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Asymptomatic myocardial ischemia in stable angina, unstable angina, and myocardial infarction: Current status and future directions

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Myocardial ischemia or infarction may occur in the absence of symptoms; however, more recently it has been appreciated that symptomatic manifestations are often extremely inconsistent and heterogeneous within a particular patient. For example, patients who experience typical angina with ischemia or with myocardial infarction (MI) may also experience episodes that are entirely asymptomatic or silent.[1] Episodes of asymptomatic ischemia occur in 25% to 50% of patients with coronary syndromes (ie, stable angina,unstable angina, acute MI),and may outnumber symptomatic episodes by more than 20 to 1. The development of ambulatory ECG (AECG) or Holter recording techniques has provided a method to identify episodes of asymptomatic ischemia during routine daily activities and has led to extensive investigation of their clinical significance. It is well known that prognosis is not based on the presence or severity of angina pectoris.[2] The risk associated with myocardial ischemia relates to the number and severity of coronary artery obstructions and to the underlying biologic instability of the coronary plaque (ulcerated plaques, acute thrombus formation, and endothelial dysfunction) and not to whether the brain perceives the sensation described as "angina." The purpose of this report is to review the pathophysiology, incidence, treatment, and prognostic significance of asymptomatic ischemia in coronary syndromes, and to provide an overview of the current and future direction of research in these areas.

Nature of anginal symptoms associated with ischemia

Why certain episodes of ischemia are associated with angina, while others are asymptomatic, remains unknown. Individual manifestations of myocardial ischemia follow a consistent temporal course with abnormalities of myocardial relaxation occurring first, followed by abnormalities in contraction, ST-segment changes, and ultimately, but not necessarily, the perception of angina. Some studies suggest that episodes of asymptomatic ischemia simply represent less severe ischemia in which the "anginal threshold" is not reached.[3-6] Other studies indicate that symptomatic and asymptomatic ischemic episodes are similar in all respects, including duration or depth of ST-segment depression during AECG monitoring, magnitude of reversible thallium defects during exercise testing, and number and severity of coronary obstructions.[7-9] Differences in the magnitude of ischemia cannot adequately account for the presence or absence of anginal pain.

Different neurohumoral mechanisms may be responsible for the presence or absence of symptoms associated with myocardial ischemia. Myocardial pain is provoked when afferent nerve fibers are activated by noxious stimuli.[10] Afferent impulses travel through the cardiac sympathetic nerves and sympathetic ganglia to the dorsal roots at upper thoracic levels. These impulses, together with some sensory innervation that travels along the vagus nerves, are conducted to the thalamus and cerebral cortex.

Disorders of peripheral autonomic nerves have been considered responsible for silent ischemia in some patients, such as diabetics. Diabetics are reported to have a higher prevalence of asymptomatic ischemia during exercise testing or AECG monitoring than nondiabetics.[11-13] However, recent experience indicates that diabetics may have similar, or even less asymptomatic, ischemia than nondiabetics.[15,16] Many of these conflicting observations may be due to small sample sizes, as well as to selection bias for inclusion in the different studies. Although peripheral neuropathy may be responsible for the lack of angina perception in a small number of patients, it is not responsible for the inconsistency of angina perception in the majority of coronary patients.

A number of studies have shown that patients whose myocardial ischemia is asymptomatic have a more generalized disorder of pain perception.[16] Increased beta-endorphin levels, naturally occurring opiates,have been demonstrated in patients with asymptomatic myocardial ischemia during exercise.[17] However, the failure of naloxone to initiate chest pain during exercise-induced asymptomatic ST-segment depression suggests that endorphins do not have much influence.[18]

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A recent study using PET brain scanning of nondiabetic patients with exercise-induced ischemia may explain why some episodes of ischemia are asymptomatic. Rosen and colleagues found that bilateral activation of the thalamus was similar both in patients who experienced angina during ischemia, and in those whose ischemia was asymptomatic.[19] The patients with asymptomatic ischemia had significantly less cortical activation,compared to those who experienced angina. These findings show that afferent stimuli from the heart reach the central nervous system even if ischemia is not perceived as angina. The lack of perception of anginal pain appears to be related to abnormal central processing of afferent pain messages from the heart. According to the "gate theory," nonmyocardial factors may exert a critical influence on the central processing of afferent stimuli. Amplifying and abating influences may include analgesic effects arising from concurrent exercise or vagal stimulation,[10] emotional status, and personality characteristics. Thus, the modulation of pain sensation, together with physiologic and cortical influences, may account for patients who never develop angina and those with angina during only a proportion of their ischemic episodes.[10]

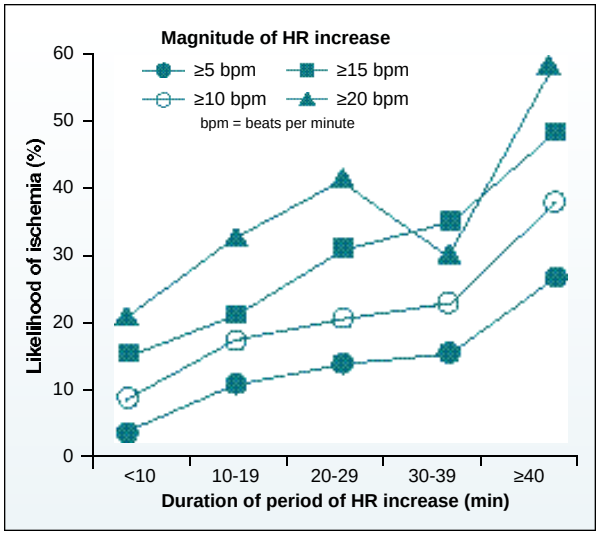
Further support of the cortical influences on the perception of angina may be different personality characteristics in patients with different symptomatic manifestations of ischemia.[20] Patients who consistently experienced angina with ischemia scored higher on the Beck Depression Inventory and the Spielberger State Anxiety scale than did those whose ischemia was consistently asymptomatic, and patients who inconsistently experienced angina at the time of ischemia had higher State Anxiety scores than did those who were consistently asymptomatic. More investigation is necessary to determine if psychophysiologic factors are fundamental to the ultimate perception of angina.

Stable coronary artery disease

There has been substantial controversy concerning the mechanisms responsible for asymptomatic ischemia in patients with stable coronary disease. Daily life ischemia, as identified by AECG monitoring, occurs at a heart rate threshold that is 10% to 20% lower than that for ischemia occurring during an exercise treadmill test (ETT). This suggests that episodes of daily life ischemia may, at least in part, be related to intermittent coronary vasoconstriction. There is also substantial variability in the heart rate threshold for ischemia throughout the day within a given patient supporting the role of varying degrees of coronary vasoconstriction contributing to ischemia. Andrews et al related the minute-by-minute heart rate profile of stable coronary patients to episodes of daily life ischemia. They found that only 20% of ischemic episodes occurred in the absence of a heart rate increase (which would be the case if vasoconstriction were the primary pathophysiologic mechanism), while approximately 80% of ischemic episodes were preceded by an increase in heart rate. The likelihood of developing ischemia throughout the day was proportional to the magnitude and duration of the heart rate increase and the baseline heart rate before the increases in heart rate (Figure 1).[21] Thus, the vast majority of daily life ischemia is preceded by some evidence of an increase in myocardial O_2 demand.

Understanding the pathophysiology of ischemia in stable coronary disease is complicated by the current appreciation that many routine daily activities can both increase myocardial demand and provoke coronary vasoconstriction (Figure 2). Furthermore, other important pathophysiologic considerations may influence the development of myocardial ischemia such as hypercholesterolemia and the hormonal milieu in postmenopausal women. Elevated serum low-density lipoprotein (LDL) cholesterol, particularly oxidized LDL cholesterol, and estrogen deprivation create and may exacerbate the endothelial dysfunction that is responsible for atherosclerosis and perhaps for episodic vasoconstriction as well.

Figure 1: Graph showing likelihood of developing ischemia after a heart rate (HR) increase by the duration and magnitude of the preceding heart rate increase. Likelihood of developing ischemia was directly proportional to both the magnitude and duration of heart rate increases ($p < 0.001$). (Adapted from Andrews et al,[21] with permission.)

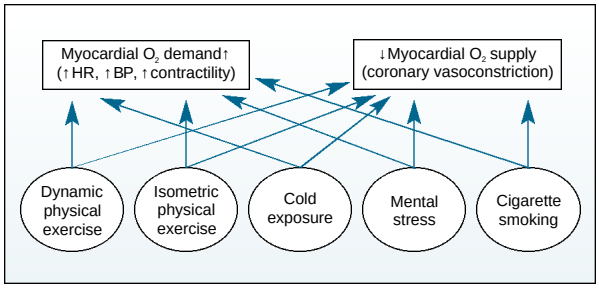


Mental stress and episodes of ischemia in patients with stable CAD

Mental stress can trigger ischemia in 40% to 70% of stable coronary patients and is reported to be a frequent trigger for development of asymptomatic ischemia,[22] acute MI, and cardiac death.[23-25] In fact, the development of ischemia in response to mental stress in the laboratory is independently associated with significantly higher rates of fatal and nonfatal cardiac events and predicts events over and above exercise-induced ischemia.[26] It is disconcerting that mental stress-induced ischemia is almost always asymptomatic. Gottdeiner et al found that while 43% of stable coronary patients experienced angina during exercise-induced ischemia, only 4% experienced angina during mental stress-induced ischemia.[27]

Experimental studies in chronically instrumented animals provide direct evidence that mental stress or anger leads to coronary vasoconstriction and myocardial ischemia.[28] In stable patients with coronary disease, mental stress induces

Figure 2: Effects of routine daily activities on the myocardial oxygen supply/demand balance. (Adapted from Stone,[69] with permission.)



transient vasoconstriction which can further obstruct the coronary lumen by up to 25%.[29] Mental stress-induced ischemia occurs at a lower heart rate and double product than exercise-induced ischemia, further suggesting that vasoconstriction may be responsible for such events. Patients with mental stress-induced ischemia experience more episodes of daily life ischemia compared to patients who do not develop ischemia in response to mental stress.[30] Behavioral studies indicate that patients most likely to develop mental stress-induced ischemia, both in the laboratory and during routine daily life activities, have higher scores of "aggressive responding," trait anger, hostile affect, behavioral reactivity, reward dependence, and a lower score on anger control.[31-33]

Physiologically, patients who experience ischemia during mental stress in the laboratory develop a significantly higher systemic vascular resistance, heart rate, blood pressure, and a significantly greater fall in ejection fraction in response to mental stress compared to patients who do not develop ischemia.[34] Similarly, patients who experience daily life ischemia have different responses to mental stress than patients who do not have daily life ischemia; they have higher ejection fraction, stroke volume, and cardiac output, and lower systemic vascular resistance.[30] These observations suggest that patients with daily life ischemia may be in a chronic state of increased sympathetic arousal and more prone to an exaggerated sympathetic systematic response to mental or exercise stress as well (ie, so-called "hot reactors").[30] The adverse outcome identified in stable coronary patients with mental stress-induced ischemia,[26] may be related to this chronic hyperdynamic state.

Incidence of asymptomatic ischemia during AECG monitoring

Asymptomatic ischemia identified by AECG monitoring during routine daily activities is extremely common, occurring in approximately 40-60% of patients. These patients generally have more threatening coronary anatomy, including more severe epicardial obstructions, more proximal lesions, and more "complex" plaques, characterized by the presence of thrombus, ulceration, and irregular lumen borders.[35] There is a correlation between the development of a progressively more abnormal exercise test and an increased likelihood of experiencing more frequent and more prolonged episodes of AECG ischemia.[36] The magnitude of the correlation, however, between the severity of ischemia during exercise testing and the severity of ischemia during routine daily activities, is very low.[37] Furthermore, the relationship between the measures of ischemia severity during exercise testing, AECG monitoring during daily activities, and even the frequency of angina and NTG consumption is also very poor.[37] Thus, although each of these indices reflects severity of ischemia, each reflection is different. One index of ischemia severity cannot be used as a surrogate to represent a comprehensive assessment of ischemia activity.

Pharmacologic treatment of asymptomatic ischemia

Therapies that are effective at reducing myocardial O_2 demand are most effective at suppressing episodes of asymptomatic myocardial ischemia in stable coronary patients.

Beta adrenergic blockers

As a class, beta adrenergic blockers are extremely effective in treating episodes of silent ischemia during AECG monitoring. In a recent cumulative analysis, beta-blockers were found to reduce the frequency of ambulatory ischemic events by 60%, reduce the cumulative duration of events per 48 hrs by 70%, and abolish ischemia entirely in 50%.[38] When beta-blockers are used in combination with other agents such as calcium channel blockers, there is an even greater anti-ischemic efficacy: 71% reduction in frequency, 77% reduction in duration, and complete resolution of ischemia in 60%.

Diltiazem and verapamil

Diltiazem has generally been effective in the treatment of episodes of silent ischemia. However, heart rate reduction observed during diltiazem treatment is less than that observed during propranolol therapy. As well,diltiazem has been correspondingly less effective than propranolol. In the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, the reduction in ischemic episodes was similar using a regimen either of diltiazem or atenolol, as long as the mean heart rate was reduced to a similar degree.[39] Verapamil, which is similar to diltiazem in its effect on heart rate and coronary vasomotor tone, has been found to have efficacy similar to that of diltiazem.

Dihydropyridines

Clinical trials using conventional release nifedipine as single agent therapy have generally not observed a therapeutic benefit. Recent studies with sustained-release nifedipine, which may not be associated with as significant a reflex tachycardia, have shown a 30% to 50% reduction in frequency and duration of silent ischemia episodes compared to placebo.[40] In the recent TIBBS study, nifedipine GITS reduced the number of ischemic events by 24% and their duration by 12%, although it had no effect on heart rate. In contrast, bisoprolol in the same study substantially reduced both heart rate and ischemia by 49% and 39%, respectively.[41]

The addition of amlodipine to a background regimen of a beta-blocker reduced the frequency and duration of ischemia by 62% and 56%,respectively, compared to adding placebo to the beta-blocker which reduced ischemia frequency and duration by 50%.[42] In the recent CASIS trial, amlodipine alone reduced the frequency of ischemic episodes by 28% (pNS), compared to 57% by atenolol alone ($p<0.001$), and by 72% using a combination regimen ($p<0.001$).[43]

Nitrate preparations

There have been remarkably few studies investigating the role of nitrates in the treatment of silent ischemia. Von Arnim and Erath[44] compared isosorbide-5-mononitrate tablets 20 mg t.i.d. in the usual formulation, and 50 mg in the sustained-release formulation, and found that each reduced the frequency and duration of episodes of silent ischemia by about 70% compared to placebo. High-dose transdermal nitroglycerin patches (mean dose 52 mg/day) have been associated with a 46% reduction in the daily frequency of episodes of silent ischemia ($p<0.05$) and a 51% reduction in the daily duration of ischemia (p=NS) on the first day of treatment compared to placebo, but the beneficial effect is lost by the second day.[45] Use of intermittent dosing with a 12-hour nitrate-free period did not prevent the development of tolerance.

Lipid-lowering therapy

Recent studies suggest that therapies directed at improving coronary endothelial function and atherogenesis may also improve the incidence of daily life ischemia. Much, if not all, of the beneficial effect of lipid lowering may be due to prevention of plaque rupture and restoration of a more healthy coronary arterial endothelium. Patients with ischemia during daily life activities frequently have ulcerated, irregular coronary plaques, or minor thrombi,[35] and their daily ischemia may be improved with restoration

of normal endothelial function. Recent pilot studies support the hypothesis that marked lipid lowering is associated with a marked reduction in the number and duration of daily life ischemic episodes.

Andrews et al have shown that therapeutic lowering of serum LDL cholesterol using statins in coronary patients with asymptomatic daily life ischemia resulted in resolution of ischemia in 13 of 20 treated patients over six months.[47] In contrast, only two of 20 patients in a placebo group showed resolution of ischemia over the same time (p=0.05). These preliminary studies have led to the formation of a large scale, NHLBI-funded clinical trial, the "Vascular Basis for the Treatment of Myocardial Ischemia," to determine whether improvement in endothelial function, using atorvastatin, antioxidant vitamins C and E, or a combination, will lead to a decrease in ischemia during daily life and to an improvement in exercise capacity. Seventy-five of the projected 300 patients have been enrolled at this time and it is anticipated that the results will be available in the year 2001.

Prognosis of transient asymptomatic ischemia during AECG monitoring

Most observational studies have demonstrated that the presence of asymptomatic ischemia during AECG monitoring of routine daily life activities is associated with an adverse cardiac prognosis (Table 1). There is a linear association between the number of ischemic episodes that are present off medications and the subsequent one-year incidence of death, MI, revascularization, or an ischemic event requiring hospitalization in patients subsequently treated medically (p=0.003) (Figure 3). The Total Ischemic Burden Bisoprolol Study (TIBBS) indicated that patients with ≥6 episodes of AECG ischemia/48 hours at baseline had a 32% event rate at one year (death, MI, unstable angina, or revascularization) compared with 25% for patients with 2 to 5 episodes and 13% for patients with < 2 episodes (p<0.001).[48]

In some studies comparing the significance of ischemia detected by AECG, ETT, and angiographic and clinical variables in stable coronary patients, the presence of daily life ischemia (detected by AECG monitoring) is the most powerful predictor of cardiac mortality in follow-up to two years (p=0.003), and of all cardiac events (death, MI, PTCA, CABG) for up to five years (p=0.009).[49,50]

A fundamental problem with virtually all the previous prognosis studies is that the event rates for 'hard end points' such as cardiac death or MI are very low in these stable patients and consequently, essentially all the studies have relied on much less definitive end points such as revascularization procedures, worsening angina, or unstable angina, to obtain statistical power. Use of these softer endpoints opens up these studies to important biases.

Figure 3: Relationship between AECG ischemic episodes and incidence of combined cardiac events (death, MI,coronary revascularization procedure, or hospitalization for an ischemic event) between week 12 and 1 year in ACIP. Patients in the two medical groups are indicated by closed circles and patients in the revascularizaiton group are indicated by open triangles. The r values represent the correlation between the number of AECG ischemic episodes and the incidence of combined cardiac events in the respective groups. (Adapted from Stone et al[56] with permission.)

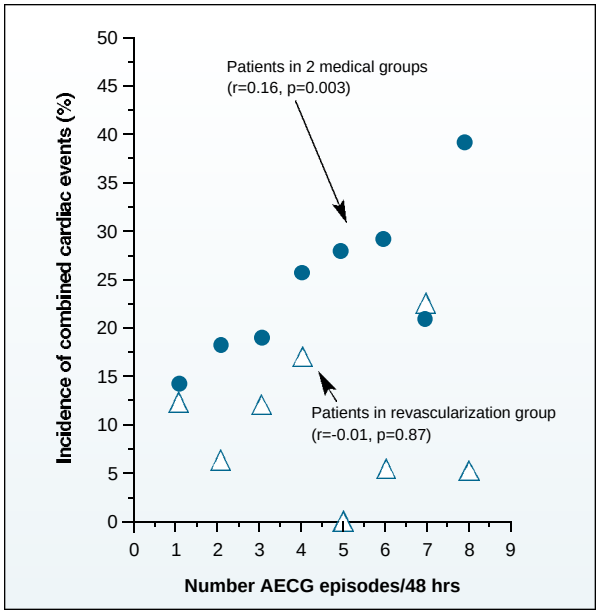


Table 1: Observational studies defining the incidence and prognostic significance of daily life ischemia in patients with stable CAD.

Authors, year	No. patients	Incidence of AECG ischemia (%)	End points	Mean follow-up (months)	Event rates (%) With AECG ischemia	Event rates (%) Without ischemia	P-value	Comments
Rocco, 1988[64]	86	57	Death, MI UA, revasc	12.5	40	3	0.003	Patients monitored once off Rx
Tzivoni, 1988[65]	118	33	Cardiac death, MI, UA, revasc	28	51	20	<0.001	All patients with previous MI
Hedblad, 1989[66]	394	25	Cardiac death, nonfatal MI	43	15	3	<0.001	
Deedwania, 1990[8]	107	43	Cardiac death	23	24	8	0.02	Monitored on Rx
Raby, 1990	176	18	Cardiac death, nonfatal MI	20	38	7	<0.0001	Patients with peripheral vascular disease
Yeung, 1991[49]	138	59	Death, MI, revasc	37	56	42	0.02	Monitored off Rx
Deedwania, 1991[50]	86	45	Cardiac death	24	23	4	<0.008	Monitored on Rx which controlled symptoms
Quyyumi, 1993[5]	116	39	MI, UA, revasc	29	13	15	NS	Very low-risk patients
Moss, 1993[67]	936	5	Cardiac death, nonfatal MI, or UA	23	27	24	NS	Very low-risk patients
de Marchena, 1994[68]	50	32	Cardiac death, MI, UA, revasc	10	56	21	<0.02	All patients monitored on Rx which controlled symptoms
Madjilessi-Simon, 1996[51]	331	27	Death, MI, revasc, or worsening angina	21	33	17	0.004	All patients initially treated with a beta-blocker

Table 2: Randomized clinical trials to assess the effect of anti-ischemic strategies on prognostic significance of daily life ischemia.

Authors, year	No. patients	End points	Follow-up	Event rate by treatment group	P-value
Pepine, 1994[52]	306	Death, MI, UA, worsening angina, or revascularization	1 year	25% placebo 11% atenolol	0.001
Rogers, 1995[54]	558	Death, MI, revascularization, hospital admission	1 year	32% angina-guided medical strategy 31% ischemia-guided medical strategy 18% revascularization strategy	0.003
Dargie, 1996[53]	682	Cardiac death, nonfatal MI, and UA	2 years	13% atenolol 11% nifedipine 8% combination	NS
		Revascularization, worsening angina		8% atenolol 9% nifedipine SR 3% combination	NS
von Armin, 1996[48]	520	Death, MI, UA, or revascularization	1 year	32% for non-100% responders 18% for 100% responders	0.008
				33% for nifedipine 22% for bisoprolol	0.03

Randomized clinical trials that assess the effect of anti-ischemia strategy

The ability of anti-ischemic therapies to improve the adverse prognosis associated with AECG ischemia has been inadequately studied (Table 2).

Pepine et al[52] studied 306 patients with ischemia detected both by ETT and by AECG and found that patients treated with atenolol had improved event-free survival and increased time to the occurrence of a first adverse event compared with patients treated with placebo. The most powerful univariate and multivariate correlate of event-free survival was the absence of AECG ischemia after 4 weeks of treatment. The control group, however, received no antianginal therapy, and the study consequently does not address the question of the incremental value of treating asymptomatic ischemia detected by AECG monitoring, in addition to treating asymptomatic ischemia.[52]

In the TIBBS study, patients whose AECG ischemia was entirely abolished by bisoprolol or nifedipine had a 17.5% event rate at 1 year compared with 32.3% for patients who had at least one episode of residual ischemia (p=0.008).[48]

The Total Ischemic Burden European Trial (TIBET) found no difference in the occurrence of cardiac events after an average follow-up of 2 years in patients treated with fixed doses of either atenolol, nifedipine, or the combination, but there was no dose titration to determine the incremental benefit of escalation of anti-ischemic therapy, and there was substantial withdrawal (up to 40%) of assigned medication over the 2-year follow-up.[53]

The Asymptomatic Cardiac Ischemia Pilot (ACIP) study was designed to determine the feasibility of performing a large-scale clinical trial to assess the prognostic significance of daily life ischemia. In the pilot study, 558 patients with coronary anatomy amenable to revascularization, one or more episodes of daily life ischemia on a 48-hour AECG, and ischemia on an ETT, were randomized to one of three treatment strategies: medication to suppress angina alone (angina-guided strategy, n = 183); medication to suppress both angina and daily life ischemia (ischemia-guided strategy, n= 183); revascularization strategy (angioplasty or bypass surgery, n= 192).[56]

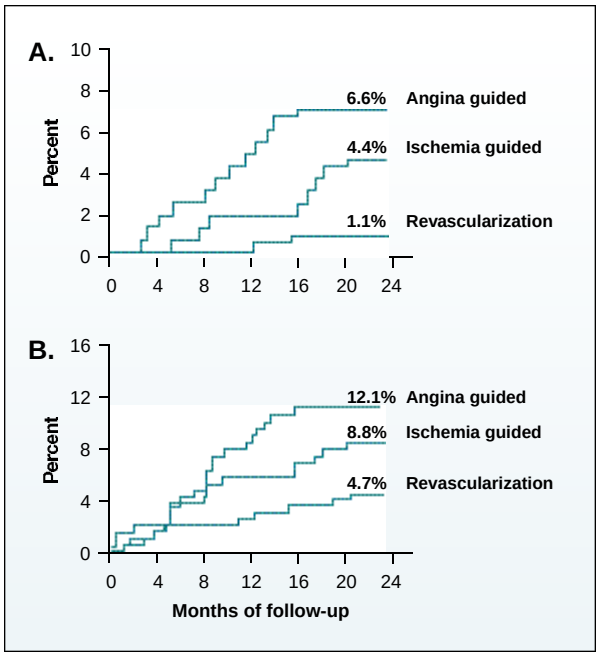
Patients were evaluated with serial AECGs and medication was titrated to reduce anginal symptoms (all patients) and to eliminate daily life ischemia (ischemia guided strategy patients). At the 12-week, 6-month, and 1-year follow-up, daily life ischemia was suppressed in each of the three treatment groups, but was more often completely suppressed in patients assigned to revascularization ($p < 0.001$ at each follow-up interval). The escalation of medication regimens in the ischemia-guided group was minimal and better ischemia reduction might have been achieved with more aggressive dose titration.[56]

Although not powered to be a prognosis study, the ACIP pilot study provides important suggestions concerning the prognostic value of treating daily life ischemia.[54,55] While the number of fatal events was small, the percentage of patients who died during the 2-year follow-up was significantly lower than for patients assigned to the revascularization strategy (1.1%), and those assigned to the angina-guided strategy (6.6%; $p< 0.005$) (Figure 4A). Ischemia-guided strategy patients had an intermediate mortality rate (4.4%) between the revascularization strategy and the angina-guided strategy. There was no difference in mortality rate between the revascularization and the ischemia-guided strategies. Similar results were found combining the end points of death or MI (Figure 4B). The incidence of either death, MI, or nonprotocol revascularization was less common with revascularization than with either of the two medical strategies, but there was no significant difference between the two medical strategies. Medical titration in the ischemia-guided strategy patients was not aggressive enough to eradicate ischemia, however, and a better prognostic effect might have been achieved if the medical regimen had been more effective.

Nevertheless, in the two medical strategies, there was a trend associating greater reduction in AECG ischemia at 12 weeks with an improved subsequent prognosis ($p = 0.04$).[56] This trend was evident primarily in the ischemia-guided group ($p = 0.06$) compared to the angina-guided group ($p = 0.32$). These observations constitute the first suggestion that AECG-guided treatment of ischemia enhances prognosis in patients with stable coronary disease.

In contrast to the observations in the two medical groups in ACIP, in the revascularization group there was no association between the number of AECG ischemic episodes at baseline and the incidence of subsequent cardiac events, nor in the change in ischemic episodes from the baseline to the week 12 AECG (Figure 3).[56] These observations suggest that revascularization is effective in lowering the incidence of subsequent cardiac events, regardless of the number of ischemic episodes present prior to revascularization. The clinical benefit resulting from revascularization may not be due to suppression of ischemia *per se*, but instead to an improvement in the underlying anatomic substrate that is responsible for the subsequent development of cardiac events.

Figure 4: A. Two-year cumulative mortality rates for three treatment strategies in ACIP. Significant differences were seen between revascularization and angina-guided strategies (p<0.005) and between revascularizatin and ischemia-guided strategies (p<0.05). Angina-guided and ischemia-guided strategies were not significantly different from each other (p=0.34).
B. Two-year cumulative rates of death and MI. Revascularization strategy was significantly different from angina-guided strategy (p<0.01). Differences were not significant between revascularization and ischemia-guided strategies (p=0.12) and between angina-guided and ischemia-guided strategies (p=0.30).
(Adapted from Davies[65] with permission)



Although small observational studies and randomized, prospective, pilot studies indicate that the presence of daily life ischemia exerts an independent prognostic effect, these findings must be confirmed in a large-scale clinical trial with sufficient power to identify a benefit using reliable and accepted end points such as cardiac death and MI. It seems likely that daily life ischemia also indicates increased risk because of its association with "active" or "complex" coronary lesions, as well as severe lesions. Therefore, large-scale randomized trials that aim to benefit patients with daily life ischemia should select therapies that improve the dysfunctional cell biology that characterizes atherosclerotic coronary lesions, as well as therapies to improve the myocardial O_2 supply/demand balance. Such a trial is currently being planned by the NHLBI.

Until the prognosis studies are completed, routine clinical use of AECG monitoring to identify the high risk stable coronary patient and to tailor optimal therapy is probably not justified. AECG monitoring remains valuable nevertheless to assess ischemia in patients who cannot exercise because of peripheral vascular disease and in patients in whom Prinzmetal's variant angina is suspected. AECG monitoring has also become an established ischemia endpoint in clinical investigations of new anti-ischemic strategies.

Unstable angina pectoris

With the advent of AECG monitoring in the early- and mid-1980s, it became clear that many patients with unstable angina exhibited refractory episodes of asymptomatic ischemia, which persisted despite adequate control of symptoms with an intense medical regimen. In the era of treatment with a combination regimen of nitrates, beta-blockers, and calcium channel blockers, approximately 50% to 70% of patients exhibited transient episodes of asymptomatic ST-segment deviation. Since heparin, aspirin, and even GP IIb/IIIa inhibitors are now included in current regimens, the incidence of asymptomatic ischemia has dramatically decreased to approximately 10% to 20%.

As noted earlier for patients with stable angina, patients with unstable angina who exhibit episodes of transient asymptomatic ischemia have high risk coronary anatomy and a corresponding adverse prognosis. Although the presence of asymptomatic ischemia is often among the most important predictors of an adverse outcome in unstable angina,[57-60] the infrequent incidence of this abnormality in the recent TIMI IIIB study casts doubt on the widespread utility of AECG monitoring to identify risk in the current therapeutic era. Among 733 patients with unstable angina or non-Q-wave MI treated medically, only 10% exhibited >1 episode of asymptomatic ischemia, and only 4% exhibited ischemia >20 minutes/ 24 hrs.[61] Furthermore, patients with a high risk AECG were generally identified by other risk stratifying tests. The AECG uniquely identified risk in only 3% of the patients, the exercise thallium test uniquely identified risk in 34% of patients, and the exercise test alone identified risk in 33% of patients.[61]

Thus, although AECG monitoring identifies unstable angina patients at risk, the low incidence of AECG abnormalities in the current therapeutic era and the higher incidence of abnormalities using other simple risk-stratifying tests suggests that AECG monitoring should not be routinely recommended for clinical risk assessment. It does remain, however, a valuable research tool to assess anti-ischemic strategies.

Acute myocardial infarction

The largest study designed to systematically investigate the incidence and significance of asymptomatic ischemia detected by AECG monitoring compared with other risk-stratifying tests was performed in 406 patients who were studied 5-7 days after MI.[62] Ischemia detected by AECG monitoring was the most powerful predictor of adverse cardiac events. In contrast to the prognostic value of AECG monitoring, the development of ischemia during the ETT did not predict an adverse cardiac event although the rates for all cardiac events were markedly higher among the patients in whom exercise testing was not performed.[66] Among clinical variables, ejection fraction variables, ETT and AECG monitoring variables, the presence of AECG ischemia contributed the most significant prognostic information.[66] Although AECG ischemia had a low predictive value for death alone (12%), it had a 44% predictive value when nonfatal MI and unstable angina were included as outcomes.

Despite published reports of the value of AECG monitoring post-MI, such testing has not been performed on a widespread basis. The reluctance of the medical community to incorporate AECG monitoring for risk stratification post-MI is multifactorial. Most published results include relatively small numbers of patients and the endpoints in many of the series include outcomes such as revascularization, which is notoriously subject to important biases. The incidence of AECG ischemia is also often quite low, and its positive predictive value may also be quite low. Resting QRS and ST-T wave abnormalities post-MI also often preclude meaningful interpretation of additional ST-segment deviation. Lastly, AECG

monitoring requires dedicated and experienced personnel to distinguish artifact from genuine ischemia. Further experience must be gained before widespread use of this risk-stratifying test can be recommended for all patients following acute MI.

Conclusion

Asymptomatic ischemia is common in patients with stable coronary disease during routine daily activities, exercise, and mental stress. The perception of ischemic pain (angina) may be modulated in part by peripheral neuropathic changes or modulated by central processing of afferent stimuli by physiologic and psychologic influences. Since asymptomatic ischemia is not associated with symptoms or discomfort, the detection of ischemia by AECG monitoring would be of clinical significance only if its presence were independently associated with an adverse prognosis.[63] Observational studies and small-scale randomized clinical trials suggest that more aggressive and thorough treatment of ischemia would lead to an improved outcome, but a more definitive large-scale study is necessary to confirm this relationship. Such a trial is currently in final planning stages by the NHLBI.

The incidence of ischemia in patients with unstable angina has declined dramatically with use of aspirin, heparin, and the more powerful antithrombotic agents. Identification of AECG ischemia in unstable angina patients indicates high risk, but the unique contribution of AECG monitoring to identify high risk is not great. Other risk-stratifying tests such as exercise testing or exercise perfusion scintigraphy may be more appropriate than AECG monitoring for widespread clinical use. In patients risk-stratified following acute MI, AECG monitoring to detect asymptomatic ischemia appears to be quite useful, but experience is somewhat limited. As with patients with unstable angina, the unique contribution of AECG ischemia will need to be confirmed prior to recommendation for widespread use of AECG monitoring.

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