Prevalence, Predictors, and Impact of Conservative Medical Management for Patients With Non–ST-Segment Elevation Acute Coronary Syndromes Who Have Angiographically Documented Significant Coronary Disease

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Objectives We sought to characterize the utilization and impact of a conservative medical management strategy for patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS) and significant coronary artery disease on early angiography.

Background Practice guidelines recommend an early invasive management strategy for NSTE ACS, but revascularization procedures may not always be performed after early angiography, even when significant coronary artery disease is present.

Methods We evaluated 8,225 intermediate- to high-risk NSTE ACS patients with at least 1 coronary lesion >50% stenosis on early angiography from the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors) trial (2001 to 2003), comparing patients treated with conservative medical management with those who underwent in-hospital percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within 7 days of randomization.

Results A total of 2,633 patients (32%) were medically managed, 4,294 (52%) underwent PCI, and 1,298 (16%) underwent CABG. The strongest independent predictors of conservative medical management versus any intervention were prior CABG, lower body weight, lack of a reinfarction between randomization and catheterization, and 3-vessel disease. With conservative medical management, the cumulative risk of 1-year mortality after discharge increased rapidly during the first 90 days and thereafter remained higher at 7.7% compared with that seen in patients treated with PCI (3.6%) or CABG (6.2%).

Conclusions One-third of patients with NSTE ACS and significant coronary disease on early angiography were managed without in-hospital revascularization in the SYNERGY trial, and these patients had an increased risk of late mortality. These findings highlight the need for novel treatment approaches for NSTE ACS patients who are not candidates for revascularization. (SYNERGY trial; NCT00043784) (J Am Coll Cardiol Intv 2008;1:369–78) © 2008 by the American College of Cardiology Foundation

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Clinical practice guidelines recommend an early invasive management treatment strategy for intermediate- to high-risk patients with non–ST-segment elevation acute coronary syndromes (NSTE ACS) (1,2). However, angiography is a diagnostic procedure that does not confer treatment benefit if patients do not undergo a subsequent revascularization procedure (3). In 4 randomized trials comparing conservative medical management with early invasive management for NSTE ACS, the majority of patients had significant coronary disease identified on angiography in the early invasive treatment arms (75% to 87%), but the use of in–hospital percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) varied from 59% to 82% (4–7). Data from a contemporary registry showed that approximately 25% of NSTE ACS patients with 3-vessel disease did not undergo revascularization (8). These data suggest that many NSTE ACS patients in contemporary practice with significant coronary artery disease (CAD) on early angiography do not undergo early revascularization, but the long-term consequences of a conservative medical management approach have not been fully explored.

We, therefore, sought to describe the prevalence and predictors of a conservative medical management treatment strategy for patients with NSTE ACS and significant CAD on early angiography, and to investigate the long-term risk of adverse outcomes in these patients compared with that seen in patients who underwent revascularization.

Abbreviations and Acronyms

- CABG = coronary artery bypass grafting
- CAD = coronary artery disease
- DES = drug-eluting stent(s)
- GRACE = Global Registry of Acute Coronary Events score
- MI = myocardial infarction
- NSTE ACS = non–ST-segment elevation acute coronary syndromes
- PCI = percutaneous coronary intervention

Methods

Study design and subjects. We performed a subgroup analysis of patients with significant disease on coronary angiography enrolled in the SYNERGY (Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIa Inhibitors) trial, which randomized 9,978 patients from 12 countries between August 2001 and December 2003 (9,10). The SYNERGY trial was an open-label trial designed to evaluate the efficacy and safety of enoxaparin versus unfractionated heparin when administered with established guidelines-recommended therapy in patients with NSTE ACS planned for an early invasive strategy. Patients were eligible for study participation if they had ≥2 of the following high-risk features: age ≥60 years, ST-segment changes, and a troponin or creatine kinase-MB level exceeding the upper limit of normal. The majority of subjects underwent cardiac catheterization during the initial hospitalization (92%).

We included only patients who underwent cardiac catheterization during the initial hospitalization with 1 or more lesions >50% severity in a native epicardial coronary artery (left main, left anterior descending, circumflex artery, or right coronary artery) or a major side branch of a native artery. Angiographic lesion severity was recorded by site investigators without utilization of an angiographic core laboratory. We excluded patients who did not undergo catheterization during the initial hospitalization (n = 880) and patients with normal coronaries on angiography or all lesions on angiography ≤50% (n = 873), as these patients would not be candidates for revascularization (Fig. 1).

Outcomes ascertainment. Data on in-hospital outcomes were obtained by reviewing clinical records for all enrolled patients. Outcomes after discharge were captured by contacting patients by telephone or through scheduled patient visits through 1 year, and 1-year mortality was ascertained through medical records or national death indexes. Adjudication was performed for all nonfatal myocardial events occurring through 6 months. The total number of subjects who were lost to follow-up for the mortality end point at 6 and 12 months were 16 and 35, respectively.

Statistical methods. UNADJUSTED ANALYSIS. We divided the study population into 3 groups: 1) those who underwent in-hospital PCI; 2) those who underwent in-hospital CABG; and 3) those who were medically managed without in-hospital revascularization performed within 7 days of randomization. Data were displayed as percentages for categorical variables and medians (25th percentile, 75th percentile) for continuous variables. Comparison of baseline characteristics, angiographic results, and outcomes was performed using the Pearson chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. The Global Registry of Acute Coronary Events (GRACE) score has been established as a robust tool for predicting 6-month post-discharge mortality in patients with ACS (11). In order to provide a single

Figure 1. Subject Flow

CABG = coronary artery bypass grafting; CAD = coronary artery disease; MM = conservative medical management; PCI = percutaneous coronary intervention.
numerical estimate of risk for each of the 3 treatment
groups, we calculated the GRACE risk scores for all
subjects studied. Unadjusted in-hospital events rates in the
3 groups were compared using the chi-square test, while
long-term event rates were estimated using the Kaplan-
Meier method with pairwise comparisons between groups
made using the log-rank test.

**PREDETERMINED OUTCOME ANALYSIS.** We developed a
cox regression model to identify significant predictors of
demographic and clinical characteristics (12). Time-dependent
covariates of in-hospital conservative medical management
versus in-hospital revascularization (Model 1) using both
stepwise and backward selection techniques on 37 candidate
covariates included from a large observational registry of
NSTE ACS patients (12). Nonfatal clinical outcomes
captured before catheterization were entered as predictors in
the model. The spline transformation method was used to
determine the functional form for continuous variables that
did not meet linearity assumptions. Whenever appropriate,
we applied piecewise linear splines as the preferred method
of transformation. A p value of 0.05 was used as the
criterion for variable entry and retention in the model.

**POST-DISCHARGE MORTALITY.** To evaluate the association
between conservative medical management and long-term
outcomes, we developed a proportional hazards model
comparing the conservative medical management group
with the PCI and CABG groups individually (conservative
medical management vs. PCI and conservative medical
management vs. CABG), as patients undergoing PCI and
CABG often have very different clinical profiles (13). We
examined the association between conservative medical
management as an independent variable and death (all-
cause mortality) or myocardial infarction (MI) at 6 months
as a dependent variable occurring after a discharge landmark
time point, defined as time of discharge, or 7 days from
randomization if hospitalization was prolonged (Model 2).
Modeling outcomes using a landmark time point enabled
accounting for the ascertainment bias expected when com-
paring early MI rates between conservative medical man-
agement patients (in whom markers were drawn only when
a suspected recurrent ischemic event occurred) and PCI or
CABG patients (in whom serial markers were recom-
mended to be routinely drawn post-procedure); as such a
comparison artificially inflates the relative rate of MI in the
PCI and CABG groups (14). The use of a discharge landmark
further permitted the modeling of nonfatal events occurring before the landmark time point, including recur-
rent ischemia, recurrent MI, acute heart failure, stroke, and
major bleeding, as time-updated covariates reflecting
changes in dynamic risk status (15). We then adjusted
Model 2 for the propensity for in-hospital conservative
medical management by including propensity scores derived
from data captured before catheterization (Model 1) as a
covariate in Model 2.

**TIME-DEPENDENT COVARIATE ANALYSIS.** We developed a
cox proportional hazards model that included conservative
medical management versus PCI and conservative medical
management versus CABG as time-dependent covariates
and death from catheterization through 1 year as the
outcome variable (Model 3). Time-dependent covariates
account for the timing of PCI and CABG relative to the
time of catheterization and the outcome of interest, there-
fore serving as a means to reduce survivor bias (16).

All p values were two-tailed and alpha set at 0.05 with
confidence intervals calculated to the 95th percentile. Sta-
tistical analyses were performed using SAS version 8.2 (SAS

**Results**

Utilization of revascularization procedures. A total of 8,225
patients were found to have significant CAD on early
angiography, and 4,752 of these patients (57.8%) were
enrolled from U.S. sites. In-hospital revascularization before
the discharge landmark time point was performed in 5,592
patients (68%), with 4,294 patients undergoing PCI
(52.2%) and 1,298 patients undergoing CABG (15.8%).

The median time from randomization to cardiac catheter-
ization was 21 (6, 42) h, while the median times from
catheterization to PCI and CABG were 0.5 (0.2, 1.2) h and
64.8 (23.5, 136.1) h, respectively. A total of 2,633 patients
(32%) were medically managed without in-hospital revas-
cularization before the discharge landmark time point
(Fig. 1).

Clinical characteristics. Compared with patients undergoing
in-hospital revascularization (PCI/CABG), patients in the
conservative medical management group were older, more
likely to be women, and more likely to have peripheral
vascular disease, prior stroke, hypertension, diabetes melli-
tus, hypercholesterolemia, prior CABG, and lower creati-
nine clearance values (Table 1). The median GRACE risk
score was similar for the CABG group at 124 (110, 141)
and conservative medical management group at 121 (106,
136), but was lower for the PCI group at 103 (90, 119).

Angiographic results. Patients in the CABG group had the
greatest frequency of left main and 3-vessel disease, while
patients in the PCI group had the greatest frequency of 1-
or 2-vessel disease (Table 2). More than half of the patients
in the conservative medical management group had 3-vessel
disease. Median left ventricular ejection fraction values were
lowest in the conservative medical management and CABG
groups.

Comorbid medication utilization. The use of aspirin,
beta-blockers, angiotensin-converting enzyme inhibitors,
and statins was high in all groups during the initial hospi-
tализация, at discharge, and at 30 days (Table 3). The use of
evidence-based medications was highest in the PCI group
followed by the conservative medical management group.
Predictors of conservative medical management. Several variables were independently associated with conservative medical management (Table 4). The strongest predictors of conservative medical management were prior CABG, lower body weight, lack of a recurrent MI from randomization until the time of catheterization, and 3-vessel disease demonstrated on angiography.

Revascularization procedures during follow-up. Overall, rates of late or repeat revascularization occurring after discharge were low (Fig. 2A). Patients who underwent in-hospital CABG before 7 days were the least likely to undergo repeat revascularization procedures, while the rate of late revascularization was similar in the conservative medical management and PCI groups. The median time to late revascularization (PCI) after discharge for the conservative medical management group was substantially shorter than the median time to repeat revascularization for those patients who had received PCI/CABG during the index hospitalization (Fig. 2B).

In-hospital outcomes. Unadjusted in-hospital events occurring between catheterization and the discharge landmark time point occurred most frequently in the CABG group (Table 5). However, the in-hospital mortality curves appeared to be similar for the 3 comparison groups (Fig. 3A).

Post-discharge outcomes. Unadjusted post-discharge events occurred most frequently in the conservative medical management group (Table 6). The post-discharge mortality curves demonstrated an early hazard for both the conservative medical management and CABG groups, but after 90
days, the curves diverged and the mortality hazard appeared higher in the conservative medical management group (Fig. 3B). Because the conservative medical management group had both an increased rate of post-discharge revascularization procedures and an earlier median time to revascularization compared with the PCI and CABG groups, we repeated the landmark analysis excluding all medically managed patients with revascularization performed after the landmark time point (discharge or 7 days) through 30 days (Table 6, bottom). We observed that the unadjusted and adjusted risk of MI declined in the conservative medical management group when events through 30 days were censored, but the adjusted risks of 6-month and 1-year mortality remained similar.

Overall outcomes. We analyzed overall mortality at 1 year over a period of observation that included both the in-hospital and post-discharge time periods (Fig. 4). The early risk of death from CABG was seen in the first 90 days, but, after that period, the risk in the medical cohort increased at a greater rate and the 2 curves cross. Thus, for those who survived the initial surgery, the risk became less than that of the medically treated patients with time. Overall mortality was highest in the medically managed group and lowest in the PCI group, with the difference persisting even after adjusting for conservative medical management as a time-dependent covariate (Table 7).

Discussion

Our study showed that, in a fairly contemporary cohort of high-risk NSTE ACS managed with an early invasive management strategy, the majority of which were from U.S. sites, a substantial proportion of patients did not receive in-hospital revascularization despite documentation of significant coronary disease on angiography. Medically managed patients had a higher risk of long-term adverse outcomes despite widespread utilization of evidence-based medications beyond the initial hospitalization.

Use of revascularization after early catheterization. Most observational studies and randomized controlled trials studying early invasive management strategies for NSTE

### Table 3. Evidence-Based Medication Use at Baseline, Discharge, and 30 Days

<table>
<thead>
<tr>
<th>Predictor</th>
<th>MM (n = 2,633)</th>
<th>PCI (n = 4,294)</th>
<th>CABG (n = 1,298)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-hospital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>94.8</td>
<td>96.0</td>
<td>94.8</td>
<td>0.032</td>
</tr>
<tr>
<td>Beta-blocker, %</td>
<td>85.7</td>
<td>87.2</td>
<td>91.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>67.6</td>
<td>61.3</td>
<td>62.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin, %</td>
<td>71.6</td>
<td>71.9</td>
<td>71.2</td>
<td>0.869</td>
</tr>
<tr>
<td>Clopidogrel, %</td>
<td>52.8</td>
<td>84.3</td>
<td>34.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>At discharge</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>90.7</td>
<td>96.1</td>
<td>89.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-blocker, %</td>
<td>85.4</td>
<td>90.1</td>
<td>80.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>75.2</td>
<td>77.5</td>
<td>55.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin, %</td>
<td>82.4</td>
<td>86.7</td>
<td>70.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clopidogrel, %</td>
<td>37.9</td>
<td>84.2</td>
<td>14.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>At 30 days</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin, %</td>
<td>90.3</td>
<td>93.5</td>
<td>88.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Beta-blocker, %</td>
<td>85.4</td>
<td>87.0</td>
<td>78.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor, %</td>
<td>72.2</td>
<td>72.9</td>
<td>57.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin, %</td>
<td>82.1</td>
<td>85.5</td>
<td>74.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clopidogrel, %</td>
<td>35.5</td>
<td>68.8</td>
<td>13.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; other abbreviations as in Table 1.

### Table 4. Independent Predictors of Conservative Medical Management (Model 1)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Wald Chi-Square</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of prior CABG</td>
<td>27.7</td>
<td>1.64</td>
<td>1.25–1.64</td>
</tr>
<tr>
<td>Body weight per 10 kg decrease</td>
<td>25.1</td>
<td>1.10</td>
<td>1.05–1.14</td>
</tr>
<tr>
<td>MI from randomization to time of catheterization</td>
<td>20.5</td>
<td>0.21</td>
<td>0.11–0.42</td>
</tr>
<tr>
<td>3-vessel disease</td>
<td>20.0</td>
<td>1.33</td>
<td>1.17–1.50</td>
</tr>
<tr>
<td>Non-U.S. site</td>
<td>18.7</td>
<td>1.69</td>
<td>1.33–2.14</td>
</tr>
<tr>
<td>History of prior heart failure</td>
<td>18.7</td>
<td>1.48</td>
<td>1.24–1.77</td>
</tr>
<tr>
<td>Time from symptom onset to presentation (per hour increase)</td>
<td>15.8</td>
<td>1.01</td>
<td>1.00–1.01</td>
</tr>
<tr>
<td>Black race</td>
<td>12.0</td>
<td>1.42</td>
<td>1.17–1.74</td>
</tr>
<tr>
<td>Killip class II–IV</td>
<td>11.7</td>
<td>1.33</td>
<td>1.13–1.56</td>
</tr>
<tr>
<td>History of prior MI</td>
<td>11.0</td>
<td>1.22</td>
<td>1.08–1.36</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6.6</td>
<td>1.15</td>
<td>1.03–1.29</td>
</tr>
<tr>
<td>Age (per 10-yr increase)</td>
<td>6.3</td>
<td>1.07</td>
<td>1.01–1.13</td>
</tr>
</tbody>
</table>

The following variables were entered into the multiple logistic regression model: age (per 10-year increase); gender; race; nationality; smoking status; creatinine clearance (per 10 ml/min); body weight per 10 kg decrease; diabetes; hypertension; hyperlipidemia; family history of coronary artery disease; history of prior myocardial infarction (MI); prior heart failure; prior coronary artery bypass grafting (CABG); prior percutaneous coronary intervention and prior peripheral vascular disease; pre-randomization use of aspirin, clopidogrel, warfarin, and/or beta-blockers; Killip class II to IV; systolic blood pressure per 10 mm Hg decrease; ST-T changes on electrocardiography; positive cardiac biomarkers; triple-vessel disease on coronary angiogram; and in-hospital events occurring from randomization to the time of catheterization (i.e., MI, stroke, new-onset heart failure, cardiogenic shock, TIMI [Thrombolysis In Myocardial Infarction] flow grade major, or GUSTO [Global Use of Strategies To Open Occluded Coronary Arteries] severe bleeding). Model chi-square = 367.6, degrees of freedom = 17, c-index = 0.64, Hosmer and Lemeshow goodness-of-fit test, p = 0.8.
ACS have focused on early catheterization rather than early revascularization as a management strategy (4–7). The potential consequences of this approach were highlighted by a recent meta-analysis of clinical trials of early invasive management in NSTE ACS in which the survival benefit with an early invasive strategy was most evident when there was proportionally greater use of revascularization in the invasive versus conservative treatment arms (17). While a recent analysis from the SYNERGY trial examined outcomes in NSTE ACS patients undergoing CABG for intermediate- to high-risk NSTE ACS, this analysis did not focus upon patients with angiographically defined significant coronary disease, so the medical management population was diluted with patients with insignificant coronary disease (18). Our study demonstrates that many patients with NSTE ACS and significant coronary disease are determined to not be candidates for revascularization procedures, and these patients have a significantly increased risk of adverse events, despite widespread use of evidence-based medications.

**Reasons for nonuse of revascularization procedures.** Possible reasons for patients not undergoing in-hospital revascularization despite significant coronary disease include death before planned revascularization, unfavorable coronary anatomy, serious comorbidities, resource availability, socioeconomic disparities, and patient refusal. Practice guidelines recommend consideration of early invasive management for patients with NSTE ACS who have had prior revascularization (1), but our data show that patients with prior CABG were least likely to undergo in-hospital revascularization after early catheterization. Patients with prior CABG comprise a subgroup in which repeat revascularization may be technically challenging due to diffuse native vessel and graft disease (19). Despite the availability of 1 subgroup analysis of a randomized trial to guide selection of revascularization strategies in these patients (20), the risk of periprocedural adverse events with any revascularization strategy remains high for patients with prior CABG. Additionally, many unmeasured variables likely contributed to decision-making regarding revascularization procedures, as reflected in the relatively poor c-index (0.64) of the model we developed to determine predictors of conservative medical management. This matter requires prospective study to understand whether there are opportunities to expand the utilization of PCI and CABG for these patients.

**Table 5. In-Hospital Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>MM (n = 2,633)</th>
<th>PCI (n = 4,294)</th>
<th>CABG (n = 1,298)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.9</td>
<td>0.5</td>
<td>1.2</td>
<td>0.027</td>
</tr>
<tr>
<td>MI</td>
<td>2.0</td>
<td>9.6</td>
<td>26.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.3</td>
<td>0.3</td>
<td>1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>0.6</td>
<td>0.9</td>
<td>3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New onset heart failure</td>
<td>9.9</td>
<td>4</td>
<td>15.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GUSTO severe bleed</td>
<td>1.0</td>
<td>0.9</td>
<td>5.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TIMI major bleed</td>
<td>1.6</td>
<td>2.1</td>
<td>34.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Events occurring from catheterization through discharge, or 7 days if hospitalization was prolonged.

PCI = percutaneous coronary intervention; other abbreviations as in Table 4.
Data from the CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the American College of Cardiology/American Heart Association guidelines) trial showed that the widespread availability of drug-eluting stents (DES) from 2003 to 2005 was associated with a sharp increase in PCI use in patients with NSTE ACS and significant CAD, while the rate of CABG procedures remained relatively stable (8). This was accompanied by a concordant decline in the proportion of medically managed patients, from 49% in 2002 to 36% in 2005, suggesting that physicians had become more willing to offer percutaneous revascularization options to patients who might have been considered poor candidates for PCI before the advent of DES. The high rate of off-label DES usage since its introduction, primarily for complex lesion subsets, supports this conclusion (21). Given recent safety concerns about DES and uncertainty over the actual benefit of an early invasive strategy (22), the proportion of medically managed patients may remain stable, or actually even increase over time.

Evidence-based medications. The risk-treatment paradox refers to progressive diminution in the use of evidence-based therapies as baseline risk and future probability of death increases (23). However, treatment intensification in high-risk patients remains a major challenge because these

Figure 3. In-Hospital and Post-Discharge Mortality

(A) Death from catheterization through discharge. (B) Death from discharge* through 1 year. Log-rank p values: conservative medical management versus PCI, p < 0.0001; conservative medical management versus CABG, p = 0.08. *Landmark time point of discharge, or 7 days if hospitalization was prolonged. Abbreviations as in Figure 1.
patients have an increased susceptibility to drug toxicity and treatment complications (24). The greatest difference in medication use among the comparison groups was with clopidogrel, which was targeted for patients who underwent PCI. A subgroup analysis of the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial showed a similar benefit of clopidogrel in patients treated with conservative medical management compared with the benefit seen in patients treated with revascularization (25). However, in the recent TRITON (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel) study, older patients and those with lower body weight were also more likely to have serious bleeding complications and less likely to derive a net treatment benefit with more potent thienopyridine treatment (26).

Similar challenges face the widespread implementation of intensive lipid-lowering in the medically managed population because of their greater prevalence of comorbid conditions. In a meta-analysis of 4 large clinical trials that included the PROVE-IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial (27), investigators confirmed the safety and efficacy of high-dose statin therapy compared with standard-dose statin therapy (28). However, patients with serum creatinine >2.5 mg/dl were excluded from the aforementioned

<table>
<thead>
<tr>
<th>Table 6. Post-Discharge Events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Death/MI at 6 months</td>
</tr>
<tr>
<td>MI at 6 months</td>
</tr>
<tr>
<td>Death at 1 yr</td>
</tr>
</tbody>
</table>

**Adjusted HR + 95% CI for MM vs. PCI (Model 2)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted for Baseline Characteristics + In-Hospital Events + Propensity for MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG (n = 1,298)</td>
<td>Adjusted for Baseline Characteristics + In-Hospital Events + Propensity for MM</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Death/MI at 6 months</td>
<td>3.80 (2.65–5.47)</td>
</tr>
<tr>
<td>MI at 6 months</td>
<td>6.65 (3.74–11.83)</td>
</tr>
<tr>
<td>Death at 1 yr</td>
<td>1.77 (0.98–3.19)</td>
</tr>
</tbody>
</table>

**Adjusted HR + 95% CI for MM vs. CABG (Model 2)**

*Only events occurring from discharge, or 7 days if hospitalization was prolonged, were considered. †Patients in the conservative medical management group who underwent PCI or CABG within 30 days were censored in this end point analysis. Outcomes for the in-hospital PCI and CABG groups are the same as under the “All Patients” analysis in the top rows.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

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**Figure 4. Overall Mortality From Randomization Through 1 Year**

Log-rank MM versus PCI, <0.0001; MM versus CABG, 0.52. Abbreviations as in Figure 1.
clinical trials, limiting generalizability of the findings to this population. Impaired renal function is a key concern, and the majority of NSTE ACS patients with renal impairment are managed medically (29). Hence, questions remain about the efficacy, safety, and correct dosing of guidelines-recommended medications in medically managed patients excluded from landmark randomized controlled trials because of excess comorbidity. Dedicated trials with alternative dosing strategies may be a step toward resolving concerns regarding drug metabolism and the increased likelihood of medication side effects in this population.

**Study limitations.** Several limitations were present with this analysis. First, detailed lesion-level angiographic findings were not captured, so we were not able to characterize angiographic suitability for revascularization. Second, significant lesions in the major coronary arteries were recorded in a dichotomized approach (>50% vs. ≤50%) on the SYNERGY case report form, so we could not assess different classification schemes for significant coronary disease such as stenoses >70%. Third, details about physician decision-making regarding revascularization were not captured. However, patients with clinical contraindications to catheterization and revascularization were excluded from the SYNERGY trial, so the study population represented an ideal group of patients for early invasive management at the time of randomization (30). Fourth, despite our best efforts to adjust for confounding, the conservative medical management group represents a particularly high-risk cohort in whom survival is unlikely to approximate that of the SYNERGY trial, so the study population represented an ideal group of patients for early invasive management at the time of randomization (30). Fourth, despite our best efforts to adjust for confounding, the conservative medical management group represents a particularly high-risk cohort in whom survival is unlikely to approximate that of the lower-risk PCI group because of unmeasured confounders making it difficult to draw definitive conclusions about the benefits of early revascularization procedures. Nonetheless, our intent was not to show that early revascularization was associated with improved outcomes, but rather to fully characterize the short- and long-term risks associated with a conservative medical management strategy. Last, the 7-day landmark analysis, although necessary for the investigation of MI outcomes in this particular study, may introduce biases associated with left censoring of longitudinal data.

**Conclusions**

Almost one-third of patients with NSTE ACS documented to have significant coronary disease on angiography did not undergo revascularization procedures in the SYNERGY trial. These patients have a higher risk of long-term adverse outcomes compared with those who undergo PCI or CABG despite widespread utilization of guidelines-recommended medications. These findings highlight the need for novel strategies to mitigate the increased risk of adverse outcomes in this population and for additional prospective studies to examine patient and physician decision-making regarding revascularization decisions.

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**REFERENCES**


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