ORIGINAL ARTICLES

The Effect of Comorbidity on Use of Thrombolysis or Aspirin in Patients with Acute Myocardial Infarction Eligible for Treatment

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OBJECTIVE: **Growing evidence indicates that life-sustaining therapies for the treatment of acute myocardial infarction (AMI) are underused among patients eligible for therapy, including the elderly and women. We examined the effect of a patient's comorbidity burden on use of these highly effective therapies in eligible populations of individuals with AMI.**

DESIGN: **Retrospective cohort design.**

SETTING AND PATIENTS: **We reviewed the medical records of 2,409 individuals at 37 Minnesota hospitals from October 1992 through July 1993 with an admission diagnosis of AMI, suspected AMI, or rule-out AMI, who met electrocardiographic, laboratory, and clinical criteria for AMI.**

MEASUREMENTS AND MAIN RESULTS: **Using multivariate logistic regression models, we determined the association between a validated comorbidity measure and the proportion of eligible patients who received thrombolysis or aspirin. Controlling for other factors previously reported to influence rates of study treatment, the odds of receipt of thrombolysis among patients with severe comorbidity was 0.49 (95% confidence interval [CI] 0.27, 0.88) when compared with individuals without such limitation. Similarly, the odds of aspirin treatment among study patients with severe comorbidity was 0.46 (95% CI 0.30, 0.72), compared with individuals without severe comorbidity. We did not distinguish any differences in patterns of treatment with either study treatment among patients with mild or moderate comorbidity when compared with individuals without any concomitant comorbidity.**

CONCLUSIONS: **This study indicates that patients with severe mental and physical comorbidities are less likely to receive standard therapies for AMI recommended in national treatment guidelines.**

KEY WORDS: **acute myocardial infarction; drug treatment; comorbidity; quality of care.**
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The past decade has witnessed rapid growth in the development and use of evidence-based clinical practice guidelines by public and private health care organizations in attempts to improve quality of care and reduce costs.[1,2] Despite the dissemination of practice guidelines for acute myocardial infarction (AMI) from the American College of Cardiology and the American Heart Association recommending use of several highly effective and lifesaving drugs among eligible patients with AMI,[3] there is growing evidence that these treatments are underused.[4,5]

Consistent evidence exists from numerous randomized controlled trials that appropriate use of aspirin and thrombolytics in eligible populations substantially reduces morbidity and mortality.[6,7] These medications differ, however, in two respects. Aspirin is inexpensive with a relatively low side-effect risk profile while thrombolytic agents are costly and can cause rare but potentially catastrophic side effects, such as hemorrhagic strokes or other serious bleeding.[8,9] Thus, it is possible that physicians will use these drugs differently in the presence of severe comorbidity.

Previous studies have indicated that patients' comorbidity—especially their premorbid cognitive function, the likelihood of surviving the current illness, and prognosis—has an impact on whether life-sustaining treatment is withheld or withdrawn.[10–12] In addition, greater severity of illness has been associated with reduced use of intensive care in critical care settings.[13] However, little information is available on the effects of patients' comorbidi-

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ties on physician decision making regarding standard therapeutic options for conditions such as AMI. In this study, we examined whether acutely ill patients eligible for highly effective drug therapies for AMI (aspirin and thrombolytic agents) were less likely to be treated if they had coexisting physical or mental illnesses.

METHODS

Setting and Study Population

As more fully described in a previous report,[4] this investigation included 37 Minnesota hospitals, representing a broad cross of urban and nonurban hospitals (54% and 46%, respectively), with a wide range of number of beds. Two study hospitals were academic medical centers; the remainder were urban, suburban, or rural community hospitals.

We measured adherence of physician prescribing practices with guideline recommendations during the initial phase of the hospitalization for AMI. Potential patients were identified through admission diagnosis (International Classification of Diseases-9 codes 410 and 786) during the study period October 1992 through July 1993, and the medical records of these individuals were then reviewed. Using clinical and laboratory findings in the first 24 hours of hospitalization found in the medical record, we included for study patients meeting at least two of the following criteria: (1) explicit documentation by the physicians that electrocardiographic findings were consistent with an AMI; (2) enzyme evidence of AMI based on individual hospital criteria (elevation of serum creatine kinase and its isoenzyme muscle-brain subfractions); and (3) clinical symptoms consistent with an acute coronary syndrome (arm or shoulder pain, chest pain, diaphoresis, dyspnea, nausea or vomiting, and neck or jaw pain). We excluded patients who were transferred from other nonstudy hospitals, individuals who were dead on arrival, or those who had suffered a myocardial infarction within 2 weeks of the index admission. Absolute and relative contraindications as well as indications for administration of thrombolytics and aspirin conformed to the most recent (1990) American College of Cardiology/American Heart Association practice guidelines for AMI.[3]

Data Sources

Our previously described instrument for medical record abstraction was used to retrieve data on demographics; admission dates and times; inclusion and exclusion criteria; time from onset of symptoms to hospital presentation; identities of all preadmission medications; electrocardiographic, clinical, and laboratory evidence of AMI; medical history at admission; and identity and time of administration of all drugs in the first 48 hours following admission (including emergency transport and emergency department treatment). Individuals were classified as having heart failure if they experienced any of the following in the first 24 hours of hospitalization: either rales or increased jugular venous pressure; they had any two of the following—cyanosis, diminished peripheral pulses, poor capillary filling, cold or clammy extremities, and a systolic pressure less than 90 mm Hg; or if there was any documentation of "cardiogenic shock" or "pump failure" in the medical record. Trained nurse abstractors with cardiology experience and blind to all study hypotheses performed data collection for this study; interrater reliability was 95%.[4] Clinical, electrocardiographic, and medical history information required for the determination of indication and contraindication for thrombolytic therapy and aspirin use was present for 98% of the 2,409 patients. For the construction of the Greenfield Index only 8 (0.3%) of the 2,409 patients had missing data. Patients with missing data elements were excluded from analysis for the variable affected.

Comorbidity Measures

Comorbidity was measured with the Greenfield Index of Coexistent Disease (ICED),[14] using information recorded at the time of admission and information collected at the time of chart abstraction. This measure consisted of two dimensions: (1) severity levels of 14 coexistent medical conditions, graded on a 4-point ordinal scale; and (2) a 3-point ordinal rating of the severity of 11 dimensions of physical and mental impairment. Coexistent medical conditions included cerebrovascular accident; peripheral vascular disease; diabetes mellitus; respiratory problems; malignancies; hepatobilary, renal, or gastrointestinal disease; arthritis; and nonischemic cardiovascular disease consisting primarily of organic cardiac disease, arrhythmias or conduction defects, hypertension without ischemic or organic heart disease, and ventricular dysfunction. Impairment levels were estimated for the following: neurologic status; and respiratory, urinary, fecal, auditory, visual, speech, ambulatory, mental, and feeding functions. Levels of coexistent medical conditions and impairment were then collapsed into a final 4-point scale according to the method of Greenfield,[14] with ranges from no comorbidity (ICED = 0) to severe comorbidity (ICED = 3).

Description of Analytical Models

We defined eligibility for aspirin or thrombolytics as the absence of absolute or relative contraindications to receipt of these agents. Thrombolytic eligibility was further restricted to patients without medical contraindications who came to medical attention within 12 hours of onset of symptoms and with an ST-segment elevation of at least $\geq$1 mm.[4] For the purposes of these analyses, we only considered medications (thrombolytic therapy or aspirin) received within 24 hours of first hospital contact.

To examine the association between an individual's comorbidity burden and guideline adherence rates, we analyzed patient-level data for each study drug using a logistic regression model that controlled for correlation of

binary observations (use or no use of treatment) within hospitals.[15] Models included control variables consisting of patient age interval (<65, 65–74, >74 years), gender, teaching status of hospital, and time from symptom onset to hospital presentation (which have been previously reported to be associated with variation in treatment patterns),[4] as well as Greenfield's ICED score. Odds ratios (OR) and 95% confidence intervals (CI) were calculated directly from the estimated regression coefficients and their standard errors. Adjusted proportions of eligible patients receiving each of the study drugs were estimated from the multivariate logistic regression models, which controlled for age, gender, hospital teaching status, and time from onset of symptoms, by calculating the predicted probability of outcome. Predicted probabilities were aggregated by variable of interest and reported as adjusted proportions.

RESULTS

Patient Sample

Table 1 indicates that the demographics of study patients (N = 2,409) reflected the epidemiology of AMI with a preponderance of older (59% ≥ 65 years of age) and male (62%) patients. Sixty percent of all patients came to the hospital within 6 hours of onset of symptoms; approximately 30% of study patients came after 12 hours. As previously described,[4] 32% of patients had an absolute or relative contraindication to aspirin, and 34% to thrombolytic treatment. The main reasons for exclusion from eligibility for aspirin were history of serious bleeding, history of peptic ulcer disease, or asthma with nasal polyps. For thrombolytic therapy, only 569 patients had a medical contraindication to therapy; of those without medical

Table 1. Baseline Characteristics of Study Patients (N = 2,409)

Demographics	Number Overall (%) (N = 2,409)	Number with Severe Comorbidity (%) (n = 583)
Age, years		
<65	970 (40)	146 (25)
65–74	661 (27)	167 (29)
>74	778 (32)	270 (46)
Male Gender	1,485 (62)	304 (52)
Time from symptom onset, hours		
≤6	1,435 (60)	313 (54)
6–12	223 (9)	49 (8)
>12	751 (31)	221 (38)
Medical contraindications for thrombolytics	569 (24)	248 (43)
Indication for thrombolytics*	1,226 (51)	251 (43)
Medical contraindication for aspirin	782 (32)	285 (49)
DNR status at admission	48 (2)	37 (6)
Heart failure†	503 (21)	170 (29)
Comorbidity‡		
No comorbidity	356 (15)	
Mild comorbidity	864 (36)	
Moderate comorbidity	606 (25)	
Severe comorbidity (n = 583)	583 (24)	
Mental impairment§		111 (19)
Malignancy ‖		82 (14)
Renal impairment¶		76 (13)
Hypertension#		64 (11)
Respiratory dysfunction**		59 (10)
Diabetes mellitus††		58 (10)

**ST-segment elevation ≥ 1 mm.*

†Occurring any time in first 24 hours of admission.

‡No comorbidity is defined as Greenfield Index of Coexistent Disease (ICED) score = 0; mild as ICED = 1; moderate as ICED = 2; severe as ICED = 3.

§Chronic condition: confused; oriented ×1, ×2; psychotic; long-term depression; intellectual deterioration.

‖End-stage or terminal cancer.

¶End-stage renal failure.

#Hypertensive crisis or coma, not related to another disease.

***Chronic obstructive pulmonary disease: documented FEV_1 < 60%; tracheotomy; O_2 tank; respirator.*

††Diabetic coma, shock, severe ischemic heart disease, end-stage renal disease (creatinine > 6 mg/dl).

contraindications, 620 were lost to eligibility owing to presentation after 12 hours of symptom onset. The electrocardiographic criterion for the indication of thrombolytics (1-mm ST-segment elevation) was met for 710 patients without medical contraindications who presented within 12 hours. Thirty percent of patients (n = 723) had evidence of heart failure at admission or during the first 24 hours of hospitalization. Two percent of all patients had do-not-resuscitate orders at admission.

Approximately one quarter (n = 583) of all study subjects had at least one item from the Greenfield ICED scored as indicating severe comorbidity (ICED = 3). These individuals tended to be older than the overall study population and had more contraindications for aspirin or thrombolysis. For these patients, the leading causes of comorbidity included mental impairment (19%), malignancies (14%), renal impairment (13%), hypertension (11%), respiratory dysfunction (10%), and diabetes (10%) (Table 1). Other causes of cardiac and noncardiac comorbidity included history of disabling stroke (7.5%), peripheral vascular disease (5.8%), gastrointestinal or hepatobilary disease (4.1%), and disturbances of heart rhythm (2.4%).

Association of Comorbidity with Use of Thrombolysis or Aspirin

Of the entire study sample, 29.5% (n = 710) were considered eligible for thrombolytic therapy, and 65.2% (n = 1,571) for aspirin. These patient groups comprised the study samples for the examination of the relation between comorbidity burden and treatment with thrombolytics or aspirin.

Controlling for patient demographics and hospital characteristics as well as heart failure, patients with mild comorbidity (ICED = 1) or moderate comorbidity (ICED = 2) did not differ from those without any comorbidity (ICED = 0) in their likelihood of receiving aspirin or thrombolytics (Table 2). However, an ICED score indicating severe comorbid illness (ICED = 3) was strongly associated with lack of treatment with either aspirin or thrombolytics among eligible patients. For patients with severe comorbidity scores (ICED = 3), the adjusted odds of treatment (compared with individuals with no impairment) was 0.46 for aspirin (95% CI 0.30, 0.72) and 0.49 for thrombolytics (95% CI 0.27, 0.88).

DISCUSSION

This study describes the relation between decisions to use effective, lifesaving drugs (thrombolytics or aspirin) to treat patients with AMI and the severity of the patients' comorbid illness. Controlling for other patient and hospital factors previously reported to influence rates of adherence to national treatment guidelines for AMI,[4] the OR of treatment with thrombolytics or aspirin for patients with severe comorbidity was approximately half that of comparable patients without significant cormorbidities (Table 2). We did not detect any differences in aspirin or thrombolytic treatment patterns among patients with mild to moderate comorbidity when compared with individuals without comorbid conditions, suggesting that physician decision making was influenced by high levels of concomitant illness but not by less severe comorbidities.

The results of this study suggest that the observed patterns of undertreatment of eligible patients with AMI may be influenced by a prognostic judgment which takes into account levels of comorbidity. Only 2% of the study patients had do-not-resuscitate orders at the time of admission, suggesting that other patient or physician factors predominated in decisions not to treat patients with more severe comorbid illness. A questionnaire survey of 524 physician medical directors of adult chronic dialysis units throughout the United States asked about decisions to withdraw or withhold dialysis from a competent, severely demented, or permanently unconscious patients.[16] The greatest variation in responses was associated with the decision to discontinue dialysis for demented patients, suggesting that a patient's cognitive function was an important factor influencing some providers' decision making. In the current study, the leading cause of limitation among study subjects was impaired mental status

Table 2. Adjusted Proportions and Odds Ratios for Receipt of Thrombolytics and Aspirin According to Greenfield Comorbidity Score, Among Eligible Patients Controlling for Age, Gender, Hospital Type (Teaching/Nonteaching), and Heart Failure*

Covariate	Thrombolytics (n = 710) Adjusted Proportion, OR (95% CI)	Aspirin (n = 1571) Adjusted Proportion, OR (95% CI)
Comorbidity Measures		
No severe comorbidity	0.79	0.85
Mild comorbidity	0.73, 0.71 (0.43, 1.18)	0.83, 0.82 (0.54, 1.23)
Moderate comorbidity	0.73, 0.72 (0.41, 1.26)	0.86, 1.07 (0.68, 1.70)
Severe comorbidity	0.64, 0.49 (0.27, 0.88)	0.73, 0.46 (0.30, 0.72)

**Probabilities, odds ratios, and confidence intervals are estimated from multivariate regression models. Probabilities are reported as adjusted proportions.*

(19%), consisting of chronic conditions characterized by confusion, disorientation, psychosis, long-term depression, or intellectual deterioration. It is possible that mental disability could influence explicit or implicit decisions to undertreat a life-threatening illness such as AMI. In an analysis of the relation between use of the two study drugs and severe mental comorbidity that controlled for severe comorbidity not related to mental function (data not shown), we observed that severely mentally impaired patients exhibited nonsignificant trends toward reduced use of thrombolytics (OR 0.45) or aspirin (OR 0.36). However, because of small sample sizes and limited power, further research is needed to assess directly the relative importance of mental dysfunction in the decision not to treat.

Increasingly, physicians treating seriously ill patients are deciding with patients and families whether to forgo or withdraw life-sustaining treatment. However, little is known about physicians' or patients' decision making in the context of illnesses such as AMI for which standard therapeutic options exist. The relative paucity of research regarding the decision to withhold standard treatment is undoubtedly influenced by the complexity and consequences of such decisions. In recent years, several studies have reported an association between physicians' decisions to provide care for incompetent or critically ill elderly patients and patients' quality of life, prognosis, anticipated survival time, and reversibility of the illness. However, few studies have examined the reasons underlying these associations. One notable exception is a study that examined physicians' perceptions about quality of life following treatment as a possible factor in explaining variability in physician decision making. In an interview of 205 physicians presented with a case management problem involving an elderly male patient with an acute deterioration of chronic obstructive pulmonary disease and mild pulmonary hypertension, major reasons for withholding therapy (respirator support) from an otherwise eligible patient included "end-stage" disease and poor quality of life.[17] No attempt was made, however, to compare physicians' stated responses for withholding treatment with actual behaviors, which could be quite different.[17] In addition, we are not aware of any previous studies that investigated the role of such comorbid illness in management of acute, reversible illness.

Our findings also have implications for the measurement of physician adherence to treatment guidelines. Apparent noncompliance with the growing number of evidence-based guidelines is commonly interpreted as reflecting gaps in knowledge or lack of acceptance of guideline recommendations. And consistent with this perception, continuing medical education and quality management interventions are intended to improve adherence to guidelines by educating providers about state-of-the-art information or by creating strategies to improve acceptance of treatment recommendations. However, this research suggests that undertreatment may reflect conscious or unconscious considerations to withhold standard therapeutic options in the context of adequate knowledge and acceptance of the findings about the efficacy of a specific therapy.

In summary, our study indicates that patients with severe mental and physical comorbidities are less likely to receive two highly effective therapies for AMI recommended in national consensus guidelines. Moreover, despite aspirin's low cost-risk profile, underuse of therapy was approximately the same as that of thrombolytic agents, which, although highly effective in reducing morbidity and mortality, also carry a greater risk of major adverse effects than does aspirin. Future research is needed to determine the generalizability of these relations to other patient populations and treatments, and to better identify other patient, family, physician, and system factors that may explain variations in adherence to evidence-based guidelines.

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