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Association of Mortality With Years of Education in Patients With ST-Segment Elevation Myocardial Infarction Treated With Fibrinolysis

Rajendra H. Mehta, MD, MS,* J. Conor O'Shea, MD,† Amanda L. Stebbins, MS,* Christopher B. Granger, MD,* Paul W. Armstrong, MD,‡ Harvey D. White, MB, DSc,§ Eric J. Topol, MD,‖ Robert M. Califf, MD,*¶ E. Magnus Ohman, MD*

Durham, North Carolina; Cork, Ireland; Edmonton, Alberta, Canada; Auckland, New Zealand; and La Jolla, California

Objectives The purpose of this study was to examine the association between lower socioeconomic status (SES), as ascertained by years of education, and outcomes in patients with acute ST-segment elevation myocardial infarction (STEMI).

Background Previous studies have shown an inverse relationship between SES and coronary heart disease and mortality. Whether a similar association between SES and mortality exists in STEMI patients is unknown.

Methods We evaluated 11,326 patients with STEMI in the GUSTO-III (Global Use of Strategies to Open Occluded Coronary Arteries) trial study from countries that enrolled >500 patients. We evaluated clinical outcomes (adjusted using multivariate regression analysis) according to the number of years of education completed.

Results One-year mortality was inversely related to years of education and was 5-fold higher in patients with <8 years compared with those with >16 years of education (17.5% vs. 3.5%, $p < 0.0001$). The strength of the relationship between education and mortality varied among different countries. Nonetheless, years of education remained an independent correlate of mortality at day 7 (hazard ratio per year of increase in education: 0.86; 95% confidence interval: 0.83 to 0.88) and also between day 8 and 1 year (hazard ratio per year of increase in education: 0.96; 95% confidence interval: 0.94 to 0.98), even after adjustment for baseline characteristics and country of enrollment.

Conclusions When the number of years of education was used as a measure of SES, there was an inverse relationship such that significantly higher short-term and 1-year mortality existed beyond that accounted for by baseline clinical variables and country of enrollment. Future studies should account for and investigate the mechanisms underlying this link between SES and cardiovascular disease outcomes. (J Am Coll Cardiol 2011;57:138–46)

Coronary heart disease (CHD) has emerged as a global epidemic and is currently the major cause of death and disability (1–3). In the first half of the 20th century, CHD and its attendant consequences seemed for the most part to afflict affluent members of society and residents of developed countries. Beginning in the mid-1960s, advances in coronary care and treatments were associated with decreasing death

From the *Duke Clinical Research Institute and Duke University Medical Center, Durham, North Carolina; †Bon Secours Hospital, Cork, Ireland; ‡University of Alberta, Edmonton, Alberta, Canada; §Auckland City Hospital, Auckland, New Zealand; ‖Scripps Clinic, La Jolla, California; and the ¶Duke Translational Medicine Institute, Durham, North Carolina. Funded by the Duke Clinical Research Institute, Durham, North Carolina. Dr. Granger has received research grants from Astellas Pharma US, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Lilly, Medtronic Vascular Inc., Merck & Co., Sanofi-Aventis, and The Medicines Co.; and consulting fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Hoffmann-La Roche, Novartis Pharmaceutical Co., Otsuka Pharmaceuticals, Sanofi-Aventis, and The Medicines Co. Dr. White has received research grants from Sanofi-Avenits, Eli Lilly, The Medicines Co., NIH, Pfizer, Roche, Johnson & Johnson, Schering-Plough, Merck Sharpe & Dohme, AstraZeneca, GlaxoSmithKline, Daiichi Sankyo Pharma Development, and Bristol-Myers Squibb; and consulting fees from Regado Biosciences. Dr. Califf has received research grants from J&J-Scios, Lilly, Merck, Novartis, and Schering-Plough; consulting fees from Annenberg, Aterovax, Bayer/Ortho McNeil, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, WebMD, J&J-Scios, Kowa Research Institute, McKinsey & Co., Medtronic, Merck, Novartis, Sanofi-Aventis, and Schering-Plough; and has equity in NITROX LLC. Dr. Ohman has received research grants from Bristol-Myers Squibb, CV Therapeutics, Daiichi Sankyo, Datascope, Eli Lilly & Co., Sanofi-Avenits, Schering-Plough, and The Medcines Co.; and consulting fees from Abiomed, CV Therapeutics, Datascope, Gilead Sciences, Liposcience, Northpoint Domain, Pozen Inc., Response Biomedical, The Medicines Co., and WedMD. All other authors have reported that they have no relationships to disclose.

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rates in countries such as the United States and the United Kingdom (3–7). In contrast, the burden of disease shifted to persons at the lower end of socioeconomic hierarchy and to less developed countries where CHD incidence and rates of mortality are currently higher (2,8–11).

The gap in CHD and its attendant morbidity and mortality between wealthier and economically underprivileged individuals and between developed and less developed countries continues to widen in the recent era (2,12–15). In fact, >80% of CHD mortality has been shown to occur in poor and less developed countries (1). Thus, the relationship between socioeconomic status (SES) and CHD is both complex and dynamic, stimulating considerable interest and serving as the focus of previous investigations. These earlier studies have shown that lower SES is linked with significantly higher prevalence of cardiovascular risk factors such as hypertension (16); diabetes (17); dyslipidemia (18); cigarette smoking (19); obesity, metabolic syndrome, and lack of physical activity (2,20,21); and hemostatic factors (22), accounting for most if not all of the excess risk of CHD in this population.

Although previous work has evaluated the relationship of SES with CHD and the risk of myocardial infarction (MI), few studies have isolated the association between social class and risk of MI from the relationship of social class with outcomes after the occurrence of this event (23). In addition, the vast majority of research in this area has reflected single-country or regional experiences, predominantly involving populations in the United States or Scandinavian countries (24). Thus, the extrapolation of these findings to other regions of the world remains unclear.

Accordingly, the goal of the present study was to examine the association of SES, as ascertained by years of education, with short- and long-term outcomes in a large, international group of patients after acute ST-segment elevation myocardial infarction (STEMI). For the purpose of this study, the patient's level of education, defined as years of completed education or level of education attained—a generally acceptable and widely used surrogate of SES (25)—was used as a measure of this parameter.

Methods

Study population. Data from patients enrolled in the GUSTO-III (Global Use of Strategies to Open Occluded Coronary Arteries) trial (26) from October 13, 1995, through January 13, 1997, were analyzed for this study. The details of the design, methods, and results of the GUSTO-III trial were previously published (26). In brief, GUSTO-III investigators enrolled 15,059 patients of any age who presented within 6 h after the onset of ischemic symptoms with electrocardiographic evidence of STEMI. Exclusion criteria for the trial included active bleeding, a history of stroke or central nervous system damage, recent major surgery, systolic blood pressure >200 mm Hg or diastolic blood pressure >110 mm Hg at any time after arrival, recent noncompressible vascular puncture, and concomitant use of an oral anticoagulant with an international normalized ratio >2. Patients were randomly assigned in a 2:1 ratio to receive reteplase (Boehringer Mannheim, Gaithersburg, Maryland, and Mannheim, Germany) in 2 bolus doses of 10 MU given 30 min apart or an accelerated infusion of alteplase (Genentech, South San Francisco, California, and Boehringer Ingelheim) in a bolus dose of 15 mg, followed by the infusion of 0.75 mg/kg body weight over a 30-min period (not to exceed 50 mg) and the infusion of 0.5 mg/kg (up to 35 mg) over the next 60 min on an open-label basis. Aspirin (160 mg) was given as soon as possible and then in a daily dose of 160 to 325 mg. With the assigned fibrinolytic therapy, patients received a bolus dose of 5,000 U of heparin given intravenously, followed by an infusion of 1,000 U/h. Other medications, including beta-blockers and nitrates, were given at the discretion of the investigator.

Abbreviations and Acronyms

CHD = coronary heart disease

MI = myocardial infarction

SES = socioeconomic status

STEMI = ST-segment elevation myocardial infarction

For the present analyses, we excluded subjects from countries with <500 patients enrolled (n = 1,806) and subjects for whom information on level of education was missing (n = 1,927). The remaining 11,326 subjects form the basis of this study. Baseline characteristics and clinical outcomes were compared according to years of education before hospital admission.

Data collection, definitions, and outcomes. Data on demographics, baseline characteristics, medical therapies during hospitalization and at discharge, invasive procedure use, in-hospital adverse clinical events, and 30-day and 1-year mortality were collected prospectively (26). All instances of stroke were centrally adjudicated and bleeding was defined using GUSTO-III criteria (26). In addition, information on years of education (defined as the number of full years of school education completed, beginning with first grade) was prospectively collected.

The primary end point of GUSTO-III was mortality at 30 days of follow-up (26). Other prospectively defined secondary end points of the trial included net clinical benefit defined as freedom from death or disabling stroke, death or nonfatal stroke, reinfarction, congestive heart failure, and mortality at 24 h (26). Unadjusted in-hospital clinical outcomes and in-hospital, 30-day, and 1-year mortality, as well as adjusted 1-year mortality (data available for 1 full year in 97% of patients) were analyzed.

Statistical analyses. For display purposes, we categorized patients according to years of education as <8 years, 8 to 12 years, >12 to 16 years, and >16 years. All statistical analyses were performed using nonparametric tests with years of education as a continuous variable. Discrete factors were displayed as frequencies and percentages. Continuous

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variables were summarized as medians and 25th and 75th percentiles. The Spearman rank correlation test was performed to evaluate the relationship of years of education with continuous factors. The association between categorical demographics, history, and baseline characteristics variables and years of education was assessed using Wilcoxon rank-sum test. The likelihood ratio test statistic p values from logistic regression models were reported for the association between drug therapies, procedures, and complications and years of education. A model was generated to assess the relationship among baseline variables (age, systolic blood pressure, heart rate, Killip class at enrollment, and MI location), years of education, and 1-year mortality. The proportional hazards assumption was not met for years of education because of a very high proportion of patients with education <8 years dying early. Hence, 2 models were created—one to assess predictors of 0 to 7 days post-randomization and a second to assess 8 to 365 days post-randomization. Together, these 5 variables were associated with 90% of prognostic information in the baseline data from the previously published model (27). Years of education (as a continuous variable) and country of enrollment were then added to this model to assess whether these contributed independently to predicting outcome. Chi-square values, p values, hazard ratios, and 95% confidence intervals (CIs) were reported. In addition, an interaction term of country by years of education was also tested in the model described. However, interaction terms were not included in final models that were reported. Although New Zealand enrolled >500 patients in the trial, it was excluded from all models due to the fact that information on years of education was available for <500 patients. All other countries each contributed >500 patients to the model. For all analyses, a 2-tailed p value <0.05 was considered statistically significant. All analyses were performed using SAS statistical software version 8.2 (SAS Institute, Cary, North Carolina).

Results

Baseline characteristics, medical therapy, and procedure use. Of the 11,326 participants in this study, 19.8% had completed 7 years of school, 61.6% had completed high school (or equivalent), and 14.4% had between 12 and 16 years of education; the remaining 4.4% had >16 years of education. Differences in baseline demographics, medical history, presenting clinical features, medical therapies, and in-hospital procedures used in STEMI patients according

Table 1 Baseline Demographics and Medical History by Years of Education

Characteristics	Years of Education				p Value
	<8 yrs (n = 2,249)	8–12 yrs (n = 6,982)	>12–16 yrs (n = 1,633)	>16 yrs (n = 462)	
Demographics					
Age (yrs)	67.9 (60.0, 74.9)	62.1 (52.6, 70.6)	58.3 (49.6, 68.3)	57.7 (50.6, 67.5)	<0.0001
Female sex	666 (29.6)	2,021 (28.9)	348 (21.3)	61 (13.2)	<0.0001
White race	2,131 (94.8)	6,625 (94.9)	1,510 (92.5)	408 (88.5)	0.0030
Height (cm)	170 (163, 175)	172 (165, 177)	173 (167, 180)	175 (168, 180)	<0.0001
Weight (kg)	75 (67, 84)	78 (70, 89)	80 (72, 90)	80 (73, 91)	<0.0001
Medical history					
Hypertension	838 (37.3)	2,677 (38.4)	637 (39.0)	194 (42.0)	0.9389
Diabetes mellitus	374 (16.6)	1,052 (15.1)	230 (14.1)	59 (12.8)	<0.0001
Current smoking	795 (35.8)	3,029 (43.5)	667 (40.9)	156 (33.9)	<0.0001
Elevated cholesterol	545 (24.5)	2,459 (35.4)	636 (39.0)	190 (41.2)	0.0008
Previous CHF	76 (3.4)	175 (2.5)	30 (1.8)	7 (1.5)	<0.0001
Previous MI	499 (22.2)	1,275 (18.3)	281 (17.2)	59 (12.8)	0.0008
Previous cerebrovascular disease	64 (2.8)	170 (2.4)	29 (1.8)	15 (3.2)	0.3718
Previous PCI	61 (2.7)	353 (5.1)	100 (6.1)	31 (6.7)	<0.0001
Previous CABG	72 (3.2)	260 (3.7)	71 (4.3)	16 (3.5)	0.0002
No. of patients by country of enrollment					
United Kingdom	522	794	89	3	—
Germany	221	937	83	2	—
Sweden	602	347	76	16	—
Italy	275	135	73	27	—
New Zealand	15	325	30	2	—
Poland	132	396	64	33	—
Canada	164	1104	309	129	—
Australia	153	727	48	9	—
United States	165	2217	861	241	—

Data are presented as median (25th, 75th percentile) or n (%) unless otherwise noted.
CABG = coronary artery bypass graft; CHF = congestive heart failure; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2 Baseline Clinical Features by Years of Education

Characteristics	Years of Education <8 yrs (n = 2,249)	8–12 yrs (n = 6,982)	>12–16 yrs (n = 1,633)	>16 yrs (n = 462)	p Value
Presenting heart rate (beats/min)	73 (62, 87)	74 (62, 86)	72 (62, 84)	74 (62, 85)	<0.0001
Presenting SBP (mm Hg)	137 (120, 153)	135 (120, 150)	134 (118, 150)	136 (118, 151)	<0.0001
Presenting DBP (mm Hg)	80 (70, 90)	80 (70, 90)	80 (70, 90)	80 (70, 91)	0.1569
Killip class ≥II	458 (20.6)	959 (13.8)	151 (9.3)	30 (6.5)	<0.0001
Location of MI					<0.0001
Anterior	1,141 (50.7)	3,307 (47.4)	720 (44.1)	221 (47.8)	—
Inferior	997 (44.3)	3,417 (48.9)	863 (52.8)	227 (49.1)	—
Time to hospital (h)	1.8 (1.1, 2.8)	1.6 (1.0, 2.5)	1.4 (0.8, 2.3)	1.3 (0.8, 2.0)	<0.0001
Time to treatment (h)	2.9 (2.0, 4.0)	2.6 (1.8, 3.8)	2.4 (1.7, 3.5)	2.3 (1.6, 3.2)	<0.0001
Time to randomization (h)	2.6 (1.8, 3.8)	2.3 (1.6, 3.5)	2.2 (1.4, 3.2)	2.0 (1.3, 3.0)	<0.0001
Time from hospital arrival to treatment (h)	1.0 (0.7, 1.5)	0.9 (0.7, 1.4)	0.9 (0.6, 1.3)	0.8 (0.6, 1.3)	<0.0001

Data are presented as median (25th, 75th percentile) or n (%) unless otherwise noted.
DBP = diastolic blood pressure; MI = myocardial infarction; SBP = systolic blood pressure.

to level of education are shown in Tables 1 and 2. Subjects with the least education tended to be older and were more likely to be women with a history of diabetes, previous congestive heart failure, and MI; however, they were less likely to have had previous percutaneous coronary interventions compared with those with more years of education. Presenting features associated with poor prognosis, such as Killip class II or higher and anterior MI location, were also more frequent in subjects with the least education. This cohort also had a greater delay in time to fibrinolytic therapy, not only because of a longer time from onset of ischemic symptoms to hospital arrival, but also due to longer door-to-needle time.

Use of aspirin in-hospital and at time of discharge was lower in patients with fewer years of education (Table 3). Beta-blockers were used less frequently and angiotensin-converting enzyme inhibitors were used more frequently among subjects with less education. Use of coronary angiography was more common among subjects with fewer years of education, but percutaneous or surgical coronary revascularization was performed less frequently in this group compared with subjects with more years of education (Table 3).

Clinical outcomes. In-hospital and 1-year outcomes according to years of education in subjects with STEMI are shown in Table 4. With the exception of in-hospital bleeding, almost all other in-hospital adverse events were inversely related to years of education. In particular, early mortality (at 24 h and 30 days) and 30-day mortality and in-hospital nonfatal stroke were approximately 4- to 13-fold higher in subjects with <8 years of education compared with those with >16 years of education. Similarly, 1-year mortality was inversely related to number of years of

Table 3 In-Hospital Medications, Medications at Discharge, and In-Hospital Procedures by Years of Education

	Years of Education <8 yrs (n = 2,249)	8–12 yrs (n = 6,982)	>12–16 yrs (n = 1,633)	>16 yrs (n = 462)	p Value
In-hospital drug therapy					
Aspirin	2,206 (98.3)	6,929 (99.3)	16,151 (99.0)	460 (99.6)	0.0085
Beta-blockers	1,450 (64.5)	5,207 (74.6)	1,321 (80.9)	378 (81.8)	<0.0001
Heparin, any	2,198 (97.7)	6,827 (97.8)	1,593 (97.6)	447 (96.8)	0.0058
ACE inhibitors	1,085 (48.2)	3,215 (46.0)	676 (41.4)	179 (38.7)	<0.0001
Drug therapy at discharge					
Aspirin	1,785 (87.6)	6,132 (90.0)	1,451 (90.0)	384 (84.4)	<0.0001
Beta-blockers	1,184 (52.6)	4,257 (61.0)	1,095 (67.1)	296 (64.1)	<0.0001
ACE inhibitors	922 (41.0)	2,719 (38.9)	586 (35.9)	157 (34.0)	<0.0001
Procedures					
Coronary angiography	1,744 (77.5)	3,857 (55.3)	663 (40.6)	198 (42.9)	<0.0001
PCI	226 (10.1)	1,514 (21.7)	495 (30.5)	133 (29.0)	<0.0001
CABG	64 (2.8)	522 (7.5)	178 (10.9)	49 (10.6)	<0.0001
IABP	26 (1.2)	169 (2.4)	61 (3.7)	20 (4.3)	<0.0001
Pulmonary artery catheter	40 (1.8)	250 (3.6)	69 (4.2)	25 (5.4)	0.0432

Data are presented as n (%).
ACE = angiotensin-converting enzyme; IABP = intra-aortic balloon pump; other abbreviations as in Table 1.

Table 4 Clinical Outcomes by Years of Education

Characteristics	Years of Education <8 yrs (n = 2,249)	8–12 yrs (n = 6,982)	>12–16 yrs (n = 1,633)	>16 yrs (n = 462)	p Value
In-hospital					
Any bleeding	579 (25.8)	2,167 (31.1)	579 (35.6)	171 (37.0)	<0.0001
Severe bleeding	16 (0.7)	56 (0.8)	20 (1.2)	12 (2.6)	0.0199
Stroke	54 (2.4)	69 (1.0)	16 (1.0)	7 (1.5)	<0.0001
Reinfarction	115 (5.1)	284 (4.1)	59 (3.6)	13 (2.8)	0.0002
Congestive heart failure	477 (21.2)	1,104 (15.8)	239 (14.6)	77 (16.7)	<0.0001
Cardiogenic shock	139 (6.2)	214 (3.1)	42 (2.6)	14 (3.0)	<0.0001
24-h mortality	117 (5.2)	65 (0.9)	9 (0.6)	2 (0.4)	<0.0001
In-hospital mortality	248 (11.0)	246 (3.5)	37 (2.3)	7 (1.5)	<0.0001
30-day mortality	270 (12.0)	290 (4.2)	43 (2.6)	9 (2.0)	<0.0001
30-day mortality or in-hospital stroke	294 (13.1)	339 (4.9)	55 (3.4)	16 (3.5)	<0.0001

Data are given as n (%). Bleeding was assessed according to GUSTO III trial criteria (26).

education (Fig. 1) and was more than 5-fold higher in subjects with <8 years of education, compared with those with >16 years of education (17.5% vs. 3.5%, p < 0.0001) (Fig. 2). Finally, patients missing information regarding years of education had the highest rates of 1-year mortality (Fig. 2).

Country of enrollment, years of education, and mortality. The number of compulsory years of education and the number of subjects in each education category varied among countries in the current study (Table 5). Similarly, there was wide variation in 1-year mortality rates among countries (Table 5). Nonetheless, for most countries included in this study, 1-year mortality was consistently higher among subjects with <8 years of education compared with those with >16 years of education (Table 5). Years of education remained independently correlated with mortality at day 7 (hazard ratio per year of increase in education: 0.86; 95% confidence interval: 0.83 to 0.88) and also between day 8 and 1 year (hazard ratio per year of increase in education: 0.96; 95% confidence interval: 0.94 to 0.98), even after adjusting for important baseline variables and country of enrollment (referent United States) (Table 6). The strength of the association of years of education with 1-year mortality differed among various countries compared with the United States, as suggested by significant p values for the interaction of some countries and years of education with 1-year mortality.

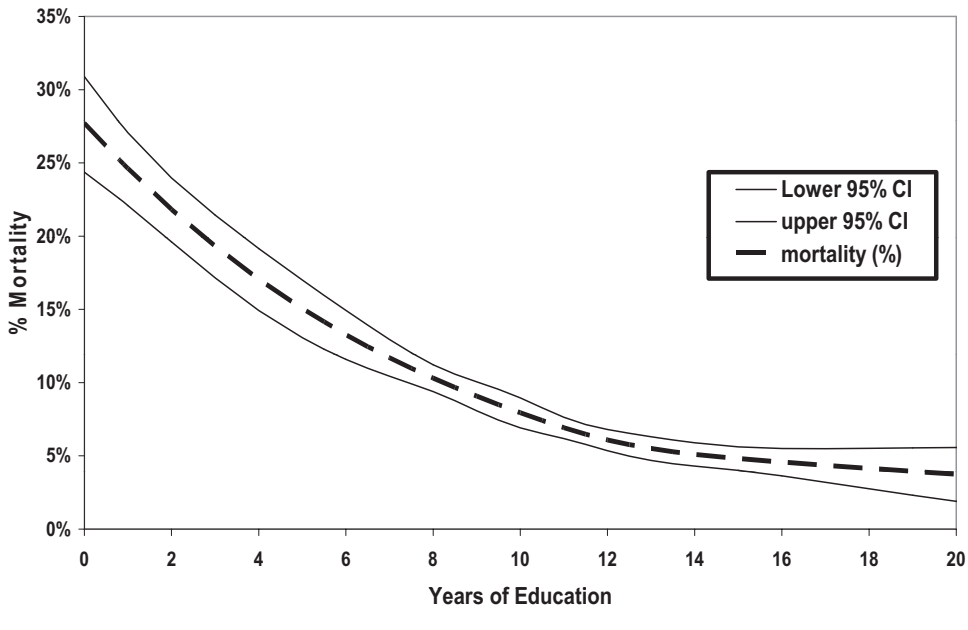

Figure 1 Relationship of Years of Education With 1-Year Mortality in Patients With STEMI

Note that increasing years of completed education were associated with decreasing 1-year mortality. CI = confidence interval; STEMI = ST-segment elevation myocardial infarction.

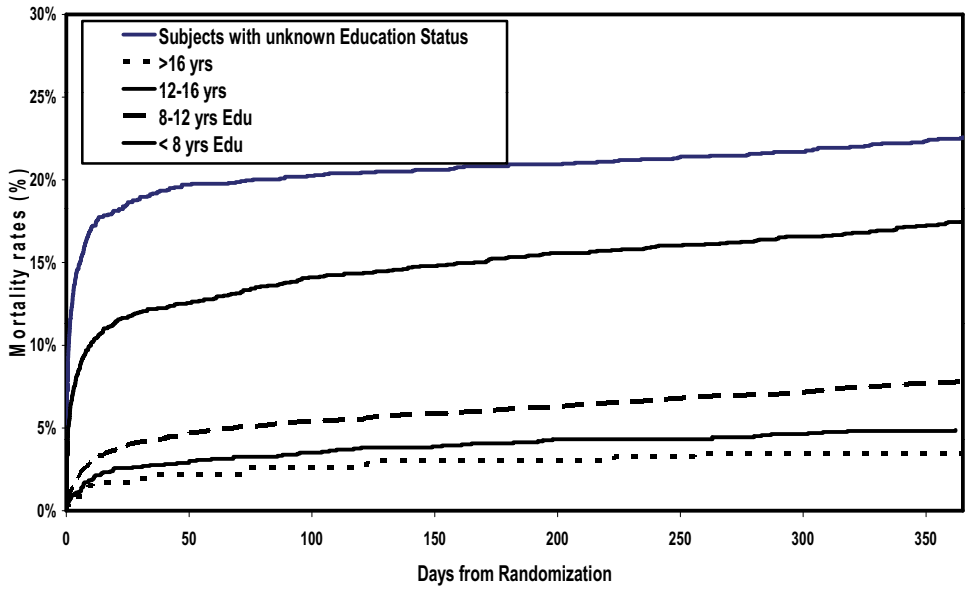

Figure 2 Relationship of Years of Education With 1-Year Mortality

Note the significantly early hazard in those with education <8 years as well as in those with information on years of education missing.

Discussion

Our study findings. This study demonstrates that lower SES, as ascertained by years of completed education, was associated with significantly poorer outcomes in subjects who received fibrinolysis after hospitalization for acute STEMI. Particularly, mortality at 24 h, 30 days, and 1 year were all increased among subjects with STEMI with fewer years of education compared with those with more years of education. Although fewer years of education was associated with adverse demographic, clinical, and presenting features that have been shown to portend a poor prognosis in STEMI patients (27), years of education remained independently correlated with mortality, even after accounting for these high-risk characteristics.

Additionally, our data indicate that the strength of the relationship between years of education and mortality in patients with STEMI varies among participating countries compared with the association observed among patients enrolled in the United States. Nonetheless, for most countries that participated in the trial and reported information on level of education for >500 subjects, years of education showed a consistent inverse relationship with 1-year mortality in subjects with STEMI. Even after adjusting for baseline characteristics and country of enrollment, years of education still remained significantly associated with increased mortality at day 7 as well as from day 8 through 1 year.

Thus, our data show that years of education is either an important predictor of mortality or a surrogate marker of measured or unmeasured variables that are strongly associ-

Table 5 Relationship Between Years of Education and 1-Year Mortality Rates by Enrolling Country

	Years of Education				
Country (Compulsory Years of Education)	<8 yrs	8–12 yrs	>12–16 yrs	>16 yrs	p Value*
Overall 1-year mortality	17.5 (16.0–19.1)	7.8 (7.2–8.5)	4.9 (3.9–6.1)	3.5 (2.2–5.6)	<0.0001
United Kingdom (12 yrs)	22.1 (18.8–26.0)	10.4 (8.5–12.8)	3.5 (1.1–10.4)	0	<0.0001
Germany (13 yrs)	23.1 (18.0–29.4)	8.6 (7.0–10.7)	3.8 (1.3–11.5)	0	<0.0001
Sweden (10 yrs)	17.8 (14.9–21.2)	5.8 (3.8–8.8)	2.6 (0.7–10.1)	0	<0.0001
Italy (9 yrs)	16.9 (12.9–21.8)	11.9 (7.5–18.7)	1.4 (0.2–9.3)	3.7 (0.5–23.5)	0.0025
New Zealand (12 yrs)	0	6.2 (4.0–9.4)	3.5 (0.5–22.1)	0	0.4684
Poland (9 yrs)	17.6 (12.1–25.3)	11.5 (8.7–15.1)	14.2 (7.8–25.6)	9.3 (3.1–26.2)	0.2523
Canada (11 yrs)	12.8 (8.5–19.0)	7.3 (5.9–9.0)	4.3 (2.5–7.2)	1.6 (0.4–6.1)	0.0002
Australia (11 yrs)	8.5 (5.0–14.2)	5.6 (4.1–7.5)	6.3 (2.1–18.1)	0	0.4765
United States (12 yrs)	9.9 (6.2–15.6)	7.3 (6.3–8.5)	5.1 (3.8–6.8)	4.2 (2.3–7.6)	0.0233

*p value reflects differences across the 4 categories of years of education within a country. Data are given as event rates (95% confidence intervals).

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Table 6 Independent Correlates of 0- to 7-Day and 8- to 365-Day Mortality Derived Using Cox Proportional Hazard Model

Variable	0- to 7-Day Mortality Model				8- to 365-Day Mortality Model			
	Model Chi-Square	HR	95% CI	p Value	Model Chi-Square	HR	95% CI	p Value
Age (yrs)	172.3	1.07	1.06–1.08	<0.0001	284.6	1.07	1.07–1.08	<0.0001
Education (yrs)	131.5	0.86	0.83–0.88	<0.0001	12.3	0.96	0.94–0.98	0.0005
Killip class (vs. I)	58.1	—	—	<0.0001	46.9	—	—	<0.0001
II	—	1.67	1.32–2.11	—	—	1.72	1.41–2.10	—
III	—	2.50	1.62–3.87	—	—	2.61	1.70–4.02	—
IV	—	4.83	3.03–7.69	—	—	3.36	1.56–7.25	—
SBP (mm Hg)	95.9	0.97	0.96–0.97	<0.0001	3.02	0.99	0.98–1.00	0.0818
Country of enrollment (vs. United States)*	54.9	—	—	<0.0001	12.7	—	—	0.0788
Australia	—	0.29	0.14–0.57	0.0004	—	0.93	0.66–1.30	0.6544
Canada	—	0.50	0.32–0.79	0.0027	—	1.08	0.82–1.41	0.5895
Germany	—	1.06	0.75–1.52	0.7353	—	0.83	0.60–1.14	0.2438
Italy	—	1.03	0.65–1.61	0.9149	—	1.21	0.81–1.79	0.3551
Poland	—	2.32	1.57–3.43	<0.0001	—	1.61	1.13–2.30	0.0090
Sweden	—	0.91	0.63–1.30	0.5938	—	0.95	0.70–1.29	0.7445
United Kingdom	—	1.10	0.77–1.58	0.6042	—	1.06	0.79–1.43	0.6868
Heart rate (beats/min)	25.9	1.01	1.01–10.2	<0.0001	66.6	1.02	1.01–1.02	<0.0001
MI location (vs. anterior)	13.6	—	—	0.0011	16.4	—	—	0.0003
Inferior	—	0.68	0.55–0.84	—	—	0.70	0.58–0.83	—
Other (nonanterior and noninferior)	—	0.75	0.46–1.23	—	—	0.93	0.63–1.36	—

Reference cell for country by years of education is the United States. The 0- to 7-day model: interaction term for years of education and country were statistically significant for Sweden ($p < 0.0001$), United Kingdom ($p = 0.0003$), and Germany ($p = 0.0011$). New Zealand was excluded from the statistical models because there were <500 patients with data on education from this country. The model reported here excluded the interaction terms for years of education and country. The United States was the reference cell for these comparisons. The 8- to 365-day model: interaction term for years of education and country was statistically significant for Poland ($p = 0.0415$). New Zealand was excluded from the statistical models as there were <500 patients with data on education from this country. The model reported here excluded the interaction terms for years of education and country. The United States was the reference cell for these comparisons.

CI = confidence interval; HR = hazard ratio; other abbreviations as Table 2.

ated with death up to 1 year after hospitalization for STEMI. In fact, the prognostic importance of years of education with mortality is further highlighted by the fact that the model chi-square for years of education (131.5) is second only to the model chi-square for age (172.3)—the factor with the strongest relationship with early mortality.

Comparisons with previous studies. Some previous studies have evaluated the relationship of years of education with patient outcomes. Tofler et al. (28) examined data from MILIS (Multicenter Investigation of the Limitation of Infarct Size), comparing 453 patients who had completed at least high school with 363 who had not finished high school; all patients were from the United States and younger than 76 years of age and had experienced acute MI. The authors found that the in-hospital and 4-year mortality rates were markedly higher for less educated patients than for those with more education (in-hospital mortality 13% vs. 5%, $p < 0.001$; 4-year mortality, 36% vs. 17%, $p < 0.001$). Fewer years of education remained an independent correlate of long-term mortality after adjustment for baseline features ($p = 0.024$ after adjustment). Some of the higher mortality among the less educated group was thought to be related to lower rates of smoking cessation in this cohort (38% vs. 49%; $p < 0.05$).

Ruberman et al. (29) evaluated 1,739 male survivors of acute MI in the United States who were enrolled in the BHAT (Beta-blockers in Heart Attack Trial). The authors demonstrated an inverse relationship between education and mortality in this population, and further showed that this relationship reflected the gradient in prevalence of defined psychosocial characteristics (e.g., social isolation and high degree of life stress were most common in the less-educated cohort).

Finally, in a small (n = 197) study of hospitalized survivors of MI in North Carolina, Kottke et al. (30) demonstrated higher reinfarction rates and lower rates of return-to-work among patients with less education. Others have examined different domains of SES, including poverty (31), income (32), occupation (30), race and ethnicity (33), address and country of residence (34,35), insurance status (36), marital status (37), or a more complex deprivation score consisting of overcrowding, unemployment, no car, and low occupational social class (35). Each of these parameters has been shown to be related to mortality in patients with acute MI.

Our study demonstrated a similar inverse relationship between lower SES, as measured by years of education, and mortality in STEMI. Nonetheless, unlike previous investigations that included only a small number of patients (with very few events) and that in many cases relied on administrative data that did not allow for appropriate adjustments for baseline confounders, our study involved a large number of STEMI patients in whom data on education, baseline features, treatments, procedure use, and events (1,026 deaths at 1 year) were prospectively collected, allowing reasonable adjustments for baseline variables. Additionally, previous investigations mainly focused on single centers, regions, or countries. Because the GUSTO-III was a multinational trial, we were able to examine and demonstrate the consistency for most parts of the relationship between years of education and mortality among STEMI patients with substantially different lifestyles, cultural influ-

ences, and health care systems that ranged from the technology-driven multipayer system in the United States to the more conservative government-regulated single-payer system in Canada.

Mechanisms underlying the relationship between years of education and mortality in patients with STEMI. Our study was not specifically designed to address mechanisms underlying the propensity for worse clinical outcomes in STEMI patients with fewer years of education. Nonetheless, we were able to provide some insight into the contributions of some factors and possibly speculate on other explanations that link lower levels of education and mortality in STEMI patients. As described previously, the increased comorbid conditions and adverse presenting features associated with fewer years of education may have accounted for some of the observed relationship with poorer outcomes in STEMI patients. Longer time to treatment, differences in medical therapies, and lower revascularization rates (percutaneous coronary intervention or coronary artery bypass graft) may also have contributed to some of the excess mortality in the cohort with fewer years of education. Moreover, factors not collected in our study such as social isolation (living alone), life stress, poverty, lack of insurance and inability to afford medications and/or lack of access to subsequent care, lack of compliance with strategies of secondary prevention including lifestyle changes may also have played an important role in the relationship between educational status and outcomes in patients with STEMI. Finally, education is closely linked with "health literacy," defined as the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions (38). Health literacy is regarded as fundamental to patients' quality of care and safety; it is also a stronger predictor of health than age, income, employment status, or race (38) and may explain some of the association between education and outcomes seen in the current study.

Clinical implications. Our study has a number of potential clinical implications. These data indicate that years of education may be a predictor of short- and intermediate-term mortality or a surrogate marker of measured or unmeasured variables that are strongly related to mortality in patients with STEMI. Future research should certainly focus on understanding the behavioral, social, biological, and physiological mediators that link SES with cardiovascular disease and its outcomes. Efforts to include measures of SES in all research on cardiovascular disease in humans, including cross-sectional and longitudinal studies, clinical trials, and, when feasible, community interventions, may help facilitate understanding of the complex link between SES and outcomes, as well as what measure of SES has the strongest link to prognosis. Improving education has the potential to improve health literacy and the health outcomes of patients.

Finally, current comparisons of in-hospital mortality in patients with CHD that adjust for baseline variables without accounting for educational status or other SES measures (39,40) may place institutions that care for large numbers of socially underprivileged patients at a significant and inappropriate disadvantage, given that such comparisons are typically used as part of measuring, publicly reporting, and rewarding quality. Our study shows educational status/SES to be the most important factor, after age, associated with early mortality. Adjusting for education/SES could help level the playing field for providers by recognizing differences among their patient populations and allow fairer comparisons of outcome measures as a surrogate for quality.

Study limitations. This was a retrospective analysis, and our findings are best viewed as hypothesis generating. We used years of education as a marker of SES because it was most commonly used in previous studies, is easily obtainable, and seldom changes beyond young adulthood. As such, we are unable to provide insights into the relative strengths of the association between other markers of SES, as noted earlier, and mortality in patients with STEMI. All patients were enrolled in a clinical trial with strict inclusion and exclusion criteria and received fibrinolytic therapy. Furthermore, almost all countries in our study were developed countries. Thus, the applicability of our study findings to STEMI patients in general or to those in less developed countries remains to be evaluated in future studies. Finally, 1,927 patients were excluded from all our analyses as noted previously, predominantly because of incomplete data on years of education. However, to demonstrate the relationship of the missing information on education with outcomes, we compared 1-year mortality in patients with missing information on education with those for whom this information was available. Patients with missing information on education had an almost 2-fold higher mortality compared with those included in this study (17.2% vs. 9.1%, $p < 0.0001$) that was even higher than those with <8 years of education (Fig. 2). It is likely that early mortality in the excluded group may have precluded the time needed to obtain socioeconomic data. Although the effect of the bias that may have been inherited by their exclusion on the results of our study cannot be ascertained, we believe that because missing information on education was more common in patients who had higher mortality and because overall mortality was inversely linked to education, the missing data on education were more likely to have biased our study findings toward failing to reject the null hypothesis (i.e., no relationship between education level and mortality).

Conclusions

Among GUSTO-III STEMI patients treated with fibrinolysis, years of completed education (a measure of SES) was inversely associated with significantly higher early and 1-year mortality. Although the strength of relationship between years of education and mortality in these patients varied among different countries, education remained independently related to mortality, even after adjusting for baseline clinical variables and country of enrollment. Future studies should account for and investigate the behavioral, social, biological, and physiological mechanisms underlying this link between SES and cardiovascular disease outcomes.

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Reprint requests and correspondence: Dr. Rajendra H. Mehta, Duke Clinical Research Institute, Box 17969, Durham, North Carolina 27715. E-mail: mehta007@dcri.duke.edu.

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