm), were excluded from analysis. The percentage of patients undergoing appropriate evidence-based therapy among those considered eligible was then calculated at hospital discharge. For each patient, there were 4 possible recommended drugs: antiplatelet agents, lipid-lowering therapy, ACE inhibitors, and β -blockers. A composite appropriateness score was calculated for each patient on the basis of the number of the drugs used at discharge divided by the number of the drugs indicated, expressed as a percentage. Composite appropriateness level was determined for each patient on the basis of the following algorithm: 0, none of the indicated medications used (score, 0); I, 1 medication used if 3 or 4 medications indicated (score, 25 or 33.3); II, 2 medications used if 3 or 4 medications indicated or 1 medication used if 2 medications indicated (score, 50 or 66.7); III, 3 medications used if 4 medications indicated (score, 75); and IV, all indicated medications were used (score, 100) (Table 1).

Statistical Analysis

Baseline characteristics were summarized by the use of frequencies and percentages for categorical factors and means and SD for continuous factors. A multivariable logistic regression analysis was performed for 6-month follow-up death in ACS patients with the composite appropriateness variable adjusted for age, gender, positive biomarker, new ST elevation, left ventricular ejection fraction, history of diabetes, renal failure, heart failure, and revascularization. The composite appropriateness for each patient was expressed as the composite appropriateness level from 0 to IV. Both a c-index (measure of model discrimination) and Hosmer-Lemeshow test (measure of model calibration) were used to determine the performance of the multivariate models. All analyses were performed using SAS version 8.2 (SAS Institute).

Results

The baseline characteristics of the study cohort are shown in Table 2. The mean age was 63.7 ± 13.3 years, and 63% were men. Comorbidities included a history of angina in 60.4%, prior myocardial infarction in 42.9%, a history of diabetes mellitus in 30.5%, hypertension in 66.8%, and hyperlipidemia in 60.6%. Approximately 15% presented with ST-segment elevation myocardial infarction, 55% with non-ST-segment elevation myocardial infarction, and 30% with unstable angina. Most patients were in Killip class I or II on presentation.

Two thirds of the patients underwent coronary angiography, and approximately 48% underwent either percutaneous or surgical coronary revascularization (Table 3). The use of antiplatelet medications at discharge was $\approx 95\%$, use of β -blockers was $\approx 82\%$, and, among appropriate patients, use of ACE inhibitors was 60% and lipid-lowering drugs were prescribed in 84% (Table 4).

The odds ratio for death for all indicated medications used (appropriateness level IV) versus none of the indicated medication used (appropriateness level 0) was 0.10 (95% CI, 0.03 to 0.42; $P < 0.0001$); similarly, odds for mortality for appropriateness level III versus level 0 was 0.17 (95% CI, 0.04 to 0.75; $P = 0.0018$), odds for appropriateness level II versus level 0 was 0.18 (95% CI, 0.04 to 0.77; $P = 0.019$), and odds for appropriateness level I versus level 0 was 0.36 (95% CI, 0.08 to 1.75; $P = 0.20$) (Table 5, Figure). Higher ejection fraction was associated with significantly better survival, and use of revascularization was associated with a strong trend toward improved survival. The c-index for the model was 0.84, suggesting excellent model discrimination, and the Hosmer-Lemeshow test statistic was 0.44, suggesting adequate model calibration and goodness of fit.

Discussion

Cardiovascular disease remains the leading cause of morbidity and mortality in the United States.¹ The past decade has seen a significant increase in pharmacological therapies with proven efficacy in reducing morbidity and mortality in patients with vascular diseases. These agents, including antiplatelet agents, statins, β -blockers, and ACE inhibitors, are individually very effective in reducing secondary cardiovascular events. However, when prescribed together, they may be even more effective and may have incremental and even synergistic benefits in eligible patients.⁹ Despite strong and unequivocal benefits of these pharmacological agents,

TABLE 2. Diagnosis, Baseline Characteristics, and Clinical Presentation of Patients Presenting With Acute Coronary Syndromes (n=1264)

Diagnosis	
ST-elevation myocardial infarction	194 (15.35)
Non-ST-elevation myocardial infarction	695 (54.98)
Unstable angina	375 (29.67)
Demographics	
Mean age $\pm$ SD, y	63.7 $\pm$ 13.26
Male gender	804 (63.61)
Body mass index $\pm$ SD	28.7 $\pm$ 7.18
Prior angina	762 (60.48)
Prior myocardial infarction	540 (42.89)
Prior stroke	148 (11.76)
Prior heart failure	260 (22.60)
Previous coronary intervention	338 (26.83)
Previous bypass surgery	291 (23.06)
Smoker (current or former)	798 (63.28)
Diabetes	386 (30.54)
Hypertension	840 (66.88)
Hyperlipidemia	763 (60.60)
Clinical presentation	
Pulse, bpm	80.1 $\pm$ 22.64
Systolic blood pressure, mm Hg	141.0 $\pm$ 28.21
Diastolic blood pressure, mm Hg	78.9 $\pm$ 17.64
Cardiac arrest	22 (1.74)
Killip class	
I	994 (78.76)
II	174 (13.79)
III	57 (4.52)
IV	26 (2.06)
Positive cardiac biomarkers	876 (69.30)
Serum creatinine, mg/dL	1.25 $\pm$ 1.01
Electrocardiogram	
New ST-segment depression	185 (14.64)
New ST-segment elevation anterior	84 (6.65)
New ST-segment depression anterior	71 (5.62)
New significant Q wave	39 (3.09)
Other ECG changes*	2 (0.16)

Values are given as n (%) or mean $\pm$ SD.

*Other ECG changes include atrioventricular block, ventricular paced rhythm, atrial fibrillation/flutter, right ventricle infarction, posterior infarction, and left ventricular hypertrophy.

TABLE 3. Management of Patients Presenting With ACS (n=1264)

Cardiac catheterization	832 (65.82)
Coronary intervention	505 (39.95)
Bypass surgery	91 (7.20)
Noninvasive stress test	358 (28.32)
Pulmonary artery catheter	107 (8.47)
Ventilator	121 (9.57)
Intra-aortic balloon pump	64 (4.22)

Values are given as n (%).

tinuous quality-improvement initiatives, such as the ACS Guidelines Applied in Practice project,¹¹ are particularly relevant to this concept, because the creation of effective care systems serves to maximize secondary prevention after ACS.

Multiple studies have demonstrated effectiveness of statin therapy in patients presenting with ACS.^{12–20} Statins not only lower lipids but also have salutary effects on platelet adhesion, thrombosis, endothelial function, inflammation, and plaque stability. The Heart Protection Study (HPS) has provided additional evidence for clinical benefits for a wide range of high-risk patients with coronary and vascular diseases.²¹ The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study²² randomized 19 342 patients with hypertension and at least 3 other cardiovascular risk factors to a combination of old (β -blocker and diuretic) or new (ACE inhibitor and calcium antagonist) therapies. A total of 10 305 patients who were not undergoing cholesterol-lowering therapy and who had high cholesterol were then rerandomized, double-blind, to placebo or atorvastatin. There were 32 fewer strokes with atorvastatin therapy (1 less for every 1000 treated per year) in this study.²²

Antiplatelet therapy has been demonstrated to be significantly beneficial in patients with ACS, with a survival advantage demonstrated with aspirin by the Antithrombotic Trialists Collaboration meta-analysis.²³ Our study predates recent recommendations regarding dual antiplatelet therapy with clopidogrel, and most patients received aspirin monotherapy.

The Heart Outcomes Prevention Evaluation study demonstrated that ramipril, an ACE inhibitor, significantly reduced the rate of cardiovascular death, myocardial infarction, and stroke in patients at high risk of cardiovascular events.²⁴ Ellis et al²⁵ recently demonstrated benefit of ACE inhibitors in patients undergoing coronary stenting. One study has demonstrated that ACE inhibition reduces troponin release in non-ST-elevation ACS, perhaps mediated by the beneficial effects of ACE on vascular reactivity and the coagulation system.²⁶ The EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) demonstrated that among patients with stable coronary heart disease without apparent heart failure, perindopril can significantly improve outcome.²⁷ Approximately 50 patients need to be treated for a period of 4 years to prevent 1 major cardiovascular event.²⁷ Present ACC/AHA guidelines suggest that ACE inhibitors should be considered for secondary prevention for all patients with known coronary disease⁷ and

secondary preventive therapies continue to be underutilized.¹⁰ In the present study, we demonstrate that combination evidence-based medical therapy was independently and strongly associated with lower 6-month mortality in patients with ACS. On the basis of the number of appropriate agents used, there was a 72% to 87% reduction in mortality in these individuals. Evidence-based medical therapies, most of which are generic and inexpensive today, when used in combination may have a striking survival advantage. Our findings thus have significant clinical and health policy implications. Con-

TABLE 4. Use of Evidence-Based Pharmacological Therapy at Hospital Discharge After ACS

Pharmacological Therapy	No. of Patients Indicated to Use the Medication	No. of Patients Given Agent at Discharge* (%)	No. of Patients Not Receiving Agent (%)
Antiplatelet therapy	1264	1200 (94.94)	64 (5.06)
β -Blockers	1264	1037 (82.04)	237 (17.96)
ACE inhibitors	1104	661 (59.87)	443 (40.13)
Lipid-lowering agents	1002	841 (83.93)	161 (16.07)

*The percentages are based on the number of patients these drugs were indicated for according to ACC/AHA guidelines.

offered to patients with clinical heart failure, left ventricular dysfunction, or ACS accompanied by hypertension.

β -Blockers have been shown in many clinical trials to improve the survival rate of patients with recent ACS. These agents have also been shown in several large randomized trials to improve the survival rate and prevent stroke and heart failure in patients with coronary artery disease.²⁸ In the Atenolol Silent Ischemia Trial (ASIST), patients with documented coronary disease and angina were treated with 100 mg of atenolol daily.²⁹ After 1 year, fewer patients in the atenolol group experienced the combined end point of death, ventricular tachycardia and fibrillation, myocardial infarction, hospitalization, aggravation of angina, or revascularization.²⁹ The atenolol-treated patients also had a longer time until their first adverse event. β -Blockers are presently indicated in all patients with ACS in the absence of contraindications.³⁰ The absolute cardiac contraindications for the use of β -blockers are severe bradycardia, preexisting high-grade AV block, sick sinus syndrome, and severe, unstable heart failure (mild to moderate heart failure is actually an indication for β -blockers). Asthma and bronchospasm are relative contraindications.

Thus, medications such as statins, antiplatelet agents, β -blockers, and ACE inhibitors have been associated with significantly improved outcomes in patients presenting with ACS. However, data on the efficacy of these agents when used in combination in appropriately indicated patients are not available. In this study, we have shown significant

synergistic effects of antiplatelet therapy, statins, ACE inhibitors, and β -blockers when used together in patients with ACS. Combined treatment correlated with a striking survival advantage at just 6 months of follow-up. A recent hypothetical analysis using Markov modeling of a polypill strategy to simultaneously reduce 4 cardiovascular risk factors (low-density lipoprotein cholesterol, blood pressure, serum homocysteine, and platelet function) demonstrated that combination strategy may reduce cardiovascular disease by >80%.³¹ Our study also demonstrated a strong trend toward improved survival at 6 months with revascularization, consistent with the Fast Revascularization during Instability in Coronary artery disease-II (FRISC II) study, which demonstrated a survival advantage with revascularization at 2 years of follow-up.³²

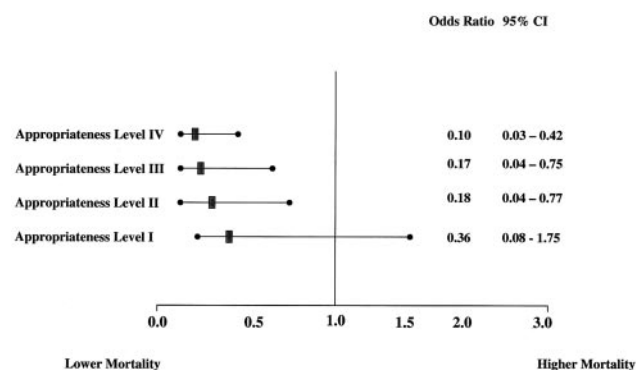
There are several potential limitations of our study. The appropriateness assessment for evidence-based therapy was based on ACC/AHA class I guidelines by retrospective review. If patients had previously experienced untoward reactions or contraindications to therapy, which was not documented, this may have been underrepresented with our sampling methodology. This might significantly overestimate the potential opportunity to improve secondary preventive measures.

Patients presenting with ACS represent an important high-risk cohort, where secondary vascular disease prevention is likely to be particularly effective and cost-effective. Clinicians have an opportunity to provide high-quality and appro-

TABLE 5. Multivariable Predictors of 6-Month Mortality After Acute Coronary Syndrome

	Adjusted Odds Ratio	95% CI	P
Age	1.05	1.03–1.07	<0.0001
Biomarker (+)	1.91	1.19–3.06	0.007
Diabetes mellitus	1.28	0.74–2.22	0.37
Renal insufficiency	1.65	0.86–3.15	0.12
Heart failure at presentation	2.87	1.60–5.14	0.004
Ejection fraction	0.96	0.94–0.98	<0.0001
Revascularization	0.24	0.05–1.24	0.08
Appropriateness level			
IV	0.10	0.03–0.42	<0.0001
III	0.17	0.04–0.75	0.0018
II	0.18	0.04–0.77	0.0195
I	0.36	0.08–1.75	0.2042

C-index for the model was 0.84; Hosmer-Lemeshow test statistic was 0.44.



Effect of combined use of evidence-based medical therapies on 6-month mortality in patients with ACS. Composite appropriateness levels (I through IV) are compared with level 0 (nonuse of any of the indicated medications) and show a gradient of survival benefit in this cohort. The number of patients in each appropriateness category was as follows: appropriateness level 0, n=21; level 1, n=91; level 2, n=302; level 3, n=314; and level 4, n=630.

appropriate evidence-based care to this high-risk cohort and to seize this opportunity in aggressively treating the underlying atherosclerotic process through lifestyle modifications and effective pharmacological therapies. However, despite strong and unequivocal benefits of these agents, secondary preventive therapies continue to be underutilized, as demonstrated in previous studies^{10,33} and in the present study. Attention to these disease-management opportunities has significant survival advantage in this high-risk cohort and underscores the importance of ACC- and AHA-initiated projects, such as the Guidelines Applied in Practice¹¹ and the Get with the Guidelines program, to improve utilization of appropriate therapies.

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