Silent Myocardial Ischemia

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Silent myocardial ischemia is defined as objective documentation of myocardial ischemia in the absence of angina or anginal equivalents. Since its original description in the 1970s, it has undergone intensive investigation, and its clinical significance is now well established. This review will serve as an update on the pathophysiology, detection, prevalence, prognosis, and treatment of silent ischemia in both asymptomatic patients and those with angina, whether stable or unstable.

Pathophysiology

Pain Studies

No discussion of silent ischemia is complete without consideration of the cardiac pain mechanism. Although much has been learned about this subject, much is still uncertain. The afferent fibers that run in the cardiac sympathetic nerves are usually thought of as the essential pathway for the transmission of cardiac pain (Figure 1). The atria and ventricles are abundantly supplied with sympathetic sensory innervation; from the heart, the sensory nerve endings connect to afferent fibers in cardiac nerve bundles, which in turn connect to the upper 5 thoracic sympathetic ganglia and the upper 5 thoracic dorsal roots of the spinal cord. Within the spinal cord, impulses mediated by this sympathetic afferent route probably converge with impulses from somatic thoracic structures onto the same ascending spinal neurons. This would be the basis for cardiac pain referred to the chest, wall, arm, back etc. In addition to this “convergence-projection theory,” the contribution of vagal afferent fibers must be acknowledged for an explanation of cardiac pain referred to the jaw and neck. How these vagal fibers are activated remains unclear. Furthermore, somatic localization of ischemic pain cannot predict the site of myocardial ischemia (anterior, inferior, or lateral) from one patient to the next.

The actual “trigger” that stimulates the sensory nerve endings remains elusive. If a chemical pain stimulus is involved, the substance that has been most recently linked to the production of angina-like chest pain is adenosine. Sylven et al observed that an adenosine infusion resulted in chest pain even in patients without obstructive coronary artery disease. Subsequently, they gave varying amounts to healthy volunteers and caused dose-dependent chest pain in all of the volunteers. Concomitant dipyridamole administration (which reduces cellular uptake of adenosine) increased the pain response, whereas theophylline (a nonspecific adenosine antagonist) reduced the pain response. When Crea et al gave adenosine via intracoronal infusion to 22 angina patients, it reproduced chest pain significantly in 20 of 22 patients but without electrocardiographic evidence of ischemia. When the drug was infused into the right atrium, it failed to reproduce the pain. From these studies and others, it appears that adenosine is a mediator of cardiac and muscular ischemic pain. At one time, a mechanical stimulus (stretching of the coronary arteries) was also proposed as a cause of pain even when ischemia itself was not induced. This was suggested after watching the behavior of laboratory animals whose coronary arteries were stretched. This theory has received increased support because of the observation that during percutaneous transluminal coronary angioplasty (PTCA) in humans, the greater the balloon inflation pressure, the more intense pain in the same individual.

The pioneering somatic pain threshold studies of Droste and Roskamm suggested differences between coronary patients either with or without angina during a positive exercise test. They studied 3 different modalities of somatic pain perception. When pain perception was determined by an electrical current applied to the thigh, asymptomatic patients had a significantly higher threshold. Subsequent studies from other laboratories confirmed their findings. A central mechanism was suggested in 1996, by Rosen et al, using PET scanning to measure cerebral blood flow in patients with and without silent ischemia. On the basis of their data, the authors postulated that abnormal central processing of afferent cardiac pain signals could be involved in the pathophysiology of this syndrome.

A possible role for endorphins in cardiac pain responses also has been studied. Varying concentrations of these opioid-like substances exist in plasma and cerebrospinal fluid and may be important in mediating pain sensitivity. The issue is not clear cut, as different laboratories that have measured plasma endorphin levels during and after exercise tests have produced conflicting results, and considerable overlap exists in values between patients with and those without silent ischemia. Data from PTCA studies by Falcone et al have suggested a link between endorphin levels and symptoms, but Oldroy et al found endorphin release to be common during both spontaneous and provoked acute myocardial ischemia.

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and to have no correlation with intensity of chest pain. Thus, the evidence linking endorphins to silent myocardial ischemia is suggestive but not conclusive. This is true in nondiabetics as well as diabetics. Diabetics also have overt neuropathy as an additional contributing factor to their silent ischemia, although in many instances the neuropathy is subclinical and can only be detected by demonstration of autonomic impairment. According to a recent study,8 the combination of microalbuminuria and silent ischemia in asymptomatic diabetics identifies a particularly high-risk subgroup for future cardiac events (Figure 2).

Benzodiazepines have been shown to interact with opioid antinociception. Considering the importance of inflammation and leukocytes in myocardial ischemia, could the expression of peripheral benzodiazepine receptors on leukocytes be different in patients with and without angina during myocardial ischemia? This is the question Mazzone et al9 asked recently in a study of 57 patients. They found that the expression of these receptors was indeed higher in patients with silent ischemia. This same group of investigators also studied production of inflammatory cytokines in a similar patient population and reported that an “anti-inflammatory pattern” of cytokine production was observed in the patients with silent ischemia.10 The authors concluded that the activation of the immune-inflammatory system may be crucial for production of anginal symptoms.

**Hemodynamic Abnormalities During Silent Ischemia**

Unlike the endorphin controversy, this is an area where increasing data have proven useful in clarifying physiological mechanisms. To begin with, PTCA has allowed the sequence of ischemic events to be precisely defined in a controlled setting. In their classic study, Sigwart et al11 placed a catheter in the pulmonary artery and a high-fidelity micromanometer in the left ventricle via the transseptal approach in 12 patients. Based on their findings and those of others in subsequent studies, it is apparent that hemodynamic abnormalities occur first and that pain follows electrocardiographic changes and is the final event in the sequence of events that characterizes an episode of myocardial ischemia.

The amount of myocardium rendered ischemic in humans is difficult to quantify, but comparisons between symptomatic and silent ischemia have been attempted using a variety of techniques. For example, Hirzel et al12 reported on both wall-motion disorders and hemodynamic changes in their series of 36 patients with exercise-induced ischemia. Under similar exercise conditions, comparable hemodynamic and wall-motion abnormalities indicative of ischemia were observed in patients with and without angina. Most, but not all, subsequent studies agreed with their findings. Some myocardial perfusion studies using radionuclear agents also tend to refute the hypothesis that lesser amounts of myocardium are injured during painless ischemia.13

Holter monitoring has also proven useful in clarifying pathophysiologic mechanisms during silent ischemia. Early studies of ambulatory ischemia noted that almost 80% of total ischemic episodes were silent and that most of the asymptomatic episodes were short, whereas the symptomatic ones were just as likely to be long as short.13,14 As more and more studies using the Holter monitor have been published, it is apparent that there is a circadian variation in ischemic episodes, with most coming after arousal in the morning, or waking and rising at night. This circadian variation is the same in both men and women. What triggers myocardial ischemia during certain activities and not during others? This is a question to which ambulatory ECG monitoring has
helped provide answers by correlating ECG data to diaries of daily events, concurrent drawing of blood catecholamines, etc. A relation to enhanced platelet aggregation or variations in vascular tone has been suggested. The importance of physical exertion, anger, smoking, and mental stress have all been well documented with the latter receiving special attention. Recently, Kop et al19 measured heart rate variability using Holter monitoring 60 minutes before and after each of 68 ischemic events, most of which were silent. They concluded that “autonomic change consistent with vagal withdrawal can act as a precipitating factor for daily life ischemia in episodes triggered by mental activity.” One of the most intriguing physiological observations has been the steady increase in heart rate preceding the ischemic episode.16 Even when not frankly tachycardia, this increased heart rate varies suggests more of a “demand” than “supply” imbalance as a basis for many of the episodes that were once thought to be vasospastic in origin. Documenting silent ischemia in patients with true variant angina represents a unique problem because in its purest form ST elevation is the predominant finding. Criteria for ST elevation on the ambulatory ECG are not as well developed as for ST depression, but it is generally accepted that the abnormality should be profound (>2 mm) to be considered significant.

Detection and Prevalence
As proposed in the 1980s,17 a useful scheme is to consider 3 separate populations, as follows: (1) totally asymptomatic individuals; (2) those who are asymptomatic after having a myocardial infarction (MI); and (3) those with both symptomatic and asymptomatic ischemic episodes, ie, patients with stable or unstable angina. Alternatively, groups 2 and 3 can be merged so that group 1 consists of patients without known coronary artery disease and group 2 with known disease.

Asymptomatic Populations
Exercise tests have long formed the main tool for detection and prevalence. In one of the earliest studies, the United States Air Force18 conducted studies in 1390 men, 111 of whom had positive exercise tests. Thirty-four of these 111 (≈2.5%) had coronary arteriographic lesions of at least 50% stenosis. Thaulow et al19 studied 2014 Norwegian male office workers between 40 and 59 years of age (mean age 50). Coronary arteriography in men with positive exercise test demonstrated that 69 had stenosis of at least 50% in one coronary artery, and 50 of these (2.7% of the total) were completely asymptomatic. This percentage is very similar to that in the United States Air Force study. Combining positive thallium scans and ECG findings, (but without arteriography) Fleg et al20 reported a progressive increase in the prevalence of exercise-induced silent ischemia in apparently healthy individuals from one decade to the next in the Baltimore Longitudinal Aging Study; prevalence was 2.5% for those under age 60 and >10% for those above age 70. In 2000, He at al21 reported that the severity of coronary artery calcification by electron-beam CT can predict silent myocardial ischemia on stress photon emission CT. When the calcium score was between 11 to 100, 2.6% had silent ischemia compared with 11.3% with scores between 101 to 399, and 46% with scores above 400. Nearly 4000 subjects were studied.

Specific Patient Populations
One of the inherent problems in interpreting ST-segment shift on ambulatory monitoring involves the type of patient studied. For example, in asymptomatic hypertensives (with apparently normal coronary arteries), elevations in blood pressure can trigger episodes of ST-segment depression. Is this truly silent ischemia or an ECG “artifact” related to ventricular hypertrophy? Patients with renal disease are another group in whom clinically silent ST-segment changes are common, occurring in up to 30% of patients with end-stage renal disease.22 This is a population with a high prevalence of latent cardiac disease and cardiovascular risk factors, including diabetes, as well as overt coronary disease. However, other putative explanations exist for the frequent occurrence of ST shift particularly during dialysis or peridialysis besides ischemia per se, including dramatic fluctuations in electrolytes and blood pressure. The occurrence of ST-segment changes during ambulatory ECG monitoring or ECG monitoring during dialysis in patients with renal disease is more likely to occur in patients with coronary disease, but reports of the predictive value of silent ischemia in this setting are conflicting.22–24 Patients with peripheral vascular disease are another population with a high prevalence of latent coronary disease. Such patients have been shown to have a prevalence of silent ischemia on ambulatory monitoring almost equal to that of a population with known coronary artery disease, and its presence has been shown to be an independent predictor of future cardiac morbidity and mortality.25

Patients Who Have Had MIs
When we reviewed this data previously,26 we estimated that ≈50 000 patients per year who were asymptomatic after an MI had silent myocardial ischemia in the initial 30-day period after the MI, based on stress test data. Holter monitoring can also be used to document the occurrence of silent ischemia. By either technique, the reported frequency of silent ischemia varies from 30% to 43%.

Patients With Angina
Although Stern and Tzivoni27 pioneered the use of Holter monitoring to record ischemic episodes in general, the classic Holter study that specifically evaluated the significance of asymptomatic episodes in patients with chronic angina was that of Schang and Pepine.28 Twenty patients with angiographically confirmed coronary artery disease and positive exercise tests were each monitored for several 10-hour periods over the course of 16 months. In the total of 2286 hours of technically adequate recordings, 411 episodes of transient ST-segment abnormalities were documented, of which 308 (75%) were asymptomatic. Schang and Pepine28 indirectly “proved” that the silent ST-segment episodes were truly ischemic by markedly reducing their occurrence with the use of prophylactic nitrate preparations.

It is currently estimated that the number of patients with angina who also have asymptomatic episodes of myocardial
ischemia is large, but the exact percentage is unknown. In general, approximately half of the patients with angina (stable or unstable) have silent ischemia on Holter monitoring, with some series reporting much higher frequencies. In apparently adequately treated patients, the figure drops to approximately one quarter to one third.

**Prognosis**

The prognostic importance of silent ischemia is still controversial despite a wealth of data on the subject, perhaps because the term loosely encompasses such a wide range of findings from different investigative modalities. Silent ischemia ranges from transient, predominantly asymptomatic ST-segment deviation detected during continuous ambulatory electrocardiographic monitoring to stress-provoked asymptomatic electrocardiographic changes during exercise tolerance test, and inducible perfusion defects or reversible regional wall-motion abnormalities during stress imaging techniques. The problem is further compounded by the variation in prognostic importance of silent ischemia in different clinical settings. To tease out the true value of silent ischemia in determining clinical outcome, and in the interests of constructing a broad outline of the subject in which the results of specific investigations can be appreciated in context, continuous ECG monitoring and stress testing techniques have been dealt with separately in the 3 patient groups cited earlier (asymptomatic, post-MI, and angina).

**Continuous ECG Monitoring**

Although detection of ischemia during continuous electrocardiographic monitoring was described in one of Holter’s original papers, it was not until the 1970s, starting with the seminal work of Stern and Tzivoni, that investigation of the potential impact of ischemia during ambulatory monitoring began. As the majority of episodes of ambulatory ischemia are silent, in the majority of studies, with few exceptions, the effect of “silent ischemia” on prognosis refers in fact to the effect of ambulatory ST-segment changes. Keen interest in silent ischemia spawned a multitude of studies on the topic and the development of the concept of the “total ischemic burden” encompassing all episodes of ischemia both silent and symptomatic. It was hoped that evaluation of the total ischemic burden would provide both prognostic insights and a therapeutic target superior to those in existence.

**Asymptomatic Populations**

There are few prognostic studies of silent ischemia in the general population or in truly asymptomatic populations. In a substudy of the Baltimore Longitudinal Aging Study involving 98 subjects, the presence of ST changes on ambulatory monitoring were associated with a significantly higher rate of

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>n</th>
<th>Population</th>
<th>Follow-Up</th>
<th>Annual Event Rate, Death/MI</th>
<th>Transient Ischemia</th>
<th>Death/MI, ST Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottlieb et al²⁷</td>
<td>1988</td>
<td>103</td>
<td>High risk after infarction</td>
<td>12 months</td>
<td>18%</td>
<td>29%</td>
<td>37%</td>
</tr>
<tr>
<td>Ouyang et al²⁸</td>
<td>1990</td>
<td>59</td>
<td>3–5 days after uncomplicated MI</td>
<td>In hospital</td>
<td>46%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Bonaduce et al²⁹</td>
<td>1991</td>
<td>165</td>
<td>After uncomplicated myocardial infarction</td>
<td>1 year</td>
<td>15%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Langer et al³⁰</td>
<td>1992</td>
<td>109</td>
<td>Thrombolysis study</td>
<td>18 months</td>
<td>1.8%</td>
<td>32%</td>
<td>27%</td>
</tr>
<tr>
<td>Petretta et al³¹</td>
<td>1992</td>
<td>270</td>
<td>Consecutive after MI</td>
<td>2 years</td>
<td>1.3% MI</td>
<td>24%</td>
<td>26.4%</td>
</tr>
<tr>
<td>Curne et al³²</td>
<td>1993</td>
<td>203</td>
<td>Before MI, before and after discharge</td>
<td>14 months</td>
<td>14%</td>
<td>14%</td>
<td>34%</td>
</tr>
<tr>
<td>Jereczek et al³³</td>
<td>1993</td>
<td>173</td>
<td>After MI, able to exercise</td>
<td>1 year</td>
<td>7.5%</td>
<td>23%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Silva et al³⁴</td>
<td>1993</td>
<td>453</td>
<td>GISSI-2 trial, single-lead monitoring</td>
<td>6 months</td>
<td>...</td>
<td>8%</td>
<td>26% in hospital</td>
</tr>
<tr>
<td>Solimene et al³⁵</td>
<td>1993</td>
<td>40</td>
<td>Asymptomatic after first uncomplicated MI</td>
<td>24 months</td>
<td>1.25%</td>
<td>15%</td>
<td>...</td>
</tr>
<tr>
<td>Stevenson et al³⁶</td>
<td>1993</td>
<td>244</td>
<td>After MI, excluding reinfection within 24 hours of monitoring</td>
<td>8 months</td>
<td>11%†</td>
<td>41%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Stevenson et al³⁷</td>
<td>1994</td>
<td></td>
<td></td>
<td>8 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mickley et al³⁸</td>
<td>1993</td>
<td>123</td>
<td>Consecutive MI survivors &lt;70 with predischarge ETT</td>
<td>1 year</td>
<td>9.8%</td>
<td>19%</td>
<td>4%</td>
</tr>
<tr>
<td>Mickley et al³⁹</td>
<td>1995</td>
<td></td>
<td></td>
<td>5 year</td>
<td>4%</td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td>Gill et al³⁰</td>
<td>1996</td>
<td>406</td>
<td>5–7 days after MI</td>
<td>1 year</td>
<td>12.8%</td>
<td>23.4%</td>
<td>23.2%</td>
</tr>
<tr>
<td>Langer et al³¹ (GUSTO)</td>
<td>1998</td>
<td>734</td>
<td>6–24 hours after thrombolysis</td>
<td>1 year</td>
<td>32%</td>
<td>10.3% death only</td>
<td></td>
</tr>
<tr>
<td>Lotze et al³²</td>
<td>1999</td>
<td>97</td>
<td>After thrombolysis with or without early PCI</td>
<td>31 months</td>
<td>3%</td>
<td>10%</td>
<td>30%</td>
</tr>
</tbody>
</table>

RR indicates unadjusted risk ratio. Brackets grouping studies together indicate analysis of data from same cohort followed up over longer time period or on a subset of the original cohort.

*Difference not statistically significant.
†Mortality rate during follow-up period.
subsequent cardiac events. However, half of these events were the development of angina, and ischemia on ambulatory monitoring was not significantly associated with hard events, death and MI. However, in a larger study of asymptomatic individuals, the Swedish study of “men born in 1914,” the presence of silent ischemia during normal daily activity was a strong predictor of cardiac mortality and acute cardiac events including unstable angina and nonfatal MI. There was a >4-fold increase in the relative risk of combined events among patients without a prior history of coronary disease who demonstrated evidence of silent ischemia, and a 16-fold increase in the subgroup of subjects with a prior history of coronary disease. However, the vast majority of events occurred in the larger portion of the population without silent ischemia. This poor negative predictive value diminishes the value of ambulatory monitoring as a screening tool for the general population.

Patients Who Have Had MI
Silent ischemia during the acute phase of MI, with continuous ECG monitoring of the patient in the coronary care unit rather than when ambulatory, is associated with an adverse inhospital prognosis in terms of death and reinfarction and is dealt with under acute coronary syndromes. With regard to the convalescent phase of MI, silent ischemia is more frequent at this time than in the acute phase, but it seems its presence does not portend adverse outcome to the same extent, when restricted to death and MI. Silent ischemia in the postinfarct phase does predict cardiac events when revascularization is included as an event, and although the prognostic importance of silent ischemia in the postinfarct phase is attenuated during long-term follow-up, the presence of silent ischemia remains predictive of all cardiac events up to 5 years after the index infarct. When subjected to multivariate analysis, ambulatory ischemia fails to outperform clinical indices such as Killip class in predicting acute events. The addition of other variables such as heart rate variability and the detection of ventricular tachycardia to silent ischemia to create a combined index of abnormal ambulatory ECG responses can improve the sensitivity and predictive value of the test. However, for patients in the convalescent phase of MI, the value of ambulatory ECG as an additional noninvasive method of risk stratification is limited to those who cannot exercise. For the majority of patients who are discharged after infarction and who are able to exercise, silent ischemia on ambulatory monitoring does not add incremental information to that gleaned from clinical assessment and exercise testing concerning the risk of acute events.

Acute Coronary Syndromes (Unstable Angina to Acute MI)
Persistence or recurrence of pain despite medical therapy has long been recognized as a predictor of adverse outcome in unstable angina. The discovery that as many as two thirds of patients with unstable angina may have silent episodes of ischemia detected during Holter monitoring prompted the investigation of silent ischemia as a means of assessing prognosis in these patients (Table 2). These studies identify
the presence of ischemia, particularly of long duration, as a significant predictor of in-hospital outcomes including death, infarction, and need for revascularization, independent of other significant variables, and most also identify silent ischemia as a predictor of more restricted end points (death and infarction). The 3- to 5-fold increase in risk of death, infarction, and revascularization has been shown to continue out to 1- and 2-year follow-up. Transient ischemia, much of which is silent, is also detectible during Holter monitoring in the acute phase after MI, and in this setting it is associated with an adverse “in-hospital” and medium-term prognosis in terms of death and reinfarction in addition to combined end points including revascularization and angina (Table 1). The time delay inherent in the Holter monitoring technique is a disadvantage in acute patient care, which has been overcome by the advent of continuous vector-derived computer-assisted 12-lead or multilead ECG monitoring systems more suited to the acute coronary care unit. Technology now allows ongoing analysis of ST-segment trends and enhances the ability to quantify the extent and duration of ischemia. Studies of acute coronary syndromes including patients with non-ST elevation MI and unstable angina and those with ST elevation MI have demonstrated that the presence of transient ischemia is predictive of increased mortality and infarction during short- and long-term follow-up. The negative prognostic impact of transient ischemia is independent of other important prognostic factors including troponin level, and there is a graded relationship between the duration of ischemia or number of episodes and progressive deterioration in event-free survival.

Transient ischemia in unstable angina treated with maximal antianginal therapy has been shown to be associated with intracoronary thrombus and lesion complexity. Antiplatelet and antithrombin therapies reduce transient ischemia and, fittingly, have been shown to be of greater therapeutic benefit in those patients who demonstrate transient ischemia.

### TABLE 2. Summary of Studies of the Prognostic Value of Continuous ECG Monitoring in Unstable Angina/Acute Coronary Syndromes

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>n</th>
<th>Population</th>
<th>Follow-Up</th>
<th>Transient Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al</td>
<td>1982</td>
<td>92</td>
<td>Consecutive unstable angina</td>
<td>3 months</td>
<td>23%</td>
</tr>
<tr>
<td>Gottlieb et al</td>
<td>1986</td>
<td>70</td>
<td>Unstable angina</td>
<td>30 days</td>
<td>53%</td>
</tr>
<tr>
<td>Gottlieb et al</td>
<td>1987</td>
<td>70</td>
<td>Unstable angina</td>
<td>2 years</td>
<td>53%</td>
</tr>
<tr>
<td>Wilcox et al</td>
<td>1990</td>
<td>66</td>
<td>Unstable angina</td>
<td>13 months</td>
<td>11%</td>
</tr>
<tr>
<td>Nademane et al</td>
<td>1987</td>
<td>49</td>
<td>Unstable angina</td>
<td>6 months</td>
<td>60%</td>
</tr>
<tr>
<td>Von Arnim et al</td>
<td>1988</td>
<td>38</td>
<td>Consecutive unstable angina</td>
<td>30 days</td>
<td>42%</td>
</tr>
<tr>
<td>Langer et al</td>
<td>1989</td>
<td>135</td>
<td>Consecutive unstable angina</td>
<td>In hospital</td>
<td>66%</td>
</tr>
<tr>
<td>Pozzati et al</td>
<td>1992</td>
<td>86</td>
<td>Unstable angina</td>
<td>1 year</td>
<td>57%</td>
</tr>
<tr>
<td>Bugiardini et al</td>
<td>1991</td>
<td>88</td>
<td>Unstable angina</td>
<td>In hospital</td>
<td>...</td>
</tr>
<tr>
<td>Romeo et al</td>
<td>1992</td>
<td>76</td>
<td>Unstable angina</td>
<td>6 years</td>
<td>56% had &gt;1 hour of ischemia</td>
</tr>
<tr>
<td>Amanullah et al</td>
<td>1993</td>
<td>43</td>
<td>Unstable angina</td>
<td>40 months</td>
<td>51% &gt;30 min of ischemia</td>
</tr>
<tr>
<td>Patel et al</td>
<td>1996</td>
<td>212</td>
<td>Unstable angina</td>
<td>In hospital</td>
<td>15%</td>
</tr>
<tr>
<td>Kootwijk et al</td>
<td>1998</td>
<td>332</td>
<td>Refractory unstable angina undergoing PCI</td>
<td>30 days</td>
<td>21%</td>
</tr>
<tr>
<td>Jernberg et al</td>
<td>1999</td>
<td>630</td>
<td>All patients admitted to CCU with suspected ACS without ST elevation</td>
<td>30 days and 6 months</td>
<td>15.9%</td>
</tr>
<tr>
<td>Akkerhuis et al</td>
<td>2001</td>
<td>216</td>
<td>Patients with unstable angina or non-ST-elevation MI</td>
<td>30 days and 6 months</td>
<td>15.9%</td>
</tr>
</tbody>
</table>

RR indicates unadjusted risk ratio; CCU, critical care unit; and ACS, acute coronary syndrome.

*Difference not statistically significant.
†Includes revascularization and unstable angina.
‡Studies of continuous computer assisted 12-lead ECG ST-segment monitoring in patients with acute coronary syndromes, but not vector cardiography.
§Acute coronary syndromes including non-ST-elevation MI.
Patients With Angina
In stable patients with clinical or angiographic evidence of coronary disease, the prognostic value of silent ischemia on ambulatory monitoring is variably reported as either significant or of no consequence (Table 3). Early studies, conducted for the most part in small numbers of highly selected and usually exercise test–positive patients, support the position of the presence and extent of ischemia as a prognostic indicator of some merit. In these initial studies, silent ischemia is extolled as a powerful and independent risk predictor in stable coronary disease. However, some of these studies included revascularization or the development of anginal symptoms as end points. Those studies in which silent ischemia was a strong and independent risk factor for coronary mortality and/or MI displayed an exceptionally high attrition rate for studies conducted in stable angina. For example, the mortality of 7.5% per annum in the study of Deedwania and Carbajal is substantially higher than the 1% to 2% routinely expected in stable angina, indicating the highly selected nature of the population studied. Studies in low-risk or unselected patient cohorts failed to identify ambulatory ischemia as an adverse prognostic indicator during mid- or long-term follow-up. Also, although one small study found the presence of ambulatory ischemia after coronary artery bypass graft surgery to be associated with a significant excess of adverse clinical events, this finding was disproved by further larger studies.

The problem of small size, which plagued earlier investigations, was resolved with the publication during the 1990s of a number of studies of sufficient magnitude and statistical power (300 to 1000 patients followed up over 1 to 3 years) to answer with confidence the question of the importance of silent ischemia on ambulatory monitoring. The largest of these studies was the Multicenter Study of Myocardial Ischemia (MSMI) study, which demonstrated no significant increase in primary cardiac events associated with ambulatory ischemia in stable patients in the first month (1 to 6 months) after MI or unstable angina. The Total Ischemic Burden Bisoprolol Study (TIBBS), Atenolol and Silent Ischemia Study (ASIST) and the Asymptomatic Cardiac

### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Death/MI, ST Positive</th>
<th>Death/MI, ST Negative</th>
<th>RR, Death/MI</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>19% 7% 2.7</td>
<td></td>
<td>Ischemia associated with significant increase in myocardial infarction</td>
<td></td>
</tr>
<tr>
<td>16% 3% 5.3</td>
<td></td>
<td>Ischemia associated with 5-fold increase in risk of infarct or revascularization</td>
<td></td>
</tr>
<tr>
<td>27% 3% 9</td>
<td></td>
<td>Ischemia associated with significantly increased rate of death and infarction</td>
<td></td>
</tr>
<tr>
<td>29% 10% 2.9*</td>
<td></td>
<td>Ischemia associated with only nonsignificant trend toward increased risk of hard events</td>
<td></td>
</tr>
<tr>
<td>17% 5% 3.4</td>
<td></td>
<td>Ischemia associated with increased event rate including hard event rate, death or MI</td>
<td></td>
</tr>
<tr>
<td>31% 9% 3.4*</td>
<td></td>
<td>Ischemia not significantly predictive of death/MI at 1 month (trend toward increased risk) but significant when revascularization included</td>
<td></td>
</tr>
<tr>
<td>20% (&gt; 60 minutes) 4%</td>
<td></td>
<td>Ischemia significantly associated with unfavorable outcome when revascularization included as outcome; OR = 3.79</td>
<td></td>
</tr>
<tr>
<td>56%† 10%† 5.6†</td>
<td></td>
<td>Ischemia at 2–4 days associated with adverse in-hospital and 1 year outcome</td>
<td></td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>Ischemia associated with particularly poor prognosis when associated with complex angiographic lesion</td>
<td></td>
</tr>
<tr>
<td>58% with &gt;1 hour of ischemia 36% with &gt;1 hour of ischemia 1.6</td>
<td>Ischemia of &gt;1 hour duration associated with increased risk of death/MI/revascularization, but not presence of ischemia &lt;1 hour ischemia associated with significantly higher rate of MI and revascularization, but increase in death/MI not significant; Holter ischemia did not offer incremental prognostic information to ETT and/or thallium perfusion imaging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18% 0% 18*</td>
<td></td>
<td>Ischemia significantly associated with unfavorable outcome, death or MI OR 2.94 by multivariate analysis</td>
<td></td>
</tr>
<tr>
<td>19% 1.6% 11</td>
<td></td>
<td>Ischemia, both symptomatic and asymptomatic, detected by vector-derived ECG associated with increased event rate (OR 3.2), and ischemia reduced by abciximab</td>
<td></td>
</tr>
<tr>
<td>15%</td>
<td>...</td>
<td>Ischemia significantly associated with adverse outcome (death and MI) at 1 month and longer follow-up</td>
<td></td>
</tr>
<tr>
<td>0% (30 day) 1.5% (30 day) 6</td>
<td></td>
<td>Ischemia significantly associated with adverse outcome (death and MI) at 1 month and 6 month follow-up</td>
<td></td>
</tr>
<tr>
<td>29% (30 days) 34% (6 months) 13% (30 days) 15% (6 months) 2.2</td>
<td>Ischemia (&gt;2 ST episodes) significantly associated with adverse outcome, (death and MI) at 1 month and 6 month follow-up</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Ischemia Pilot\textsuperscript{79} (ACIP) reported a significant association between ambulatory ischemia either before or during treatment, and adverse outcome. The combined end points used included not only objective end points such as death and MI, but also more subjective end points such as revascularization for deteriorating symptoms and aggravation of angina requiring medical therapy. By contrast, the Angina Pectoris Study In Stockholm\textsuperscript{80} (APSIS) identified the extent of ambulatory ischemia as a predictor of cardiac events during 2-year follow-up, but the finding only held true in those patients with >2-mm ST depression when exercise variables were also considered. TIBET (Total Ischemic Burden European Trial)\textsuperscript{77} reported transient ischemia to be of no significant prognostic value when considering either the hard end points of death, MI, or unstable angina, or all end points including revascularization.

Despite considerable heterogeneity in study design and analysis (Table 4), prognostic studies in stable coronary disease seem to identify silent ischemia on ambulatory monitoring as a harbinger of hard clinical events only in highly selected patients with ischemia detectible on exercise testing. Although silent ischemia may be associated with
greater revascularization rates in low-risk populations, this may be confounded by its known association with ischemia on exercise testing, and there is little evidence to support its routine deployment as a prognostic implement in this clinical setting.

**Silent Ischemia During Stress Testing**

**Asymptomatic Populations**

As with the detection and prevalence of ischemia, support for the prognostic importance of silent inducible ischemia in the asymptomatic population comes predominantly from studies involving exercise electrocardiography. Participants in the Seattle Heart Watch study and the Lipid Research Clinics Program, United States Air Force personnel, Norwegian office workers and Indiana State Police employees are among the “normal” asymptomatic populations who have been subjected to exercise testing and followed prospectively to investigate the prognostic significance of electrocardiographic evidence of ischemia. Epstein et al combined results of the studies of Bruce and Eriksson to estimate that of 10,000 asymptomatic individuals, 500 (5%) had an abnormal exercise test; of these individuals, 50% had angiographic coronary disease. These subjects demonstrated an annual event rate of 0.7% in contrast to the 0.06% annual mortality rate of the normal population. The data from these studies are summarized in Table 3.

<table>
<thead>
<tr>
<th>Transient Ischemia</th>
<th>Death/MI, ST Positive</th>
<th>RR, Death/MI</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>46%</td>
<td>2.7%</td>
<td>0%</td>
<td>2.7</td>
</tr>
<tr>
<td>34%</td>
<td>65%</td>
<td>39%</td>
<td>1.6</td>
</tr>
<tr>
<td>77%</td>
<td>28%</td>
<td>0%</td>
<td>28</td>
</tr>
<tr>
<td>43%</td>
<td>26%</td>
<td>10%</td>
<td>2.6</td>
</tr>
<tr>
<td>45%</td>
<td>26%</td>
<td>4%</td>
<td>6.5</td>
</tr>
<tr>
<td>57%</td>
<td>12%</td>
<td>0%</td>
<td>12</td>
</tr>
<tr>
<td>59%</td>
<td>10%</td>
<td>0%</td>
<td>10</td>
</tr>
<tr>
<td>42%</td>
<td>2.7%</td>
<td>7%</td>
<td>0.4†</td>
</tr>
<tr>
<td>42%</td>
<td>7%</td>
<td>13%</td>
<td>0.5†</td>
</tr>
<tr>
<td>39%</td>
<td>2.2%</td>
<td>8.5% (MI)</td>
<td>0.25†</td>
</tr>
<tr>
<td>41%</td>
<td>9%</td>
<td>11%</td>
<td>0.8†</td>
</tr>
<tr>
<td>52%</td>
<td>14%</td>
<td>9%</td>
<td>1.6†</td>
</tr>
<tr>
<td>32%</td>
<td>6%</td>
<td>3%</td>
<td>2.0†</td>
</tr>
<tr>
<td>48%</td>
<td>11%</td>
<td>9%</td>
<td>1.2†</td>
</tr>
<tr>
<td>100%</td>
<td>3.7% with 2 episodes</td>
<td>1% in pts&lt;2 episodes</td>
<td>3.7†</td>
</tr>
<tr>
<td>27%</td>
<td>9.5%</td>
<td>6.5%</td>
<td>...</td>
</tr>
<tr>
<td>100%</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>58%</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>17%</td>
<td>15%</td>
<td>10%</td>
<td>1.5†</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>33%</td>
<td>16.2%</td>
<td>7.3%</td>
<td>2.2</td>
</tr>
<tr>
<td>8%</td>
<td>...</td>
<td>...</td>
<td>1.24†</td>
</tr>
<tr>
<td>32%</td>
<td>18%</td>
<td>15% all events</td>
<td>1.2†</td>
</tr>
</tbody>
</table>

Ischemia associated with greater incidence of events when hospitalization for angina and worsening angina included. Ischemia strongly associated with adverse outcome in elderly patients with stable CAD. Ischemia strongly associated with all cardiac events, including combined end points of death and MI. Ischemia not associated with adverse outcome. Ischemia not associated with increased risk of hard events. Ischemia not associated with increased risk of hard events. Ischemia not predictive of adverse outcome. Ischemia not associated with increased rate of death and infarction. Ischemia not associated with significantly higher rate of death and MI. Ischemia not significantly associated with hard outcomes but predictive of all cardiac events including revascularization and unstable angina. Ischemia 4 weeks into randomization associated with increased event rate 26.9% vs 11.2% mostly accounted for by worsening angina. Ischemia not associated with increased event rate. Ischemia not associated with increased risk of hard events. Ischemia not associated with significantly higher rate of death and MI. Ischemia associated with hard events including revascularization and unstable angina. Ischemia not associated with increased rate of death/MI, as well as all events including revascularization and unstable angina. Ischemia not associated with increased rate of death/MI, or of all events including unstable angina and revascularization. No difference in patients over 70. Ischemia associated with adverse outcome only when unstable angina or unstable ischemia on Holter and ETT comprised highest risk group with cardiac event rate (including unstable angina) of 30%. Ischemia on Holter not predictive of future events, fatal or nonfatal. Ambulatory monitoring at 4–8 weeks after MI is inferior to ETT in predicting events.
TABLE 4. Heterogeneity in Design and Analysis Hinders Interpretation of Results of ECG Monitoring Studies

<table>
<thead>
<tr>
<th>Factor</th>
<th>Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient selection</td>
<td>Relationship between transient ST segment changes during continuous monitoring and outcome varies considerably depending on the population studied and selection process as outlined in the text in relation to asymptomatic vs CAD populations</td>
</tr>
<tr>
<td>Baseline ECG</td>
<td>Most, but not all, studies exclude patients with resting ECG abnormalities affecting ST segment interpretation such as left ventricular hypertrophy, bundle branch block, or an implanted pacemaker</td>
</tr>
<tr>
<td>Definition of ischemic episode</td>
<td>Variable definitions of ischemic episodes; The most widely accepted criteria for ischemic episode include: ST elevation generally of shorter duration, greater amplitude, and more often associated with chest pain than ST depression, but not measured consistently</td>
</tr>
<tr>
<td>Duration of monitoring</td>
<td>Duration of monitoring varies from 12 to 48 hours and longer but the relative merits of longer vs shorter duration of monitoring period for prognostic assessment have not been formally addressed</td>
</tr>
<tr>
<td>Anti anginal medication</td>
<td>Withdrawal or continuation of antianginal medication during period of monitoring not standard between studies</td>
</tr>
<tr>
<td>Adjustment for confounding variables</td>
<td>Multivariate analysis not performed on all studies</td>
</tr>
<tr>
<td>Choice of end points</td>
<td>Definition of outcome highly variable between studies</td>
</tr>
<tr>
<td></td>
<td>Some studies restrict outcomes to the hard events of death or MI; others include unstable angina</td>
</tr>
</tbody>
</table>

enjoyed by those with a normal response to exercise. In the Lipid Research Clinics prevalence follow-up report, asymptomatic individuals with a positive exercise test had an almost 5-fold increase in cardiovascular mortality even when the data were adjusted for age and other risk factors. In this cohort, electrocardiographic evidence of ischemia was an independent predictor of mortality approximately equivalent to a 17.4-year increment in age. Other studies have shown the presence of silent ischemia to be predictive of the advent of angina rather than death or MI90 and that the coexistence of at least one conventional risk factor in addition to ST depression substantially increases the relative risk of coronary events.86

Patients Who Have Had MI or Have Angina
It is not surprising that the presence of ischemia on exercise, a moderately sensitive indicator of the presence of coronary disease, would identify a subgroup of the general population at higher risk of cardiovascular death. The impact of silent ischemia on exercise testing in the population with suspected or confirmed coronary disease is a more challenging question. Over the past 30 years, a large number of studies have been conducted on patients with a history of angina, with or without prior MI,75,87,88 and in patients after MI,89 which serve to answer just this question. The presence of inducible ECG features of ischemia, either symptomatic or asymptomatic, on exercise testing has been shown to be associated with adverse outcome,76,87–89 The strength of the association is most convincing, and the predictive value of ischemia is greatest, when it occurs at low workload.88 The electrocardiographic severity of ischemia is less useful in identifying those at risk of events.

In patients with coronary disease, the effect of the presence of pain in association with electrocardiographic changes has been inconsistently reported to portend a worse prognosis, and silent ischemia is reported as an indicator of a poor prognosis is some69 but not all studies. In fact, a relatively benign prognosis (1.4% annual mortality, not substantially greater than would be expected in the overall population with coronary disease) has been reported in patients with profound (>2 mm) ischemia on exercise testing when the majority had painless ischemia.91 There are several reasons for these inconsistencies. The importance of exercise duration and the time to ischemia cannot be overemphasized. Patients with an early positive test, whether painful or painless, are consistently more likely to suffer adverse events.75,88 In patients with profound (painless) ST depression, exercise duration serves as an effective discriminator between high- and low-risk subgroups.89 Painful ischemia is associated with signif-
Ischemia can also be detected by means of stress echocardiography; positron emission tomography; radionuclide perfusion scanning; and more recently, MRI. Stress is provided by exercise or pharmacological means, either a positive inotrope and chronotrope such as dobutamine, or a selective vasodilator such as dipyridamole. The extent and severity of stress-induced ischemia observed during echocardiography and myocardial perfusion scanning influence the prognosis and renders these tests more accurate indicators of prognosis than conventional exercise testing. The presence of extensive ischemia, irrespective of whether it is silent or not, indicates an increased risk of cardiovascular events, and as with exercise testing, the threshold at which ischemia occurs carries important prognostic information.

**Treatment**

Because most of the data in this area concerns post-MI patients or those with angina (and the treatment of asymptomatic patients involves similar drugs and procedures), we will focus our remarks on those patients with known coronary artery disease. Early reports of the characteristics of silent ischemia during ambulatory monitoring document a reduction in ischemic episodes accompanying treatment with nitrates, a finding confirmed by subsequent investigators. The effects of other conventional antianginal therapies, namely β-blockers and calcium antagonists, alone and in combination, on silent ischemia have been extensively investigated. The use of ambulatory monitoring, and the discovery that ST-segment changes occur frequently during daily activities and at heart rates lower than those associated with ischemic change during formal exercise testing, led certain investigators to hypothesize that ambulatory ischemia was due to alterations in vasomotor tone (leading to reduced supply) rather than to increased heart rate and contractility leading to greater myocardial demand. The logical progression of this idea was that silent ischemia would respond more favorably to treatment with calcium antagonists, which act as vasodilators, than to β blockade. The theory was not supported, however, by the multiple studies that have unequivocally shown that β blockers reduce the incidence, frequency, duration, and severity of silent ischemia in a dose-dependent manner. Calcium antagonists, phenylalkylamine, benzothiazepine, and dihydropyridine derivatives, have demonstrated efficacy in reducing silent ischemia, but there are some inconsistencies in the reports with a small number of investigators finding deterioration in the degree of silent ischemia associated with the use of nifedipine. In fact, β-blockers are in most cases superior to calcium antagonists alone in reduction of the total ischemic burden and furthermore have been shown to blunt the circadian pattern of transient ischemia, particularly the morning peak of ischemic activity, which closely mirrors the circadian incidence of acute MI and sudden death.

However, the addition of a calcium antagonist to β blockade has been shown to improve objective measures of ischemia and the combination of both types of agents has been found to be superior to either type alone in reducing ischemia. An elegant study by Andrews et al casts some light over the possible mechanism involved in the additive effect of combination therapy. They demonstrated 3 distinct subtypes of ambulatory ischemia, 2 of which are associated with minor but significant heart rate increases and a third not associated with any increase in heart rate. The third type, probably related to vasoconstriction, responds preferentially to vasodilator therapy, whereas the first 2 respond to negative chronotropic effects.

As a considerable amount of silent ischemia remains undetectable in individuals whose symptoms are controlled with
antianginal therapy, should treatment be aimed at reducing the total ischemic burden, both symptomatic and silent? The answer to this question lies in the prognostic effect of silent ischemia. Is ischemia per se detrimental to the patient, and does the eradication of ischemia improve prognosis? The first part of the question has been answered in the preceding discussion. In the case of acute coronary syndromes, therapy directed at the underlying pathophysiology of plaque rupture and thrombus formation reduces ischemia and improves prognosis, while anti-ischemic agents do not.

As for the effect of reducing ischemia in stable coronary disease, the TIBBS trial (a study of bisoprolol and nifedipine and their combination) reported a significant prognostic advantage for 100% eradication of ischemia. This was, however, due to a significant reduction in angina requiring revascularization. Similarly, the ASIST study (atenolol versus placebo) reports a treatment benefit favoring patients with abolition of ischemia on ambulatory monitoring, but a substantial proportion of this benefit is yielded from the reduction in aggravation of angina rather than objective acute events. Objective cardiac events were not significantly reduced in 2 large trials of longer duration (APSIS and TIBET) in patients on β-blockers or calcium antagonists or their combination who showed a significant reduction in the total ischemic burden. In the 2-year follow-up of the ACIP trial, conducted in patients with ambulatory ischemia as a prerequisite for entry, revascularization, particularly surgery, was superior to pharmacological therapy in improving prognosis (Figure 4). Finally, in addition to their potent lipid-lowering effects, statins have been shown to reduce ambulatory ischemia.
develops, but far less so by the concurrent occurrence of pain during the test. The situation is different for acute coronary syndromes, including ST elevation MI, in which ongoing transient ischemia, irrespective of whether or not it is silent, is associated with an increased risk of infarction and death. The increase in risk is proportional to the duration of ischemia. Furthermore, transient ischemia may identify patients with the most to gain from treatment with antithrombotic therapy, making continuous ECG monitoring an extremely useful tool in this clinical scenario. The study of silent ischemia has illuminated our understanding of many of the pathophysiological processes underlying the natural history of coronary disease and enhanced our knowledge and practice of cardiology. Over the years it has become apparent that the detection of ischemia, whether silent or symptomatic, may be of considerable diagnostic and prognostic importance when the clinical population to be studied is clearly defined (Figure 5). Furthermore, careful selection not only of the population for study but also of the techniques for its detection are necessary for the search for silent ischemia to achieve its maximal clinical utility.111–122

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REGRESS Study Group. 


IRES (Ischemia Residual Study) Group. 


**Key Words:** ischemia — myocardial infarction — angina — prognosis