

Unrecognized Myocardial Infarction

Stuart E. Sheifer, MD; Teri A. Manolio, MD, PhD; and Bernard J. Gersh, MB, ChB, DPhil

This review addresses myocardial infarctions that escape clinical recognition. It focuses on the prevalence, predisposing factors, and prognosis of these unrecognized infarctions, and incorporates data from relevant epidemiologic studies, basic science investigations, and review articles. These data indicate that at least one fourth of all myocardial infarctions are clinically unrecognized. The demographic characteristics and coronary risk factor profiles of persons with previously unrecognized myocardial infarctions appear to be similar to those of persons whose infarctions are clinically detected. Impaired symptom perception may contribute to lack of

recognition, but both patients' and physicians' perceptions about the risk for myocardial infarction may also play an important role. Finally, mortality rates after unrecognized and recognized myocardial infarction are similar. Given the public health implications of unrecognized myocardial infarction, future studies should address screening strategies, risk stratification after detection of previously unrecognized myocardial infarction, and the role of standard postinfarction therapies in affected patients.

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For author affiliations and current addresses, see end of text.

While most acute myocardial infarctions are characterized by significant and often severe symptoms, a substantial minority are accompanied by minimal or no discomfort. Consequently, many affected patients may not seek medical attention, and the diagnosis may be delayed for months or years. These patients are unaware of any history of myocardial infarction but are ultimately identified clinically when electrocardiography shows diagnostic Q waves.

Such events, termed "unrecognized myocardial infarctions," were first described by Herrick in 1912 (1). Subsequent studies have demonstrated that unrecognized myocardial infarctions represent a significant proportion of all infarctions and that they may therefore represent a significant public health problem. Moreover, since available analyses have focused primarily on infarctions with persistent significant Q waves, the true prevalence of undetected infarctions may be even greater than available estimates.

A review of this topic is timely because recent studies have provided new information on the impact of unrecognized myocardial infarction in the contemporary era. Moreover, although the underlying causes of unrecognized infarction have not been fully delineated, several recent mechanistic investigations have shed new light on the pathophysiology of this entity. Given the potential public health implications of unrecognized myocardial infarction, we reviewed the available information and identified the clinically relevant questions that remain unanswered.

METHODS

We identified relevant publications by searching MEDLINE from 1966 to the present. All publications

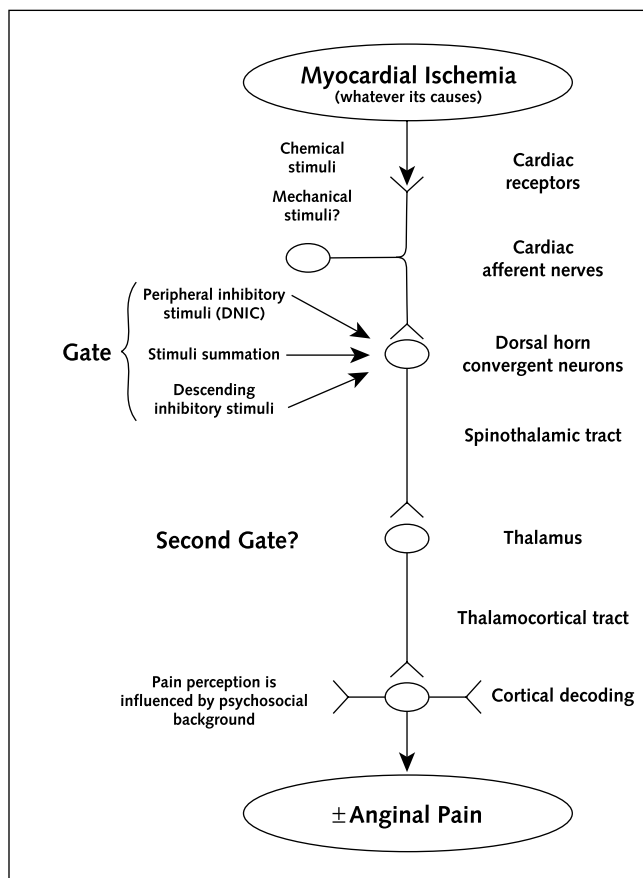
that included the text words *unrecognized* or *silent* were identified, and this grouping was then combined, by using an "AND" statement, with all publications indexed with the key word *myocardial infarction*. We reviewed the resultant list of publications for all population-based studies, basic science investigations, and review articles relevant to unrecognized myocardial infarction. We then systematically examined each of these publications and abstracted and qualitatively compared data on the epidemiology and pathophysiology of unrecognized myocardial infarction. In addition, we evaluated the reference section of each paper and systematically reviewed additional references on unrecognized infarction. We examined all references addressing the symptomatic presentation of myocardial infarction and selected for review those that addressed silent or unrecognized infarctions. Our funding sources had no role in the collection, analysis, or interpretation of these data or in the decision to submit this review for publication.

PATHOPHYSIOLOGY OF UNRECOGNIZED MYOCARDIAL INFARCTION

The Notion of a Defective Anginal Warning System

The specific course of events that leads to unrecognized myocardial infarction is not known; however, as in the case of recognized infarction, the process presumably begins with atherosclerotic plaque rupture and occlusion of a thrombotic coronary artery. According to this hypothesis, unrecognized myocardial infarction differs from recognized infarction in the translation of resultant myocardial ischemia into symptomatic discomfort. Another possibility is that interpretation of

Figure 1. Steps in the development, progression, and perception of myocardial ischemia.



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symptoms may differ between persons with unrecognized myocardial infarction and those with recognized infarction. The former patients may be less likely to conclude that their symptoms represent a significant health problem. Abnormalities in either of these steps may lead to a “defective anginal warning system” and consequently to a clinically unrecognized event (2, 3).

The Perception of Myocardial Ischemia: Proposed Mechanisms

The normal events that span the spectrum from myocardial ischemia to the perception of discomfort begin with stimulation of free nerve endings in the myocardium (Figure 1). Potential stimuli include mechanical factors, such as ischemia-induced changes in the tone of the ventricular wall, and chemical factors released by

cardiac myocytes in response to hypoxia (4, 5). One such mediator is adenosine, which has been shown to reproduce chest pain in patients with angina (6). In addition, evidence suggests that the size of the myocardial infarction is important; larger infarctions induce greater discomfort. This may relate to the number of activated receptors (7).

Once nerve endings are stimulated, the impulses progress along the cardiac sympathetic nerves to the thoracic sympathetic ganglia and then to the dorsal horn spinal neurons. From there, they travel through the spinothalamic tract to the thalamus, and then through the thalamocortical tract to the cerebral cortex. The cortex decodes the impulse, ultimately leading to the conscious perception of discomfort. Areas of the brain that have been shown to have augmented blood flow during angina include the thalamus, the hypothalamus, the periaqueductal gray area, and the prefrontal and cingulate cortex (8).

Blunted Perception of Myocardial Infarction: Potential Causes

Several factors may modulate the generation, conduction, and processing of the afferent impulse; any of these factors could lead to depressed perception of myocardial ischemia. While it is yet to be determined whether the processes that underlie silent myocardial ischemia also lead to unrecognized myocardial infarction, the two entities overlap significantly; thus, a review of proposed mechanisms for silent ischemia is relevant.

Receptor and Afferent Neuron Dysfunction

In the model described above, the anatomic and functional integrity of cardiac sensory receptors and afferent neurons is a major factor in the perception of myocardial ischemia. Inadequate receptor stimulation, or frank receptor dysfunction, may block impulse initiation and pain perception. In addition, pathologic changes of the afferent fibers may hinder impulse conduction. Autonomic neuropathy is the suggested explanation for the relatively high incidence of painless ischemia in diabetic patients (9).

Gating Mechanisms

The conduction of the afferent impulse may also be affected by various “gating mechanisms.” It has been proposed that “gates” exist both in the dorsal horn of

the spinal cord and in the thalamus (8). At these sites, multiple stimuli from varying locations may converge and effectively cancel each other. Some researchers have postulated that many patients do not perceive pain with myocardial infarction because other stimuli, such as dyspnea, saturate sensory mechanisms (10). Moreover, it appears that inhibitory inputs from peripheral nerves and higher centers are directed at these gates and that these too may modulate or abolish the afferent impulse (8).

Neuropsychiatric Factors

The translation of ischemia into discomfort may also be blunted at a supratentorial level. At least some patients with silent ischemia have completely normal function of afferent neuronal pathways; this implies a defect in the central nervous system (11). The patient's state of alertness, as well as the endogenous opioid system, may affect pain perception. Several treadmill studies have indicated that elevated β -endorphin levels may delay or prevent the onset of angina (12–14). Other investigations, however, including efforts to “unmask” silent ischemia with naloxone, have contradicted this finding, and at present the role of opioids in unrecognized ischemia and myocardial infarction has not been clearly established (15, 16).

Evidence from mental stress experiments also suggests that silent ischemic events may be associated with distinct patterns of brain activity. These studies have shown that mental stress can induce both symptomatic and asymptomatic myocardial ischemia (17–21). To investigate potential underlying mechanisms, Soufer and colleagues (22) performed simultaneous positron emission tomography brain imaging and transthoracic echocardiography during mental stress. In patients with known coronary artery disease, mental stress-induced silent ischemia was associated with a unique pattern of hyperactivation of several left-brain structures and concomitant deactivation of several right-brain structures, as well as the anterior cingulate bilaterally (22). This result expands on the findings of previous pharmacologic stress studies, which suggested that dobutamine-induced silent ischemia, as compared with dobutamine-induced angina, is associated with relatively low amounts of metabolic activity in the frontal cortex (23). Taken together, these findings suggest that failure to perceive ischemia may be based on the pattern and sequence in which brain structures are activated.

The patient's psychosocial milieu also has a complex effect, but it too may influence the degree of discomfort accompanying a myocardial infarction (24–26). Characteristics such as stoicism and denial, which have personal, social, and cultural groundings, play a substantial role in this context. Patients with painless myocardial ischemia have higher pain thresholds, as defined by reports of pain in response to noxious stimuli (27–31). Similarly, a patient's threshold for somatic pain correlates with the reported pain level during myocardial infarction (32). Finally, clinical depression may also play a role. Depression has been associated with autonomic dysfunction, medical nonadherence, and other motivational issues, and each of these has been proposed as an explanation for the relatively poor prognosis of depressed patients with coronary artery disease (33, 34). Hypothetically, each of these factors could also confound recognition of an acute infarction.

FREQUENCY OF UNRECOGNIZED MYOCARDIAL INFARCTION

The most comprehensive data available on the frequency of unrecognized myocardial infarction originate from large cohort studies. The best known is the Framingham Study, which was based on 34 years of follow-up of 5070 participants (35–39); the most recent analysis of this study was published in 1990. In this series, unrecognized myocardial infarction represented 26% and 34% of all myocardial infarctions in men and women, respectively. Approximately half of the affected patients had no symptoms whatsoever, whereas the remainder experienced nonspecific symptoms that at the time were not perceived to be the consequence of myocardial infarction (40, 41).

These data are reinforced by recent analyses of the Reykjavik and Cardiovascular Health Study samples. In the Reykjavik Study, 35% of infarctions in men and 33% of infarctions in women were initially unrecognized (42, 43). In the Cardiovascular Health Study, which is based in four U.S. field centers and is confined to persons 65 years of age or older, 22% of all prevalent Q-wave infarctions at study entry had previously gone undetected (44). The Table lists the results of published cohort studies (45–49).

For several reasons, these data probably underestimate the frequency of unrecognized myocardial infarction (50). First, the electrocardiographic diagnosis of a

Table. Cohort Studies Addressing Frequency of Unrecognized Myocardial Infarction*

Study, Year (Reference)	Patients	Mean Age	Men	Myocardial Infarctions	Unrecognized Myocardial Infarctions
	<i>n</i>	<i>y</i>	%	<i>n</i>	%
Western Collaborative Group Study, 1967 (45)	3524	46	100	73	37†
Israeli Heart Attack Study, 1976 (46)	9509	NA	100	427	40
Multiple Risk Factor Intervention Trial, 1987 (48)	12 866	46	100	460	25‡
Honolulu Heart Study, 1989 (47)	7331	55	100	135	22
Framingham Study, 1990 (40)	5070	NA	44	363	30
Bronx Aging Study, 1990 (49)	390	79	36	72	44
Reykjavik Study (men), 1995 (42)	9141	60	100	237	35
Reykjavik Study (women), 1998 (43)	13 000	NA	0	641	33
Cardiovascular Health Study, 2000 (44)	5888	72	42	901	22

* NA = not available (several studies presented age categorically and did not calculate mean age).

† Proportion of patients with coronary artery disease in whom the presentation was unrecognized myocardial infarction.

‡ Proportion of nonfatal myocardial infarctions that were unrecognized.

previous myocardial infarction is based primarily on the identification of Q waves, and thus previously unrecognized non-Q-wave infarctions will not be detected. Second, unrecognized myocardial infarctions resulting in sudden cardiac death will also be missed, in the absence of autopsy evidence of a recent infarction. Finally, the diagnosis of myocardial infarction may be missed if an electrocardiogram is not obtained shortly after the event. It has been estimated that the electrocardiographic features of myocardial infarction disappear within 2 years in 10% of patients with an anterior infarction and 25% of those with an inferior infarction (41). Others have estimated that, overall, 20% of patients who have survived an infarction have normal electrocardiograms 4 years after their event (51).

RISK FACTORS FOR UNRECOGNIZED MYOCARDIAL INFARCTION

To better understand, diagnose, treat, and ultimately prevent unrecognized myocardial infarction, identifying predisposing factors would be helpful. Several analyses have addressed this issue, but study methods have varied. In some studies, such as the Western Collaborative Group and Israeli Heart Attack studies, participants with unrecognized myocardial infarction were compared with persons drawn from the population at large (45, 46). In others, patients with unrecognized myocardial infarction were directly compared with persons who had recognized infarctions (40, 42, 44, 47). Furthermore, most studies comparing groups with recognized and unrecognized infarctions have been limited to univariate analyses and have not sought to identify

factors that are *independently* associated with infarction recognition. To address this concern, the recent analysis of the Cardiovascular Health Study used a multivariate model that tested several factors for associations with infarction recognition while controlling for potential confounding issues (44).

Hypertension

Previous research has suggested that hypertension is associated with alterations in pain perception. The baroreflex system has been shown to have the capacity to attenuate transmission of noxious stimuli, and evidence indicates that endogenous opiates may affect blood pressure, with possible depressor or pressor effects (52–54). Hypertensive patients have relatively high β -endorphin levels (55). Perhaps as a result, hypertensive patients with coronary artery disease report relatively little pain in response to somatic noxious stimuli (56, 57).

Epidemiologic studies have supported these physiologic findings. In the Western Collaborative Group Study, mean systolic and diastolic blood pressures were higher in patients with “silent” infarctions than in those with no evidence of coronary disease (45). In the Israeli Heart Attack Study, systolic blood pressure and left ventricular hypertrophy were clearly correlated with incidence of unrecognized myocardial infarction (46). Similarly, in the Reykjavik cohort, when patients with unrecognized myocardial infarction were compared with all other participants, the use of antihypertensive diuretic therapy was significantly associated with the development of unrecognized myocardial infarction, with an odds ratio of 6.2 (42).

However, direct comparisons of patients with unrecognized myocardial infarction to those with recognized infarctions have failed to confirm a unique link between blood pressure and infarction recognition. The Reykjavik and Honolulu Heart studies, as well as the most recent Framingham analysis, suggested trends toward more hypertension in the unrecognized myocardial infarction group, but these trends were not statistically significant (40, 42, 47). Also in the Cardiovascular Health Study, systolic and diastolic blood pressure were univariate predictors of infarction recognition; in multivariate modeling, however, these associations lost significance (44). Therefore, it remains uncertain whether hypertension and unrecognized myocardial infarction are specifically linked or whether the association simply reflects the fact that hypertension is a risk factor for coronary artery disease.

Age

During an evolving myocardial infarction, elderly patients appear prone to experience diminished or atypical symptoms, and they are at increased risk for delayed presentation to the hospital (58, 59). This suggests that they may also be at risk for unrecognized myocardial infarction. As with hypertension, mechanisms linking age to unrecognized myocardial infarction have not been clearly established, but several possible explanations have been postulated. These include cognitive changes, such as dementia; the degree of comorbid illness; and potential age-related decreases in sensory nerve function (49).

Most studies of unrecognized myocardial infarction have included few older patients, but the available data suggest that the incidence of unrecognized myocardial infarction increases with age. In the Reykjavik Study, the risk for unrecognized myocardial infarction increased approximately 10% per year of life (42). In the Israeli Heart Attack series, the proportion of unrecognized infarctions increased from 38% in participants 39 to 59 years of age to 49% in those 60 years of age or older (46). Similarly, in the Bronx Aging Study, which followed 390 patients who were at least 75 years of age, the percentage of unrecognized incident myocardial infarctions was higher (44%) than that in the other cohorts listed in the Table (49).

As in the case for hypertension, only a few analyses have directly compared the ages of patients who had

unrecognized myocardial infarction with the ages of those who had recognized infarction. The results are inconsistent. Unadjusted analyses in the Framingham cohort showed that among men, survivors of unrecognized myocardial infarction were significantly older than survivors of recognized infarction, but this was not the case for women (38). In addition, in the Cardiovascular Health Study, older age was a significant predictor of unrecognized myocardial infarction in unadjusted analysis; in multivariate analysis, however, the association lost statistical significance (44). Consequently, as in the case of hypertension, it remains uncertain whether there is a specific link between age and unrecognized myocardial infarction or whether their association is due simply to the effects of aging on the development of coronary atherosclerosis.

Diabetes Mellitus

Several basic science, clinical, and epidemiologic studies have suggested an association between diabetes mellitus and unrecognized myocardial infarction. For example, diabetic patients have high rates of asymptomatic myocardial ischemia (60–63). While the mechanisms have not been confirmed, evidence suggests that diabetic autonomic neuropathy plays a significant role by attenuating sensory inputs from ischemic myocardium (64–66). In diabetic patients who had had a silent infarction, autopsy has shown pathologic changes in cardiac afferent neurons that are consistent with a neuropathy (9).

Perhaps as a result of these neurologic issues, diabetic patients with suspected coronary artery disease pose a difficult challenge for clinicians. Among patients with recognized infarction, diabetic patients tend to report less pain, and in fact diabetes mellitus is an independent predictor of “painless” myocardial infarction (67, 68). Conversely, diabetic patients with myocardial infarction tend to have high rates of congestive heart failure, and their evaluation and management may be confounded by high rates of diabetic complications, including renal failure and infections (69).

However, despite all this supporting evidence, none of the existing epidemiologic analyses have identified diabetes as an independent predictor of infarction recognition. The reasons for this are unclear (70). Diabetic neuropathy may certainly impair recognition, but signif-

icant neurologic dysfunction is typically a manifestation of relatively advanced diabetes. Thus, the impact of this diabetic complication may be masked by the inclusion in epidemiologic databases of many diabetic patients with milder disease. Another possibility is that diabetic patients may receive more counseling and clinical attention for the presentations of coronary artery disease; thus, despite altered neuronal function, they may be less likely to have an infarction that escapes attention.

Finally, as suggested earlier, the pain suppression associated with diabetes mellitus may be offset by other symptoms that often accompany myocardial infarction in patients with diabetes. Diabetic patients with acute infarctions not only have high rates of congestive heart failure but also are more likely to present with shock or cardiac arrest (71). Each of these conditions typically prompts emergency clinical attention and thus infarction recognition.

Sex

Relatively few studies have evaluated potential associations between sex and infarction recognition, but the available data suggest that women are at relatively high risk for unrecognized myocardial infarction. As was seen with older age, female sex has been associated with delayed presentation to the hospital with a recognized myocardial infarction (59). In the Framingham and Cardiovascular Health Study analyses, the proportion of infarctions that were initially unrecognized was substantially higher in women than in men (42, 43). In the Framingham Study, as discussed above, 34% of infarctions in women, compared with only 26% in men, were initially undetected (40). In the Cardiovascular Health Study, although sex was not independently associated with infarction recognition, the unadjusted odds of unrecognized myocardial infarction were 45% greater in women than in men ($P = 0.02$) (44).

Here again, the explanations are probably multifactorial, and the Cardiovascular Health Study analysis suggests that confounding factors are involved. Nonetheless, misperceptions of the prevalence and manifestations of coronary artery disease in women may play a significant role. Both physicians and the general public appear to mistakenly believe that coronary artery disease and myocardial infarction are relatively uncommon in women (72, 73). Contributing factors include the under-

representation of women in clinical trials and the resultant lack of data on the results of therapy in female patients. Consequently, many women may not appreciate the significance of cardiac symptoms. This problem is compounded by other factors that complicate the clinical evaluation of women with coronary syndromes. These include a relatively high prevalence of "atypical" symptoms, including abdominal and back pain, that may inhibit infarct detection (74–76).

Other Potential Risk Factors

Relatively few data are available on other potential risk factors for unrecognized myocardial infarction, but the existing information provides valuable insights into the epidemiology of this entity. Many authors have argued that, in general, the other factors leading to unrecognized myocardial infarction are probably identical to the other established risk factors for coronary artery disease. The data from the Cardiovascular Health Study support this notion because they showed that none of the traditional coronary risk factors independently distinguished patients with prevalent unrecognized myocardial infarction from those with recognized infarction (44).

The more interesting finding of the Cardiovascular Health Study was discovery of the factors that ultimately did distinguish these two groups. In multivariate analysis, the important factors were established cardiac conditions and diagnoses (or the lack thereof). The two independent predictors of unrecognized myocardial infarction were the absence of angina and the absence of congestive heart failure. There was also a trend toward an association with low FEV₁ (44).

The absence of angina predicted unrecognized myocardial infarction not only in the Cardiovascular Health Study but also in the Framingham and Reykjavik studies. In the Framingham Study, 53% of patients with recognized infarction but only 24% of those with unrecognized infarction reported a history of angina. In women, the percentages were 45% and 33%, respectively (40). Similarly, in the Reykjavik Study (42), 58% of patients with recognized myocardial infarction, but only one third of those with unrecognized infarction, reported a history of this condition ($P < 0.001$).

This reproducible association with the absence of angina may at least partly explain the frequency and pathophysiology of unrecognized myocardial infarction.

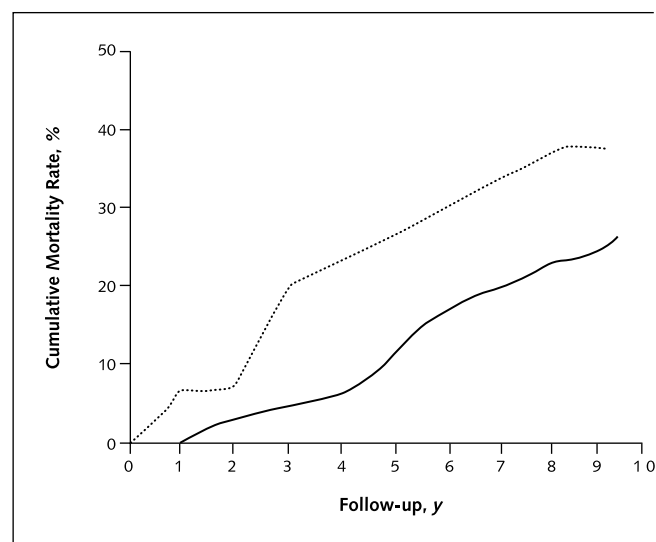
The influence of the absence of angina may simply reflect diagnosis bias: Physicians may more aggressively counsel and follow patients with angina, and they may be more likely to detect myocardial infarction in this population. Another possibility is that the central role of the absence of angina may relate to neurologic factors. More specifically, the association between the absence of angina and unrecognized myocardial infarction suggests that survivors of unrecognized infarction may have a generalized inability to perceive myocardial ischemia. This theory has also been invoked to explain detected infarctions that are manifested by symptoms other than pain. Research has shown that patients with painless detected infarctions, similar to patients with initially unrecognized infarctions, have very low rates of antecedent angina (77).

The associations of congestive heart failure and FEV₁ with unrecognized myocardial infarction are speculative and have not been shown in other cohorts. In part, they too may relate to diagnosis bias. Patients with congestive heart failure may be followed more closely for new cardiovascular events, and chest symptoms in patients with pulmonary disease may be more likely to be attributed to respiratory processes. An alternative theory is that these associations may result from neurologic conditions. Patients with unrecognized myocardial infarction may have generalized sensory dysfunction that precludes the perception not only of infarction but also of congestive heart failure (77). Meanwhile, in patients with lung disease, the afferent nervous system may be overloaded with respiratory signals and therefore block the perception of pain.

PROGNOSIS OF PATIENTS WITH PREVIOUSLY UNRECOGNIZED MYOCARDIAL INFARCTION

Intuition might suggest that an infarction accompanied by minimal or no symptoms might seem more benign than one heralded by more typical or severe findings, but this is not the case. Several of the analyses listed in the Table have thoroughly investigated the prognosis after unrecognized myocardial infarction. These investigations have an inherent “survival bias” that must be appreciated because the patients of interest had already survived the index infarction and lived to the time of study entry (78). Previous studies have shown that the risk for cardiovascular death is highest in

Figure 2. Mortality after unrecognized (dotted line) and recognized (solid line) myocardial infarction in the Honolulu Heart Program.



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the first 6 months after recognized infarction; thus, most patients in the published analyses had already emerged from the highest-risk period (79). However, in analyses of unrecognized myocardial infarction, survival bias does not diminish the relevance of the data because it is the survivor of unrecognized myocardial infarction who is encountered clinically.

In the Reykjavik Study, 15-year mortality was 55% in men with unrecognized myocardial infarction and 52% in those with a history of recognized infarction (42). Similarly, in the Honolulu Heart Program, 10-year mortality rates were 45% and 35% in the unrecognized and recognized infarction groups, respectively (Figure 2) (47).

In male participants in the Framingham Study, unrecognized myocardial infarction carried a significantly higher risk for cardiovascular death than did recognized myocardial infarction; in women, however, the difference was not significant (40). Overall, the risk for death from any cause was similar between the unrecognized and recognized infarction groups (80). Of interest, among patients with unrecognized myocardial infarction, those who had abrupt-onset Q waves across serial electrocardiograms fared worse than those in whom unexplained Q waves developed gradually (81). In the Car-

diovascular Health Study, 7-year mortality did not significantly differ between the unrecognized and recognized myocardial infarction subsets (21% vs. 25%; $P > 0.2$), and recognition status did not predict death in multivariate analysis (44). The only major cohort study that has reported a significantly better prognosis with unrecognized myocardial infarction than with recognized infarction (pooled annual mortality, 1.7% vs. 3.6%) has been the Israeli Heart Attack Trial (46).

Taken in total, these data indicate that the prognosis after detection of a previously unrecognized myocardial infarction does not significantly differ from that after recognized infarction. Inherent delays in diagnosis and treatment probably contribute to an adverse prognosis after unrecognized myocardial infarction. Furthermore, in the Cardiovascular Health Study, although survivors of unrecognized myocardial infarction had significantly lower cardiovascular mortality, they also showed a trend toward an increased rate of noncardiovascular death; this finding hints that these patients have greater noncardiovascular comorbidity (44).

CONCLUSIONS AND IMPLICATIONS

The data presented in this review confirm that unrecognized myocardial infarction is a common and clinically significant event. This entity accounts for at least one fifth, and probably a much greater fraction, of all infarctions. Moreover, it carries a prognosis that is as poor as that for recognized myocardial infarction. Consequently, it merits, to the extent possible, thorough investigation.

However, this review also reveals that the available information, much of which was accumulated 10 to 20 years ago, leaves several clinically relevant questions unanswered. First, to develop prevention and education efforts, we need a better understanding of factors predisposing to unrecognized myocardial infarction. It remains uncertain whether hypertension, age, and sex are uniquely linked to unrecognized myocardial infarction, or whether instead their associations merely reflect the associations of these factors with coronary artery disease. Even if research finds these factors to be specifically linked to unrecognized myocardial infarction, the underlying mechanisms are poorly understood; elucidation of these mechanisms might provide important new insights into the relationships between myocardial isch-

emia and pain. In addition, the apparent contradiction between common clinical perception and cohort studies with regard to the role of diabetes merits further evaluation. Finally, the independent association of the absence of previous angina must be further explored. Diagnosis bias, which may play a key role in the consideration and detection of infarction, may explain this association. Another possibility is that unrecognized myocardial infarction survivors may have neuropsychological abnormalities that lead to defective anginal warning systems; this theory argues strongly for further investigation into potential neurologic explanations.

In addition, future studies should focus on detecting and managing unrecognized myocardial infarction, with a view toward improving the outcomes of affected patients, who typically have not had access to acute reperfusion therapy. The costs and benefits of routine screening electrocardiography in all patients with significant coronary risk should be investigated. To date, the available data are insufficient to determine whether such a strategy would be clinically beneficial or cost-effective. However, given the prevalence and prognosis of unrecognized myocardial infarction, screening electrocardiography during scheduled health maintenance visits should be considered for high-risk subsets of patients, such as elderly patients with coronary risk factors. Moreover, for patients in whom a previous unrecognized myocardial infarction is detected, clinically beneficial management protocols need to be identified. The prognostic ability of conventional noninvasive and invasive cardiac diagnostic tests and the role of standard postinfarction medications merit investigation.

Until these issues are delineated, it appears reasonable to apply to these patients strategies that have been shown to reduce morbidity and mortality from coronary artery disease. These include thorough screening for conventional coronary risk factors and aggressive risk factor modification. In addition, for stable patients, noninvasive testing for residual myocardial ischemia and left ventricular function, with stress testing and echocardiography, appear reasonable because these factors are powerful predictors of outcome in patients with recognized myocardial infarction (79, 82–84). In this regard, myocardial perfusion imaging may be particularly useful because nuclear stress testing has been shown to be superior to conventional exercise treadmill testing in pre-

dicting recurrent cardiac events after myocardial infarction (85, 86).

For patients with unstable ischemia, heart failure, ventricular arrhythmias, or results on noninvasive tests that suggest high risk, invasive testing should be considered. An alternative approach might be routine coronary angiography and possible coronary revascularization on *all* affected patients, based on the notion that any recurrent events will also lack symptomatic warning. However, this hypothesis has yet to be confirmed, and this management strategy has no proven clinical benefit. Finally, unless contraindicated, treatment with aspirin, a β -blocker, an angiotensin-converting enzyme inhibitor, and lipid-lowering medication seems logical because each of these therapies has been demonstrated to improve survival after myocardial infarction (87–91).

From Georgetown University Medical Center, Washington, D.C.; the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland; and Mayo Clinic, Rochester, Minnesota.

Requests for Single Reprints: Stuart E. Sheifer, MD, Division of Cardiology, Georgetown University Medical Center, 3700 Joseph Siewick Drive, Suite 102, Fairfax, VA 22033.

Current Author Addresses: Dr. Sheifer: Division of Cardiology, Georgetown University Medical Center, 3700 Joseph Siewick Drive, Suite 102, Fairfax, VA 22033.

Dr. Manolio: Epidemiology and Biometry Program, National Heart, Lung, and Blood Institute, Room 8160, MSC 7934, 6701 Rockledge Drive, Bethesda, MD 20892-7934.

Dr. Gersh: Cardiovascular Diseases and Internal Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905.

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