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Asymptomatic CAD & Silent Ischemia: Roles of Stress Testing, Myocardial Imaging, Optimal Medical Therapy, and Myocardial Revascularization

Mandeep S. Sidhu, William Boden

I. Silent Myocardial Ischemia: What every physician needs to know.

Silent myocardial ischemia (SMI)—also referred to as asymptomatic ischemia—highlights that SMI is common in different clinical populations. These populations include patients with no prior history of coronary artery disease (CAD), with a prior history of CAD, and with diabetes.

Most definitions of SMI include objective evidence of myocardial ischemia without symptoms of angina or classic chest discomfort. This definition, however, does not take into consideration that many patients exhibit a myriad of atypical symptoms such as dyspnea, while other patients do not experience any symptoms at all. The lack of these symptoms—chest discomfort or angina—as a dominant feature can create clinical challenges in evaluating patients with SMI.

A. History Part I: Pattern Recognition:

N/A

B. History Part 2: Prevalence:

To reduce the possible risks associated with silent ischemia, it is important to identify, diagnosis, and provide therapy to these individuals. Depending on the population studied and the modality used to diagnose SMI, studies estimate that the incidence of SMI ranges from 0.52% to 22% and the prevalence ranges from 12% to 33% in the U.S.

A population of apparently healthy subjects without risk factors for CAD demonstrated a 24% rate of abnormal stress on an ECG or on myocardial perfusion imaging studies. The prognostic significance of SMI has previously been debated; however, studies have demonstrated a worse prognosis and higher risk of unfavorable outcomes in each patient subset, including patients without history of known CAD, stable angina, unstable angina, and post–myocardial infarction. For example, in one study of a CAD population, SMI occurred far more frequently than anginal episodes. SMI is also known to have increased risk of coronary disease and events.

These findings support earlier Framingham Study data suggesting that asymptomatic patients with multiple risk factors have an annual cardiac death rate of approximately 3%. Further data

from the Multiple Risk Factor Intervention Trial (MRFIT) and Lipid Research Clinic's Coronary Primary Prevention Trial (LRCPPT) demonstrated individuals with asymptomatic ischemia on exercise treadmill testing (ETT) in a population of patients without known CAD was predictive of a five-fold increase in risk for coronary events and cardiac death in long-term follow-up.

C. History Part 3: Competing diagnoses that can mimic Silent Myocardial Ischemia.

Mechanism

Understanding that the mechanism and pathophysiology of silent ischemia has not been established and remains controversial, it is necessary to explore the proposed mechanisms for an imbalance in myocardial oxygen supply and demand to better understand the pathophysiology underlying SMI. The increase in the rate pressure product leads to an increase in myocardial demand, which likely leads to the manifestation of anginal episodes in patients with known CAD and similarly the presence of SMI without overt angina.

It has been demonstrated that the blood pressure (BP) and heart rate (HR) components of the double product are both increased immediately prior to onset of ST depressions on ambulatory electrocardiography. Other possible mechanisms involved in silent ischemia may include abnormal endothelial function and abnormal microvascular physiology.

The controversy regarding the role of increased demand with ambulatory electrocardiography is furthered by data suggesting that a majority of silent ischemic episodes occur at rest or with minimal activity, instead of the widely held notion that these episodes occur with higher levels of physical activity studies regarding increased HR and BP immediately preceding the electrocardiographic findings of ischemia.

Studies that analyzed additional factors—including circadian rhythm and mental stress—show an increase in myocardial demand. These studies also looked at the role of the physiologic effects of circadian rhythm and revealed that the silent ischemic events showed a circadian pattern with a high density (34% of total events) between 6:00 AM and noon.

Another study explored whether the ischemic threshold during daily activity exhibits a circadian pattern that might relate to the frequency of ischemic episodes. The study also examined the time of occurrence and the heart rate at onset of ischemia in 1,371 ischemic episodes recorded in 41 patients. These data demonstrated an occurrence of ischemic episodes that exhibited the typical bimodal circadian distribution with a prominent peak between 7:00 and 11:00 AM and a second less prominent peak between 6:00 and 9:00 PM.

In addition, studies have further examined the role of mental stress in silent ischemia in patients with CAD. The relationship between mental stress and the induction of silent ischemia in patients with coronary artery disease was first described in 1983 by Rozanski and colleagues.

Subsequently, further investigation in a stable angina population demonstrated mental stress resulting in a significant increase in plasma epinephrine and norepinephrine levels during each treatment phase. This would increase afterload (blood pressure) and preload (wall tension),

thereby increase myocardial demand. Although these data do not reflect an SMI population, the underlying pathophysiology and mechanisms of disease may be similar.

In the Psychophysiological Investigation of Myocardial Ischemia(PIMI) trial, patients with daily life ischemia exhibited a heightened generalized response to mental stress. Additionally, ST segment depression in response to mental or exercise induced stress was more predictive of ST segment depression during routine daily activities than other laboratory-based ischemic markers.

The effects of mental stress highlight that atherosclerosis disturbs the normal vasomotor response (no change or dilation) of large coronary arteries; in patients with atherosclerosis paradoxical constriction occurs during mental stress, particularly at points of stenosis. These data support the hypothesis that the physiologic effects of circadian rhythm and mental stress are likely to play a role in the mechanisms underlying silent ischemia.

Pain modulation, perception by neurologic pathways, and signaling also play a role in the mechanism of silent ischemia. It remains unclear why some patients with confirmed ischemia do not perceive the sensation of pain or discomfort while other patients do perceive these symptoms.

D. What diagnostic tests should be performed?

There are many ways to diagnose silent ischemia, including ambulatory ECG; resting ECG; exercise treadmill testing; stress imaging modalities; and electron beam computed tomography (EBCT), when patients have no symptoms, but have objective evidence of ischemia such as ST segment deviation, regional wall motion abnormalities, perfusion imaging defects, or presence of coronary calcium.

Traditionally, the diagnosis of silent ischemia has been made with ambulatory monitoring. However, the availability of ETT has largely supplanted ambulatory monitoring. Stress imaging studies have largely supplanted ETT in clinical practice despite the guidelines favoring ETT for appropriate populations, such as patients without paced rhythms, left bundle branch block (LBBB), left ventricular hypertrophy (LVH), baseline ST depression, or preexcitation.

The use of ambulatory electrocardiography was first established in healthy active subjects in 1961 and was first described in SMI in 1977 by Schang et al., who demonstrated the presence of transient asymptomatic ST segment depression during daily activity. Subsequently, ambulatory electrocardiography was studied with transient ST segment depression as a marker of myocardial ischemia during daily life to validate the physiology in patients with angina and coronary disease.

More recently, the reliability of ambulatory monitoring has been challenged and it has been shown that there is a marked variability in ischemic activity for the frequency of ST segment depression and in duration of ischemia. Therefore, based on this study conducted with 48 hours of continuous monitoring performed twice on patients 5 days apart, ambulatory ST segment

monitoring outside the hospital is not a reliable method for assessing the therapeutic effects of antiischemic agents.

Criteria for diagnosing ischemia with transient ST segment depression on ambulatory electrocardiography should demonstrate at least 0.5 mV of ST segment shift, with changes lasting 60 seconds in duration followed by ST segments returning to baseline, as false positives can occur since ST segment deviation can be nonspecific.

Exercise testing with ETT can detect silent ischemia in patients with a history of CAD or exertional angina. This testing has also proven useful in the asymptomatic population and particularly high-risk patients with multiple cardiac risk factors.

ETT is readily available in clinical practice and has similar diagnostic accuracy as ambulatory monitoring, with low specificity and a high false positive rate in certain subgroups such as women. ETT can identify most patients with significant ischemia during their daily activities and therefore remains the most important screening test for significant CAD.

Myocardial perfusion imaging (MPI) with stress thallium or pharmacologic stress nuclear imaging and stress echocardiography with dobutamine stress echocardiography (DSE) are useful tests to evaluate certain patient populations who would have limited diagnostic accuracy with ETT. This limited accuracy is usually due to either a baseline electrocardiographic abnormality (LBBB, paced rhythm, baseline ST depression >1 mm, or preexcitation) or an inability to exercise, which would preclude them from reaching the target HR for a diagnostic study.

The potential for radiation exposure of MPI, potential adverse effects of dobutamine, and the costs of these stress imaging modalities need to be factored in when making the decision to further evaluate a patient for silent myocardial ischemia. Patients with a total of >7.5% myocardium ischemic were found to be consistent with high-risk silent ischemia.

This study also showed that 60%of patients had evidence of high-risk silent ischemia. The high percentage of SMI could be predicted with classic clinical risk factors—such as gender, age, diabetes, and hypertension—as well as electrocardiographic or stress related factors—such as abnormal resting ECG, angina with stress, peak HR, peak BP, ST depression with stress, and lower Duke treadmill score (DTS). These are all independent predictors of relevant silent ischemia.

Furthermore, this study demonstrated that in 3,664 consecutive asymptomatic patients without prior diagnosis of CAD undergoing myocardial perfusion SPECT (MPS), 21% had ischemia and 6% had high-risk ischemia. This translated into a worse prognosis than in patients with less silent ischemia—such as hard events of MI or cardiac death present in 3.1% in patients with high-risk ischemia and 0.4% in patients with less silent ischemia. The role for MPI modalities is well established in clinical practice and supported by the literature in specific patient populations.

Electron beam computed tomography (EBCT) may also have a role as the initial screening tool for identifying individuals at various stages of CAD development including SMI. This modality

was first studied prospectively in 3,895 generally asymptomatic subjects with EBCT, of whom 411 had single photon emission computed tomography (SPECT) within a close time period (mean of 17 days) to compare coronary artery calcium scores with SPECT and ETT and demonstrated that EBCT calcium scoring predicted an abnormal SPECT regardless of subject age or gender. Furthermore, 46% of patients with scores >400 had an abnormal SPECT (*P* <.0001).

III. Management.

Management: Role of optimal medical therapy (OMT) and myocardial revascularization

OMT, as studied in the COURAGE trial, is fundamentally based on antiischemic pharmacologic therapy aimed at double product control with both BP and HR reduction being a central principle.

The reduction in BP and HR can be accomplished with AV nodal blocking agents (including beta-blockers, such as atenolol, bisoprolol, Carvedilol, or metoprolol and nondihydropyridine CCBs, such as verapamil or diltiazem, which have a negative inotropic effect to decrease the force of contraction, as well as a negative chronotropic effect) and vasodilator agents (LANs and dihydropyridine CCBs, such as amlodipine, nicardipine, and nifedipine, which reduce systemic vascular resistance and arterial pressure, thereby reducing afterload).

These effects on vascular resistance and inotropy can each lead to decrease in myocardial demand via reduction in afterload, preload and the force of myocardial contraction. In addition, the lipid lowering and endothelial function effects of statin therapy in primary and secondary prevention is necessary along with antiischemic therapy to optimally treat silent ischemia and subsequent cardiac events.

Silent Ischemia has been shown, despite ongoing debate, to increase the risk of coronary events and cardiac mortality. The prognostic importance of SMI has been further elucidated in patients with CAD, as well as in patients without known CAD. Therefore, based on the proposed mechanisms by which cardiac ischemia may increase this risk of major cardiac events, silent ischemia can be treated based on the well understood pathophysiology of CAD with a mismatch of coronary supply with myocardial demand.

This pathophysiology is likely similar in silent ischemia along with the role of endothelial dysfunction and arterial vasomotor response. Therefore, the cornerstones of optimal medical therapy (OMT)—namely beta-blockers, calcium channel blockers (CCB), long-acting nitrates (LAN), and newer antiangina agents, such as ranolazine—can also be employed in treatment of silent ischemia in a manner similar to the treatment of symptomatic ischemia.

Beta-blocker and calcium channel blocker therapy were studied in multiple small trials for silent ischemia, including Angina and Silent Ischemia Study (ASIS) and Atenolol Silent Ischemia Study (ASIST). The ASIS trial evaluated the most effective monotherapy for patients with stable angina and a high frequency of asymptomatic ischemic episodes on ambulatory electrocardiography.

Patients were randomized to propranolol-LA (mean daily dose of 293 mg), diltiazem-SR (mean daily dose of 350 mg), nifedipine (mean daily dose 79 mg), with each compared with a placebo. Of note, 94% of all episodes of ambulatory ischemia were asymptomatic to support the earlier data regarding the prevalence of asymptomatic ischemia in a stable angina population.

Compared with the placebo, only propranolol was associated with a marked reduction in all manifestations of asymptomatic ischemia during ambulatory electrocardiography (2.3 vs. 1.0 episodes in 24 hours, mean duration of ischemia per 24 hours was 43.6 vs. 5.7 minutes with P <.0001 for both). Diltiazem's reduction of frequency of episodes was associated with a trend (P = .08) in the per protocol completed analysis and had a significant reduction (P = .03) in the intention to treat analysis.

Nifedipine had no significant effect on either measured variable for ambulatory ischemia. Frequency of angina was significantly decreased by both propranolol and diltiazem. Study limitations included small sample size (63 patients were eligible of the 194 patients screened and only 50 patients completing all four treatment phases), as well as tolerance of high doses of each therapy, limiting the patient's ability to complete all phases.

Despite these limitations, the study first demonstrated a role for beta-blocker and calcium channel blocker therapy to reduce frequency and duration of silent ischemia in the stable angina population. Subsequently, atenolol was studied versus nifedipine in 24 patients with stable exertional angina and transient silent ischemia during ambulatory electrocardiography.

Both atenolol and nifedipine were effective in reducing the average number and duration of transient ischemic events. In addition, the atenolol group had a significant decrease in duration of early morning silent ischemia.

The use of beta-blocker therapy as first-line antiischemia therapy was further studied in the ASIST and Total Ischemic Burden Bisoprolol Study (TIBBs) trials. The ASIST trial included a slightly larger population of 306 patients who were asymptomatic or minimally symptomatic with daily silent ischemia during ambulatory monitoring for 4 weeks randomized to atenolol (100 mg/day) or a placebo.

The trial revealed that the number and duration of ischemic episodes per 48 hours of ambulatory monitoring decreased in the atenolol group compared with the placebo group (number of episodes [P <.001] and duration of episodes [P <.001], respectively), and event-free survival time improved in atenolol-treated patients (P <.0066), with both increased time to onset of first adverse event (120 vs. 79 days) and fewer total first events compared with the placebo (RR 0.44; 95% CI 0.26 to 0.75; P = .001), while there was a nonsignificant trend toward fewer serious events (death, MI, VT/VF, hospitalization for U.S.) in the atenolol treated group (RR 0.55; 95% CI of 0.22 to 1.33; P =.175).

The ASIST trial demonstrated that atenolol treatment reduced daily ischemia and was associated with reduced risk for adverse outcome in asymptomatic and mildly symptomatic patients compared with the placebo. Other beta-blockers, such as bisoprolol, have been studied, as in Total Ischemic Burden Bisoprolol Study (TIBBS), which was an 8-week randomized comparison

of bisoprolol and nifedipine on transient ischemic episodes in 520 patients with stable angina. The TIBBS trial demonstrated a correlation between the number of episodes and event rates, as well as a greater reduction of ischemia with bisoprolol than nifedipine followed by an improved outcome at 1 year (22.1% vs. 33.1%, *P* = .033), which supports data with different beta-blocker agents.

The Asymptomatic Cardiac Ischemia Pilot Study (ACIP) also evaluated beta-blockers and calcium channel blockers in combination with other pharmacologic agents in comparison with myocardial revascularization as discussed below. The pharmacologic treatment aims for an angina-guided strategy and for an ischemia-guided strategy, including atenolol plus nifedipine if needed, versus diltiazem plus isosorbide dinitrate if needed.

Both strategies were effective in reducing the number of episodes and total duration of ischemia on ambulatory electrocardiography, which further supports earlier work regarding the efficacy of these pharmacologic agents in an asymptomatic cardiac ischemia population with both short-term ischemia suppression and long-term improvement in outcomes out to 2 years.

The debate regarding pharmacologic therapy versus myocardial revascularization has continued despite earlier trials (ACIP and SWISSI II), which originally established the benefits of coronary revascularization. The Asymptomatic Cardiac Ischemia Pilot (ACIP) pilot study initially demonstrated that 55% of patients assigned to the revascularization strategy (PTCA or CABG) no longer had ambulatory ECG evidence of ischemia compared with 41% of patients assigned to the ischemia-guided strategy and 39% of patients assigned to the angina-guided strategy at 12 weeks.

Follow-up of outcomes to 1 year in ACIP reaffirmed that the revascularization group received less medication and had less ischemia on serial ambulatory ECT recordings and exercise testing than those assigned to medical strategies. Despite the relatively small sample size, the mortality rates at 1 year were 4.4% in the angina-guided group compared with 1.6% in the ischemia-guided group and 0% in the revascularization group (overall, *P* = .004) and for the angina-guided versus revascularization (*P* = .003).

The incidence of death, MI, or nonprotocol revascularization or hospital admissions at 1 year was 32% with the angina-guided medical strategy, 31% with the ischemia-guided medical strategy, and 18% with the revascularization strategy (P = .003). Therefore, revascularization better suppressed asymptomatic ischemia and was associated with better outcome at 1 year.

The revascularization strategies were compared as the patients assigned to bypass surgery had more severe coronary disease (*P* = .001) and more ischemic episodes at baseline (*P* = .01) when compared with those assigned to PTCA. It is important to note that this trial was performed prior to the advent of PCI with stenting, which is a limitation for modern day applicability.

Endpoints, including ambulatory ECG ischemia using ST segment depression on exercise ECG, total exercise time, and the presence of angina at 12 weeks were all improved with CABG as compared with PTCA, despite having more severe coronary disease. At 2 years, the ACIP trial, these data were reaffirmed as the initial revascularization strategy improved prognosis of the

population compared with the angina-guided pharmacologic therapy. The intensity of the pharmacologic therapy was also an issue compared with modern day optimal medical therapy.

Coronary revascularization in the ACS population was evaluated by the SWISSI II trial, which evaluated 201 patients with ACS and recent STEMI or NSTEMI, who were found to be asymptomatic and had evidence of silent ischemia on stress imaging and underwent angiography where they were randomized to PTCA versus medical management. The study revealed a persistent benefit of revascularization with PTCA compared with antiischemic pharmacologic therapy, including secondary preventive measures for the long-term outcome of asymptomatic patients with silent ischemia post MI.

There was a significant reduction in long-term mortality (out to 10.3 +/– 2.6 years) in this trial, although like other contemporary (1991-1997) studies the intensity of pharmacologic therapy may not have been as intensive during the study period. Follow-up from this trial population has demonstrated that the rate of sudden cardiac death (SCD) corresponded to an average annual event rate of 0.6%.

Additionally, on multivariate regression analysis, the decline in left ventricular ejection fraction (LVEF) was greater in patients receiving medical management than in those who had received revascularization (P <.001), as well as in patients with residual myocardial ischemia (P <.001) or recurrent MI (P = .001) during follow-up. These findings have confirmed earlier data, once again reinforcing the importance of silent myocardial ischemia from a prognostic standpoint and reaffirming the increased risk of hard endpoints such as sudden cardiac death (SCD).

More recently, the common practice of using stress myocardial perfusion scintigraphy (MPS) to identify ischemia in patients with prior revascularization in the era of contemporary optimal medical therapy was studied in 769 patients who had asymptomatic ischemia from 2005 to 2007 and followed for a median of 5.7 years to define the benefit of repeat revascularization versus medical therapy.

Of the study group, 15% (N = 115) underwent revascularization at a median of 13 days after MPS and there were 142 deaths with no statistically significant difference between medical therapy (18.3%) and revascularization (19.1%) with P = .84. The analysis was performed with development of a propensity score to express the associations of revascularization.

After adjusting for baseline characteristics, type of prior revascularization, MPS data and propensity scores, only age and hypercholesterolemia (but not revascularization) were associated with mortality. Therefore, asymptomatic patients with history of revascularization and inducible ischemia on MPS had no significant benefit from repeat revascularization and an ischemia-based strategy did not alter mortality or improve survival compared with medical therapy.

These data suggest that intensive pharmacologic therapy from contemporary trials likely impact the net benefit when comparing medical therapy with revascularization. Unlike earlier studies, this analysis also uses modern percutaneous coronary intervention with use of drug eluting stent technology and therefore closely reflects current clinical practice. Although prior studies have evaluated the symptomatic population with ischemia post-revascularization, which is supported

by literature and clinically appropriate, the current study raises an important point in the asymptomatic post-revascularization subgroup with ischemia.

The COURAGE trial demonstrated that a strategy of initial revascularization with optimal medical therapy had no survival benefit over optimal medical therapy alone in patients with stable ischemic heart disease and angiographically documented CAD. The nuclear substudy of the COURAGE trial demonstrated that patients with extensive inducible ischemia at baseline did not seem to benefit with revascularization plus OMT compared with OMT alone. The event rates were not significantly increased with OMT alone and these data were discordant with earlier studies, demonstrating that the extent of ischemia was associated with greater benefit in all-cause mortality, with early revascularization compared with optimal medical therapy in earlier trials. Use of a different stress modality in stress echocardiography did not show a survival benefit with repeat revascularization in the asymptomatic population.

A recent post hoc analysis of the COURAGE Trial evaluated clinical outcomes in patients with silent myocardial ischemia as compared to those with symptomatic ischemia during a 5-year follow-up. There were 283 SIHD patients who qualified for enrollment on the basis of objective baseline findings of inducible ischemia and significant flow-limiting coronary stenoses (>70%) but who lacked anginal symptoms.

When compared to the 1997 symptomatic patients, there were no major differences in baseline clinical characteristics nor were there differences in death or MI as compared with symptomatic patients. There were, however, significantly fewer hospitalizations for ACS and a lower rate of subsequent revascularization in the patients with silent ischemia.

When outcomes were compared as a function of treatment strategy, there were no overall differences among the silent ischemia patients between those randomized to PCI or medical therapy for the endpoints of death or MI. However, there were numerically fewer all-cause deaths in the PCI-treated patients (n = 7) vs. medically treated patients (n = 16), which was of borderline statistical significance.

When these results were combined with the previously-noted ACIP trial, and the earlier SWISSI-II study, the pooled analysis of 1,042 silent ischemia patients revealed a statistically significant 64% reduction in the composite endpoint of death or MI in PCI-treated patients, and a significant 56% reduction in death alone. While these data should be interpreted as hypothesis-generating, they do suggest that myocardial revascularization may play a potential role in improving prognosis in these patients.

IV. Management with Co-Morbidities

Diabetics and SMI

Silent ischemia is also a challenging clinical dilemma in the diabetic patient population, which is known to have increased cardiac risk and often silent myocardial ischemia (because they possess a “defective anginal warning system” due to the effects of diabetic neuropathy on autonomic nerve endings in myocardial tissue).

It is well established that coronary artery disease (CAD) is a major complication of diabetes mellitus and CAD is leading cause of death in patients with type II diabetes mellitus. The risk is validated and guidelines have deemed type 2 diabetes as a coronary artery disease risk equivalent.

The issue of SMI and DM has been studied in the Detection of Ischemia in Asymptomatic Diabetics (DIAD) randomized controlled trial in which patients were randomly assigned either to be systematically screened with stress myocardial perfusion imaging (MPI) or not to be screened with the hypothesis that systematic screening would identify higher risk individuals and beneficially affect their risk of myocardial infarction or death. Some 1,123 patients, aged 50 to 75 years with type II DM were enrolled with no known or suspected CAD, and the prevalence of ischemia was assessed by adenosine tehnetium-99m sestamibi single-photon emission computed tomography myocardial perfusion imaging.

A total of 113 patients (22%) had silent ischemia and 33 had moderate or large perfusion defects. The strongest predictors for abnormal tests were abnormal Valsalva (HR 5.6), male gender (HR 2.5), and diabetes duration (HR 5.2).

The authors pointed out that only selecting patients who met the American Diabetes Association guidelines would have failed to identify 41% of patients with silent ischemia. However, in follow-up (mean 4.8 years) the cumulative cardiac event rate was 2.9% for an average of 0.6% per year.

Seven nonfatal MIs and 8 cardiac deaths (2.7%) occurred among the screened group and 10 nonfatal MIs and 7 cardiac deaths (3.0%) occurred among the unscreened group (HR 0.88 with 95% CI 0.44-1.88, $P = .73$). The positive predictive value of having moderate or large MPI defects was only 12%.

The overall rate of coronary revascularization was low in both groups with 31 (5.5%) in the screened group and 44 (7.8%) in the unscreened group (HR 0.71;95% CI 0.45-1.1; $P = .14$). The outcomes study concluded that in the contemporary population (2000-2002) of patients with diabetes, the cardiac event rates were low and were not significantly reduced by MPI screening for myocardial ischemia over 4.8 years.

Diabetic patients continue to pose a challenging clinical scenario as to how best to screen the asymptomatic high-risk patient for silent ischemia and whether there is any clinical benefit compared with standard control of cardiovascular risk factors. The Do You Need to Assess (DYNAMIT) trial was a prospective, randomized, open, blinded end point, multicenter trial run between 2000 and 2005 with a mean follow-up of 3.5 years in ambulatory care in 45 French hospitals. The study included 631 male and female patients with diabetes aged 63.9 +/– 5.1 years, with no evidence of coronary artery disease and at least 2 additional risk factors, receiving appropriate medical treatment.

The patients were randomized centrally to either screening for silent ischemia using a bicycle exercise test or dipyridamole single photon emission computed tomography (N = 316), or follow-up without screening (N = 315).

The main study endpoint was time to death from all causes, nonfatal myocardial infarction, nonfatal stroke, or heart failure requiring hospitalization or emergency service intervention. The study was discontinued prematurely because of difficulties in recruitment and a lower than expected event rate.

Follow-up was complete for 98.9% of patients regarding mortality and 97.5% regarding the main study end point. Silent ischemia detection was positive or uncertain in 68 (21.5%) of the screening group.

There was no significant difference between the screening and the usual care group for the main outcome (HR 1.00, 95% CI 0.59 to 1.71). A meta-analysis combining these data and the DIAD data gave similar results, with narrow confidence intervals for each endpoint, and suggesting overall that the systematic detection of silent ischemia in high-risk asymptomatic patients with diabetes is unlikely to provide any major benefit on hard outcomes in patients whose cardiovascular risk is controlled by optimal medical treatment.

In diabetic patients, with a defective anginal warning system, it is reasonable to assume that asymptomatic ischemia has a prognostic significance similar to that of symptomatic ischemia and that their management with respect to disease-modifying preventive therapy, coronary angiography, and revascularization should be similar.

Although suppression of ischemia in patients with asymptomatic ischemia appears to be a worthwhile objective, whether treatment should be guided by symptoms or by ischemia as reflected by the ambulatory ECG has not been established. Nevertheless, it seems reasonable to use antiischemic pharmacologic therapy in patients with well-documented myocardial ischemia, even if symptoms are lacking. Aggressive secondary prevention with lipid-lowering therapy has also been shown to reduce ischemia on ambulatory monitoring.

What's the Evidence for specific management and treatment recommendations?

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