Volume Title: Medical Care Output and Productivity

Volume Author/Editor: David M. Cutler and Ernst R. Berndt, editors

Volume Publisher: University of Chicago Press

Volume ISBN: 0-226-13226-9

Volume URL: http://www.nber.org/books/cutl01-1

Publication Date: January 2001

Chapter Title: Trends in Heart Attack Treatment and Outcomes, 1975-1995 -- Literature Review and Synthesis

Chapter Author: Paul Heidenreich, Mark B. McClellan

Chapter URL: http://www.nber.org/chapters/c7635

Chapter pages in book: (p. 363 - 410)

9

Trends in Heart Attack Treatment and Outcomes, 1975–1995
Literature Review and Synthesis

Paul Heidenreich and Mark McClellan

9.1 Introduction

Age-adjusted mortality rates for ischemic heart disease have fallen for the last three decades (Goldman and Cook 1984). The reasons for the decline—which include primary prevention of coronary events, secondary prevention, improved outcomes of the events themselves, and changes in event severity—have been the subject of considerable debate. Much of the debate centers on the relative importance of medical technology versus lifestyle changes or other sources of reductions in risk factors. The debate has important implications for priorities in health care research and policymaking: If medical interventions have been relatively unimportant, then the direction of more resources to research and education on preventive care may be worthwhile. But resolving the debate is very difficult due to the complexity of health care interventions and disease processes.

Several well-known studies have assessed the contribution of broad categories of explanatory factors by synthesizing evidence from clinical trials, changes in medical practices, and changes in population risk characteristics. Risk factor reduction leading to primary and secondary prevention of fatal coronary events, including acute myocardial infarction (AMI) and ischemia-induced ventricular arrhythmias, appears to have been respon-

Paul Heidenreich, a practicing cardiologist, is assistant professor of medicine at Stanford University. Mark McClellan is associate professor of economics and medicine at Stanford University and a research associate of the National Bureau of Economic Research.

The authors thank David Cutler, Alan Garber, and Jack Triplett for helpful discussions and comments, and the National Institute on Aging and the Veterans Administration for financial support. All errors are the authors'.

sible for most of this decline up to the early 1980s. Goldman et al. (1982) estimated that changes in lifestyle leading to disease prevention accounted for 54 percent of the decline in ischemic heart disease mortality between 1968 and 1976. Medical interventions accounted for 40 percent; among these interventions, 13.5 percent of the decline was attributed to coronary care unit treatments, 7.5 percent to treatment of hypertension, 4 percent to prehospital resuscitation, 3.5 percent to coronary artery bypass surgery, and 10 percent to other medical treatments of ischemic heart disease (IHD), particularly chronic beta-blockade therapy.

Weinstein and colleagues (1987) have developed the Coronary Heart Disease model, a state-transition computer model of outcome from ischemic heart disease for patients in the United States, to address this question more comprehensively. The first study using the model concluded, like Goldman et al., that the bulk of mortality improvement prior to 1980 was the result of lifestyle-related changes in risk factors. However, recent results indicated that lifestyle improvements could explain less than 20 percent of the total reduction in heart disease mortality between 1980 and 1990. Moreover, primary and secondary prevention through risk factor reduction may be increasingly associated with treatment changes as well, such as increased use of lipid-lowering and antihypertensive agents with better side-effect and compliance profiles. Thus, medical interventions seem to be growing increasingly important in explaining IHD mortality improvements.

Despite the apparent increasing importance of changes in medical technology, few studies have sought to identify the contributions of specific treatment changes. For example, Goldman et al. considered only five major medical interventions in their analysis (and some of these, like coronary care unit adoption, actually consisted of a bundle of new medical treatments); and the recent Coronary Heart Disease model report (Hunink et al. 1997) attributed approximately half the IHD mortality reductions to unspecified "treatment changes." One reason for this lack of evidence on the contributions of particular interventions is the difficulty of separating out the contribution of each. Even less evidence exists on the cost implications of these different interventions.

Yet identifying the contribution of specific treatments to the observed improvements in outcomes is important for several reasons. First, it is only at the level of specific treatments that the contribution of medical care to the overall outcome improvements can be determined explicitly. Second, examining specific factors may provide insights about which types of medical treatments have made the greatest contributions to both outcome improvements and cost increases. For example, "high-tech" treatment use has changed in substantially different ways in different hospitals (Cutler and McClellan 1998) and around the world (McClellan et al., in press). Do such differences have any important consequences for health outcomes?

Moreover, this analysis might identify the most cost-effective opportunities for future changes in heart disease outcomes, and help forecast future improvements in heart disease outcomes.

In this study, we provide a first step toward synthesizing evidence from the clinical literature and a range of empirical databases to try to identify the contributions of particular changes in medical treatment in acute myocardial infarction (AMI) over the last twenty years. Deaths classified as due to AMI make up a relatively small share, perhaps 10 percent, of total IHD mortality. Even though its apparent share is small, there are several important reasons to study this condition carefully. IHD treatments and mortality are closely related to AMI, even though deaths are generally classified as caused by AMI if the death occurs during or soon after the AMI hospitalization. Many more IHD deaths reflect longer-term consequences of AMI; for example, arrhythmias resulting from unstable conduction pathways, in turn the result of permanent heart damage from a prior AMI. Another reason is that the available clinical trial and medical practice evidence on the outcomes of "AMI episodes" is far more extensive than that available for more chronic forms of IHD treated on an outpatient basis. Finally, previous studies of long-term outcome trends for AMI patients show that most of the improvement in outcomes for AMI patients, and all of the improvement attributable to hospital care, arises within the first week after an AMI (McClellan and Noguchi 1988; McClellan and Staiger 1998). After we present our detailed analysis of trends in AMI outcomes, we consider the implications of our results for IHD and other illnesses.

In this review, we estimate the reduction in age-adjusted thirty-day mortality rates for hospitalized AMI patients, place this improvement in the context of overall improvements in population AMI mortality, and summarize the impact on AMI mortality trends of the most notable specific changes in AMI treatment, from 1975 to 1995. Thrombolytic therapy, primary angioplasty, aspirin, early beta blockade, and ACE-inhibition, among other treatments, have been shown to reduce mortality in AMI patients (Lau et al. 1992; ISIS-4 Collaborative Group 1995). How much of the reduction in thirty-day mortality rates is explained by changes in medical and surgical therapies during the AMI episode? What other factors are likely to have contributed to the observed improvements? Changes in prehospital or posthospital care? Changes in the characteristics of AMI patients? We find that identifiable changes in these factors, especially in acute treatment, can explain the bulk of the observed improvements in AMI mortality for hospitalized patients. Published evidence is insufficient to reach exact conclusions on the contributions of these improvements to overall IHD mortality trends, and on improvements in the long-term quality of life of AMI survivors. We review qualitative evidence on these issues, which also suggests that the changes in medical treatments reviewed here

have been among the principal factors responsible for improvements in these outcomes as well.

9.2 Methods

9.2.1 Trends in Incidence, Treatments, and Thirty-Day Mortality

We performed searches of the MEDLINE database and reviewed the bibliographies of review articles to identify studies describing treatment for AMI. We used population-based studies with at least a ten-year range whenever possible to determine changes in incidence, thirty-day mortality rates, and intervention rates during this period. We reviewed studies describing trends in prehospital, in-hospital, and posthospital treatments of acute myocardial infarction. Published results from randomized controlled trials were used to estimate the probable average benefit from changes in these various interventions. These estimates of benefit were considered an upper limit for effectiveness, given that the patients enrolled in the trials and the trial settings themselves are often not representative of the general population. Data were also obtained from large databases of Medicare patients, including the Cooperative Cardiovascular Project (CCP) and Medicare claims files.

We obtained estimates of AMI incidence and case fatality rates (CFRs)[1] from the National Hospital Discharge Survey (NHDS). NHDS trends may not accurately reflect true trends in AMI case fatality for two reasons. First, length of stay increased in the late 1970s, but has decreased somewhat since the early 1980s. Other things equal, patients remaining in the hospital longer are more likely to die in the hospital, so that some of the apparent CFR decline may be the result of reduced length of stay. Second, transfers have also increased over time, and until recent years (after 1990) transfer AMI patients were not reliably distinguishable from new AMI patients based on diagnosis codes. Thus, trends in the apparent number and mortality of AMI cases from the NHDS may be misleading. We identified AMI discharges that met the NHDS definition from 1982 onward, which includes all patients with primary diagnosis of AMI or secondary diagnoses of AMI if the reported primary diagnosis was a circulatory disease.[2] To improve the comparability of results across time periods that differed in average length of hospitalization and transfer rates, and thus in

1. Here we follow the convention of most of the literature and use the term *case-fatality rate* to describe the mortality rate during the initial AMI hospitalization (possibly including transfers).

2. This coding convention reflects the fact that, even if the non-AMI circulatory diagnosis was a principal reason for admission to the hospital, it was probably a consequence of the AMI. For example, diagnoses of ischemic heart disease complications or heart failure probably resulted from the accompanying AMI, even if these diagnoses were regarded as the principal reason for admission.

their apparent CFRs, we converted case-fatality rates based on all AMI admissions to standardized thirty-day mortality rates (MRs) that account for trends in transfers and readmissions. That is, we developed a conversion factor $F(N)$ based on the average length of stay in the study:

$$F(N) = [\text{Estimated true MR at 30 days}]/[\text{Observed CFR at } N \text{ days}].$$

To form this conversion factor, we used longitudinal data including transfers for Medicare patients in 1984 and subsequent years, which provides complete information on mortality at one, seven, and thirty days after AMI (McClellan and Noguchi 1988). Because it fit the data well, we assumed a logarithmic relationship between the number of days following AMI and AMI CFRs after day one to approximate the relationship between the expected thirty-day CFR and a reported CFR for average length of stay N. That is,

$$F(N) = [\text{Medicare FR at 30 days}]/[\text{Estimated Medicare CFR at } N \text{ days}],$$

where estimated Medicare CFR at N days is given by

$$[\text{Medicare CFR}(1)] + [\ln(N - 1)/\ln(29)][\text{Medicare MR}(30) - \text{Medicare MR}(1)].$$

Thus standardized thirty-day CFR for a study with average length of stay N was calculated as

$$\text{Standardized 30-day mortality} = (\text{Reported CFR}) \times F(N).$$

Such CFRs were constructed using NHDS data for 1975, 1980, 1985, 1990, and 1995.

9.2.2 Contributions of Treatments to Changes in Case-Fatality Rates

The contribution of each technology to the reduction in case-fatality rate was estimated from the absolute mortality benefit reported for each technology (primarily obtained from meta-analyses of published studies), accounting for important interactions with other technologies, and from the estimated change in use of each technology over time. Because AMI treatments have been evaluated separately and at different times, the reported benefit of the therapies evaluated earlier (beta blockade) may not be equal to their benefit when used with therapies that have been applied more recently, such as thrombolysis and aspirin.

To estimate the contribution of each treatment, we first calculated the adjusted odds ratio $\text{AOR}_j(t)$ for each therapy j in each year t. If the published odds ratio $\text{POR}_j(Y)$ from meta-analyses of trials performed around year Y was less than 1 (i.e., the therapy was beneficial), then

$$\text{AOR}_j(t) = 1 - [1 - \text{POR}_j(Y)] \times (\text{Interaction effect})_{jt},$$

where

$$(\text{Interaction effect})_{jt} = \Pi_i\{1 - [\text{Use}_{ij}(t) - \text{Use}_{ij}(Y)] \times \text{Factor}_{ij}\},$$

and $\text{Use}_{ij}(t)$ is the joint usage of drug i with drug j in year t, $\text{Use}_{ij}(Y)$ is the joint usage in the (approximate) trial period Y, and Factor_{ij} is the relative decrease in effectiveness of drug j when used with drug i. In other words, we model the impact of changes in other treatments since the treatment of interest was studied as a relative reduction in the benefit compared to the time of the study; joint effects are generally somewhat less than their individual effects. Where possible, we used published evidence on interactions of treatment effects to guide our assumptions about the magnitudes of the interaction effects.[3] Where empirical evidence was lacking but clinical considerations suggested that interactions were probably nontrivial, we assumed that the effect of a second treatment on the treatment of interest was proportional to the published benefit of the second therapy, using the following formula: $\text{Factor}_{ij} = 0.2 \times |1 - \text{POR}_i|$. We conducted a sensitivity analysis by reducing the assumed interaction to 0. Our "base case" interaction assumptions resulted in noticeable but modest reductions in the effectiveness of individual treatments over time. For example, in our analysis, the use of aspirin with beta blockade decreases the effectiveness of beta blockade by 5 percent (in relative terms) and the effectiveness of aspirin by 2 percent.

If the published odds ratio was greater than 1.0 and the interaction effect was greater than 1, then

$$\text{AOR}_j(Y) = (\text{POR}_j)/(\text{Interaction effect})_{jt},$$

and if the published odds ratio was greater than 1.0 and the interaction effect was less than 1, then

$$\text{AOR}_j(Y) = 1 - [(1 - \text{POR}_{(j)}) \times (\text{Interaction effect})_{jt}].$$

Evidence on the joint usage of medications over time is also scant; virtually all studies report only univariate trends in treatment rates. Conse-

3. For example, the majority of studies of beta blockade were performed prior to the use of thrombolysis. The TIMI-2 trial (McClellan and Staiger 1999), which evaluated beta blockade in conjunction with thrombolysis, found a decrease in recurrent myocardial infarction but not in mortality (overall hospital mortality in the substudy was only 2 percent). Similarly, nitrate therapy was found to have a positive mortality benefit in studies prior to the use of thrombolysis (Van de Werf et al. 1993). In the postthrombolysis era, ISIS-4 (McClellan et al., in press) found a minimal benefit which is consistent with a lack of independence between the effects of nitrates and more recently used agents (thrombolysis and aspirin). We assumed that the absolute benefit for thrombolysis and aspirin was reduced by 2 percent when the two drugs were given together based on the ISIS-2 trial. There were no data describing the interactions between other medications. We assumed the reduction in published benefit would be proportional to the published benefit of the added drug.

quently, we also conducted sensitivity analyses on our assumptions about the frequency with which drugs are used together. In our base case, we assumed that use was independent; that is, $\text{Use}_{ij}(t) = \text{Use}_i(t) \times \text{Use}_j(t)$. For sensitivity analysis, we alternatively assumed that use was as correlated as possible; that is, $\text{Use}_{ij}(t) = \min[\text{Use}_i(t), \text{Use}_j(t)]$.

The absolute benefits from interventions were then calculated from the AORs for 1975, 1985, and 1995, using the mortality rate from 1975 and the AMI hospitalization rate in the comparison year. For example, we calculated the absolute change in thirty-day AMI deaths attributable to treatment j as follows. The relative outcome change attributable to the change in use of treatment j between 1995 and 1975 is given by

$$\text{AOR}_j(95) \times \text{Use}_j(95) - \text{AOR}_j(75) \times \text{Use}_j(75).$$

Multiplying this relative outcome change (which accounts for changes in the use of other treatments) by the standardized thirty-day mortality rate for 1975 gives the absolute thirty-day mortality benefit attributable to the change in use of the intervention. Multiplying this estimated absolute mortality benefit times the number of patients hospitalized with AMI in 1995 gives the total number of 1995 AMI deaths averted because of the change in treatment.

9.2.3 Cost-Effectiveness Calculations

To estimate the overall cost-effectiveness of all AMI treatments combined, we determined the total cost of care and the expected quality-adjusted life years gained for patients following myocardial infarction. Medicare data were used to determine changes in acute (thirty-day) cost of care from 1984 to 1994. All costs were adjusted to 1995 dollars using the gross domestic product deflator. Rates of change in acute care costs over this period were used to extrapolate costs to 1975 and 1995. We estimated long term expenditures ($2,000 per year) for survivors of myocardial infarction based on Medicare data. We estimated the acute survival by using the difference in thirty-day mortality rate from 1975 to 1995 as described above. Long-term survival was determined using several different expected survival periods following MI (five years to fifteen years). We adjusted years of life gained for quality of life using the time-trade-off utility of 0.88 (Tsevat et al. 1993). All future costs and benefits were discounted using a rate of 3 percent. We assumed that changes in MI treatments were responsible for all increases in cost per case, but that they provided only a fraction of the total benefit as calculated above. All costs were adjusted to 1995 dollars using the GDP deflator.

9.3 Results

9.3.1 Trends in the Incidence and Mortality of AMI

Trends in AMI Hospitalizations

The decline in the incidence of new AMI *hospitalizations* has been more modest. The total number of hospitalized admissions for AMI, as reported in the NHDS, actually increased over the 1975–95 time period, especially between 1975 and 1985 (table 9.1, line 1). As we described in section 9.2, we used the ratio of new AMIs to all AMI discharges from Medicare for individuals aged sixty-five to sixty-nine in 1984–94 (table 9.1, line 2) to estimate the share of reported AMI admissions that represented new patients, rather than transfers or readmissions.[4] The increase in transfers and readmissions over time accounts for much of the apparent increase in AMIs in NHDS, though this adjustment does not completely account for an anomalous bulge in AMI hospitalization rates in the early- to mid-1980s (table 9.1, line 3). This change may be due in part to idiosyncrasies in the reporting of AMI discharges around the introduction of Medicare's Prospective Payment System in 1983, as well as improved diagnostic techniques for detecting AMI (we analyze this hypothesis in more detail below). To compute AMI incidence rates over time, we accounted for growth in the at-risk population aged thirty-five and over (summarized in table 9.1, line 4). The resulting estimated trend in AMI incidence, based on the population distribution in either 1995 (table 9.1, line 5) or 1975 (table 9.1, line 6), suggests that the incidence of new AMI hospitalizations in the U.S. population has declined substantially, from 613 per 100,000 population aged thirty-five and over in 1975 to 437 per 100,000 in 1995 (1995 population). Because of population aging and population growth, the total number of new hospitalizations with true AMIs in the United States has remained relatively constant, around 540,000 per year, and our benchmark analyses are based on this figure.[5]

Trends in Mortality for Hospitalized AMI Patients

In 1975 the case fatality rate (CFR) per AMI admission (not counting transfers) according to NHDS was 19 percent (table 9.1, line 7, and fig. 9.1). To develop a measure more comparable to the clinical literature, which typically considers transfers in case fatality rates, we adjust for the share of admissions not transferred (table 9.1, line 8) and for population trends. The result is an estimate of a true, age- and sex-adjusted case fatal-

4. Our results were not sensitive to alternative reasonable assumptions about transfer rates and readmission rates within thirty days, for example by using a readmission correction based on all Medicare beneficiaries rather than sixty-five-to sixty-nine-year-old beneficiaries.

5. This estimated number of AMIs is smaller than the estimated number of "coronary events" leading to hospitalization that are reported by the American Heart Association; these estimates may include many unstable angina patients as well.

Table 9.1 **Calculations of CFR, Incidence Including Age Breakdown**

	1975	1980	1985	1990	1995	Source
1. AMI hospital discharges (thousands, unadjusted)[a]	577	572	710	652	679	Calculated from NHDS
2. Fraction due to new patients[b]	0.94	0.91	0.88	0.83	0.80	Calculated from Medicare
3. New AMI hospital discharges (thousand unadjusted)[c]	542	521	625	545	540	Line 1 × Line 2
4. Adult U.S. population age 35+ (millions)	90	94	102	111	124	*Statistical Abstract of the United States*
5. New AMI discharge rate (age/gender adjusted to 1995)	613	527	591	481	437	Lines 3, 4
6. New AMI discharge rate (age/gender adjusted to 1975)	603	527	583	472	431	Lines 3, 4
7. Case fatality rate (%) (no age/gender adjustment)	19.2	20.4	17.0	14.1	11.9	Calculated from NHDS
8. Fraction of MI admissions not transferred[b]	1.0	0.99	0.95	0.90	0.85	Calculated from Medicare
9. Case fatality rate (%) (adjusted for transfers, age/gender adjusted to 1995)	23	32.4	19.3	16.3	14	Lines 3, 4, 8; NHDS
10. Estimated 30-day fatality rate (%) (age/gender adjusted to 1995)[c]	27.0	27.9	24.1	20.4	17.4	Line 9, adjusted for dying in 30 days
11. Total AMI deaths	325	299	274	239	218	NCHS
12. Inpatient AMI deaths in thousands (no age/gender adjustment)	111	109	111	84	77	Lines 3, 4, 9
13. Estimated deaths in 30 days among hospitalized AMI patients in thousands, no age/gender adjustment	158	130	146	117	112	Line 12, adjusted for dying within 30 days
(% of all AMI deaths)	(49)	(44)	(53)	(49)	(52)	

[a]Adjusted for coding changes, discharged alive with length of stay less than three days and age < thirty-five excluded.

[b]Age group sixty-five to sixty-nine, data for 1975 and 1980 are extrapolated from the 1985–94 trends.

[c]Based on an exponential decline in daily mortality from day seven to day thirty (see text).

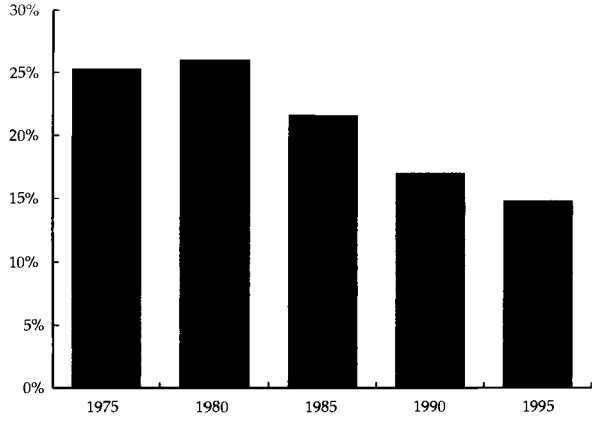

Fig. 9.1 Change in thirty-day acute MI mortality rate over the last twenty years

ity rate per new (nontransfer) AMI admission (table 9.1, line 9). Using the extrapolations described above based on Medicare data, this CFR corresponds to a thirty-day mortality rate of 27 percent (table 9.1, line 10). By 1995 the admission CFR had declined 12 percent, corresponding to a new-case CFR of 14 percent and a thirty-day mortality rate of 17 percent. Because length of stay decreased during the last twenty years, the reduction in CFR (40 percent) is greater than the reduction in thirty-day mortality rate (36 percent). This absolute drop in thirty-day mortality of 9.6 percentage points corresponds to approximately 52,000 more patients per year surviving to thirty days. Much of our subsequent analysis focuses on the factors explaining this substantial mortality trend since 1980.

Overall (In-Hospital and Out-of-Hospital) AMI Incidence and Mortality

We were unable to identify any published studies that permitted us to quantify long-term trends in the number of out-of-hospital AMIs and of AMI deaths in patients who were not hospitalized for AMI directly. However, using estimates of total AMI deaths and our results for hospitalized AMI patients, we were able to estimate these trends indirectly.

The remainder of table 9.1 places the mortality trend for hospitalized AMI patients in the context of overall AMI mortality trends, including deaths in patients who do not survive to hospitalization. According to the National Death Index, the total number of AMI deaths among Americans thirty-five and over was approximately 325,000 in 1975 and 218,000 in 1995 (table 9.1, line 11). To explore the contribution of the mortality decline among hospitalized AMI patients to this overall mortality decline, we calculated the total deaths among hospitalized patients implied by our analysis, which was based on data independent of the death index. In 1975, our estimate of in-hospital case fatalities (before discharge, but possibly after transfer) was 111,000, and the corresponding number for 1995

was 77,000 (table 9.1, line 12). Because death index records should generally classify AMI patients who die acutely (within thirty days) as AMI deaths, an increasing number of patients who die after discharge or readmission will be missed using the case-based approach. Consequently, the final line of table 9.1 (line 13) reports our estimate of the total number of deaths within thirty days after AMI, based on our estimated trends in thirty-day fatalities. These deaths declined from 158,000 in 1975 to 112,000 in 1995.

Because total AMI deaths consist of prehospital deaths and of deaths in hospitalized patients, our findings provide an indirect approach for quantifying trends in prehospital deaths.[6] Our estimates of trends in death for hospitalized AMI patients imply that approximately 214,000 AMI patients died before hospitalization in 1975 and 106,000 did so in 1995, and that hospitalized AMI patients accounted for 49 percent of the total AMI deaths in 1975 and 52 percent in 1995. These findings on the relative importance of prehospitalization and posthospitalization deaths are consistent with estimates from earlier years (Goldman et al. 1982) that 50 to 60 percent of acute MI deaths occurred outside the hospital.

They are also consistent with previously published studies on the decline in out-of-hospital deaths from ischemic heart disease. Because of these difficulties in quantifying out-of-hospital AMI deaths separately,[7] most published studies consider trends in out-of-hospital IHD deaths generally, including deaths from cardiac arrest as well as AMI. The number of such deaths has declined impressively over the last twenty years. The incidence of out-of-hospital IHD deaths in the Minneapolis area was approximately 150 per 100,000 in 1990, a reduction of more than 50 percent compared to the 1970 rate of 330 per 100,000 (McGovern et al. 1996; Gillum et al. 1983). This community study concludes that the reduction in out-of-hospital deaths, which include a substantial number of AMI deaths, accounts for the bulk of the observed improvements in overall IHD mortality rates. Our results imply a similar conclusion for AMI: The improvements in mortality for hospitalized AMI patients, impressive as they were, accounted for only around 30 percent[8] of the total decline in AMI deaths between 1975 and 1995—though they were relatively more important in

6. Note that this cannot be done directly from death records, even though they report whether a death occurred in or out of the hospital. The out-of-hospital group includes those dying of AMI prior to hospitalization, as well as the increasing number of patients dying after their initial hospitalization.

7. We emphasize that it is difficult to quantify reliably the number of deaths from AMI without hospitalization. Especially if autopsy of an individual "found down" is not performed, it may be difficult to determine whether patients with IHD died from a new AMI or from a ventricular arrhythmia. As a result, most out-of-hospital deaths in the setting of IHD are classified with a nonspecific IHD diagnosis (McClellan and Staiger 1999). One reason that reported AMI mortality rates are so low relative to IHD mortality rates is that such nonspecific out-of-hospital deaths are relatively common.

8. Total deaths among hospitalized patients declined by 46,000, while total prehospital deaths declined by 108,000.

1985–95 than in the previous decade. Part of this decline resulted from an increasing share of AMI patients being hospitalized—according to our estimates, 72 percent in 1975 compared to 84 percent in 1995. But this increasing rate of hospitalization accounts for only a small fraction of the more than 100 percent decline in prehospital deaths.

Our estimates imply a decline in the number of AMI events resulting in either prehospital deaths or hospitalization from 757,000 in 1975 to 646,000 in 1995. With the growth and aging of the population during this period, this trend implies a decline in the rate of serious AMI events of more than 40 percent over the twenty-year period. The true decline in both the rate and number of serious AMI events may be even larger. Trends in the number of individuals who have a mild AMI but do not seek treatment cannot be estimated from any reported health statistics. With public education campaigns about the importance of responding to classic AMI symptoms, it is possible that patients are increasingly seeking out medical care, but the magnitude of this trend toward patient-initiated hospitalization for AMI is unclear. More clear, as we describe below, is the effect of changes in technology for diagnosing AMI on the detection, and probably the hospitalization, of patients with mild AMIs. In any case, as we turn to our detailed analysis of changes in treatment and outcomes given the occurrence of AMI, it is worth noting that a decline in the rate of serious AMI events was the most important contributing factor to the reduction in AMI mortality over the past twenty years.

9.3.2 Mortality Consequences of Changes in Acute In-Hospital Treatment

Thrombolysis

By 1995 thrombolytic use was 31 percent, according to data from the National Registry of Myocardial Infarction (NRMI) (Rogers et al. 1996) (table 9.2). The use of thrombolytic therapy in 1975 was effectively 0 percent. After adjustment for concomitant use of other drugs, we estimated that the absolute mortality reduction due to thrombolytics in 1995 was 4.6 percent. This would explain 16 percent of the reduction in the AMI thirty-day mortality rate from 1975 to 1995.

Time from symptom onset to treatment is a major determinant of successful thrombolysis. If thrombolysis can be initiated within one hour then the relative risk reduction is near 50 percent, which would lead to an absolute mortality reduction of as much as 9.5 percent. If we assume that in 1995 such rapid treatment was actually achieved, then thrombolysis could explain 35 percent of the overall reduction in thirty-day mortality. However, this estimate is likely to be much too high. Data from Worcester in 1985 (median time to hospitalization 2.0 hours) (Yarzebski et al. 1994a), NRMI (2.8 hours to treatment in 1990 and 2.7 hours in 1993) (Rogers et

Table 9.2 **Use of Interventions for Acute Myocardial Infarction**

	1973–77	1978–82	1983–87	1988–92	1993–96	Source/Comment
Medications						
Beta blockers	20.6	41.5	47.5	47.3	49.8	Goldberg et al. (1987b); Gurwitz et al. (1994); McLaughlin et al. (1996)
ASA	15	14.1	20.1	62	75	Rogers et al. (1994); Goldberg et al. (1987b); Burns et al. (1997)
Nitrates	55.8	83.1	93.2	93	93	Goldberg et al. (1987b). 1990–1995 values are assumed equal to 1985.
IV nitroglycerin	29.1[a]	40.9	76.4		59	Rogers et al. (1994); McGovern, Burke, et al. (1992)
Heparin/anticoagulants			53	75	70	McGovern et al. (1996); Rogers et al. (1994)
Calcium antagonists	0	0	63.9	59	31	Rogers et al. (1996); McGovern, Burke, et al. (1992); Gurwitz et al. (1994); Pashos et al. (1994)
Lidocaine	30	48.2	46.5		16.2	Goldberg et al. (1987b); Chandra et al. (1996)
Other antiarrhythmics	30.7	22.5	21.9			Goldberg et al. (1987b)
Magnesium					8.5	Ziegelstein et al. (1996)
ACE inhibitors	0	0	0		24	Cooperative Cardiovascular Project
Thrombolytics	0	0	9.3	24.5	30.6	Rogers et al. (1996); Chandra et al. (1997)
Procedures						
Cardiac catheterization	3	5	10	35	42	Gore et al. (1987); Paul et al. (1996); Tu et al. (1997)
Primary PTCA	0	0	0		9.1	Rogers et al. (1996)
Any PTCA	0	0	6	21	15	McGovern et al. (1996); Paul et al. (1996)
CABG	3[a]	6	8	10	14	McGovern et al. (1996); McGovern, Folsom et al. (1992); Medicare

Note: In-hospital or thirty-day use.

[a]Average of 1970 and 1979 values.

al. 1994), and GUSTO (median time to treatment 2.7 hours) (GUSTO III Investigators 1997) suggest that there has been little improvement in time from symptom onset to thrombolysis up to 1995. Largely anecdotal results since 1995 suggest that time to thrombolytics may be declining, perhaps accounting for very recent mortality improvements.

Beta Blockade

In 1985 and 1990, beta blockade use was stable at 47 to 48 percent of MI cases (table 9.2). Data from Minnesota in 1992–93 indicate a slight increase to 53 percent use. This is more than double the 1975 value of 21 percent. The published odds ratio demonstrating a survival benefit with beta blockade is 0.88. However, the majority of data regarding the benefit of beta blockade was collected prior to the use of thrombolysis and primary pecutaneous transluminal coronary angioplasty (PTCA). Thus, the benefit may not be as great in conjunction with other current treatments (Becker 1994; Van de Werf et al. 1993). After adjustment for interactions with other therapies, we estimate that increased use of beta blockers accounts for an absolute mortality reduction of 2.0 percent, or 6 percent of the reduction in the thirty-day mortality rate.

Aspirin

Aspirin use in 1995 was estimated to be 75 percent, in contrast to 15 percent use in 1975 (table 9.2). If we assume that the absolute survival benefit from aspirin after adjustment for use of thrombolysis is 4.0 percent (ISIS-2 Collaborative Group 1988), then aspirin use would explain 28 percent of the reduction in thirty-day mortality rates. These results suggest that the increase in aspirin use had a far greater impact on the acute MI thirty-day mortality rate than thrombolysis or beta blockade. A major reason for aspirin's estimated importance is the magnitude of its increase in use, perhaps because of less physician concern about complications compared to thrombolytics or beta blockers.

Calcium Channel Blockers

It is unclear whether calcium channel blockers provide any benefit in AMI. Meta-analyses by Lau et al. (1992) and Teo, Yusuf, and Furberg (1993) have demonstrated a harmful nonsignificant trend with the use of these drugs (table 9.3). We assumed that 1995 use was similar to 1993 use of 31 percent based on data from NRMI (Rogers et al. 1994)—it may in fact be somewhat lower. Use in 1975 was zero, as these drugs had not yet been developed. Based on Lau et al.'s summary odds ratios, greater calcium channel antagonist use would account for a 7 percent absolute increase in mortality, leading to 4,700 more deaths (assuming 540,000 myocardial infarctions in 1995). However, newer calcium channel blockers have not been evaluated in these meta-analyses. Their effect on AMI mortality is unclear, and possibly favorable.

Table 9.3 **Effects of Interventions for Acute Myocardial Infarction**

	Published Odds Ratio		Calculated Odds Ratio			
	Estimate	Upper, Lower	No Other Treatments	1975	1995	Source
Medications						
Beta blockers	0.88	0.80, 0.98	0.88	0.88	0.91	Lau et al. (1992)
ASA	0.77	0.70, 0.89	0.74	0.75	0.78	Lau et al. (1992)
Nitrates	0.94	0.90, 0.99	0.91	0.92	0.94	ISIS-4 Collaborative Group (1995); Hennekens et al. (1996)
Heparin/anticoagulants	0.78	0.65, 0.92	0.77	0.78	0.83	Lau et al. (1992)
Calcium antagonists	1.12	0.92, 1.39	1.14	1.13	1.10	Lau et al. (1992)
Lidocaine	1.38	0.98, 1.95	1.40	1.38	1.29	Teo, Yusuf, and Furberg (1993)
Magnesium	1.02	0.44, 1.08	1.03	1.03	1.02	ISIS-4 Collaborative Group (1995); Hennekens et al. (1996)
ACE inhibitors	0.94	0.89, 0.98	0.91	0.92	0.94	ISIS-4 Collaborative Group (1995); Hennekens et al. (1996)
Thrombolytics	0.75	0.71, 0.79	0.71	0.73	0.77	Lau et al. (1992)
Procedures						
Primary PTCA[a]	0.5	0.35, 0.71	0.46	0.48	0.50	Weaver et al. (1997)
CABG[b]	0.94	0.71, 1.26	0.93	0.93	0.95	Koshal et al. (1988)

[a]Calculated assuming an odds ratio of 0.75 for thrombolytics and an odds ratio with benefit of PTCA vs. thrombolysis of 0.66.

[b]Absolute benefit assumed equal to nitrate therapy and ACE inhibition. Upper absolute benefit estimate assumed equal to thrombolysis. Lower absolute estimate = base estimate (0.01) − upper estimate (0.052) = −0.42.

Nitrates

It is also unclear if nitrates still provide any survival benefit in acute MI. A meta-analysis reported with the results from ISIS-4 demonstrated a small survival benefit with oral nitrates (ISIS-4 Collaborative Group 1995). A metanalysis of IV nitroglycerin in acute MI in the prethrombolytic era found a more substantial mortality reduction of 20 percent (Yusuf et al. 1988). An explanation for these seemingly contradictory findings is that the nitrate effect is not independent of the effect of thrombolysis and aspirin. Another possible explanation is that the intravenous route is more beneficial than the oral route. We used the more conservative ISIS-4 value for our analysis (odds ratio 0.94), which reflected interaction effects with other treatments that were less prominent in earlier years. Because the increase in use of more potent therapies that interacted with nitrate effects was large, the incremental contribution of nitrates to AMI survival in 1995 was slightly less than in 1975.

Heparin

In studies performed before widespread use of thrombolytics, heparin and other anticoagulants have been shown to reduce mortality (summary odds ratio 0.78, equivalent to a 3.9 percent absolute benefit with 1975 overall mortality) (Lau et al. 1992). In 1993 NRMI, 70 percent of patients receive heparin. Because heparin is now often considered part of "thrombolytic therapy" we assumed that all patients receiving thrombolytics would receive heparin and that heparin provided no substantial additional benefit in these patients. Of the 69 percent that did not receive thrombolytics in 1995, 57 percent were estimated to have received heparin, that is, $(69 - 31)/(100 - 31)$. No data were available on heparin use in 1975; data from 1985 (Minnesota) showed that 53 percent of patients received heparin (McGovern et al. 1996). Summary data from the Worcester cohort from 1975 through 1988 found that 65 percent of patients received anticoagulants (Goldberg et al. 1991), suggesting that heparin use did not increase markedly from 1975 to 1985. If the increase in use over the last twenty years was only 4 percent (53 percent to 57 percent) then less than 1 percent of the improvement in MI thirty-day mortality rates is explained by heparin use. However, if heparin use was in fact much lower in 1975, then it would explain more of the mortality improvement: If 1975 use were 20 percent, then the increased use would explain 15 percent of the 1975–95 mortality reduction.

Lidocaine

It is now known that prophylactic lidocaine is not beneficial and is probably harmful in the setting of AMI (Teo, Yusuf, and Furberg 1993). Lidocaine use was 31 percent in 1975 (Goldberg et al. 1987b), increased in the early 1980s, and subsequently dropped to 16.2 percent in 1995 ac-

cording to NRMI (Chandra et al. 1996). Data from Minnesota (which did not include patients of age seventy-five years or older) suggested an even greater use of lidocaine (43 percent in 1970 and 67 percent in 1979) (McGovern, Folsom, et al. 1992). If we assume that nonprophylactic, potentially beneficial use remained constant from 1975 to 1995, then the absolute decrease in prophylactic use is approximately 15 percent (31 − 16, according to Worcester data). Meta-analyses have suggested that the lidocaine increases mortality by an absolute 6 percent, assuming a 22.6 percent overall mortality (Teo, Yusuf, and Furberg 1993). Thus the substantial decline in the use of prophylactic lidocaine since 1975 would have explained 11 percent of the reduction in thirty-day mortality rates.

Magnesium

Early studies of intravenous magnesium suggested an absolute survival benefit for patients with AMI (Teo et al. 1991). However, a large recent trial (ISIS-4 Collaborative Group 1995) found no benefit and a slight harmful trend. Because there is no evidence that the recent finding reflects an interaction of newer therapies with the magnesium benefit, we used the estimated effect from ISIS-4. Magnesium use was 8.5 percent in 1995 according to NRMI data, and we assumed it to be 0 percent in 1975. Thus in any case, because so little magnesium is used, the effect on overall mortality is very small (<1 percent). If an absolute harm of 0.3 percent is assumed, then magnesium use would have led 180 extra deaths within thirty days following MI in 1995.

Primary PTCA

Primary PTCA use in 1995 was estimated to be 10 percent based on data from NRMI (Rogers et al. 1996) and 0 percent in 1975. Using a 3.8 percent absolute benefit of primary PTCA (assumed equal to thrombolysis [Every et al. 1996], table 9.3) the increased use would explain 4.6 percent of the reduction in thirty-day mortality rates. A meta-analysis by Weaver et al. (1997) suggests that PTCA has an absolute survival benefit over thrombolysis. If this is true (absolute benefit 9.9 percent) then 9.8 percent of the reduction in the acute MI mortality rate is attributable to primary PTCA.

Immediate or Urgent Coronary Artery Bypass Graft (CABG)

One small randomized trial suggested no benefit to urgent CABG versus waiting (Koshal et al. 1988). Data from NRMI suggest that use of CABG during acute MI has not increased markedly (5.7 percent in 1995) compared to an estimate of 2.3 percent for 1975 (average based on Minnesota data from 1970 and McGovern et al. 1996; McGovern, Folsom, et al. 1992). If we assume that urgent CABG has a modest net absolute benefit (1 percent) in the additional patients who received it, then the increased use of CABG would explain 0.6 percent of observed decline in the thirty-

day mortality rate. Even if we assume a comparable benefit to early PTCA, the small increase in CABG use explains only a small share of the mortality improvement.

Acute Revascularization

Use of catheterization and revascularization, particularly angioplasty, within thirty days of AMI has increased markedly in use since 1975. The mortality benefits of these changes in treatment are not clear. Several recent studies have documented no survival benefit (and possible harm) from routine catheterization and revascularization soon after AMI in cases without recurrent chest pain or other ischemic symptoms (Boden et al. 1998). Thus, for most AMI patients, thirty-day mortality benefits of early revascularization are probably zero. However, a subset of AMI patients who experience recurrent ischemic symptoms soon after infarct are generally viewed as appropriate candidates for revascularization (Ryan et al. 1996). Unfortunately, no trial results are available regarding urgent revascularization for patients presenting with MI. Both PTCA and CABG may have longer-term mortality benefits that are greater than their acute benefits; we return to this issue below.

Few patients hospitalized for AMI underwent CABG or angioplasty within thirty days in 1975. According to Medicare data, 5.8 percent underwent revascularization in 1985; assuming that the relative odds of procedure use were constant, this corresponds to a rate of 7.3 percent of nonelderly patients. In 1994 the elderly rate was 14.8 percent, compared with 18.6 percent among the nonelderly in California. If we assume an average absolute thirty-day mortality benefit of 1 to 2 percent in these patients—which probably consists of a more substantial benefit for a small share of patients, and little benefit for others—then increased revascularization explains 0.6 to 1.2 percent of the reduction in acute mortality.

Pulmonary Artery Catheterization

Use of pulmonary artery catheterization increased from 1975 to 1984, then declined thereafter among all patients with AMI studied. Among high-risk patients with AMI complicated by heart failure or hypotension, use of pulmonary artery catheterization increased until 1988, then declined in use from 1990. For the combined study periods, 14.7 percent of all patients with AMI studied and 25.4 percent of those with complicated AMI underwent pulmonary artery catheterization (Yarzebski et al. 1994b; Gore et al. 1987). To date there is no evidence that pulmonary artery catheterization improves mortality in patients with myocardial infarction (Zion et al. 1990). In fact, there is concern that these procedures may increase mortality, possibly by causing infection or by direct cardiac injury (Connors et al. 1996; Dalen and Bone 1996). For our analysis, we assumed no mortality effect from pulmonary artery catheterization.

Coronary Care Units

The diffusion of coronary care units was largely complete by the late 1970s. Although we cannot rule out a subsequent mortality benefit from improvements in arrhythmia detection and complex AMI management, other changes in CCU technology are unlikely to have made a substantial contribution in themselves to the drop in thirty-day mortality rates from 1975 to 1995. We discuss the harder-to-measure benefits of increasing skill and experience in CCU and other decisions below.

Overall Effect of Changes in Acute Inpatient Treatments

The contribution of each of these treatments to the overall reduction in mortality rates during the last twenty years is summarized in table 9.4 and figure 9.2. This analysis compares benefit and use in 1995 with benefit and use in 1975. An alternative analysis is displayed in table 9.5, which examines the impact of increasing treatment use from 1975 to 1995 levels holding all other drug use constant at 1995 levels. Table 9.4 shows that increased use of beta blockers, aspirin, thrombolysis, primary PTCA, and ACE inhibitors can explain 62 percent of the reduction in thirty-day mortality from 1975 to 1995. Including the treatment changes in lidocaine, calcium channel blockers, nitrates, magnesium, and revascularization increases the share of the reduction explained to 60 percent, or approximately 6 percentage points lower mortality.

Our findings are mildly sensitive to the assumed joint effects and uses of therapies. If no interaction between therapies is assumed, then 79 percent of the reduction would be explained. Our base-case analysis also assumes that therapies are used independently. If we instead assume that drugs are always given together (patients receive many therapies, or almost no therapies), then the consequences of interactions between treatments will be larger. If this assumption is true, then the five major therapies would explain only 59 percent of the decline in mortality, and all of the therapies would explain about 56 percent.

To explore whether the treatments we identified made different contributions over different time periods, we examined the time periods from 1975 to 1985 and 1985 to 1995 separately (table 9.4). From 1975 to 1985, increased use of the five major MI therapies explained 42 percent of the reduction in mortality during this period. The moderate increase in therapies mirrored the moderate drop in mortality during this decade. Increased use of beta blockers accounted for 20 percent of the drop in mortality, followed by thrombolysis (16 percent) and aspirin (6 percent). Nitrate therapy may have had a greater impact on mortality during this period when little thrombolysis or aspirin were used. If the survival benefit for nitrate therapy is as estimated by Yusuf et al. (1988) (odds ratio 0.79 for oral nitrates), then the increased use of nitrates from 1975 to 1985 would

Table 9.4 **Calculation of Benefit from Acute Myocardial Infarction Therapies**

	Odds Ratio			Increase in Use (%), 1995–75	Reduction in Mortality Explained[a] (%)				
	Published	1975	1995		Major Therapies, 1975–95	Major Therapies, 1975–85	Major Therapies, 1985–95	All Therapies, 1975–95	All Therapies, No Interaction, 1975–95
Medications									
Beta blockers	0.88	0.88	0.89	29	6.1	20	−0.7	6.1	7.3
ASA	0.77	0.76	0.77	60	27.5	5.8	33.3	27.5	30.2
Nitrates	0.94	0.87	0.92	30				−5.5	4.7
Heparin/anticoagulants	0.78	0.78	0.79	4				−0.5	1.9
Calcium antagonists	1.12	1.12	1.12	31				−7.3	−7.4
Lidocaine	1.38	1.38	1.38	−15				10.7	10.6
Magnesium	1.02	1.02	1.02	8.5				−0.3	−0.3
ACE inhibitors	0.94	0.87	0.92	24	2.7	0	3.6	2.7	3.0
Thrombolytics	0.75	0.74	0.76	31	16.1	16.1	14.5	16.1	17.1
Procedures									
Primary PTCA	0.5	0.48	0.50	9.1	9.8	0.0	12.8	9.8	10.8
CABG	0.94	0.92	0.94	6.7				0.6	0.8
Total					62	42	64	60	79

[a]Percent of 1995–75 decrease in acute MI thirty-day mortality rates explained by each intervention. "No Interaction" assumes no interaction between drugs.

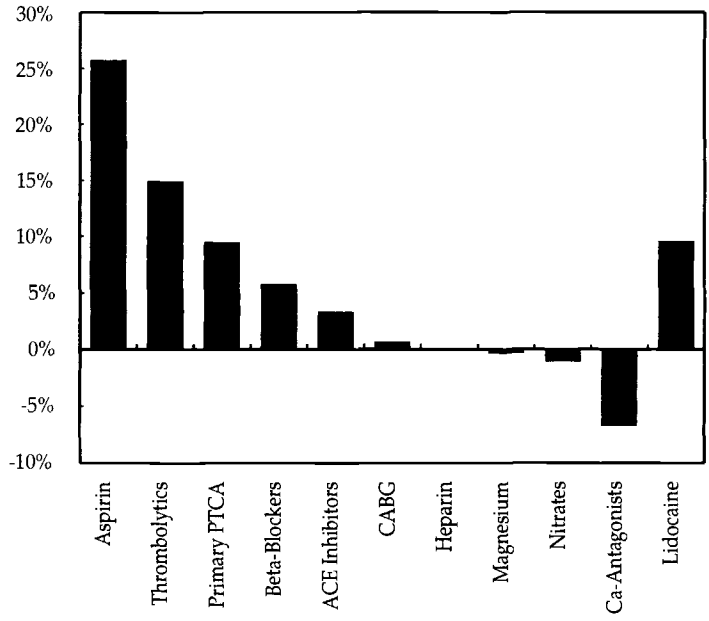

Fig. 9.2 Contribution of the change in usage of individual therapies to the reduction in case-fatality rate from 1975 to 1995

Note: The total percent explained is 61 percent. This analysis assumes that point estimates of effect size from the meta-analysis are correct. The contribution of lidocaine was due to a reduction in use.

Table 9.5 Reduction in Mortality Explained Due to Increasing Drug Use from 1975 to 1995 Levels (%)

	Direct Effect	Indirect Effect (Interactions)	Total Effect
Medications			
Beta blockers	6.6	−0.75	5.9
Aspirin	27.5	−1.83	26.5
Nitrates	4.2	−0.49	3.7
Heparin/anticoagulants	1.8	−0.17	1.6
Calcium antagonists	−7.3	0.08	−7.2
Lidocaine	10.5	−0.09	10.4
Magnesium	−0.3	0.01	−0.3
ACE inhibitors	2.7	−0.33	2.4
Thrombolytics	16.1	−0.83	15.3
Procedures			
Primary PTCA	9.8	−0.83	8.9
CABG	0.7	−0.09	0.6

Note: Percent of 1995–75 decrease in acute MI thirty-day mortality rates explained by increasing an individual drug usage from 1975 to 1995 levels. All other drugs are assumed to be used at 1995 levels. Indirect effects are opposite to direct effects because of negative interactions with other drugs.

have explained a much larger share (22 percent) of the decline in thirty-day mortality rate during this period.

From 1985 to 1995, a more substantial drop in thirty-day mortality occurred compared to the 1975–85 period (approximately 6.7 versus 3.7 percentage points, table 9.1). This greater improvement was associated with a large increase in the use of the major therapies shown to be effective in AMI care (tables 9.1 and 9.2). The relative contribution of different treatments to the drop in mortality also changed substantially. Beta blockers, the use of which increased only modestly during this time period, were unimportant. Aspirin explained 33 percent of the decline, the increased use of thrombolysis explained 15 percent, primary PTCA explained 13 percent, and ACE inhibition explained 4 percent.

In contrast to our base case, if we assume the average harm from calcium channel blockade is as reported in the meta-analyses, then the impact of changes in interventions on the overall mortality rate during these two time periods differs markedly. Because there was a large increase in calcium blockade from 1975 to 1985, the benefit from proven therapies is largely offset by the harm from rapid diffusion of calcium channel blockers.[9] Conversely, because calcium channel blockers (and to a lesser extent lidocaine) were used less frequently by 1995, the overall contribution of effective treatments to the reduction in mortality from 1985 to 1995 increases to 84 percent. We find these average effects for potentially harmful treatments to be implausible. In any case, all of our estimates suggest that medical treatments for acute MI were much more important in reducing AMI mortality during the ten years following 1985 compared to the prior ten years.

The major changes in inpatient AMI treatment we evaluated do not include all of the changes in the acute hospital management of AMI that have occurred in the past two decades. Other treatment changes that may have contributed to the reduction in AMI mortality include improved supportive care for heart failure and shock, improved arrhythmia monitoring and defibrillation, stenting and other treatments to improve vessel patency after angioplasty, and miscellaneous other therapies. The importance of these additional changes in the mortality trends is unclear, because of the absence of published information on effects from randomized controlled trials or other studies on effectiveness, and on trends in treatment use over time. Even though none of these treatments are used on a large share of AMI patients, they may nonetheless account for part of the residual unexplained mortality trends. However, the following sections describe explanations for the remaining mortality improvement other than these additional changes in hospital care.

9. Lidocaine also accounts for a less substantial adverse change in outcomes from 1975 to 1985, but the effect is smaller since its change in use was smaller.

Changes in Appropriateness of Care

In the preceding subsections, we have focused on changes in treatment *rates* in AMI patients. Even if treatment rates and AMI patient characteristics remain unchanged, outcomes may nonetheless improve if treatments are allocated to patients more effectively. Treatment allocation may improve as clinical knowledge improves (e.g., with the publication of new studies on large benefits or adverse effects of treatment) or as clinical experience increases (e.g., as cardiologists become more familiar with the types of patients likely to benefit from intensive procedures).

Unfortunately, obtaining longitudinal information on appropriateness of treatment is very difficult. Though many studies report information on the clinical characteristics of enrolled patients, they generally do not report statistics on treatment rates in particular clinical subgroups of patients at the level of detail required for appropriateness judgments. Even if they did, the sample sizes involved would likely be too small to reach definitive conclusions about changes in appropriateness over time. Finally, studies designed to examine appropriateness of care at a point in time often classify a large share of patients into a "possibly appropriate" category, where benefits of treatment are uncertain, and judgments about appropriateness may differ (Ayanian et al. 1998). For all of these reasons, the clinical-trial literature and our analysis necessarily focus on average effects of treatment across broad groups of patients. Though we must treat it as a residual, we suspect that improvement in appropriateness of care also contributed to the observed improvements in outcomes.

9.3.3 Prehospital Treatment Changes

As we noted above, much of the decline in out-of-hospital deaths from AMI (and IHD-associated ventricular arrhythmias) appears to be the result of a decline in the total incidence of AMI and cardiac-arrest events. In this section, we review evidence on the prehospital treatment of AMI and AMI- and IHD-related cardiac arrest. If more AMI patients survive to hospitalization as a result of improved prehospital treatment, then the share of AMI hospitalizations among total AMIs will increase. The substantial decline in out-of-hospital IHD death rates relative to the AMI hospitalization rate suggests that this is indeed the case. To the extent that these additional hospitalized patients have more or less severe AMIs than average, these changes may have implications for apparent survival rates after hospitalization for AMI.

Advanced Cardiovascular Life Support (ACLS) Availability

Goldman and Cook (1984) estimated that ACLS accounted for 8.4 percent of the reduction in IHD mortality between 1968 and 1976. They estimated that if ACLS had been widely available, 36,000 deaths per year

during this period could have been prevented. However, only 600 lives per year were actually saved, because most people had access to basic life support only. The availability of ACLS may have increased over the last twenty years due to increased use of ambulances by the public and the diffusion of the 911 system. It is now estimated that over 90 percent of the U.S. population has emergency medical services available within ten minutes (Cummins 1993), and that most have access to basic 911 services (Hunt et al. 1989).

Although improved access to defibrillation has probably improved outcomes of cardiac arrest victims, it is unclear if the improved access to care has had an effect on mortality from AMI for patients without a cardiac arrest (tables 9.6 and 9.7). There is little evidence that rates of ambulance use by AMI patients have increased. According to a review by Ho et al. (1989), 30 to 50 percent of MI patients used an ambulance in 1975, compared with 42 percent for the Minneapolis metropolitan area in 1990. Even though ACLS availability has increased substantially, its actual emergent use for AMI patients has probably increased only modestly. Thus, the share of mortality improvement for hospitalized AMI patients explained by changes in ACLS availability up to 1995 is probably small.

Cardiac Arrest Treatments

Several studies have documented improvement in survival from out-of-hospital cardiac arrest following implementation of systems using paramedics or defibrillation-trained emergency medical technicians (EMTs) (Vukov, White, and Bachman 1988; Weaver et al. 1986). In Seattle, the percent of patients discharged alive increased from 10 percent in 1971 to 25 percent in 1973 following the establishment of a comprehensive program to improve access to advanced cardiac life support including defibrillation (Weaver et al. 1986). Little improvement occurred during the subsequent ten years (26 percent survival to discharge in 1983) despite implementation of new treatments such as automated defibrillators (Cummins et al. 1987), and dispatcher-assisted cardiopulmonary resuscitation (CPR) (Eisenberg et al. 1985). A similar improvement in survival (2.5 percent to 12 percent) for cardiac arrest patients with ventricular fibrillation was observed following the use of defibrillators by EMTs (Vukov, White, and Bachman 1988). The focus of cardiac arrest treatment has been on defibrillation because 50 to 80 percent (Eisenberg et al. 1990; American Heart Association 1992) of patients are found in this rhythm (Cummins 1993).

A few additional treatments have been noted to improve survival in cardiac arrest. Bystander CPR, when performed correctly, has been associated with an increased probability of the patient's being in ventricular fibrillation when emergency personnel arrive, and with an improved outcome (4.6 percent survival with effective CPR versus 1.4 percent with ineffective

Table 9.6 Trends in Prehospital Treatment for Myocardial Infarction

	1973–77	1978–82	1983–87	1988–92	1993–95	Source
Patient-Related						
Time to call 911 (hours)			2–2.6	2.1	> 6 in 40%	Ho et al. (1989); Sharkey et al. (1989)
Use of ambulance (%)	33–50		50	44	42	Ho et al. (1989); Sharkey et al. (1989); Kereiakes et al. (1990)
Time to hospitalization (hours) mean (median)	> 4 in 40–50%		4.1 (2.0)	4.6 (2.0)	(2.7)	Yarzebski et al. (1994a); GUSTO III Investigators (1997); Ho et al. (1989); Maynard et al. (1995)
Hospital						
Arrival-lytics (minutes) mean (median)			90		99 (57)	Sharkey et al. (1989)
Arrival-lytics CCU (minutes)			102	73		Sharkey et al. (1989); Maynard et al. (1995)
Arrival-lytics ER (minutes)			67	47		Sharkey et al. (1989); Maynard et al. (1995)

Table 9.7 **Effects of Different Prehospital Technologies for Acute Myocardial Infarction and Cardiac Arrest**

Effects	Estimate: Absolute Benefit	Source/Comment
Use of paramedics or EMT-D[a] (%)	15	Survival increased from 10% to 25% (Weaver et al. 1986)
Effective bystander CPR (5)	3.2	4.6% survival with effective CPR vs. 1.4% with ineffective CPR (Gallagher, Lombardi, and Gennis 199)
Media campaign to increase use of EMS[b] (%)	0	No effect on time delay or use of ambulance (Ho et al. 1989; Blohm et al. 1996)
Prehospital thrombolysis (%)	2.2	(Weaver 1995)
Prehospital ECG (%)	4.3	Decreased time to lytics by 40 mins (Barbash et al. 1990; Canto et al. 1996)
Lytics in 1 hour (%)	6.9	(Boersma et al. 1996)
Lytics in 6 hours (%)	2.6	(Boersma et al. 1996)
Paramedics vs. EMT (%)	8	24% paramedics vs. 16% EMTs (all benefit in hypotensive patients) (Pressley et al. 1988)

[a] EMT-D: emergency medical technicians with defibrillation training.

[b] EMS: emergency medical services.

CPR) (Gallagher, Lombardi, and Gennis 1995). In contrast, other treatments such as the use of high-dose epinephrine (Callaham et al. 1992), transcutaneous pacing (Cummins et al. 1993), and active compression-decompression CPR (Schwab et al. 1995) have not been shown to improve survival to hospital discharge.

It is unclear if the 911 system has an effect on acute MI mortality apart from improved access to defibrillation. A study of trauma patients in North Carolina found no improvement in trauma death rates following institution of the system (Patsey et al. 1992). A comparison with counties that lacked 911 also did not show a benefit. Although similar data for AMI patients are lacking, the time from symptoms to hospitalization, an important determinant for benefit from thrombolysis, has not changed dramatically (table 9.6). Taken together, these improvements in prehospital care for AMI and arrest appear to account for a small part of the overall IHD and AMI mortality reduction.

Overall Changes in Survival to Hospitalization of AMI Patients

The changes in out-of-hospital treatment probably had a relatively modest effect on the higher rates of survival to hospitalization of AMI patients. In this section, we compare this evidence on prehospital treatment changes to the overall changes in survival of out-of-hospital arrests and severe AMI events.

Different studies have reported widely divergent survival rates for out-of-hospital events, and Becker, Smith, and Rhodes (1993) demonstrated a striking inverse relationship between reported incidence and survival. Studies with an incidence of 120 per 100,000 had survival rates of 2 to 3 percent. Other studies with higher survival rates (5 to 18 percent) had much lower incidence rates (40 per 100,000) (Cummins et al. 1985). Although these differences may be related to differences in patient populations, the threefold variation in reported incidence among studies strongly suggests that different inclusion criteria were used to identify the population receiving prehospital care. After adjustment for differences in incidence rates, there was no clear trend in survival rates over time from the data reported between 1970 and 1990. This observation is limited by publication bias: Areas with advanced prehospital care programs may be more likely to report data. If we assume that lower incidence rates in some areas result from more patients receiving no prehospital care before death, we can assume that the rate of out-of-hospital events is approximately 150 cases of arrest and AMI-related cardiogenic shock per 100,000. The survival rate for out-of-hospital events (using an incidence of 150 arrests per 100,000) is 1 to 5 percent. As our review of changes in prehospital technologies suggested, the actual improvements in prehospital treatment appear to account for only a modest increase in the number of AMI patients reaching the hospital alive.

Though they may have modestly improved population AMI survival rates, these prehospital treatment changes did not necessarily improve the thirty-day survival rate for hospitalized AMI patients. The "marginal" patients saved in the field may be relatively ill when reaching the hospital. In support of this hypothesis are data from Minnesota, which demonstrate an increase in the death rate from ischemic heart disease in the emergency room from 1970 to 1978 (Gillum et al. 1983). Partly for this reason, we examine trends in the characteristics of hospitalized AMI patients to assess their contribution to the apparent trends in AMI survival rates.

9.3.4 Changes in Characteristics and Reporting of AMI Hospitalizations

Outcomes of hospitalized AMI patients will change over time in the absence of changes in effective treatment if the characteristics of the AMI populations change. Changes in survival to hospitalization are one source of changes in patient characteristics, but changes in the health risks of patients hospitalized with AMI, diagnostic accuracy, and other factors may also have contributed. In this section, we review the evidence on whether changes in the nature or severity of hospitalized AMIs have affected outcome trends.

Presenting Characteristics

Data on all hospitalized AMI patients from NHDS show some changes in AMI patient demographics (table 9.8).[10] The average age of the acute MI patient has increased from sixty-four to sixty-nine years. The proportion of MI patients that are female has increased from 33 percent in 1975 to over 40 percent in the 1990s (Goldberg et al. 1986; Chandra et al. 1997). Data from Minnesota demonstrate some reduction in the risk-factor profile (cigarette smoking, hypercholesterolemia, systolic blood pressure) from 1985 to 1990, which might lead to better outcomes. The precise extent to which these modest changes in risk factors have affected thirty-day AMI mortality is unclear, but the impact has probably not been substantial.

Infarct Type, Location, and Severity

According to data from the Worcester Heart Attack Study, between 1975 and 1981 the rate of non-Q-wave MI increased relative to the Q-wave MI rate (Goldberg et al. 1986). A likely reason for this increase is the improved detection of MI with creatine kinase (CK) cardiac enzymes. In 1975 medium serum creatine kinase (CK-MB) fractions and other chemistry tests for AMI confirmation were used in 5 percent of infarcts, compared to 58 percent in 1981 (Goldberg et al. 1986) and in over 90 percent of cases by the late 1980s. This increased use of cardiac enzymes may in part explain the observed increase in acute MI discharges at a time when overall mortality from MI was decreasing. In addition, improved initial detection and treatment of AMI may decrease the myocardial damage, resulting in a greater share of non-Q-wave infarcts. Non-Q-wave infarctions have better short-term mortality than Q-wave infarcts, although this difference does not appear to persist for long-term outcomes (Goldberg et al. 1987a; Behar et al. 1996). If we assume that two-thirds of the decline in Q-wave MI is due to improved treatment, then the remaining decline due to improved detection would explain 27 percent of the overall decline in thirty-day mortality.

Anterior location of the infarct appears to have dropped, perhaps also because of increased diagnosis of nonanterior infarcts, from 58 percent in 1975 to 43 percent in the early 1990s (Goldberg et al. 1986; Chandra et al. 1997). However, recent data from the GUSTO trials (GUSTO III Investigators 1997) suggest that the proportion of patients with anterior infarcts may have increased somewhat since 1993 (40.9 percent to 47.5 percent in 1996). Past studies have shown that mortality from an anterior MI is 50

10. Because we have used age-specific incidence rates to calculate the overall death rate, the impact of changing distributions of ages does not account for the unexplained reduction in our reported case-fatality rates. However, these demographic changes may be associated with other changes in case characteristics.

Table 9.8 **Trends in Patient Characteristics**

	1973–77	1978–82	1983–87	1988–92	1993–95	Source
Age (years)	64.1	65.5	67.5	68.4	69.1	NHDS
Female gender (%)	33	37	40	40	40	NHDS
Anterior or lateral location	58	58		44	46	GUSTO III Investigators (1997); Goldberg et al. (1986); Chandra et al. (1997); Mickelson, Blum, and Geraci (1997)
Q-wave MI	72	57		48	32	Goldberg et al. (1986); Mickelson, Blum, and Geraci (1997); McGovern et al. (1997)
Shock	7.6	7.3	7.6	9.1	2.9	Goldberg et al. (1991); Goldberg et al. (1986); Canto et al. (1996)

Note: The presence of Q-waves is a function of both patient characteristics and treatment.

Table 9.9 **Infarct Characteristics and Mortality**

Effect Size	Odds Ratio
Age	1.05
Male	n.s.
Anterior location	1.52
Q-wave MI	2.32
Shock (Killip IV)	7.89

Source: Canto et al. (1996).
Note: All $p < 0.001$; n.s. = not significant.

percent greater regardless of Q-wave or non Q-wave type, and anterior MIs have higher mortality than inferior infarcts even after adjusting for size of infarction (table 9.9) (Behar et al. 1993, 1996; Haim et al. 1997; Kornowski et al. 1997). If we assume that the relative death rates for anterior and inferior infarcts did not change, then the change in distribution of MI (more inferior) would explain 12 percent of the decrease in case-fatality rates.

A final source of evidence on changes in severity of infarcts is the share of patients who experience symptoms of cardiogenic shock. There is some evidence that average AMI severity given distribution increased through the late 1980s. According to the Worcester series, the incidence of shock increased slightly, from 7.6 percent in 1975 to 9.1 percent in 1988 (Goldberg et al. 1991). However, data from NRMI suggest that the prevalence of shock in more recent years is less than 5 percent, and shows no clear trend. If the NRMI data are correct, then decreasing MI severity over the entire time period can explain up to 30 percent of the reduction in AMI mortality.

Available data on patient characteristics and infarct severity do not permit definitive conclusions, but the bulk of the evidence suggests that the changes in the nature of AMIs in hospitalized patients accounts for a significant part of the observed improvements in outcomes, especially between 1975 and 1985. Taken together, the changes in infarct type, severity, and location would plausibly explain around one-third of the thirty-day mortality improvement for AMI between 1975 and 1995.

Changes in Reporting

Changes in coding practices and consequent increases in noncardiovascular death rates may explain some of the decline in IHD death rates (Pankow et al. 1994). A mathematical model of the decline in ischemic heart disease mortality estimated that 5 to 10 percent of the decline in mortality from 1970 to 1989 is due to definitional changes in the cause of death (Gilbertson et al. 1992). However, this model applied to all AMI deaths, including the predominant out-of-hospital deaths that are difficult to clas-

sify precisely. Studies based on clinical audits of Medicare discharge records suggest that the discharge diagnosis of AMI has a positive predictive value of 95 percent or higher for true AMIs (Green and Wintfeld 1993). This high level of accuracy for AMI does not appear to have changed much over time. Thus, it appears unlikely that changes in reporting practices have had a substantial impact on observed AMI trends.

9.3.5 Changes in Postacute Care and Long-Term Outcomes

Our results suggest that most of the substantial improvement in thirty-day AMI mortality over the past twenty years can reasonably be attributed to changes in medical treatments. An important question is the extent to which the thirty-day mortality improvements translate into long-term reductions in mortality for AMI patients. Medicare beneficiaries hospitalized with AMI between 1984 and 1994 had larger mortality reductions up to three to five years after AMI than they did at thirty days (McClellan and Noguchi 1988). However, variations in hospital treatment explained a significantly smaller share of one-year than thirty-day mortality variations for these patients (McClellan and Staiger 1999), suggesting that the long-term mortality improvements required the interaction of changes in hospital treatment with changes in subsequent treatment and behavior that led to secondary prevention. Unfortunately, less quantitative evidence exists on the effectiveness of postacute treatments, and especially on trends in their use in post-AMI patients. We review the available evidence here, which permits only qualitative estimates of the sources of improvements in long-term outcomes after AMI.

Reductions in mortality with beta blockers (odds ratio 0.81, 95 percent confidence interval [CI] 0.73–0.89), antiplatelet agents (0.90, 0.82–1.0), cholesterol lowering agents (0.86, 0.79–0.94), anticoagulants (0.78, 0.67–0.90) and rehabilitation programs (0.80, 0.65–0.95) have been demonstrated by multiple randomized trials. The benefit of calcium channel blockers is unclear (odds ratio 1.01, 95 percent CI 0.90–1.12), while class 1 antiarrhythmic agents appear to be harmful (1.28, 1.02–1.61) (see Lau et al. 1992 for a summary of these trials).

Changes in the use of these and other postacute treatments are less clear than the evidence on their likely effectiveness. A survey of internists by Hlatky et al. (1988) found increased long-term beta blockade, from 35 percent in 1979 to 82 percent in 1987, for a patient with an uncomplicated MI. Actual use is likely to be considerably lower because many patients have complicating factors that make them less than ideal candidates, and because of compliance problems. Data from outside the United States show an increase in postdischarge beta blockade use from 30 to 40 percent in the early 1980s to over 60 percent in the 1990s (Myers 1985, Thompson et al. 1992). Our analysis of data from the Cooperative Cardiovascular Project (CCP) has found that although beta blockers were given during

admission to 46 percent of Medicare patients, only 27 percent received them at discharge.

A substantial increase in long-term aspirin use was also reported in Hlatky et al.'s (1988) physician survey, from 35 percent in 1979 to 82 percent in 1987. Data from Medicare beneficiaries in 1992–93 found that 76 percent of patients without a contraindication received aspirin (Krumholz et al. 1996). Non-U.S. data also suggest that postdischarge aspirin use has increased significantly worldwide, from 33 percent in 1985 to over 80 percent in the early 1990s (Thompson et al. 1992; Smith and Channer 1995). The increase in long-term aspirin use may be an important contributor to long-term outcome improvements.

Data from Medicare (CCP) in 1994 reveal that 26 percent of patients received calcium channel blockers, 24 percent received ACE inhibitors, and 11 percent received warfarin at discharge. NRMI results also show that use of ACE inhibitors at discharge appears to be increasing slowly but steadily in the United States, to around one-fourth of AMI patients by 1995 (McClellan et al., in press). International data document increasing use of calcium channel blockers from their first use in the early 1980s to a peak in the mid- to late 1980s of 40 to 50 percent, followed by a subsequent decline (Smith and Channer 1995; Zuanetti et al. 1996; Heller et al. 1992). Long-term use of nitrates and anticoagulants show no dramatic trends following AMI, at least over the past decade (Myers 1985; Thompson et al. 1992; Smith and Channer 1995; Heller et al. 1992).

In 1990 an estimated 10 to 15 percent of MI survivors participated in a supervised outpatient cardiac rehabilitation program (Wittels, Hay, and Gotto 1990; American College of Physicians 1988). This is less than the fraction of MI survivors (38 percent) in the GUSTO trial who were enrolled in cardiac rehabilitation programs (Mark et al. 1994). However, the GUSTO patients were a select group whose use of rehabilitation services may differ from that of the general population. The use of rehabilitation appears to be increasing over time, but little quantitative data exist on the magnitude of these trends.

Post-AMI catheterization and revascularization procedures, particularly angioplasty, became much more widespread between 1975 and 1995. Clinical trials have only documented a clear long-term mortality benefit from revascularization for a small fraction of IHD patients (Yusuf et al. 1994), and even in these cases the mortality differences were not evident until six months following surgery. Several recent trials have found no mortality benefit and possibly increased mortality risk with routine catheterization after AMI (Boden et al. 1998). Thus the limited available clinical trial evidence suggests that the additional procedures have had a modest impact on overall mortality trends. International comparisons of trends in long-term outcomes for AMI patients find results consistent with this conclusion: Countries like Canada that have had far less rapid growth in

procedure use have had near-identical trends in mortality improvements (McClellan et al., in press). Some observational evidence suggests that more intensive procedure use may lead to improved quality of life (Rouleau et al. 1993). But few studies have evaluated trends in quality of life for AMI patients, so that conclusions about the contribution of more intensive procedures to long-term quality of life would be highly speculative.

Risk factors have also improved over the last several years for the general population, and improvements are likely to be similar if not greater for patients following MI. Smoking rates have dropped steadily between 1975 and 1995. Cholesterol levels dropped between 1960 and the mid-1980s, largely due to changes in diet (Goldman and Cook 1984), and they have dropped more substantially since the late 1980s, probably as a result of increased use of cholesterol lowering agents (statins). Data from the National Health and Nutrition Examination Survey (NHANES) indicate a yearly drop in total and LDL (low-density lipoprotein) cholesterol of 0.25 to 0.6 percent. Hypertension is also better controlled, particularly systolic hypertension in the elderly, again probably as a result of both behavioral changes (especially before 1980) and new drug treatments. Diastolic blood pressure has also decreased approximately 0.15 to 0.2 percent per year according to data from Minnesota (McGovern, Burke, et al. 1992). Obesity rates, in contrast, have increased from the mid-1980s onward. Data from NHANES suggest a 0.25 to 0.4 percent increase in body mass index per year. Taken together, these reductions in risk factors may be important contributors to the long-term sustainability of the short-term outcome improvements that we have described in detail. Both behavioral changes, especially in the early period of our study, and more effective drug therapy in more recent years have mediated these effects.

These results on long-term outcome improvements after AMI yield several qualitative conclusions. First, the substantial improvements in short-term mortality appear to translate into long-term mortality improvements. Second, changes in both postacute treatment—increased use of drugs including aspirin, beta blockers, statins, and antihypertensive drugs, and (perhaps to a lesser extent) increased use of revascularization procedures—as well as changes in risky behaviors have contributed to these improvements. Though quantitative conclusions are not possible using published data on effectiveness and treatment trends, it is likely that behavioral changes were relatively important up to the early 1980s, and that changes in medical treatments have accounted for the bulk of the improvements since. These qualitative conclusions about long-term mortality are generally consistent with our findings on the sources of acute mortality improvements, as well as with the conclusions of more general studies of IHD mortality trends (Goldman and Cook 1984; Weinstein et al. 1987; Hunink et al. 1997).

9.3.6 Cost-Effectiveness of Technological Change for AMI Care

Our results indicate that changes in medical technology have accounted for the bulk of improvements in acute AMI mortality, and probably of long-term AMI mortality, over the past two decades. With the cost of AMI treatment increasing substantially over the same period (McClellan and Noguchi 1988; Cutler et al. 1998), an important policy question is whether these changes have been cost-effective. A comprehensive approach to this question would require a detailed analysis of the cost of each of the technologies that we have studied, including their downstream impact on other expenditures. Such an analysis is beyond the scope of this paper. Here, we review some of the overall changes in thirty-day and longer-term expenditures on AMI patients, and discuss their implications for cost-effectiveness.

Resource Use, Costs, and Expenditures

The length of stay for patients hospitalized with myocardial infarction has declined consistently since 1975 (table 9.10). Data from discharge surveys and GUSTO I-III (GUSTO III Investigators 1997) show a drop from fifteen days in 1976 to seven or fewer in 1995. Medicare data on total length of stay for the thirty days and year after AMI show a similar, though slightly less dramatic, decline in total hospital days over the past decade. The decline is slightly less dramatic due to the increasing use of readmissions and transfers documented in table 9.1.

Despite the reduction in use of hospital days, total resource use in AMI care has increased substantially over the past two decades. Because of increasing use of intensive cardiac procedures, thrombolytics, other drugs, and intensive procedures during the initial AMI episode of care, the cost of each hospital day has grown more than enough to offset the reduced length of stay. Hospital list charges for AMI care have increased enormously: $4,752 in 1975 in Boston (Cretin 1977), $15,900 in San Francisco in 1982 (Sawitz et al. 1988), and $30,000 in Midwestern community hospitals (Leimbach et al. 1988) to $39,000 in Ann Arbor (Chapekis, Burek, and Topol 1989) in 1987. List charges are increasingly misleading measures of resource use, particularly since the late 1980s, because of managed-care contracting and government price regulation. However, studies based on estimated resource costs and actual reimbursements for medical services have qualitatively similar results. Studies from Boston hospitals using detailed cost per charge ratios to estimate costs have found an increase in mean costs from $10,638 in 1986 (Tosteson et al. 1996) to $15,073 in 1992 (Di et al. 1996). These trends are reflected in provider payments for AMI care: The thirty-day DRG payments for the Medicare population have increased steadily since 1985, and their growth may have accelerated since 1992 (McClellan and Noguchi 1988).

Table 9.10 **Trends in Resource Utilization and Cost**

	1973–77	1978–82	1983–87	1988–92	1993–95	Source
Length of stay (days)	16.5	14.0	10.5	8.3	7.1	HCIA Inc.
ICU length of stay (days)			5.8	4	3.5	Leimbach et al. 1988; Mark et al. 1995; Reeder et al. 1994
Hospital charges 1 year (1995$)	4,740	15,900	38,800			Cretin 1977; Sawitz et al. 1988; Chapekis, Burek, and Topol 1989
Hospital costs 1 year (using cost-charge ratio) (1995$)			12,100	15,000		Tosteson et al. 1996; Paul et al. 1995
Hospital costs 30-day (using Medicare reimbursements) (1995$)			8,100	9,500	12,300	Medicare data from 1985, 1990, 1994
Hospital costs 1 year (using Medicare reimbursements) (1995$)			12,100	14,200	18,200	Medicare data from 1985, 1990, 1994

Cost-Effectiveness

Using Medicare data on thirty-day expenditures for treatment, we estimated the aggregate cost-effectiveness of interventions for MI by determining the total cost of care and the expected quality-adjusted life years gained from all acute MI treatments. If we extend the 5.0 percent yearly real increase in total thirty-day medical expenditures observed between 1985 and 1995 (McClellan et al. in press) back to 1975, we would have observed a total increase in medical expenditures of $8,500 over the last twenty years. Because a greater percentage of patients are surviving their AMI, their long-term medical and nonmedical costs also rise. If we assume that the quality-of-life adjustment for surviving post-AMI has remained constant at 0.88 (Tsevat et al. 1993), then the discounted (3 percent per year) quality-adjusted life years (QALYs) over five years are forty QALYs per 100 patients treated (table 9.11). If quality of life of AMI survivors has actually improved over time, for example through better symptomatic relief from medications and revascularization, the QALY gains would be even larger.

Our estimates indicate that changes in AMI technology accounted for over 60 percent of the increase in QALYs. If we further assume that the changes in technology were responsible for all of the expenditure growth (Cutler and McClellan 1998), then the marginal cost-effectiveness for all

Table 9.11 Cost-Effectiveness Calculations

	5-Year Survival	10-Year Survival	15-Year Survival
Increase in MI cost (1995–75) per 100 patients ($)	8,500	8,500	8,500
Increase in MI survivors (1995–75) per 100 patients	8.3	8.3	8.3
Quality adjustment for living post-MI	0.88	0.88	0.88
Increase in long-term health costs due to MI survivors per 100 patients (assumes $4,000/year/survivor) ($)	181,000	337,000	472,000
Increase in total costs per 100 patients ($)	1,029,000	1,185,000	1,319,000
Increase in quality-adjusted life years (QALYs) per 100 patients	40	77	108
· costs/· QALYs ($)	26,000	15,000	12,000
QALYs due to interventions (QALYs × 0.62) per 100 patients[a]	25	48	67
Adjusted · costs/· QALYs ($)	42,000	25,000	20,000
Adjusted · costs/· Life years ($)	35,000	20,000	15,000

Note: All long-term costs and utilities are discounted at 3 percent per year (1995 dollars).

[a] Uses estimate of reduction in mortality from medical technologies from table 9.4.

treatments combined is $42,000 per QALY if patients survive five years post-MI, and $25,000 per QALY if patients survive ten years. Assuming a fifteen-year life expectancy following AMI (Mark et al. 1995), the cost per QALY gained is $20,000 and the cost per year of life gained is $16,000. These values cluster toward the low end of commonly accepted thresholds for cost-effectiveness of $25,000 to $100,000 per year of life saved (Laupacis et al. 1993).

The favorable results on the average value of all the changes in medical technology for AMI care do not imply that all of the many particular changes in AMI treatment have been cost-effective. For example, greater use of catheterization and revascularization can explain almost all of the growth in hospital payments for Medicare beneficiaries with AMI over the past decade (Cutler and McClellan 1998). But the evidence reviewed here suggests that these procedures account for only a small part of the short- and long-term mortality improvements, and these particular treatments may not have favorable cost-effectiveness ratios in themselves. In contrast, the cost-effectiveness of aspirin is extremely favorable.

9.4 Discussion

The treatment of AMI has changed enormously during the past twenty years. The use of interventions that have been shown to be effective in randomized clinical trials (aspirin, beta blockers, primary PTCA, thrombolytics) have increased, while the use of possibly harmful technologies (lidocaine, calcium channel blockers) has declined. Many other technologies with uncertain effectiveness have also become more widely used.

Recently, Hunink et al. (1997) reported the results of a Markov model of coronary heart disease to evaluate the importance of such changes in care for understanding the decline in IHD deaths from 1980 to 1990 (see also Weinstein et al. 1987). The study estimated that improvements in the thirty-day mortality rate for acute MI explained 15 percent (19,000 deaths) of the drop during this period. The coronary heart disease policy model did not incorporate individual treatment for acute myocardial infarction such as thrombolytic therapy or primary angioplasty, thus, the particular contributions of these interventions could not be determined.

Our goal was to understand the extent to which specific changes in AMI treatment and other factors could explain outcome trends for AMI patients. We developed quantitative estimates of changes in overall AMI mortality, including both hospitalized patients and those who die before hospitalization. Though we explored the likely consequences of changes in prehospital treatment and postacute AMI care, published studies were adequate to provide quantitative estimates only of the consequences of changes in acute mortality for hospitalized AMI patients. For this important group of AMI patients, we quantified the likely effects of all of the

significant medical and nonmedical factors that might explain the decline. We found that changes in medical technology explain around two-thirds of the decline in thirty-day mortality rates. A small part of the residual decline in thirty-day mortality rates may be due to other treatments for which quantitative evidence on effectiveness and use was not available. But changes in AMI patient characteristics are probably responsible for the bulk of the residual one-third reduction. Among the nontreatment factors, improvements in diagnosis appear to have led to improved case-fatality rates as more patients with small, mild infarcts are being identified. However, improved early diagnosis, leading to more rapid use of effective technologies and thus more "incomplete" non-Q-wave AMIs, may also have contributed to this effect.

Technologies differed substantially in their impact on the reduction in thirty-day mortality rates. The use of beta blockade and anticoagulants increased only slightly and minimally contributed to the decline in case-fatality rates. Thrombolysis and primary PTCA have also become much more widespread since 1985, contributing significantly to the mortality improvement over the past decade. The greatest contributor to the decline in case-fatality rates was the diffusion of aspirin. Clinical trials have documented a substantial effect of aspirin on mortality, even in the postthrombolytic era. More importantly, aspirin use increased enormously, from around 15 percent in 1975 to 75 percent in the early 1990s. The use of aspirin for secondary prevention of MI has also increased in the United States. Thus aspirin appears to be the most important factor in explaining the cost-effectiveness of technological change in AMI care for both short- and long-term mortality improvements. Other changes in technology have probably been less cost-effective, and may not have been worth their additional resource costs.

To our knowledge, this is the most detailed quantitative analysis of the contribution of specific changes in medical technology to changes in population outcomes. Our findings suggest that the medical treatment changes can explain over 60 percent of the observed improvements in mortality for hospitalized AMI patients, and have been particularly important since 1985. The remainder of the mortality improvement can probably be attributed to reductions in the average severity of hospitalized AMI patients, in association with improvements in techniques for diagnosing mild non-Q-wave MIs. Important as the changes in acute treatment collectively appeared to be, we found that they accounted for only a minority—less than one-fourth—of the overall decline in population AMI mortality rates during the 1975–95 period. Most of the observed reduction in AMI mortality was associated with a large decline in the number of serious AMI events resulting in either prehospital deaths or hospitalization. Further studies could extend our detailed decomposition techniques to explaining "primary prevention" trends, building on the general descriptive work of Hun-

ink et al. and others. Fewer quantitative clinical studies have examined the use of preventive medical treatments and their individual effects on outcomes, so a quantitative analysis of the contribution of particular preventive treatments to the reductions in AMI event rates that we estimate may be difficult. The same problem applies to understanding the specific factors responsible for improvements in long-term AMI outcomes. Nonetheless, a careful review of the changes in treatments and outcomes for primary and secondary prevention could provide important insights into why these outcomes have changed and the cost-effectiveness of these changes, as well as identifying key areas of uncertainty for future clinical studies.

Our results demonstrate that changes in medical treatment are becoming more important, and changes in behavior are becoming relatively less important, in accounting for the substantial improvements that have occurred in acute and long-term AMI outcomes. Steady growth in the use of particular technologies suggests that the use of beneficial acute therapies may become even more widespread over the next several years. To explore the consequences of increased use of beneficial therapies, we determined the improvement in thirty-day mortality rate that would occur if (1) aspirin use increased to 90 percent, (2) beta blockade increased to 80 percent, and (3) thrombolysis or primary PTCA increased to 50 percent. These changes in treatment, which may occur over the next five to ten years if current trends continue, would reduce thirty-day mortality to 15 percent (14 percent relative decrease, 2.5 percent absolute decrease relative to 1995 mortality). Because these therapies are relatively underused in the elderly, who still have relatively high mortality rates, even larger reductions might be possible.

Changes in prehospital care also remain a potential source of outcome improvements. Treatment of cardiac arrest with early defibrillation has become more readily available. However, few studies have suggested that other aspects of prehospital treatments for AMI have changed substantially between 1975 and 1995. For example, studies of 1975 and 1990 AMI patients found similar rates of ambulance use, and several studies have failed to document improvements in death rates for urgent conditions following activation or enhancement of 911 systems. Improving these emergency responses and reducing time to effective therapy remains a policy priority through initiatives such as the National Heart Attack Alert Program and the Cooperative Cardiovascular Project. Perhaps these initiatives are beginning to pay off: In the last few years, evidence from particular hospitals suggests that time between hospital arrival and the delivery of key AMI treatments (thrombolytics, primary angioplasty) is declining. Even though they do not appear to have played a large role in the improvements between 1975 and 1995, it is possible that changes in prehospital care and reductions in time to treatment will also lead to further improvements in AMI mortality.

Many unanswered questions about technological change in AMI care remain. The lack of quantitative evidence on postacute care for AMI patients complicates forecasts of future changes in AMI patient outcomes. The enormous apparent variation in the cost-effectiveness of the various changes in AMI treatment that have occurred suggests there is considerable room for further improvements in the "productivity" of AMI care. Have any changes in AMI treatment been clearly cost-ineffective, and why did they occur? Which economic incentives encourage the most rapid adoption of cost-effective innovations in treatment? Have changes in appropriateness of treatment choices and the expertise of providers been important contributors to outcome trends? Our results suggest that further integration of studies on treatment effectiveness with descriptive studies on trends in actual patient characteristics, treatments, and outcomes holds considerable promise for addressing these questions.

References

American College of Physicians. Health and Public Policy Committee. 1988. Cardiac rehabilitation services. *Annals of Internal Medicine* 109 (8): 671–73.

American Heart Association. Emergency Cardiac Care Committee and Subcommittees. 1992. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Part II, Adult basic life support. *Journal of the American Medical Association* 268 (16): 2184–98.

Ayanian, J. Z., M. B. Landrum, S. L. Normand, E. Guadagnoli, and B. J. McNeil. 1998. Rating the appropriateness of coronary angiography: Do practicing physicians agree with an expert panel and with each other? *New England Journal of Medicine* 338 (26): 1896–1904.

Barbash, G. I., A. Roth, H. Hod, H. I. Miller, M. Modan, S. Rath, et al. 1990. Improved survival but not left ventricular function with early and prehospital treatment with tissue plasminogen activator in acute myocardial infarction. *American Journal of Cardiology* 66 (3): 261–66.

Becker, L. B., D. W. Smith, and K. V. Rhodes. 1993. Incidence of cardiac arrest: A neglected factor in evaluating survival rates. *Annals of Emergency Medicine* 22 (1): 86–91.

Becker, R. C. 1994. Beta-adrenergic blockade following thrombolytic therapy: Is it helpful or harmful? *Clinical Cardiology* 17 (4): 171–74.

Behar, S., M. Haim, H. Hod, R. Kornowski, H. Reicher-Reiss, M. Zion, et al. 1996. Long-term prognosis of patients after a Q wave compared with a non-Q wave first acute myocardial infarction. Data from the SPRINT Registry. *European Heart Journal* 17 (10): 1532–37.

Behar, S., B. Rabinowitz, M. Zion, H. Reicher-Reiss, E. Kaplinsky, E. Abinader, et al. 1993. Immediate and long-term prognostic significance of a first anterior versus first inferior wall Q-wave acute myocardial infarction. Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) Study Group. *American Journal of Cardiology* 72 (18): 1366–70.

Blohm, M. B., M. Hartford, B. W. Karlson, R. V. Luepker, and J. Herlitz. 1996. An evaluation of the results of media and educational campaigns designed to

shorten the time taken by patients with acute myocardial infarction to decide to go to hospital. *Heart* 76 (5): 430–34.

Boden, W. E., R. A. O'Rourke, M. H. Crawford, A. S. Blaustein, P. C. Deedwania, R. G. Zoble, et al. 1998. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators. *New England Journal of Medicine* 338 (25): 1785–92.

Boersma, E., A. C. Maas, J. W. Deckers, and M. L. Simoons. 1996. Early thrombolytic treatment in acute myocardial infarction: Reappraisal of the golden hour. *Lancet* 348 (9030): 771–75.

Burns, M., R. Becker, J. Gore, C. Lambrew, W. French, and W. Rogers. 1997. Early and predischarge aspirin administration among patients with acute myocardial infarction: The second National Registry of Myocardial Infarction (NRMI 2). *Journal of the American College of Cardiology* 29 (2): Abstract 738–1.

Callaham, M., C. D. Madsen, C. W. Barton, C. E. Saunders, and J. Pointer. 1992. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. *Journal of the American Medical Association* 268 (19): 2667–72.

Canto, J., W. Rogers, L. Bowlby, W. French, and D. Pearce. 1996. Pre-hospital electrocardiogram in the Second National Registry of Myocardial Infarction (NRMI-2). *Journal of the American College of Cardiology* 27 (2): Abstract 1030–52.

Chandra, H., J. Yarzebski, R. J. Goldberg, J. Savageau, C. Singleton, J. H. Gurwitz, et al. 1997. Age-related trends (1986–1993) in the use of thrombolytic agents in patients with acute myocardial infarction. The Worcester Heart Attack Study. *Archives of Internal Medicine* 157 (7): 741–46.

Chandra, N., R. Ziegelstein, J. Hilbe, W. French, L. Sanathanan, and N. Investigators. 1996. Lidocaine use in acute MI: A marker for increased mortality. Observations from the National Registry of Myocardial Infarction-2 (NRMI-2). *Circulation* 94 (8): Abstract 2083.

Chapekis, A. T., K. Burek, and E. J. Topol. 1989. The cost:benefit ratio of acute intervention for myocardial infarction: Results of a prospective, matched pair analysis. *American Heart Journal* 118 (5, pt 1): 878–82.

Connors, A. J., T. Speroff, N. V. Dawson, C. Thomas, F. J. Harrell, D. Wagner, et al. 1996. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *Journal of the American Medical Association* 276 (11): 889–97.

Cretin, S. 1977. Cost/benefit analysis of treatment and prevention of myocardial infarction. *Health Services Research* 12 (2): 174–89.

Cummins, R. O. 1993. Emergency medical services and sudden cardiac arrest: The "chain of survival" concept. *Annual Review of Public Health* 14:313–33.

Cummins, R. O., M. S. Eisenberg, A. P. Hallstrom, and P. E. Litwin. 1985. Survival of out-of-hospital cardiac arrest with early initiation of cardiopulmonary resuscitation. *American Journal of Emergency Medicine* 3 (2): 114–19.

Cummins, R. O., M. S. Eisenberg, P. E. Litwin, J. R. Graves, T. R. Hearne, and A. P. Hallstrom. 1987. Automatic external defibrillators used by emergency medical technicians. A controlled clinical trial. *Journal of the American Medical Association* 257 (12): 1605–10.

Cummins, R. O., J. R. Graves, M. P. Larsen, A. P. Hallstrom, T. R. Hearne, J. Ciliberti, et al. 1993. Out-of-hospital transcutaneous pacing by emergency medical technicians in patients with asystolic cardiac arrest. *New England Journal of Medicine* 328 (19): 1377–82.

Cutler, D., and M. McClellan. 1998. Technological change in Medicare. In *Frontiers in the economics of aging,* ed. David A. Wise. Chicago: University of Chicago Press.

Cutler, D., M. McClellan, J. Newhouse, and D. Remler. 1998. Are medical prices declining? Evidence from heart attack treatments. *Quarterly Journal of Economics* 113:991–1024.

Dalen, J. E., and R. C. Bone. 1996. Is it time to pull the pulmonary artery catheter? *Journal of the American Medical Association* 276 (11): 916–18.

Di, S. T., S. D. Paul, J. D. Lloyd, A. J. Smith, L. G. Villarreal, V. Bamezai, et al. 1996. Care of acute myocardial infarction by noninvasive and invasive cardiologists: Procedure use, cost and outcome. *Journal of the American College of Cardiology* 27 (2): 262–69.

Eisenberg, M. S., A. P. Hallstrom, W. B. Carter, R. O. Cummins, L. Bergner, and J. Pierce. 1985. Emergency CPR instruction via telephone. *American Journal of Public Health* 75 (1): 47–50.

Eisenberg, M. S., B. T. Horwood, R. O. Cummins, R. Reynolds-Haertle, and T. R. Hearne. 1990. Cardiac arrest and resuscitation: A tale of 29 cities. *Annals of Emergency Medicine* 19 (2): 179–86.

Every, N. R., L. S. Parsons, M. Hlatky, J. S. Martin, and W. D. Weaver. 1996. A comparison of thrombolytic therapy with primary coronary angioplasty for acute myocardial infarction. Myocardial Infarction Triage and Intervention Investigators. *New England Journal of Medicine* 335 (17): 1253–60.

Gallagher, E. J., G. Lombardi, and P. Gennis. 1995. Effectiveness of bystander cardiopulmonary resuscitation and survival following out-of-hospital cardiac arrest. *Journal of the American Medical Association* 274 (24): 1922–25.

Gilbertson, D., P. McGovern, D. Jacobs, L. Gatewood, and H. Blackburn. 1992. A mathematical modeling approach toward explaining the decline in coronary heart disease mortality. Abstract. *Circulation* 86 (suppl.): I597.

Gillum, R. F., A. Folsom, R. V. Luepker, D. R. Jacobs Jr., T. E. Kottke, O. Gomez-Marin, et al. 1983. Sudden death and acute myocardial infarction in a metropolitan area, 1970–1980. The Minnesota Heart Survey. *New England Journal of Medicine* 309 (22): 1353–58.

Goldberg, R. J., J. M. Gore, J. S. Alpert, and J. E. Dalen. 1986. Recent changes in attack and survival rates of acute myocardial infarction (1975 through 1981). The Worcester Heart Attack Study. *Journal of the American Medical Association* 255 (20): 2774–79.

———. 1987a. Non-Q wave myocardial infarction: Recent changes in occurrence and prognosis—a community-wide perspective. *American Heart Journal* 113 (2, pt 1): 273–79.

———. 1987b. Therapeutic trends in the management of patients with acute myocardial infarction (1975–1984): The Worcester Heart Attack Study. *Clinical Cardiology* 10 (1): 3–8.

Goldberg, R. J., J. M. Gore, J. S. Alpert, V. Osganian, J. de Groot, J. Bade, et al. 1991. Cardiogenic shock after acute myocardial infarction: Incidence and mortality from a community-wide perspective, 1975 to 1988. *New England Journal of Medicine* 325 (16): 1117–22.

Goldman, L., and E. F. Cook. 1984. The decline in ischemic heart disease mortality rates: An analysis of the comparative effects of medical interventions and changes in lifestyle. *Annals of Internal Medicine* 101 (6): 825–36.

Goldman, L., F. Cook, B. Hashimotso, P. Stone, J. Muller, and A. Loscalzo. 1982. Evidence that hospital care for acute myocardial infarction has not contributed to the decline in coronary mortality between 1973–1974 and 1978–1979. *Circulation* 65 (5): 936–42.

Gore, J. M., R. J. Goldberg, D. H. Spodick, J. S. Alpert, and J. E. Dalen. 1987. A community-wide assessment of the use of pulmonary artery catheters in patients with acute myocardial infarction. *Chest* 92 (4): 721–27.

Green, J., and N. Wintfeld. 1993. How accurate are hospital discharge data for evaluating effectiveness of care? *Medical Care* 31 (8): 719–31.

Gurwitz, J. H., R. J. Goldberg, Z. Chen, J. M. Gore, and J. S. Alpert. 1994. Recent trends in hospital mortality of acute myocardial infarction—the Worcester Heart Attack Study: Have improvements been realized for all age groups? *Archives of Internal Medicine* 154 (19): 2202–8.

GUSTO III Investigators. 1997. A comparison of Reteplase with Alteplase for acute myocardial infarction. *New England Journal of Medicine* 337:1118–23.

Haim, M., H. Hod, L. Reisin, R. Kornowski, H. Reicher-Reiss, U. Goldbourt, et al. 1997. Comparison of short- and long-term prognosis in patients with anterior wall versus inferior or lateral wall non-Q-wave acute myocardial infarction. Secondary Prevention Reinfarction Israeli Nifedipine Trial (SPRINT) Study Group. *American Journal of Cardiology* 79 (6): 717–21.

Heller, R. F., A. J. Dobson, H. M. Alexander, P. L. Steele, and J. A. Malcolm. 1992. Changes in drug treatment and case fatality of patients with acute myocardial infarction: Observations from the Newcastle MONICA Project, 1984/1985 to 1988/1990. *Medical Journal of Australia* 157 (2): 83–86.

Hennekens, C. H., C. M. Albert, S. L. Godfried, J. M. Gaziano, and J. E. Buring. 1996. Adjunctive drug therapy of acute myocardial infarction—evidence from clinical trials. *New England Journal of Medicine* 335 (22): 1660–67.

Hlatky, M. A., H. E. Cotugno, D. B. Mark, C. O'Connor, R. M. Califf, and D. B. Pryor. 1988. Trends in physician management of uncomplicated acute myocardial infarction, 1970 to 1987. *American Journal of Cardiology* 61 (8): 515–18.

Ho, M. T., M. S. Eisenberg, P. E. Litwin, S. M. Schaeffer, and S. K. Damon. 1989. Delay between onset of chest pain and seeking medical care: The effect of public education. *Annals of Emergency Medicine* 18 (7): 727–31.

Hunink, M. G., L. Goldman, A. N. Tosteson, M. A. Mittleman, P. A. Goldman, L. W. Williams, et al. 1997. The recent decline in mortality from coronary heart disease, 1980–1990: The effect of secular trends in risk factors and treatment. *Journal of the American Medical Association* 277 (7): 535–42.

Hunt, R. C., J. B. McCabe, G. C. Hamilton, and J. R. Krohmer. 1989. Influence of emergency medical services systems and prehospital defibrillation on survival of sudden cardiac death victims. *American Journal of Emergency Medicine* 7 (1): 68–82.

ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. 1988. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 2 (8607): 349–60.

ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. 1995. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet* 345 (8951): 669–85.

Kereiakes, D. J., W. D. Weaver, J. L. Anderson, T. Feldman, B. Gibler, T. Aufderheide, et al. 1990. Time delays in the diagnosis and treatment of acute myocardial infarction: A tale of eight cities. Report from the Pre-hospital Study Group and the Cincinnati Heart Project. *American Heart Journal* 120 (4): 773–80.

Kornowski, R., U. Goldbourt, H. Reicher-Reiss, L. Reisin, M. Haim, Y. Moshkovitz, et al. 1997. Prognostic significance of infarction location in patients with recurrent myocardial infarction. SPRINT Study Group. Secondary Prevention Reinfarction Israel Nifedipine Trial. *Cardiology* 88 (5): 441–45.

Koshal, A., D. S. Beanlands, R. A. Davies, R. C. Nair, and W. J. Keon. 1988. Urgent surgical reperfusion in acute evolving myocardial infarction: A randomized controlled study. *Circulation* 78 (3, pt 2): I171–78.

Krumholz, H. M., M. J. Radford, E. F. Ellerbeck, J. Hennen, T. P. Meehan, M. Petrillo, et al. 1996. Aspirin for secondary prevention after acute myocardial infarction in the elderly: Prescribed use and outcomes. *Annals of Internal Medicine* 124 (3): 292–98.

Lau, J., E. M. Antman, S. J. Jimenez, B. Kupelnick, F. Mosteller, and T. C. Chalmers. 1992. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *New England Journal of Medicine* 327 (4): 248–54.

Laupacis, A., D. Feeny, A. S. Detsky, and P. X. Tugwell. 1993. Tentative guidelines for using clinical and economic evaluations revisited. *Canadian Medical Association Journal* 148 (6): 927–29.

Leimbach, W., Jr., A. D. Hagan, H. L. Vaughan, R. C. Sonnenschein, J. D. McCoy, and L. L. Basta. 1988. Cost and efficacy of intravenous streptokinase plus PTCA for acute myocardial infarction when therapy is initiated in community hospitals. *Clinical Cardiology* 11 (11): 731–38.

Mark, D. B., M. A. Hlatky, R. M. Califf, C. D. Naylor, K. L. Lee, P. W. Armstrong, et al. 1995. Cost effectiveness of thrombolytic therapy with tissue plasminogen activator as compared with streptokinase for acute myocardial infarction. *New England Journal of Medicine* 332 (21): 1418–24.

Mark, D. B., C. D. Naylor, M. A. Hlatky, R. M. Califf, E. J. Topol, C. B. Granger, et al. 1994. Use of medical resources and quality of life after acute myocardial infarction in Canada and the United States. *New England Journal of Medicine* 331 (17): 1130–35.

Maynard, C., W. D. Weaver, C. Lambrew, L. J. Bowlby, W. J. Rogers, and R. M. Rubison. 1995. Factors influencing the time to administration of thrombolytic therapy with recombinant tissue plasminogen activator (data from the National Registry of Myocardial Infarction). Participants in the National Registry of Myocardial Infarction. *American Journal of Cardiology* 76 (8): 548–52.

McClellan, M., N. Every, A. Garber, P. Heidenreich, M. Hlatky, D. Kessler, et al. In press. Technological change in heart attack care in the United States. In *Technological change in health care: A global analysis of heart attacks,* ed. M. McClellan and D. Kessler. Ann Arbor: University of Michigan Press.

McClellan, M., and H. Noguchi. 1988. Technological change in heart-disease treatment: Does high tech mean low value? *American Economic Review* 88 (2): 90–96.

McClellan, M., and D. Staiger. 1999. The quality of health care providers. NBER Working Paper no. 7327. Cambridge, Mass.: National Bureau of Economic Research.

McGovern, P. G., G. L. Burke, J. M. Sprafka, S. Xue, A. R. Folsom, and H. Blackburn. 1992. Trends in mortality, morbidity, and risk factor levels for stroke from 1960 through 1990. The Minnesota Heart Survey. *Journal of the American Medical Association* 268 (6): 753–59.

McGovern, P. G., A. R. Folsom, J. M. Sprafka, G. L. Burke, K. M. Doliszny, J. Demirovic, et al. 1992. Trends in survival of hospitalized myocardial infarction patients between 1970 and 1985. The Minnesota Heart Survey. *Circulation* 85 (1): 172–79.

McGovern, P. G., J. Herlitz, J. S. Pankow, T. Karlsson, M. Dellborg, E. Shahar, et al. 1997. Comparison of medical care and one- and 12-month mortality of hospitalized patients with acute myocardial infarction in Minneapolis–St. Paul, Minnesota, United States of America and Goteborg, Sweden. *American Journal of Cardiology* 80 (5): 557–62.

McGovern, P. G., J. S. Pankow, E. Shahar, K. M. Doliszny, A. R. Folsom, H. Blackburn, et al. 1996. Recent trends in acute coronary heart disease—mortality, morbidity, medical care, and risk factors. The Minnesota Heart Survey Investigators. *New England Journal of Medicine* 334 (14): 884–90.

McLaughlin, T. J., S. B. Soumerai, D. J. Willison, J. H. Gurwitz, C. Borbas, E. Guadagnoli, et al. 1996. Adherence to national guidelines for drug treatment of suspected acute myocardial infarction: Evidence for undertreatment in women and the elderly. *Archives of Internal Medicine* 156 (7): 799–805.

Mickelson, J. K., C. M. Blum, and J. M. Geraci. 1997. Acute myocardial infarction: Clinical characteristics, management and outcome in a metropolitan Veterans Affairs Medical Center teaching hospital. *Journal of the American College of Cardiology* 29 (5): 915–25.

Myers, M. G. 1985. Changing patterns in drug therapy for ischemic heart disease. *Canadian Medical Association Journal* 132 (6): 644–48.

Pankow, J. S., P. G. McGovern, J. M. Sprafka, D. J. Jacobs, and H. Blackburn. 1994. Trends in coded causes of death following definite myocardial infarction and the role of competing risks: The Minnesota Heart Survey (MHS). *Journal of Clinical Epidemiology* 47 (9): 1051–60.

Pashos, C. L., S. L. Normand, J. B. Garfinkle, J. P. Newhouse, A. M. Epstein, and B. J. McNeil. 1994. Trends in the use of drug therapies in patients with acute myocardial infarction: 1988 to 1992. *Journal of the American College of Cardiology* 23 (5): 1023–30.

Patsey, T., J. Messick, R. Rutledge, A. Meyer, J. M. Butts, and C. Baker. 1992. A population-based, multivariate analysis of the association between 911 access and per-capita county trauma death rates. *Annals of Emergency Medicine* 21 (10): 1173–78.

Paul, S., C. Lambrew, W. Rogers, and M. Fifer. 1996. A study of 118,276 patients with acute myocardial infarction in the United States in 1995: Less aggressive care, worse prognosis, and longer hospital length of stay for diabetics. *Circulation* 94 (8): Abstract 3576.

Paul, S. D., K. A. Eagle, U. Guidry, T. G. DiSalvo, L. G. Villarreal, A. J. Smith, et al. 1995. Do gender-based differences in presentation and management influence predictors of hospitalization costs and length of stay after an acute myocardial infarction? *American Journal of Cardiology* 76 (16): 1122–25.

Pressley, J. C., H. J. Severance, M. P. Raney, R. A. McKinnis, M. W. Smith, M. C. Hindman, et al. 1988. A comparison of paramedic versus basic emergency medical care of patients at high and low risk during acute myocardial infarction. *Journal of the American College of Cardiology* 12 (6): 1555–61.

Reeder, G. S., K. R. Bailey, B. J. Gersh, D. J. Holmes, J. Christianson, and R. J. Gibbons. 1994. Cost comparison of immediate angioplasty versus thrombolysis followed by conservative therapy for acute myocardial infarction: A randomized prospective trial. Mayo Coronary Care Unit and Catheterization Laboratory Groups. *Mayo Clinic Proceedings* 69 (1): 5–12.

Rogers, W., N. Chandra, W. French, J. Gore, C. Lambrew, and A. Tiefenbrunn. 1996. Trends in the use of reperfusion therapy: Experience from the second National Registry of Myocardial Infarction (NRMI 2). *Circulation* 194 (8): Abstract 1138.

Rogers, W. J., L. J. Bowlby, N. C. Chandra, W. J. French, J. M. Gore, C. T. Lambrew, et al. 1994. Treatment of myocardial infarction in the United States (1990 to 1993): Observations from the National Registry of Myocardial Infarction. *Circulation* 90 (4): 2103–14.

Rouleau, J. L., L. A. Moye, M. A. Pfeffer, J. M. Arnold, V. Bernstein, T. E. Cuddy, et al. 1993. A comparison of management patterns after acute myocardial in-

farction in Canada and the United States. The SAVE investigators. *New England Journal of Medicine* 328 (11): 779–84.

Ryan, T. J., J. L. Anderson, E. M. Antman, B. A. Braniff, N. H. Brooks, R. M. Califf, et al. 1996. ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *Journal of the American College of Cardiology* 28 (5): 1328–1428.

Sawitz, E., J. A. Showstack, J. Chow, and S. A. Schroeder. 1988. The use of in-hospital physician services for acute myocardial infarction: Changes in volume and complexity over time. *Journal of the American Medical Association* 259 (16): 2419–22.

Schwab, T. M., M. L. Callaham, C. D. Madsen, and T. A. Utecht. 1995. A randomized clinical trial of active compression-decompression CPR vs standard CPR in out-of-hospital cardiac arrest in two cities. *Journal of the American Medical Association* 273 (16): 1261–68.

Sharkey, S. W., D. D. Bruneete, E. Ruiz, W. T. Hession, D. G. Wysham, I. F. Goldenberg, et al. 1989. An analysis of time delays preceding thrombolysis for acute myocardial infarction. *Journal of the American Medical Association* 262 (22): 3171–74.

Smith, J., and K. S. Channer. 1995. Increasing prescription of drugs for secondary prevention after myocardial infarction. *BMJ* 311 (7010): 917–18.

Teo, K. K., S. Yusuf, R. Collins, P. H. Held, R. Peto. 1991. Effects of intravenous magnesium in suspected acute myocardial infarction: Overview of randomised trials. *BMJ* 303 (6816): 1499–1503.

Teo, K. K., S. Yusuf, and C. D. Furberg. 1993. Effects of prophylactic antiarrhythmic drug therapy in acute myocardial infarction: An overview of results from randomized controlled trials. *Journal of the American Medical Association* 270 (13): 1589–95.

Thompson, P. L., R. W. Parsons, K. Jamrozik, R. L. Hockey, M. S. Hobbs, and R. J. Broadhurst. 1992. Changing patterns of medical treatment in acute myocardial infarction: Observations from the Perth MONICA Project 1984–1990. *Medical Journal of Australia* 157 (2): 87–92.

Tosteson, A. N., L. Goldman, I. S. Udvarhelyi, and T. H. Lee. 1996. Cost-effectiveness of a coronary care unit versus an intermediate care unit for emergency department patients with chest pain. *Circulation* 94 (2): 143–50.

Tsevat, J., L. Goldman, J. R. Soukup, G. A. Lamas, K. F. Connors, C. C. Chapin, et al. 1993. Stability of time-tradeoff utilities in survivors of myocardial infarction. *Medical Decision Making* 13 (2): 161–65.

Tu, J. V., C. L. Pashos, C. D. Naylor, E. Chen, S. L. Normand, J. P. Newhouse, et al. 1997. Use of cardiac procedures and outcomes in elderly patients with myocardial infarction in the United States and Canada. *New England Journal of Medicine* 336 (21): 1500–1505.

Van de Werf, F., L. Janssens, T. Brzostek, et al. 1993. Short-term effects of early intravenous treatment with a beta-adrenergic blocking agent or a specific bradycardiac agent in patients with acute myocardial infarction receiving thrombolytic therapy. *Journal of the American College of Cardiology* 22 (2): 407–16.

Vukov, L. F., R. D. White, J. W. Bachman, P. C. O'Brien. 1988. New perspectives on rural EMT defibrillation. *Annals of Emergency Medicine* 17 (4): 318–21.

Weaver, W. D. 1995. Time to thrombolytic treatment: Factors affecting delay and their influence on outcome. *Journal of the American College of Cardiology* 25 (7, suppl.): 3S–9S.

Weaver, W. D., L. A. Cobb, A. P. Hallstrom, M. K. Copass, R. Ray, M. Emery, et al. 1986. Considerations for improving survival from out-of-hospital cardiac arrest. *Annals of Emergency Medicine* 15 (10): 1181–86.

Weaver, W. D., R. J. Simes, A. Betriu, C. L. Grines, F. Zijlstra, E. Garcia, et al. 1997. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: A quantitative review. *Journal of the American Medical Association* 278 (23): 2093–98.

Weinstein, M. C., P. G. Coxson, L. W. Williams, T. M. Pass, W. B. Stason, and L. Goldman. 1987. Forecasting coronary heart disease incidence, mortality, and cost: The Coronary Heart Disease Policy Model. *American Journal of Public Health* 77 (11): 1417–26.

Wittels, E. H., J. W. Hay, and A. M. Gotto Jr. 1990. Medical costs of coronary artery disease in the United States. *American Journal of Cardiology* 65 (7): 432–40.

Yarzebski, J., R. J. Goldberg, J. M. Gore, and J. S. Alpert. 1994a. Temporal trends and factors associated with extent of delay to hospital arrival in patients with acute myocardial infarction: The Worcester Heart Attack Study. *American Heart Journal* 128 (2): 255–63.

———. 1994b. Temporal trends and factors associated with pulmonary artery catheterization in patients with acute myocardial infarction. *Chest* 105 (4): 1003–8.

Yusuf, S., R. Collins, S. MacMahon, and R. Peto. 1988. Effect of intravenous nitrates on mortality in acute myocardial infarction: An overview of the randomised trials. *Lancet* 1 (8594): 1088–92.

Yusuf, S., D. Zucker, P. Peduzzi, L. D. Fisher, T. Takaro, J. W. Kennedy, et al. 1994. Effect of coronary artery bypass graft surgery on survival: Overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 344 (8922): 563–70.

Ziegelstein, R., J. Hilbe, W. French, L. Sanathanan, N. Chandra, and N. Investigators. 1996. Magnesium use in the treatment of acute MI: Is a little still too much? Observations from the National Registry of Myocardial Infarction-2 (NRMI 2). *Circulation* 94 (8): Abstract 1541.

Zion, M. M., J. Balkin, D. Rosenmann, U. Goldbourt, H. Reicher-Reiss, E. Kaplinsky, et al. 1990. Use of pulmonary artery catheters in patients with acute myocardial infarction: Analysis of experience in 5,841 patients in the SPRINT Registry. SPRINT Study Group. *Chest* 98 (6): 1331–35.

Zuanetti, G., R. Latini, F. Avanzini, M. G. Franzosi, A. P. Maggioni, F. Colombo, et al. 1996. Trends and determinants of calcium antagonist usage after acute myocardial infarction (the GISSI experience). *American Journal of Cardiology* 78 (2): 153–57.

This Page Intentionally Left Blank