ORIGINAL INVESTIGATION

The Underlying Risk of Death After Myocardial Infarction in the Absence of Treatment

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Background: The underlying risk of death in the absence of treatment after a myocardial infarction (MI) is poorly documented.

Methods: Analysis of 23 published studies in which 14 211 patients were followed prospectively after MI; 6817 deaths were recorded. We restricted the analysis to studies in which follow-up was completed by 1980 to quantify the underlying risk in the absence of effective treatments.

Results: After a first MI, on average, 23% of patients died before reaching the hospital and another 13% died during hospital admission; these rates increased with age. After hospital discharge cardiovascular mortality was approximately 10% in the first year and 5% per year thereafter, rates that were unrelated to age or sex. The yearly death rate of 5% persisted indefinitely; after 15 years, cumulative cardiovascular mortality was 70%. After a subsequent MI, 33% of patients died before reaching the hospital, and 20% died in hospital. After discharge, cardiovascular mortality was approximately 20% in the first year and 10% per year thereafter, rates again unrelated to age and sex. Approximately a third of all heart disease deaths occurred minutes after the first MI, a sixth during the first hospitalization, and half after a subsequent MI, which could occur many years after the first.

Conclusions: In persons with a history of MI, cardiovascular mortality in the absence of treatment is high—5% per year after a first MI and 10% per year after a subsequent MI, persisting for many years and probably for the rest of a person's life. The high mortality rate emphasizes the need to ensure that everyone who has had an MI, even years previously, receives effective preventive treatment.

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IN THIS STUDY, we used published data to determine the underlying risk of death after a myocardial infarction (MI) in the absence of modern effective treatments. This risk is poorly documented. Many published studies have followed up patients after an MI, but the data have not been collated and quantified.

Quantifying the natural history of MI in the absence of effective intervention is important. Without knowing the size of the excess risk of death after MI or for how many years it persists, it is difficult to judge how long to maintain preventive drug treatments such as aspirin, statins, and β-adrenergic blocking agents. It is also difficult to assess whether persons who have had an MI years previously and are not receiving long-term comprehensive preventive treatment should be systematically identified and offered such treatment. The lack of baseline data also hampers the interpretation of present data on mortality after an MI; only by expressing current death rates as a proportion of the baseline rates can the effectiveness of present interventions, and the likelihood of further gain, be assessed.

We therefore present an analysis of the natural history of MI before the introduction of effective preventive treatments in the early 1980s.

METHODS

We identified 23 published studies[1-30] in which patients were identified around the time of an MI and followed prospectively to determine their mortality. To identify the studies, we used MEDLINE (subject heading and text word "myocardial infarction"), *Index Medicus*, review articles, and the citations in the studies themselves. We included only studies that reported mortality according to whether the MI was a first or a subsequent event. We also included only studies that followed patients for at least 3 years so that both short- and long-term mortality rates could be determined.

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To quantify the underlying risk in the absence of intervention, our analysis was deliberately restricted to studies in which follow-up was completed by 1980. We chose that year because the widespread use of modern effective treatments began in the early 1980s (the first randomized trial showing a statistically significant effect of aspirin, for example, was published in 1979[31]). Population mortality data in European countries show that the recent sub-

Table 1. Studies of Consecutive Patients With Acute Myocardial Infarction (MI) in Which Deaths Were Recorded According to Whether the MI Was a First or Subsequent MI*

Source	Years of Recruitment	Age, Mean, y	Follow-up, y†	First MI, No.				Subsequent MI, No.			
				Before Hospital Discharge		After Hospital Discharge		Before Hospital Discharge		After Hospital Discharge	
				Patients	Deaths	Patients	Deaths (% Cardiac‡)	Patients	Deaths	Patients	Deaths (% Cardiac‡)
Patients Identified at Time of MI											
Framingham[1,2]	1950-1970	61	6	333	133	200	56 (. . .)	. . .	. . .	. . .	. . .
HIP, United States[3]	1956-1961	52	3.4	1331	399	932	160 (. . .)	. . .	. . .	. . .	. . .
HIP, New York[4,5]	1961-1965	54	4.5	1054	382	672	139 (88)	113§	63	. . .	. . .
Perth (Australia)[6,7]	1970-1971	58	8.5	862	323	498	199 (. . .)	276	141	168	111
Patients Identified on Hospital Admission											
Boston[8]	1920-1930	56	27	200	38	162	158 (86)	. . .	. . .	. . .	. . .
Mayo Clinic[9]	1920-1935	58	3.7	370	38	331	158 (94)	63	15	47	25 (100)
Chicago[10]	1932-1941	53	10	461	105	285	160 (78)	126§	78	. . .	. . .
Mayo Clinic[11]	1935-1941	62	5	279	44	168	75 (83)	. . .	. . .	. . .	. . .
US Veterans[12]	1943-1944	42	15	598	68	530	373 (. . .)	. . .	. . .	. . .	. . .
US Veterans[13]	1950-1952	53	10	503	76	427	241 (. . .)	. . .	. . .	. . .	. . .
New York[14]	c1953	53	15	484	66	418	267 (. . .)	116§	51	65	45
Ohio[15]	1967-1968	61	6	157	26	122	38 (94)	55	20	32	18 (94)
Stockholm[16]	1968-1969	65	3	400	89	308	109 (. . .)	. . .	. . .	. . .	. . .
Patients Identified on Hospital Discharge											
Malmö[17]	1935-1959	63	6	. . .	. . .	1589	779 (. . .)	. . .	. . .	. . .	. . .
Boston[18]	1937-1949	35	16.2	. . .	. . .	91	52 (83)	. . .	. . .	. . .	. . .
Kentucky[19]	1940-1945	57	10	. . .	. . .	211	142 (81)	. . .	. . .	. . .	. . .
Dublin[20,21]	1961-1968	51	4.1	. . .	. . .	252	34 (91)	. . .	. . .	. . .	. . .
Health Service, Denmark[22]	1963	64	8	. . .	. . .	523	306 (74)	. . .	. . .	119	93 (80)
Birmingham (England)[23]	1968-1972	38	9.7	. . .	. . .	142	37 (97)	. . .	. . .	. . .	. . .
Göteborg[24-27]	1968-1977	53	6.1	. . .	. . .	1521	392 (83)	. . .	. . .	76	26 (96)
Helsinki[28]	1970-1971	55	5	. . .	. . .	566	142 (77)	. . .	. . .	162	77 (88)
St Louis[29]	1971-1975	58	3	. . .	. . .	593	116 (75)	. . .	. . .	. . .	. . .
New York State[30]	1973-1976	54	3.0	. . .	. . .	761	82 (88)	. . .	. . .	179	52 (83)
All Studies		56	7.3	**3580‖ 3452¶**	**1237‖ 550¶**	**11 302**	**4215** (83)	631‖ 118¶	333‖ 35¶	**848**	447 (87)

*Ellipses indicate not reported.
†Values with a decimal point indicate the average of a variable follow-up period.
‡Omitting deaths of unknown cause.
§These subsequent MIs were observed during follow-up of first MI patients.
‖From time of MI.
¶From hospital admission.

stantial decline in age-specific death rates from ischemic heart disease, which is at least partly due to modern treatments, also began in the early 1980s. This condition necessarily excludes several recent large studies, including the reports of 28-day case-fatality rates in the MONICA populations.[32] Although some older treatments were used in some medical centers before 1980 (such as warfarin, exercise, and weight loss), selection of the year 1980 as the cutoff point for study inclusion was justified by a regression analysis showing no trend in increased survival rates (before or after hospital discharge) in more recent vs older studies across the 23 studies included in the analysis.

The 23 studies included in the analysis are listed in **Table 1**; there were 14 211 patients, 13 281 first-infarct patients (of whom 3580 were identified at the time of MI, 3452 were identified for the first time on hospital admission, and 6249 were identified for the first time on hospital discharge), together with 930 patients identified for the first time after a subsequent MI (276 at the time of the MI, 118 on hospital admission, and 536 on hospital discharge). Of the 14 211, 83% were men, and 6817 deaths were recorded. Estimates of the proportion of patients who died at any time from the occurrence of the MI up to hospital discharge (approximately the first month) were obtained from the 4 studies (3580 patients) listed in Table 1 that identified patients at the time of the MI regardless of whether they survived to be admitted to the hospital (this was possible because the study populations were taken from registers kept by health insurance or other organizations). Estimates of the proportion of patients who died between hospital admission and discharge were obtained from the 9 studies (3452 patients) in Table 1 that identified patients at the time of hospital admission. The proportion of patients who died before reaching the hospital was usually not stated in the published studies; we estimated it from the fact that the proportion dying during a period is 100% minus the proportion surviving that period, and the proportion surviving until reaching the hospital (which was not reported), multiplied by the proportion surviving between hospital admission and discharge (which was known), equals the proportion surviving to hospital discharge (which was known). Death rates from all causes after hospital discharge were reported for each separate year of follow-up in

Table 2. Death Rates After Myocardial Infarction Before and During Hospital Admission (Corresponding to About the First Month) in the Absence of Treatment

	Death Rate, % (95% Confidence Interval)
First infarct	
Before hospital admission	23 (17-29)
During hospital admission (of those admitted to the hospital)	16 (13-19)
Before and during hospital admission	36 (31-40)
Subsequent infarct	
Before hospital admission	33 (16-47)
During hospital admission (of those admitted to the hospital)	30 (19-43)
Before and during hospital admission	53 (46-60)

Table 3. Death Rates After Myocardial Infarction From the Time of Hospital Discharge, in the Absence of Treatment

	Cause of Death, %			
	All Causes	Ischemic Heart Disease	Stroke	Stroke and Heart Disease
First infarct				
First-year death rate	10.3	9.3	0.3	9.6
Annual death rate in subsequent years	5.3	4.3	0.3	4.6
5-Year death rate	28	24	1.5	25
10-Year death rate	45	39	3.0	41
Subsequent infarct				
First-year death rate	21	19	0.3	19
Annual death rate in subsequent years	12	10	0.3	10
5-Year death rate	52	47	1.5	48
10-Year death rate	75	69	3.0	70

all the studies in Table 1 except 2,[10,11] and excluding these 2, we calculated average survival rates for each year after the MI (adjusting for study differences). In most studies, the death rates from ischemic heart disease and stroke were not reported for each separate year of follow-up; we calculated these by multiplying the all-cause death rates by the proportions of all deaths in patients with first and subsequent MIs that were from heart disease (Table 1, taking the excess mortality in the first year to be entirely cardiac) and that were from stroke.[9,10,15,18,19,22,23]

In all 23 studies, the diagnosis of MI was based on a classic clinical history together with diagnostic electrocardiographic changes, including Q waves, ST-segment elevation, and T-wave changes, or, in patients who did not survive long enough to undergo an electrocardiogram, autopsy findings. In the 13 most recent studies,[1-7,15,16,20-30] elevated serum concentrations of enzymes (serum aspartate transaminase and lactate dehydrogenase) were also used.

To determine the effect of age and sex on survival, we analyzed data from 5 studies[10,12,13,17,28] reporting death rates in 10-year age groups in men after hospital discharge after a first MI and from 7 studies[2,4,10,17,19,27,28] reporting data that allowed an age-adjusted comparison of rates in men and women. Some of these studies reported only all-cause mortality; we estimated death rates from ischemic heart disease and stroke (typically approximately 85% of all deaths) according to age by subtracting from the published all-cause death rates the average age- and sex-specific death rates from all causes other than heart disease and stroke recorded in the country in which the study was conducted in the years during which the follow-up took place. We estimated coronary mortality rates in patients with angina but no history of MI from 5 studies[4,12,33-35] with mortality follow-up of 4 to 15 years (although data on nonfatal MI between recruitment and death were not reported). We calculated from these studies the relative risk of coronary death in patients with angina on recruitment compared with those with a first MI on recruitment.

Survival estimates from individual studies, expressed as the odds of survival in logarithms, were combined across studies using a random-effects model,[36] which in the absence of significant heterogeneity between studies is equivalent to weighting each estimate by the number of patients.

RESULTS

Table 2 gives the death rates after MI before and during hospital admission (corresponding to about the first month) in the absence of modern treatment. After a first MI, 36% of patients died during this period, and 53% died after a subsequent MI. The average age at death in all the studies analyzed (Table 1) was approximately 60 years (average age at entry was 56 years, and the events occurred over an average of 7 years of follow-up).

Death rates within 1 month of the MI increased with a person's age. After a first MI, death rates were 24%, 37%, and 48% in men aged 35 to 39, 60 to 64, and 70 years and older, respectively.[3,37] The rates were similar in men and women of the same age.[4]

Table 3 gives the death rates after hospital discharge. After a first MI, the average death rate in the first year was 10.3% (95% confidence interval [CI], 8.5%-12.3%) from all causes and 9.6% from ischemic heart disease and stroke. From the second year onward, the annual death rates were about half these values (the average all-cause death rate from years 2 to 10 was 5.3% [95% CI, 4.8%-5.9%]), and **Figure 1** shows that these rates remained approximately constant with increasing duration of follow-up. There was a small but statistically significant tendency for mortality rates from all causes to increase over time, which was due to the increase with age in mortality from noncardiovascular causes. Death rates from ischemic heart disease and stroke (also shown in Figure 1) showed no statistically significant tendency to increase or decrease over time; average mortality was 4.6% per year. Table 3 shows that after a subsequent MI, the death rate after hospital discharge was about twice as high as after a first MI. All-cause mortality was 21% (95% CI, 16%-26%) in the first year and 12% per year (95% CI, 10%-14%) in the second and subsequent years. The death rate from ischemic heart disease and stroke was 19% in the first year and 10% per year in subsequent years, again with no tendency to change with time since the MI.

Figure 2, based on the data in Tables 2 and 3, shows the natural history of MI in the absence of treatment in 1000 persons. An estimated 750 of the 1000 MIs are first MIs, and 250 are subsequent MIs, based on the combined data from 5 MI registries[7,37-40] recording a total of 6873 MIs. After a first MI, 36% die in the first month (most before hospital admission). A further 34% of patients die of cardiovascular disease during the next 15 years, in many cases

after a subsequent MI, for a cumulative death rate of 70%. Approximately half of all heart disease deaths, therefore, occur in the first month after the first MI (one third within minutes and one sixth in hospital), and half occur later. After a subsequent MI, 53% of patients die in the first month, and a further 39% die of cardiovascular disease during the next 15 years, for a cumulative death rate of 92%.

After a first MI, the incidence of all subsequent MIs (fatal and nonfatal) was recorded in too few of the studies to yield a reliable direct summary estimate, but it can be estimated indirectly from Figure 2. The annual death rate of approximately 5% per year after a first MI was mostly due to subsequent MI, and the case fatality in the first month after subsequent MI was about half, so the incidence of all subsequent MIs (fatal and nonfatal) is approximately double the death rate, or approximately 10% per year.

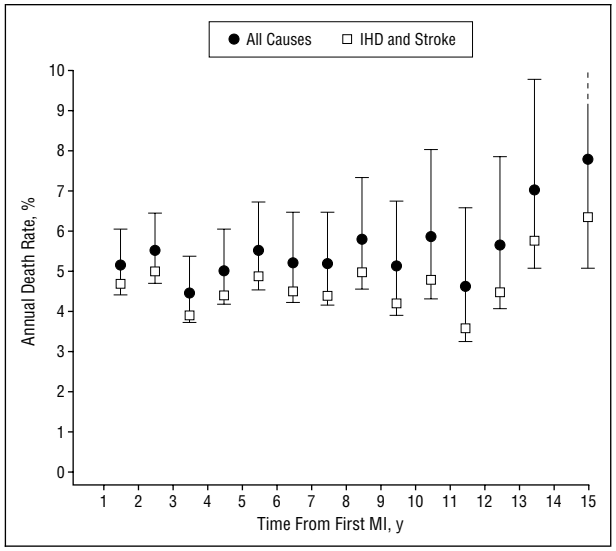

Figure 1. Annual death rates for all causes (error bars represent 95% confidence intervals) and for ischemic heart disease (IHD) and stroke from the second year after hospital discharge onward after a first myocardial infarction (MI), in the absence of treatment. Data are from the studies listed in Table 1. The death rate in the first year was 10.3%, although it was higher in the earlier months.

The mortality rate estimates in the first month shown in Figure 2 are corroborated by a series of "community studies"[37,39-45] in which all cases of MI occurring in geographically defined populations during specified periods were identified. One study[37] recorded the mortality rate in the first month in patients experiencing a first MI (33%; 24/73 patients). Six studies[39-45] did not distinguish patients with first and subsequent MIs; in all patients with a history of MI, combined mortality in the first month was 38% (2719/7164),[39-45] and the proportion who died before reaching the hospital was 27% (1586/5912).[39-43] These 3 estimates of 33%, 38%, and 27% are based on patients younger than 70 years (so that the average age is approximately 60 years, similar to that in Figure 2), and they are similar to the corresponding estimates in Figure 2 of 36%, 40%, and 26%.

A striking result from the studies listed in Table 1 is that the death rates from cardiovascular disease after hospital discharge did not increase with age. The 5 studies reporting mortality rates in 10-year age groups were all consistent in showing no association with age, and the summary result showed that the death rate at age 65 years was almost the same as at age 35 years (relative risk, 1.08; 95% CI, 0.89-1.32). A strength in the analysis was the ability to separate the effect of age per se from the fact that in older men it is more likely that an MI will be a subsequent (rather than a first) one, which itself increases mortality rates. Mortality rates after hospital discharge after a first MI were similar in men and women (relative risk, 1.20; 95% CI, 0.84-1.64), an observation confirmed in more recent data.[46]

In patients with angina but no history of MI, the annual death rate from ischemic heart disease was 2.6% per year, about half that after a first MI. The death rate from ischemic heart disease and stroke was 2.8% per year, or 12.0% in 5 years and 23.0% in 10 years.

COMMENT

In people who have had an MI at any time in the past, the death rate from cardiovascular disease in the absence of preventive treatment is high, approximately 5%

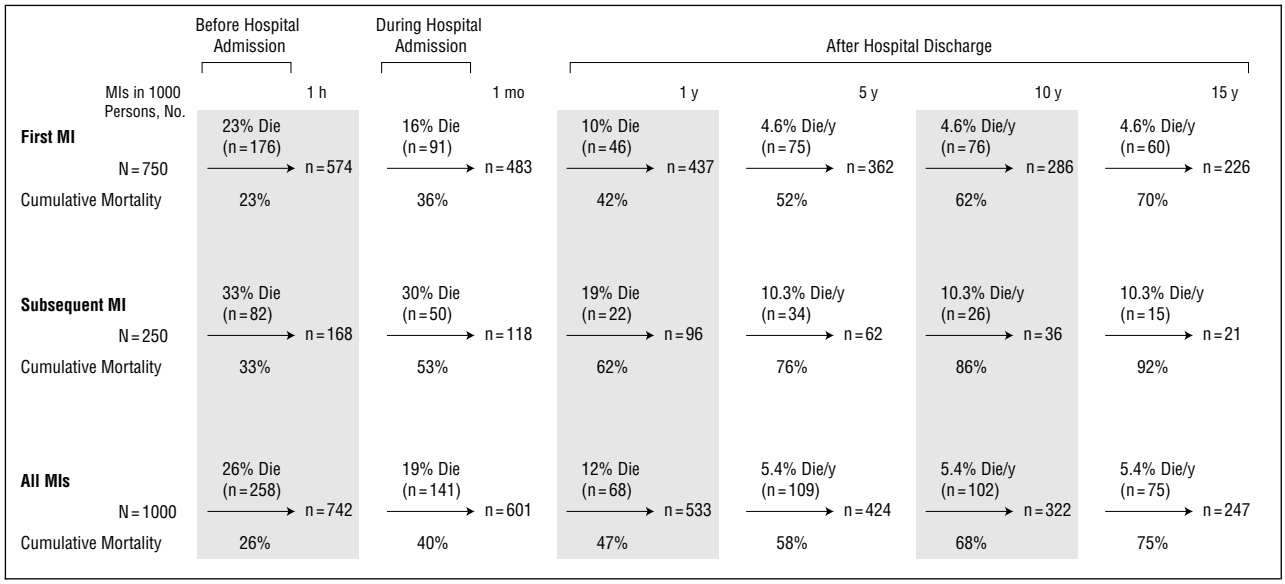

Figure 2. Number and timing of deaths in 1000 typical patients (average age, 60 years) who have experienced a myocardial infarction (MI), in the absence of treatment.

per year, and this risk persists for at least 15 years and probably for the rest of a person's life. At no time can one say that a person has "recovered" from MI with so high a recurrence rate. In the first year, the death rate after hospital discharge is approximately 10%; the excess is concentrated in the early months, with a similar increase in nonfatal reinfarction.[5,26] The high and prolonged mortality rate makes it essential that effective preventive treatments (including aspirin, statins, β-adrenergic blocking agents, and angiotensin-converting enzyme inhibitors) are maintained indefinitely.

The death rate during hospital admission reflects the quality of acute medical care. Several studies[46-49] covering defined populations have recorded estimates similar to ours for the years before 1980 (approximately 16%), with lower in-hospital mortality rates in later years, falling to about half the 1980 rate by 1995. The higher in-hospital mortality rates with increasing age have persisted despite the declining rates over time across all ages.[47,50]

In the absence of treatment, the annual death rate after hospital discharge after MI is not age related, although the incidence of a first MI is strongly age related. This is not unexpected: the incidence of MI is age related because the prevalence of severe coronary artery disease is age related, but once an event has occurred, coronary artery disease must be present, so there is little more for age to predict. Recent follow-up studies[39,40,47] that showed an increase in long-term mortality rates after an MI with increasing age did so because they combined first and subsequent MIs. At older ages, it is more likely that an MI will be a subsequent one, and this itself is associated with a higher mortality rate. Also, preventive treatments have been less widely used at older ages[51]; this may cause poorer survival at older ages.

The observation that age does not predict a recurrent event is also found for cancer: for example, among women who have had breast cancer, the incidence of a second cancer in the contralateral breast (about 0.7% per year) does not increase with age.[52] In persons with previous disease in general, the fact that the absolute risk of disease events is constant means that the relative risk of a disease event in persons with previous disease to that in persons without previous disease will vary, being greater at younger ages and in women than in men. The more familiar situation, in relation to risk factors in persons without a history of previous disease, is for the relative risk to be constant and generalizable and the absolute risk to vary with age, sex, and other factors.

Techniques for diagnosing MI have improved in recent years (with the availability of troponin and other markers). Some MIs that would be recognized now may not have been so diagnosed in the studies included in this analysis (covering the period before 1980). These infarcts lack the characteristic electrocardiographic changes—partial-thickness (non–Q-wave) MIs or those that lacked the classic persisting ST-segment elevation or deep T-wave inversion. Results of studies from before 1980, however, have shown that such MIs were not associated with better survival, indicating that our results have not overestimated mortality rates in the absence of treatment. Patients with partial-thickness (non–Q-wave) MIs showed higher rates of reinfarction and mortality (because they are at high risk of converting their partial-thickness MI to a full-thickness MI).[53-55] In patients with a history of MI without ST-segment elevation and T-wave inversion, survival rates were similar to those in patients with the classic changes.[53]

Table 4. Annual Death Rates From Cardiovascular Disease (Ischemic Heart Disease and Stroke) According to Various Risk Factors, in the Absence of Preventive Treatment

Clinical History	Annual Death Rate, %
Known cardiovascular disease (any age)	
>1 Previous myocardial infarction	10
1 Previous myocardial infarction	5
Angina without infarction	3
Previous stroke[56-58]	5
Transient ischemic attack without stroke	2
No history of cardiovascular disease (age, ≈ 60 y)	
All men	0.4
Men, nonsmokers[59]	0.3
Men, smoke >25 cigarettes per day[59]	0.7
Men, high cholesterol (>80th percentile)[59]	0.6
All women	0.2
Patients with type 2 diabetes mellitus (men and women)[60]	0.5

Table 4 summarizes the estimates of the long-term death rates in persons who have had an MI and previously published estimates of death rates in persons who have had a stroke and compares these rates with those in persons without known cardiovascular disease.[56-60] The death rates are approximately 10 times higher in persons with known disease than in those without disease but with unfavorable risk factors. Much effort is given to attempt to treat people in the latter group,[61] but it is more important to direct treatment to people with known disease in view of their higher risk.

In Western countries, approximately 6% of people aged 55 to 64 years have had a heart attack, increasing to 9% in those aged 65 to 74 years.[62] They are a large group at high risk, but they are often not placed in this category. Many people with a history of MI or angina are not maintained on adequate preventive treatment, and some will be taking none. Data from hospital surveillance records, registers maintained in primary care settings, and background data on patients recruited into randomized trials have shown that during the past few years, about two thirds of patients with ischemic heart disease did not receive statins, half did not receive β-adrenergic blocking agents and other drugs, and, in some localities, a quarter to a half did not receive aspirin.[51,63-68] It is unusual for physicians to seek out patients who have had MIs years before to advise them of their ongoing high risk and to commence or reinstate preventive treatment, although this method of screening is highly effective and preventive treatment is highly effective. Systematically identifying patients who have had an MI in the past and offering them intensive preventive treatment could prevent many heart disease deaths and should be regarded as a medical priority. It is difficult to identify any other group in the population at such high risk of death that can so readily be prevented by medical means.

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