Does More Intensive Treatment of Acute Myocardial Infarction in the Elderly Reduce Mortality?

Analysis Using Instrumental Variables

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Objective.—To determine the effect of more intensive treatments on mortality in elderly patients with acute myocardial infarction (AMI).

Design.—Analysis of incremental treatment effects using differential distances as instrumental variables to account for unobserved case-mix variation (selection bias) in observational Medicare claims data (1987 through 1991).

Main Outcome Measures.—Survival to 4 years after AMI.

Results.—Patients who receive different treatments differ in observable and unobservable health characteristics, biasing estimates of treatment effects based on standard methods of adjusting for observable differences. Patients' differential distances to alternative types of hospitals are strong independent predictors of how intensively an AMI patient will be treated and appear uncorrelated with health status. Thus, differential distances approximately randomize patients to different likelihoods of receiving intensive treatments. Comparisons of patient groups that differ only in differential distances show that the impact on mortality at 1 to 4 years after AMI of the incremental ("marginal") use of invasive procedures in Medicare patients was at most 5 percentage points; this gain was achieved during the first day of hospitalization and therefore appears attributable to treatments other than the procedures. Admission to a hospital treating a high volume of AMI patients was associated with an effect on mortality at 4 years of less than 1 percentage point, again arising on day 1. Patients living in rural areas experienced acute mortality that was an additional 0.6 percentage-point higher, after controlling for less access to intensive treatments.

Conclusions.—For elderly patients with AMI, the aspects of treatment most affecting long-term survival relate to care within the first 24 hours of admission. The survival benefits from greater use of catheterization and revascularization procedures appear minimal in marginal patients.

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DOES MORE intensive treatment of acute myocardial infarction (AMI) in the US elderly population—more aggressive use of cardiac catheterization, revascularization, and other intensive technological procedures—reduce mortality? The criterion-standard approach to this question uses controlled trials, which randomize elderly patients to different treatments. Although such trials have provided some evidence on this question,[1] they are often too costly, too difficult, or unethical to perform. As a result, trials in this and other contexts focus on narrow treatment comparisons and patient populations, so that in many respects the resulting evidence is inadequate for policy.[2,3]

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For editorial comment see p 891.

Consequently, policymakers and clinical researchers have turned to outcomes research, using observational data on real-world patient populations to analyze the relationships among provider characteristics, treatments, and health outcomes. Because increasingly large and comprehensive data sets are available to evaluate medical treatments and providers,[4] outcomes research is one of the fastest-growing fields in medical research today. Its results can potentially determine not only what effect alternative treatments have on outcomes and which practice patterns are appropriate,[5] but also which providers are "best."[6,7] Yet, despite intense policy interest in and financial support for outcomes research, prominent critics question its validity.[8]

The critics' central concern is the danger of selection bias when observational data sets are used to compare outcomes among patients receiving different treatments. The potential for selection bias arises because many factors other than the treatment may affect patient outcomes. These factors include comorbid diseases, severity of illness, and other complex details of a patient's health status, as well as patient and physician preference. Such factors are likely to influence treatment decisions but are difficult to capture fully in recorded data. Differences in outcomes between groups receiving different treatments result from the effects of the treatments plus the net effects of differences in all these characteristics between the groups.

Standard biostatistical methods can be used to adjust for observable differences between groups, but they cannot adjust for unobserved differences. One example of the inability to adjust for important residual unobserved differences is poorer case-mix adjusted mortality rates for certain hospitals, not because they provide lower-quality services but because they treat sicker patients even after adjustment.[9-12]

In this study, we describe and apply a fundamentally different approach to the selection problem in observational studies. The method, instrumental variables (IVs) estimation, is well known in econometrics[13,14] but generally has not been applied to estimate relationships between medical treatments and health outcomes. Instrumental variables estimation uses one or more IVs—observable factors that influence treatment but do not directly affect patient outcomes—to mimic a randomization of patients to different likelihoods of receiving alternative treatments. When valid, the method is analogous to randomization methods in identifying "balanced" sources of variation in treatment, so that estimates of treatment effects are not contaminated by selection bias.

The method differs from randomized trials in two key respects. First, because randomization is not deliberate, it assumes that the proposed IVs are not correlated with unobserved differences in characteristics that directly affect outcomes. Unlike randomized trials, this absence of correlation is an assumption; its validity can be explored extensively but not be proven. Second, because the groups being compared differ only in likelihoods of treatment, as opposed to a division into pure treatment and control groups, the method estimates an incremental or "marginal" effect of treatment only over the range of variation in treatment across the IV groups.

We use the IV method to study the incremental effects on short- and long-term mortality of more intensive treatments of acute myocardial infarction (AMI) in the elderly in 1987. We address a set of questions that randomized trials are unlikely ever to address: (1) the degree to which availability of certain technological capabilities at hospitals independently influences treatment decisions in the management of AMI; (2) the extent to which patients with a greater likelihood of receiving more intensive treatment after an AMI—for reasons independent of their health status—have lower mortality rates; and (3) the timing of any such survival benefits.

METHODS

Patients

We began with a cohort that consisted of the vast majority of Medicare beneficiaries older than 64 years who had an AMI in 1987 and who had not had an AMI in 1986 (N=218 427); the criteria used to identify valid AMI cases in the creation of this cohort are described elsewhere.[15] By linking claims and administrative data from the Health Care Financing Administration, we identified patient demographic characteristics (age, sex, and race), patient comorbid disease characteristics, the hospitals treating the patient for AMI, the use of cardiac catheterization, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery during the 90 days after the initial AMI admission, and survival to 4 years after AMI. We characterized the patient's residence as rural or urban, based on whether the patient resided in a metropolitan statistical area.

We then applied additional exclusion criteria that related to our use of ZIP codes to calculate distances from patient residences to the nearest hospitals with particular characteristics. Because of missing ZIP code information, we were unable to estimate distance for 1.2% of the cohort. We excluded another 4.9% of patients who were admitted initially to a hospital more than 100 miles from their place of residence; we assumed such patients were traveling at the time of their AMI. We also eliminated the small number (0.04%) of patients living in Alaska because of inaccuracies in our program for calculating distance at far northern latitudes. Our analytic sample thus consisted of 205 021 patients, approximately 94% of the initial 1987 AMI cohort.

Hospital Characteristics

We classified hospitals along two dimensions of intensity. First, we grouped them by procedure capability, based on whether the hospital performed at least five catheterization procedures on elderly AMI patients (catheterization hospital); in some analyses, we further divided catheterization hospitals into those performing 10 or more revascularization procedures (revascularization hospital) and others. To prevent coding errors from causing misclassifications, we required that a hospital perform at least five catheterizations to be classified as a catheterization hospital; results were not sensitive to alternative cutoffs between two and 10 procedures. We categorized all other hospitals with five or more Medicare AMI admissions in 1987 as noncatheterization hospitals.

Second, we grouped hospitals on the basis of volume of AMIs in the elderly, as measured by the number of patients admitted to each hospital. We defined high-volume hospitals as those treating at least 75 elderly patients with AMIs in the year; roughly half our sample was admitted to such hospitals. We associated patients with their initial admission hospital; patients initially admitted to small noncatheterization hospitals could be revascularized or treated at high-volume hospitals after being transferred.

Analytic Approach

We first compared raw (unadjusted) outcomes between patient groups that did and did not undergo catheterization after AMI; then we used fully interacted analysis of variance (ANOVA) methods to adjust the raw outcome differences for observable differences in demographic and comorbid disease characteristics between these two groups. To establish the magnitude of selection bias, we contrasted these estimates with those using IV methods.

We sketch our IV estimation methods herein; they are described in full in a technical companion paper.[16] The methods compare treatments and outcomes across groups that appear identical except for their values of the IVs, which are associated with differences in treatment. Thus, the methods isolate the effect of treatment variation in the observational data that is independent of unobserved patient characteristics. Because important aspects of health status cannot be observed, the validity of the key assumption that the IVs are uncorrelated with health status cannot be verified directly. Nonetheless, because some aspects of health status are observed and because the IV assumption has a number of statistical implications, the assumption of no correlation is partially testable.

To implement the IV estimation strategy, we hypothesized that patients' locations would independently affect hospital choice and that differences in the intensive procedures available at various hospitals would lead to differences in how similar patients were treated. Because physician and patient decisions that influence treatment choice may also influence choice among hospitals (eg, AMI patients who appear to be better candidates for catheterization may be disproportionately admitted to catheterization hospitals), comparing treatments and outcomes of patients actually treated at different hospitals risks selection bias.

To avoid such bias, we grouped patients on the basis of differential distance to alternative hospital types, defined as the difference between the patient's distance to the nearest hospital of a given type (eg, catheterization hospital) minus the patient's distance to the nearest hospital. We estimated distances in a straight-line fashion, from the geographic center of population for the patient's residence ZIP code to the center for the hospital's ZIP code.

To determine whether hospital type affects treatment intensity, and therefore whether simple comparisons of treatments and outcomes across hospital types are valid, we estimated the average effect of hospital capability on procedure use in two ways: by standard, fully interacted ANOVA methods and by IV methods. Any difference in effect size implies selection bias in hospital choice. Our IV methods, analogous to those described next for the effect of treatment on mortality, compared invasive procedure use across otherwise identical differential-distance groups that differed in the probability of initial admission to noncatheterization, catheterization, and revascularization hospitals.[17]

Because we found some selection bias in hospital choice, we developed IV methods to estimate the incremental effects of more intensive treatments on mortality without selection bias. We began by comparing two differential-distance groups of approximately equal size: patients relatively near to a catheterization hospital (differential distance ≤2.5 miles) and patients relatively far from such hospitals (>2.5 miles). This preliminary comparison provided evidence on the validity of our key assumption that the distribution of health status in elderly AMI patients is for practical purposes independent of differential distance and also illustrated the IV method. In particular, the ratio (mortality rate_{near}–mortality rate_{far})/(catheterization rate_{near}– catheterization rate_{far}) estimates the average effect of invasive treatment for all patients who are marginal from the standpoint of the near-far IVs—those who undergo catheterization in the relatively near group but not in the relatively far group—if the two groups are balanced and if catheterization is the only treatment that differs between the groups.

We then applied more general IV estimation techniques. These methods exploit more of the differential-distance variation in our data by using a larger number of groups (0, 0 to 1, 1 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 10, 10 to 12, 12 to 15, 15 to 18, 18 to 21, 21 to 25, 25 to 30, 30 to 40, and more than 40 miles). They also account for any small remaining observable differences between differential-distance groups (analogous to ANOVA methods) by estimating effects within cells of patients identical in observable demographic characteristics: age (in 5-year intervals from 65 through 69 years to 90 years and older), sex, race (black or nonblack), and urban or rural residence. Cell sizes were generally large. For nonblacks all cells contained more than 5000 patients; the smallest cell, rural black men older than 90 years, included 89 patients. Some models defined cells including state of residence and comorbid diseases. Finally, to account at least in part for the effects of treatments other than catheterization and revascularization that patients relatively near catheterization and revascularization hospitals were also more likely to receive, the general methods use additional IV groups based on differential distance to a high-volume hospital to estimate the effects of catheterization and admission to a high-volume hospital simultaneously.

Table 1.—Characteristics of Elderly Patients With Acute Myocardial Infarction in 1987*

Characteristic	All Patients (N=205 021)	No Catheterization Within 90 d (n=158 261)	Catheterization Within 90 d (n=46 760)
Demographic Characteristics			
Female	50.4	53.5	39.7
Black	5.6	6.0	4.3
Mean age, y (SD)	76.1 (7.2)	77.4 (7.3)	71.6 (5.0)
Urban	70.5	69.6	73.8
Comorbid Disease Characteristics			
Cancer	1.9	2.2	0.8
Pulmonary disease, uncomplicated	10.7	11.1	9.3
Dementia	1.0	1.2	0.1
Diabetes	18.0	18.3	17.1
Renal disease, uncomplicated	1.9	2.3	0.7
Cerebrovascular disease	4.8	5.4	2.8
Treatments			
Initial admit to catheterization hospital†	19.7	19.3	21.3
Initial admit to revascularization hospital†	26.2	21.6	41.6
Initial admit to high-volume hospital†	51.8	50.0	58.0
Catheterization within 7 d	15.9	0	69.5
CABG‡ within 90 d	7.7	0.8‖	30.8
PTCA§ within 90 d	5.3	0.6‖	21.2
Outcomes			
Mortality within 1 d	8.2	10.3	0.9
Mortality within 7 d	17.7	22.0	3.3
Mortality within 30 d	25.6	26.6	7.4
Mortality within 1 y	40.2	47.1	16.6
Mortality within 2 y	47.5	55.3	21.3
Mortality within 3 y	53.4	61.6	25.6
Mortality within 4 y	56.3	66.7	29.9

*All data entries are percentages except for mean age, which is in years.

†All US acute care hospitals were classified on the basis of procedure capacity (none, catheterization only, and catheterization and revascularization) and volume of elderly AMI patients treated.

‡CABG indicates coronary artery bypass graft.

§PTCA indicates percutaneous transluminal coronary artery angioplasty.

‖Slightly more than 1% of patients in the no-catheterization group actually underwent a revascularization procedure, suggesting catheterization occurred before acute myocardial infarction or was not recorded in our data. Reassigning this small group of patients to the catheterization group had no effect on our results.

These estimation techniques simply extend the two-group IV comparisons to comparisons across a larger number of differential-distance groups identical in terms of observable characteristics; they estimate weighted-average effects over these cells. Formally, we used nonparametric generalized method-of-moments estimation, based on the moment condition that differential distance is uncorrelated with outcome residuals.[14,18]

We estimated the effects of catheterization and high-volume hospital treatment on mortality at various times after AMI (1, 7, and 30 days and 1, 2, 3, and 4 years). By analyzing the impact of these treatments over time, we also sought to infer the role of treatments other than procedure use on survival. Specifically, effects appearing within the first day after AMI are unlikely to relate causally to catheterization and subsequent revascularization but rather to other aspects of treatment that correlate with these procedures, because fewer than 2% of elderly AMI patients in 1987 underwent catheterization on day 1. We also computed the average effect of rural residence as an indicator of the impact of advanced emergency medical response systems.

The assumption that differential distance is uncorrelated with patient health status is crucial to the validity (technically, to the consistency) of our IV estimates. We used a variety of approaches to test the assumption, which we describe in a technical companion paper[16] and summarize briefly herein.

RESULTS

Procedure Use and Outcomes: Evidence for Selection Bias

Of the sample, 23% (46 760/205 021) underwent catheterization within 90 days of AMI, and these patients had much lower mortality at all time intervals after AMI than patients who did not undergo catheterization (Table 1). The catheterized patients also differed in terms of most observable characteristics; they were younger and had fewer comorbid diseases. They probably differed in many unmeasured dimensions as well, such as AMI severity or the incidence of acute complications. Catheterized patients were more likely to have been treated initially at hospitals performing invasive procedures, suggesting large differences in patient treatment across hospital types.

Use of standard statistical techniques (ANOVA) to adjust for the observable differences between catheterized and noncatheterized patients does not reduce substantially the large mortality differences (Table 2). Adjustment for demographic characteristics decreases the estimated catheterization "effects" by 15% to 20%, and further adjustment for comorbid disease differences reduces them by another 5%.

Although these standard adjustment methods attribute the residual difference in outcomes between catheterized and noncatheterized patients to the more intensive treatment, the large differences in observed health characteristics suggest that much of the outcome difference instead may be the result of unobserved health differences between the groups. Moreover, a large difference in mortality is apparent within the first day after AMI (day 1), and the difference steadily increases over time. This pattern also suggests that unobserved health differences are important: the catheterization group simply has a lower risk of death at any and all time intervals before and after the procedures are actually performed.

Correlated Dimensions of AMI Treatment Intensity

Aspects of treatment other than catheterization and revascularization may affect outcomes, and hospital volume correlates with many of them (Table 3). More than half our sample was treated initially at the 18% of hospitals that admitted 75 or more new elderly AMI patients. These high-volume hospitals were more likely to have the capability to perform catheterization and revascularization, and patients initially admitted to them were more likely to undergo the procedures.

The higher-volume hospitals were able to provide more intensive treatment in many other dimensions. For example, they tended to have more beds, suggesting more specialized staff and equipment, and they were more likely to have dedicated coronary care units. We used hospital volume, controlling for capacity to perform invasive procedures, to summarize the effects of intensity in these other dimensions.

Preliminary Comparisons Using Differential-Distance Groups

Our IV methods do not compare outcomes for individual patients based on their actual treatments, which reflect unobserved differences in health status. Instead, we use an IV to form groups with similar distributions of health characteristics whose treatment differs substantially for reasons independent of health status. Table 4 shows the results of grouping patients by whether they lived relatively near to a catheterization hospital. Patients whose differential distance was more than 2.5 miles were more likely to live in rural areas and less likely to be black, suggesting that effects should be estimated within these demographic groups.

With respect to health characteristics such as age and the prevalence of comorbid diseases, however, the two groups are far more similar than the groups in Table 1. This balance in observable health status provides some validation of the key assumption of the IV technique: that the distribution of unobserved health characteristics is balanced across differential distances. (Across the finer differential-distance intervals used herein, age and comorbid diseases also showed no meaningful differences.)

Despite the similarity in observable health characteristics, the two groups differ substantially in AMI treatment. Patients relatively near to a catheterization hospital were much more likely to be admitted to such a hospital initially (76% vs 16%), confirming our hypothesis that differential distance is a strong independent predictor of hospital choice. As a result of the differences in medical practice patterns across hospital types, relatively near patients were almost twice as likely to undergo catheterization within 7 days as those at greater distances (20.7% vs 11.0%) and even at 90 days were almost one third more likely to have undergone catheterization (26.2% vs 19.5%).

Revascularization rates differed proportionally with catheterization rates (eg, a difference of one third in the simple two-group comparison, 14.9% vs 11.2%); percutaneous transluminal coronary angioplasty rates had relatively larger proportional responses (eg, 6.4% vs 4.3%), and coronary artery bypass graft rates had relatively smaller proportional responses (eg, 8.6% vs 6.9%). Our analyses of the effects of more aggressive use of invasive procedures thus include the effects of proportional increases in both catheterization and revascularization. These substantial differences in treatment are the basis for the IV estimates of treatment effects.

Procedure Use and Hospital Capabilities

Our data confirm that rural residents, women, and blacks receive invasive procedures less often[19-24] (Table 5; for reference, a 65- to 69-year-old nonblack, male urban resident has a 41% probability of being catheterized). Analogous to a recent study involving New York State AMI patients,[25] the second column of Table 5 presents estimates of the "ef-

Table 2.—Estimated Cumulative Effect of Catheterization, Not Accounting for Selection Bias

Adjustment for Observable Differences Using ANOVA*	Percentage-Point Changes in Mortality Rates (SE)					
	1 d	7 d	30 d	1 y	2 y	4 y
None (unadjusted differences)	−9.4 (0.2)	−18.7 (0.2)	−19.2 (0.3)	−30.5 (0.3)	−34.0 (0.3)	−36.8 (0.3)
After adjustment for demographic differences (age, sex, race, and state)	−6.7 (0.2)	−13.7 (0.2)	−18.7 (0.3)	−26.0 (0.3)	−28.7 (0.3)	−30.4 (0.3)
After adjustment for demographic and comorbidity differences	−6.8 (0.2)	−13.5 (0.2)	−17.9 (0.3)	−24.1 (0.3)	−26.6 (0.3)	−28.1 (0.3)

*ANOVA indicates analysis of variance.

Table 3.—Hospital Characteristics*

Hospital Volume	No. of Hospitals (%)	Patient Share, %	Procedure Capacity, %			90-d Catheterization Rate, %	Bed Size		Coronary Care Unit Present, %
			None	Catheterization	Revascularization		<100	>500	
<25 AMI admissions	2909 (49.8)	12.2	96.2	3.3	0.5	17.0	75.9	0.8	57.2
25-74 AMI admissions	1889 (32.3)	36.0	69.8	18.9	11.3	20.8	20.8	4.4	81.5
75-149 AMI admissions	824 (14.1)	34.2	39.7	26.3	33.9	24.6	1.0	17.0	93.7
≥150 AMI admissions	222 (3.8)	17.6	20.8	19.8	59.4	27.4	0	49.2	97.3
Total	**5844 (100.0)**	**100.0**	54.1	19.7	26.2	22.8	17.1	16.1	85.4

*Data are weighted by number of initial hospital admissions for elderly patients with acute myocardial infarction (AMI).

fect" of hospital capability on procedure use after adjusting for observed differences among patients admitted to different types of hospitals. Patients treated at catheterization hospitals are more likely to undergo catheterization after AMI (8.6 percentage points), and patients treated at revascularization hospitals are even more likely (18.5 percentage points). These methods, however, cannot adjust for any selective admission of AMI patients to catheterization or revascularization hospitals for unobserved reasons, such as the nature of their coronary disease or their preferences for more aggressive treatment.

To account for any such unobserved differences in patients admitted to different types of hospitals, the third column of Table 5 shows IV estimates of the effect of hospital type on treatment choice, using differential distances to catheterization and revascularization hospitals as IVs to predict hospital choice independent of such unobserved factors. Although these estimates are qualitatively similar to those in the second column, they show evidence of patient sorting by hospital type. The effects of catheterization and revascularization capacity remain large (7.1 percentage points and 16.0 percentage points, respectively) but are significantly smaller than those in column 2 (eg, 18.5 vs 16.0; $P<.01$). Thus, 15% to 20% of the observed difference in AMI catheterization rates across hospital types is due to unobserved differences in case mix. The remainder is due to true differences in practice patterns. Comparing columns 1 and 3 shows that the less frequent use of catheterization among rural patients is due entirely to such patients' more limited access to catheterization hospitals. In contrast, virtually none of the observed differences in rates between women and men and between blacks and nonblacks stems from such access differences; those differences occur within hospitals.

Table 4.—Patient Characteristics by Differential Distance to a Catheterization or Revascularization Hospital*

Characteristic	Differential Distance ≤2.5 Miles (n=102 516)	Differential Distance >2.5 Miles (n=102 505)
Demographic Characteristics		
Female	51.3	49.5
Black	7.1	4.3
Mean age, y (SD)	76.1 (7.3)	76.1 (7.2)
Rural	6.5	52.4
Comorbid Disease Characteristics		
Cancer	1.9	1.9
Pulmonary disease, uncomplicated	10.4	10.9
Dementia	0.99	0.94
Diabetes	18.1	18.0
Renal disease, uncomplicated	2.0	1.9
Cerebrovascular disease	4.8	4.8
Treatments		
Initial admit to catheterization hospital†	34.4	5.0
Initial admit to revascularization hospital†	41.7	10.7
Initial admit to high-volume hospital†	67.1	36.5
Catheterization within 7 d	20.7	11.0
Catheterization within 90 d	26.2	19.5
CABG‡ within 90 d	8.6	6.9
PTCA§ within 90 d	6.4	4.3
Outcomes		
Mortality within 1 d	7.5	8.9
Mortality within 7 d	16.8	18.6
Mortality within 30 d	24.9	26.4
Mortality within 1 y	39.8	40.5
Mortality within 2 y	47.2	47.9
Mortality within 3 y	53.1	53.6
Mortality within 4 y	58.1	58.5

*All data entries are percentages except for mean age, which is in years.
†All US acute care hospitals were classified on the basis of procedure capacity (none, catheterization only, and catheterization and revascularization) and volume of elderly AMI patients treated.
‡CABG indicates coronary artery bypass graft.
§PTCA indicates percutaneous transluminal coronary artery angioplasty.

Two-Group Illustrations of Procedure Use, Hospital Type, and Mortality

Table 4 shows mortality rates for the relatively near and far patients, who had virtually identical observable health characteristics. Despite large differences between the two groups in procedure use, the differences in mortality at intervals from 1 day to 4 years are much smaller than those shown in Table 1. At 7 days, the near group had an average mortality rate 1.8 percentage points lower than the far group (16.8% vs 18.6%); by 4 years this difference had decreased to 0.4 percentage point (58.1% vs 58.5%).

The two-group comparison yields preliminary IV estimates of the effect of catheterization. For example, the 6.7 percentage-point difference in catheterization rates between the two groups at 90 days is associated with a 0.4 percentage-point difference in mortality at 4 years. Thus, catheterization in the patients who are "marginal" from the standpoint of the IVs yields a 6 percentage-point reduction in the 4-year mortality rate ($-6.0=100\times[58.1-58.5]/[26.2-19.5]$; $P<0.05$).

This estimate does not control for any other differences in treatments between the two groups, such as greater access to emergency medical services associated with urban residence, or other specialized treatments more likely to be available at the larger hospitals that tend to perform catheterization. If these other treatments are nonharmful on average, the two-group estimate is a bound on the effect of catheterization in marginal patients, because it attributes all the difference in mortality to more aggressive use of invasive procedures, whereas some of the difference is probably due to these other correlated treatments.

To illustrate the importance of the correlated treatments, we group patients on the basis of differential distance to a high-volume hospital rather than to a catheterization hospital (Table 6). These patient groups are similar in terms of observable health measures. Because patients relatively near to high-volume hospitals are not much more likely to undergo invasive procedures, procedure use is unlikely to account for much difference in mortality between the groups. In contrast, patients relatively near to a high-volume hospital had a much higher probability of admission to such a hospital than did patients relatively far away (81.7% vs 20.6%). This 61 percentage-point admission differential was associated with a 0.8 percentage-point mortality differential at 4 years (57.9% vs 58.7%). A simple estimate of the effect of initial admission to a high-volume hospital is thus a 1.3 percentage-point reduction in mortality ($-1.3=100\times[57.9-58.7]/[81.7-20.6]$). Once again, the simple two-group estimate does not account for the effects of other differences in treatment intensity or of demographic (urban/rural and racial) differences between the two groups.

Multigroup, Multitreatment Analysis of Procedure Use, Hospital Type, and Mortality

Our more general IV methods extend the two-group comparisons by forming a larger number of differential-distance IV

Table 5.—Average Effects of Patient and Hospital Characteristics on Catheterization Use Within 90 Days After Acute Myocardial Infarction*

	Estimation Method		
Effect	ANOVA: Adjustment for Observable Patient Characteristics	ANOVA: Adjustment for Observable Patient Characteristics and for Hospital Type	IV: Adjustment for Observable and Unobservable Patient Characteristics and for Hospital Type
Probability of catheterization for 65- to 69-year-old male urban resident, % (SE)	41.4 (0.4)	32.8 (0.4)	34.4 (0.4)
Average rural residence effect, percentage-point change (SE)	−5.9 (0.2)	+0.7 (0.2)	−0.3 (0.3)
Average female effect, percentage-point change (SE)	−9.2 (0.4)	−8.6 (0.4)	−8.7 (0.4)
Average black race effect, percentage-point change (SE)	−14.6 (1.0)	−14.4 (1.0)	−14.5 (1.0)
Effect of initial admission to catheterization hospital, percentage-point change (SE)	Not applicable	+8.6 (0.2)	+7.1 (0.4)
Effect of initial admission to revascularization hospital, percentage-point change (SE)	Not applicable	+18.5 (0.3)	+16.0 (0.6)

*ANOVA indicates analysis of variance; IV, instrumental variables.

groups consisting of all patients identical in terms of demographic characteristics. To illustrate, the Figure plots the probability of mortality at 2 years against the probability of catheterization for specific age-gender-race-rural cells divided into 15 differential-distance subgroups. The larger number of IV groups permits estimation of a mortality effect over a somewhat larger range of catheterization rates, 15% to 27%, than does the two-group comparison. The slope of a weighted least-squares line fitted to the cells yields an estimate of the effect of greater catheterization use (again uncontrolled for other treatments), and it indicates that for each percentage-point reduction in the catheterization rate (moving left on the horizontal axis), mortality increases about 0.1 percentage point.

Our most general IV model (Table 7) jointly estimates the effects of catheterization and initial treatment at a high-volume hospital by extending the methods underlying the Figure to group patients on the basis of differential distances to catheterization, revasculariztion, and high-volume hospitals simultaneously. We also report a weighted-average effect of rural residence on AMI mortality after controlling for differences in access to intensive hospital treatments.

Catheterization effects are somewhat smaller than in the simple two-group comparisons, reflecting the correlation of invasive procedure use and high-volume hospital admission. Mortality effects of both catheterization and treatment at a high-volume hospital are concentrated in the first day after AMI. For example, the estimated effect of an additional catheterization is 8.8 percentage points at day 1; some of this effect persists for longer-term outcomes. Rural residents experience a probability of death that is 0.57 percentage point higher than urban residents on the first day after the AMI. This difference essentially disappears after 1 year, so that mortality outcomes 1 year or more after AMI are not worse for rural patients.

The estimated effects in Table 7 are unbiased if differential distances are approximately uncorrelated with health status. We presented some evidence in Tables 4 and 6 on the validity of this assumption: the lack of correlation between observable health characteristics and differential distances and the absence of a "signature" of selection bias (estimated effects that steadily increase or decrease over time). We conducted additional validity tests: we estimated models only including patients living in urban areas or with small absolute distances to hospitals (and hence likely to be treated rapidly after AMI); we estimated models including indicator variables for the presence of 22 comorbid diseases present at admission, as well as models allowing effects of patient health and demographic characteristics to vary with differential distances, to test for systematic differences in their effects; and we performed statistical overidentification tests of the principal IV assumption.[26] All these tests, which we review in detail elsewhere, failed to detect any evidence of important differences in health status as a function of differential distances.[18]

COMMENT

We have applied IV estimation methods, statistical techniques primarily developed in econometrics, to study the incremental benefits of AMI treatments and, more generally, the selection problem that biases research with nonexperimental data: differences in outcomes among patients who actually receive different treatments may be attributable to factors not observed by the analyst, who therefore estimates biased effects of alternative treatments. This is the standard rationale for using randomized trials rather than observational studies to estimate treatment effects, but randomized trials are not always feasible. We showed that IV methods are an alternative.

When valid, IV methods estimate a somewhat different effect than controlled trials: the average effect of treatment over the incremental or marginal range of probabilities of use across values of the IVs not the average effect of the treatment over an entire population or subpopulation. Instrumental variable groups based on differential distances to a high-volume hospital were associated with differences in initial admission rates to high-volume hospitals ranging from 13% to 85%; the estimated high-volume effect is thus a weighted average over most of the elderly population. In contrast, invasive procedure use in most patients was not affected by IV grouping: our catheterization effect is estimated over a range of catheterization rates varying only from 15% to 27%, so the method does not provide direct evidence on the effect of invasive procedure use in most patients.

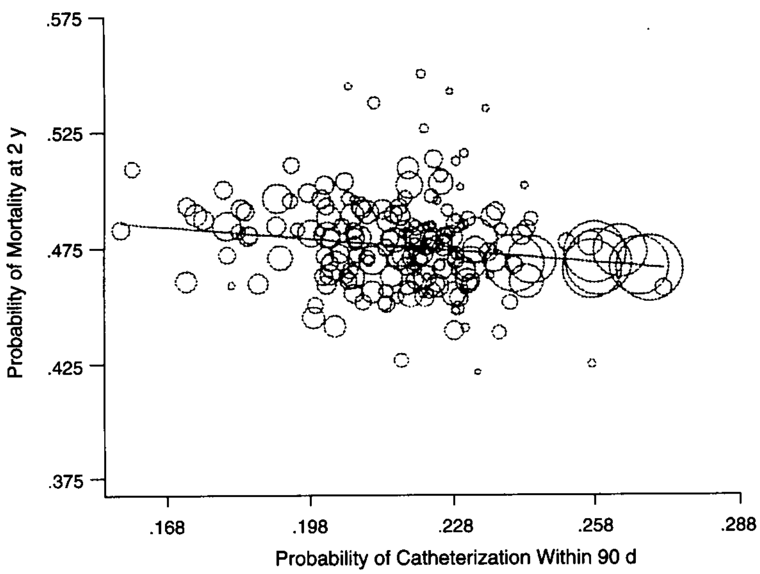
Thus, IV methods are ideally suited to address the question, "What would be the effect of reducing the use of invasive procedures after AMI in the elderly by, for example, one fourth?" They do not address the question, "What would be the expected effect of treating a particular patient aggressively rather than with noninvasive therapies alone?"[27-30] For clinical decisions involving treatment of individual patients, the answer to the latter question is more useful. For policy decisions affecting the treatment of patient populations, the answer to the former is likely to be more useful.

We draw five principal conclusions from our results. First, the selection problem can lead to large biases in studies using observational data sets, as evidenced by the substantial differences in estimated effects using standard vs IV methods. This problem is the principal reason why some believe that the contributions from outcomes research will be limited.[8] More comprehensive data on health characteristics, permitting better adjustment across groups receiving different treatments, can potentially mitigate the problem, but accurately duplicating all the information that clinicians use in making treatment decisions will be extremely costly, if it is ever feasible at all. Development of alternative approaches to the selection problem, such as IV estimation, may thus be crucial to the future of outcomes research.

Table 6.—Patient Characteristics by Differential Distance to a High-Volume Hospital*

Characteristic	Differential Distance ≤1.5 Miles (n=104 665)	Differential Distance >1.5 Miles (n=100 359)
Demographic Characteristics		
Female	51.2	49.3
Black	6.1	5.2
Mean age, y (SD)	76.0 (7.3)	76.1 (7.3)
Rural	10.8	48.9
Comorbid Disease Characteristics		
Cancer	1.9	1.9
Renal disease	1.9	1.9
Treatments		
Initial admit to high-volume hospital	81.7	20.6
Catheterization within 90 d	23.3	22.3
Revascularization within 90 d	13.2	12.8
Outcomes		
Mortality within 1 d	7.4	9.0
Mortality within 30 d	24.5	26.7
Mortality within 1 y	39.5	40.9
Mortality within 4 y	57.9	58.7

*All data entries are percentages except for mean age, which is in years.



Graphic illustration of instrumental variables (IV) approach to estimating the incremental effect of invasive procedure use on acute myocardial infarction mortality at 2 years. Each circle represents a group of patients in a particular differential-distance group with a particular set of age, gender, and race characteristics. The model is thus fully adjusted for effects of observable patient demographic characteristics, and remaining differences in probabilities of catheterization across groups are strictly the result of different IV values for patients who are identical in terms of observable characteristics. The area of each circle is proportional to the number of patients in the group. The slope of the line fitted to the cells estimates the weighted-average effect of invasive procedure use.

Second, others have documented systematic differences in practice patterns across providers,[25,31] but to our knowledge this is the first evidence that different providers treat patients who differ in both observed and unobserved dimensions. Even for an emergent admission such as AMI, the difference between estimates of the effect of hospital capabilities on treatment choice using standard and IV methods indicates that some patient selection occurs across hospitals. Unobserved patient differences across providers are likely to bias results even more for chronic and nonemergent health problems, including estimates of outcomes and costs of disease treatment as a function of physician specialty.[31] Although unobserved case-mix variation biases existing estimates of how hospital capability affects AMI treatment,[25] after accounting for selection bias we still find large effects of hospital capability. Differential access to hospitals with catheterization capability entirely explains lower catheterization rates in rural patients but none of the differentials found among blacks and women. Our methods are potentially applicable to the study of many other kinds of provider effects.

Third, in contrast to results using standard statistical methods of adjustment, our IV estimates show at most a modest and possibly no true incremental effect of catheterization and associated revascularization procedures on mortality after AMI. Over the range of catheterization use in our IV groups, an upper-bound estimate of the reduction in mortality from an additional catheterization is 5 percentage points at 1 to 4 years.

This estimate is an upper bound because the beneficial effect of catheterization appears at day 1, before the catheterization and revascularization procedures were performed in almost all cases. (During the interval when many revascularization procedures are performed—between 7 and 30 days after AMI—the initial survival benefit decreases, possibly reflecting operative mortality.) Our results show stable mortality differences between 1 and 4 years, and effects not appearing by 4 years are unlikely to be consequential in an elderly population. Thus, aspects of acute care other than greater use of invasive procedures appear to be better at catheterization and revascularization hospitals than at lower-technology hospitals, leading to lower acute mortality. This effect is in addition to the effect of higher volume, which is also associated with better outcomes.

The results of Table 7 can be used to predict the effects on mortality of a reduction in invasive procedure use by approximately one fourth, within the range of treatment differences across our IV groups. Such a reduction might be achieved, for example, by limiting catheterization capabilities to specific hospitals (as in New York State) or through other changes in practice patterns that would lead to less aggressive treatment of patients thought to have the least benefit from catheterization.

The conservative IV estimate predicts small long-term mortality effects: the 1-year rate would increase by at most 0.6% (from 40.20 to 40.46 percentage points) and the 4-year rate by at most 0.5% (from 58.30 to 58.57 percentage points). More realistically, if the long-term mortality differential is attributable in part to the other, better aspects of acute treatment that lead to lower acute mortality at catheterization hospitals, the true mortality effect of reducing invasive procedure use in the elderly is even closer to zero. Some recent studies have suggested that invasive procedure use may lead to more improvements in

Table 7.—Instrumental Variable Estimates of the Effects of Patient Location, High-Volume Hospital, and Catheterization on Mortality at Indicated Time Intervals After Acute Myocardial Infarction

Average Effect	Time After Acute Myocardial Infarction, Percentage-Point Change (SE)						
	1 d	7 d	30 d	1 y	2 y	3 y	4 y
Rural residence							
Since previous interval	+0.57 (0.19)	−0.07 (0.20)	+0.02 (0.19)	−0.68 (0.24)	+0.14 (0.18)	−0.06 (0.16)	+0.22 (0.15)
Cumulative	+0.57 (0.19)	+0.50 (0.26)	+0.52 (0.29)	−0.15 (0.33)	−0.01 (0.32)	−0.08 (0.33)	+0.14 (0.32)
Initial admission to high-volume hospital							
Since previous interval	−0.93 (0.24)	−0.31 (0.26)	−0.23 (0.24)	+0.39 (0.31)	+0.19 (0.23)	−0.09 (0.21)	+0.22 (0.19)
Cumulative	−0.93 (0.24)	−1.24 (0.33)	−1.47 (0.38)	−1.07 (0.42)	−0.88 (0.43)	−0.97 (0.42)	−0.75 (0.42)
Catheterization within 90 d							
Since previous interval	−8.8 (2.0)	−2.7 (2.0)	+4.1 (1.8)	+2.6 (2.4)	−0.6 (1.8)	+0.4 (1.6)	−0.1 (1.5)
Cumulative	−8.8 (2.0)	−11.5 (2.5)	−7.4 (2.9)	−4.8 (3.2)	−5.4 (3.3)	−5.0 (3.2)	−5.1 (3.2)

quality of life than survival time.[32] We focus on incremental mortality effects herein, but our methods can potentially be used to study whether the incremental use of intensive treatments has greater effects on morbidity outcomes.

Fourth, treatment at a high-volume hospital yields a survival benefit that begins at day 1 and persists throughout 4 years. This high-volume effect is somewhat lower acutely than estimates for many surgical procedures, which were derived using methods that did not account for unobserved selection bias.[33-34]

Fifth, controlling for use of intensive hospital treatments, rural residents have greater mortality at day 1 (0.57 percentage point), but this effect vanishes by 1 year. This effect suggests the greater availability of prehospital advanced cardiac life support systems in metropolitan areas may improve acute survival. Nonetheless, rural patients as a group have significantly worse acute and long-term outcomes as a result of their greater likelihood of receiving treatment at lower-volume, noncatheterization hospitals.

Together, our estimates of catheterization, volume, and rural-residence effects indicate that acute treatment shortly after an AMI, rather than more aggressive use of invasive procedures, has the greatest impact on long-term mortality for marginal elderly AMI patients who received the additional intensive treatments provided by more intensive hospitals. A redirection of resources from marginal catheterizations and revascularizations to characterizing and improving access to some of these acute treatments could improve AMI mortality in the elderly and may reduce costs.

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References

1. Yusuf S, Sleight P, Held P, McMahon S. Routine medical management of acute myocardial infarction. *Circulation.* 1990;82(suppl II):117-134.
2. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. *JAMA.* 1992;268:1417-1422.
3. Roper WL, Winkenwerder W, Hackbarth GM, Krakauer H. Effectiveness in health care. *N Engl J Med.* 1988;319:1197-1202.
4. Grady ML, Schwartz HA, eds. *Medical Effectiveness Research Data Methods.* Rockville, Md: Agency for Health Care Policy and Research; 1992. Publication AHCPR 92-0056.
5. Chassin M, Kosecoff J, Park RE, et al. Does inappropriate use explain geographic variations in the use of health care services? *JAMA.* 1987;258:2533-2537.
6. Physician Payment Review Commission. *Conference on Profiling.* Washington, DC: Physician Payment Review Commission; 1992. Publication 92-2.
7. Shapiro DW, Lasker RD, Bindman AB, Lee PR. Containing costs while improving quality of care. *Annu Rev Public Health.* 1993;14:219-241.
8. Anderson C. Measuring what works in health care. *Science.* 1994;263:1080, 1082.
9. Park RE, Brook RH, Kosecoff J, et al. Explaining variation in hospital death rates. *JAMA.* 1990;264:484-490.
10. Wagner DP, Knaus WA, Draper EA. The case for adjusting hospital death rates for severity of illness. *Health Aff (Millwood).* 1986;5:148-153.
11. Blumberg MS. Comments on HCFA hospital death rate statistical outliers. *Health Serv Res.* 1987;21:715-740.
12. Greenfield S, Aronow HU, Elashoff RM, Watanabe D. Flaws in mortality data. *JAMA.* 1988;260:2253-2255.
13. Bowden RJ, Turkington DA. *Instrumental Variables.* Cambridge, Mass: Cambridge University Press; 1984.
14. Imbens A, Angrist J. Identification and estimation of local average treatment effects. *Econometrica.* 1994;62:467-476.
15. Udvarhelyi IS, Gatsonis CG, Epstein AM, Pashos C, Newhouse JP, McNeil BJ. Acute myocardial infarction and the Medicare population. *JAMA.* 1992;268:2530-2536.
16. McClellan MB, Newhouse JP. *The Marginal Benefits of Medical Treatment Intensity.* Cambridge, Mass: National Bureau of Economic Research; 1994. Working paper.
17. McClellan MB. *The Effects of Hospital Technological Capabilities on Practice Patterns.* Cambridge, Mass: National Bureau of Economic Research; 1994. Working paper.
18. Chamberlain G. Asymptotic efficiency in estimation with conditional moment restrictions. *J Econometrics.* 1987;34:305-334.
19. Goldberg KC, Hartz AJ, Jacobson SJ, Krakauer H, Rimm AA. Racial and community factors influencing coronary artery bypass graft surgery rates for all 1986 Medicare patients. *JAMA.* 1992;267:1473-1477.
20. Wenneker MB, Epstein AM. Racial inequalities in the use of procedures for patients with ischemic heart disease in Massachusetts. *JAMA.* 1990;261:253-257.
21. Ayanian JZ, Epstein AM. Differences in the use of procedures between women and men hospitalized for coronary artery disease. *N Engl J Med.* 1991;325:221-225.
22. Ford E, Cooper R, Castaner A, Simmons B, Mar M. Coronary arteriography and coronary bypass surgery among whites and other racial groups relative to hospital-based incidence rates for coronary artery disease: findings from NHDS. *Am J Public Health.* 1989;79:437-440.
23. Ayanian JZ, Udvarhelyi IS, Gatsonis CA, Pashos CL, Epstein AM. Racial differences in the use of revascularization procedures after coronary angiography. *JAMA.* 1993;269:2642-2546.
24. Steingart RM, Packer M, Hamm P, et al. Sex differences in the management of coronary artery disease. *N Engl J Med.* 1991;325:226-230.
25. Blustein J. High-technology cardiac procedures. *JAMA.* 1993;270:344-349.
26. Newey WK. Maximum likelihood specification testing and conditional moment tests. *Econometrica.* 1985;53:1047-1070.
27. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. *N Engl J Med.* 1993;328:673-679.
28. Zijlstra F, deBoer MJ, Hoorntje JCA, et al. A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. *N Engl J Med.* 1993;328:680-684.
29. Gibbons RJ, Holmes DR, Reeder GS, et al. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. *N Engl J Med.* 1993;328:685-691.
30. Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. *JAMA.* 1992;268:240-248.
31. Greenfield S, Nelson EC, Zubkoff M, et al. Variations in resource utilization among medical specialties and systems of care. *JAMA.* 1992;267:1624-1630.
32. Rouleau JL, Moyer LA, Pfeffer MA, et al. A comparison of management patterns after acute myocardial infarction in Canada and the United States. *N Engl J Med.* 1993;328:779-784.
33. Showstack JA, Rosenfeld KE, Garnick DW, Luft HS, Schaffarzick RW, Fowles J. Association of volume with outcome of coronary artery bypass graft surgery. *JAMA.* 1987;257:785-789.
34. Hughes RG, Garnick DW, Luft HS, McPhee SJ, Hunt SS. Hospital volume and patient outcomes: the case of hip fracture patients. *Med Care.* 1988;26:1057-1067.