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STATE-OF-THE-ART PAPER

Silent Ischemia

Clinical Relevance

C. Richard Conti, MD, Anthony A. Bavry, MD, MPH, John W. Petersen, MD, MS

Gainesville, Florida

Myocardial ischemia can occur without overt symptoms. In fact, asymptomatic (or silent) ST-segment depression during ambulatory electrocardiogram monitoring occurs more often than symptomatic ST-segment depression in patients with coronary artery disease. Initial studies documented that silent ischemia provided independent prediction of adverse outcomes in patients with known and unknown coronary artery disease. The ACIP (Asymptomatic Cardiac Ischemia Pilot Study) enrolled patients in the 1990s and found that revascularization was better than medical therapy in reducing silent ischemic episodes and possibly cardiovascular (CV) events. However, the more recent COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial found similar CV event rates between patients treated with optimal medical therapy alone and those treated with optimal medical therapy plus percutaneous revascularization. Therefore, in the current era, medical therapy appears to be as effective as revascularization in suppressing symptomatic ischemia and preventing CV events. COURAGE was not designed to evaluate changes in the frequency of silent ischemia. Therefore, silent ischemia may persist despite current-era treatment and might still identify patients with increased risk of CV events. Also, silent ischemia is likely to occur frequently in heart transplant patients with denervated hearts and coronary allograft vasculopathy, and future study aimed at improving the management of silent ischemia in this population is warranted. Additionally, future research is warranted to study the effect of newer medical therapies such as ranolazine or selected use of revascularization (for example, guided by fractional flow reserve) in those patients with persistent silent ischemia despite optimal current-era medical therapy. (J Am Coll Cardiol 2012;59: 435–41) © 2012 by the American College of Cardiology Foundation

Preventing and reversing myocardial ischemia in an effort to protect myocardial tissue is a primary goal of cardiologists. Most often, myocardial ischemia is encountered in patients with symptoms; however, ischemia that occurs without associated symptoms also has important prognostic implications. Asymptomatic (silent) ischemia may be identified during routine daily activities or during stress testing. In the 1970s, asymptomatic ST-segment depression during ambulatory electrocardiogram (AECG) monitoring was shown to occur more often than symptomatic ST-segment depression in patients with coronary artery disease (CAD) (1). Important work in the 1980s and 1990s suggested that silent ischemia was associated with adverse events (2). Further, randomized trials at that time suggested that revascularization of patients with silent ischemia might improve clinical outcomes (3); however, more recent studies have suggested similar clinical outcomes in patients with stable CAD treated with either aggressive risk factor–directed medical therapy alone or medical therapy combined with revascularization (4). Thus, review of the clinical significance of silent ischemia in the current era is warranted.

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Definition, Diagnosis, and Mechanism

After coronary artery occlusion, left ventricular mechanical abnormalities and electrocardiogram (ECG) abnormalities precede the development of symptoms (Fig. 1) (5,6). Therefore, it is not surprising that patients can have evidence of myocardial ischemia without symptoms. Silent ischemia is typically defined as objective evidence of myocardial ischemia in patients without symptoms related to that ischemia. Silent ischemia may be detected in patients who have no symptoms during an exercise or pharmaceutical stress test but who do have transient ST-segment changes, perfusion defects, or reversible regional wall motion abnormalities. Additionally, silent ischemia may be detected with the use of AECG devices such as the Holter monitor. These AECG monitors can detect ischemia with as few as 2 leads and are typically worn for 24 to 48 h with recordings analyzed using various computer algorithms (7). ST-segment changes during AECG monitoring can be nonspecific, and false positives do occur; thus, strict criteria are necessary to support a diagnosis of silent ischemia. For

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AECG = ambulatory electrocardiogram
CABG = coronary artery bypass graft
CAD = coronary artery disease
CV = cardiovascular
ECG = electrocardiogram
PCI = percutaneous coronary intervention

example, ischemia should only be diagnosed when ST-segment depression is at least 0.5 mV and the changes last at least 60 s and reverse to normal (8). More recently, an implanted ECG monitor has been described. The AngelMed Guardian ischemia detection system (Angel Medical Systems, Shrewsbury, New Jersey) places a pacemaker lead at the right ventricular apex and continuously monitors intracardiac electrocardiogram signals (9). The system alerts the patient of abnormal ST-segment deviations, and early studies have suggested an improvement in time to presentation after an ischemic event. AECG monitoring and implantable devices have allowed for evaluation of silent ischemia over longer periods of time and during routine daily activities.

Changes in either myocardial oxygen demand or supply have been proposed as the mechanism of silent ischemia. Many studies have suggested a demand mechanism of ischemia by demonstrating an increase in heart rate prior to silent ischemic events (10). Additionally, blood pressure has been shown to increase in the minutes preceding silent ischemic episodes (11). Other studies have suggested that demand alone does not explain the cause of silent ischemia; for example, the heart rate at which asymptomatic ST-segment depression occurs during AECG monitoring is significantly lower than the heart rate at the onset of ST-segment depression during exercise testing in the same patient (12). The combination of an increasing demand and an altered supply secondary to abnormal microvascular and endothelial response is a possible explanation for the mechanism of silent ischemia.

Prevalence

Asymptomatic myocardial ischemia has been shown to occur more often than symptomatic ischemia in patients with stable CAD (1). With AECG monitoring, nearly one-half of patients with stable CAD are shown to have transient ST-segment depressions that likely represent silent ischemic events (13). Similarly, nearly one-half of patients admitted with unstable angina will have silent ischemia detected during continuous ECG evaluation (14). Silent ischemia has also been documented in patients who only have risk factors for CAD; for example, 15% of patients with mild-to-moderate hypertension who had no signs or symptoms of CAD had ST-segment depression during AECG monitoring or with exercise stress (15). Also, 12% of noninsulin-dependent diabetics with no symptoms suggestive of CAD had abnormal exercise ECGs (16), although only one-half of these patients were found to have perfusion defects during thallium scintigraphy. In another study, 33% of diabetic patients with at least 1 additional cardiovascular risk factor had silent ischemia (17). Finally, even healthy patients without risk factors for CAD have been shown to have silent ischemia. Twenty-four percent of apparently healthy individuals either had an abnormal stress ECG or stress perfusion study (18).

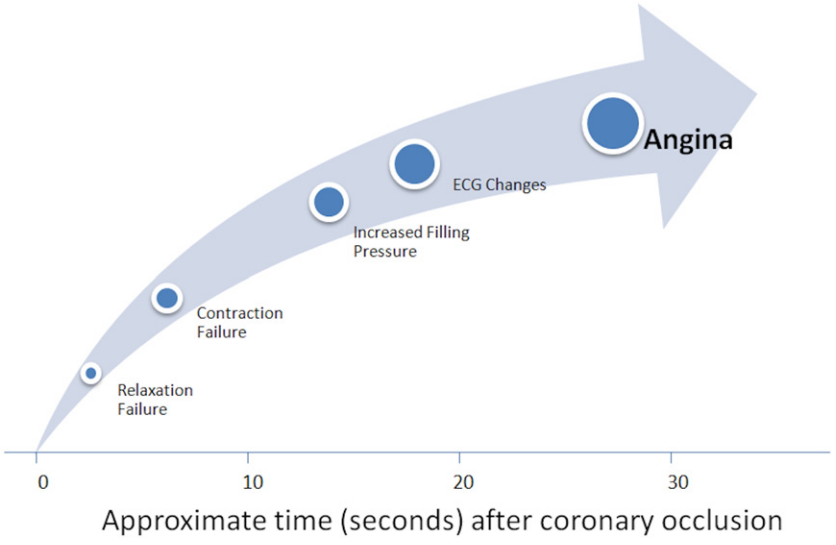

Figure 1 **Sequence of Events Following Occlusion of a Coronary Artery**

Following coronary artery occlusion diastolic, systolic, and electrocardiographic (ECG) changes precede the development of angina.

Prognosis of Patients With Silent Ischemia

Patients with stable CAD. In patients with mild-to-moderate CAD, silent ischemia provides similar prognostic information for adverse outcomes as does symptomatic ischemia. In patients with medically managed CAD, the likelihood of death or myocardial infarction during 7 years of follow-up was similar between patients with asymptomatic ST-segment depression with exercise and those patients with symptomatic ST-segment depression with exercise (Fig. 2). However, among patients with medically treated extensive CAD, silent ischemia is associated with worse prognosis than symptomatic ischemia (19).

More recent studies have suggested that ST-segment depression during AECG monitoring may be better than exercise tests in predicting outcomes. In 1 study, 86 patients with stable CAD and abnormal exercise ECGs were followed for an average of 12.5 months (20). During the follow-up period, there were 21 major cardiovascular (CV) events, and all but 1 of these events occurred in patients with AECG evidence of ST-segment depression. The number of ST-segment depression events during AECG monitoring correlated with exercise ECG findings, such as the time to onset of ST-segment depression during exercise, duration of exercise, and depth in millimeters of ST-segment depression during exercise. However, after multivariate adjustment, only ST-segment depression during AECG monitoring, and not ST-segment depression during exercise, significantly predicted worse outcomes. Similar results were provided by a different study of patients with CAD who were asymptomatic on antiangina therapies (2). Silent ischemia during AECG monitoring was a more powerful predictor of mortality than exercise duration, age, previous myocardial infarction (or resting Q waves), hypertension, diabetes, or smoking history.

Patients with unstable angina. Silent ischemia is also known to occur in patients who present with unstable coronary syndromes (14). The presence of silent ischemia in these patients provides important prediction of short- and long-term risk. In patients with unstable angina that is medically managed in a coronary care unit, evidence of silent ischemia during 48 h of continuous ECG recording was predictive of poor outcomes at 1 month and 2 years (21).

Patients after percutaneous coronary intervention. Silent ischemia has also been predictive of outcomes in patients who have undergone percutaneous coronary intervention (PCI) with stents. Six months after successful PCI, 14% of patients had evidence of silent target vessel ischemia during exercise stress perfusion imaging (22). Patients with silent ischemia had a smaller burden of ischemia (average summed difference score of 2.8) than those with symptomatic ischemia (average summed difference score of 5.9). Accordingly, compared with patients with no ischemia, silent ischemia is associated with increased adverse events but not to the extent of symptomatic ischemia (Fig. 3). Whereas this study documented a persistent, although attenuated hazard from silent ischemia after PCI, it is still unclear if detecting asymptomatic ischemia can help to improve outcomes. The ADORE (Aggressive Diagnosis Of REstenosis) trial evaluated the benefit of screening for silent ischemia with routine stress testing after PCI as compared to performing stress testing only in those with symptoms (23). Patients with PCI were randomized to either scheduled stress tests in which they had an exercise ECG at 6 weeks and an exercise ECG with nuclear perfusion imaging at 6 months versus selective stress testing, in which stress testing was only performed if patients developed a clinical indication. There was no difference in functional status,

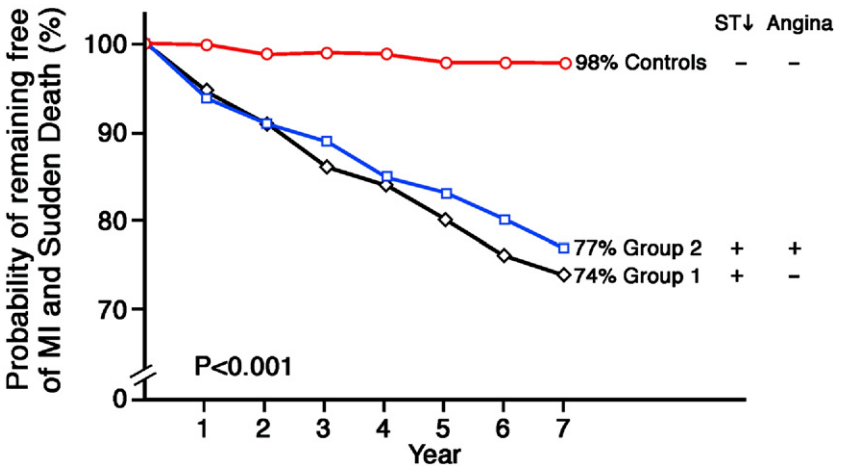

Figure 2 Prognosis of Patients With Exercise-Induced Ischemia With or Without Symptoms

Probability of remaining free of myocardial infarction and sudden death in control subjects who had no known history of coronary artery disease (CAD), and in patients with medically treated CAD and ST-segment depression during exercise with (Group #2) or without (Group #1) angina. Reprinted, with permission, from Weiner et al. (19).

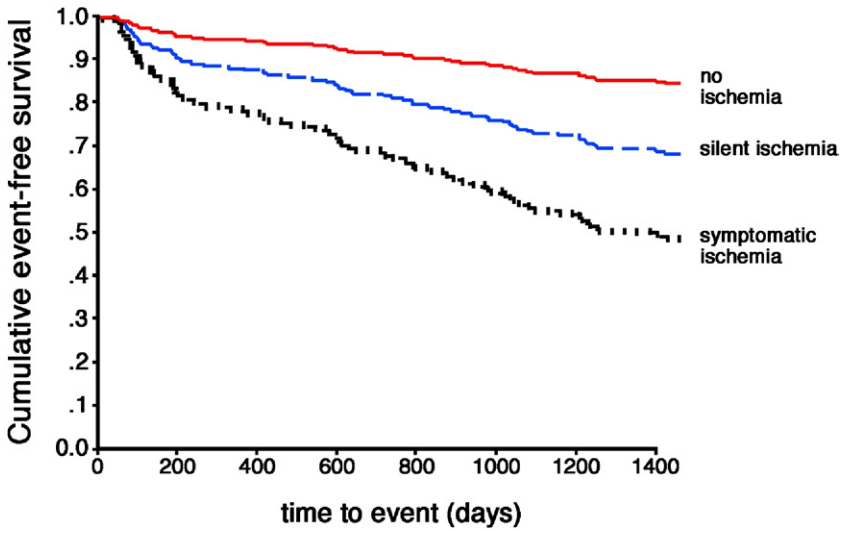

Figure 3 Survival After PCI in Patients With Ischemia With or Without Symptoms

Probability of event-free survival by symptomatic and ischemic status. Reprinted, with permission, from Zellweger et al. (22). PCI = percutaneous coronary intervention.

quality of life, or rates of invasive cardiac procedures at 9 months after PCI between the 2 groups. These findings support the American College of Cardiology/American Heart Association guideline recommendations to not routinely perform stress tests in asymptomatic patients after revascularization without specific indications (24).

Healthy subjects. Silent ischemia detected in healthy individuals with no known CAD has also been shown to predict adverse events. Among 407 healthy individuals with ages ranging from 40 to 96 years, 9.8% had a significant cardiac event during a mean follow-up of 4.6 years (18). An abnormal exercise ECG and thallium perfusion study provided independent prediction of adverse events. The degree of silent ischemia may be more important than the simple presence of silent ischemia in the prediction of future events. Zellweger et al. (25) evaluated 3,664 consecutive asymptomatic patients without known CAD who had undergone myocardial perfusion imaging. They determined that if a subject had >7.5% ischemic myocardium, then their risk of a CV event was significantly increased.

Post-transplant patients. Coronary allograft vasculopathy, which can result in myocardial ischemia, is a significant problem in patients who have had a heart transplantation (26). Because these patients have denervated hearts, they rarely present with symptoms. Instead they present with heart failure after suffering multiple small myocardial infarcts. Although the management of coronary allograft vasculopathy is beyond the scope of this manuscript, the diagnosis and treatment of these patients with silent ischemia is currently suboptimal, and further research is warranted.

Medical Therapy and Revascularization

The ACIP trial. Because silent ischemia has shown to predict poor outcomes, it is not surprising that many investigators have attempted to determine if interventions that reduce silent ischemia improve outcomes. The ACIP (Asymptomatic Cardiac Ischemia Pilot Study) tested various strategies to reduce silent ischemia. Eligible patients had evidence of asymptomatic ischemia on AECG, an abnormal exercise ECG, and stable CAD with at least a 50% stenosis (13). Whereas most of the patients had angina symptoms at study enrollment, approximately one-third were asymptomatic. Participants were randomized to medical therapy versus revascularization. Medical therapy was further divided into an angina-guided strategy with the use of antiangina medications to eliminate symptoms and an ischemia-guided strategy with the use of antiangina medications to eliminate silent ischemia on AECG monitoring. Angina or ischemia was controlled with either atenolol (with nifedipine XL if necessary) or diltiazem SR (with isosorbide dinitrate if necessary). Patients in the revascularization arm could receive either balloon angioplasty or coronary artery bypass graft (CABG) as appropriate. It is important to note that this study predated the use of coronary stents. The primary outcome at 12 weeks was the absence of ischemic episodes on AECG. At 12 weeks, patients who were revascularized had more significant suppression of ischemic events during AECG monitoring than did patients in either of the medical therapy groups (27). Specifically, 55% of patients in the revascularization group had no ischemic episodes on AECG, compared with 39% of patients in the angina-guided group and 41% of patients in the ischemia-guided group. There was no significant difference in the proportion

of patients with complete suppression of ischemic episodes between either of the 2 medical therapy groups. Importantly, the ACIP investigators demonstrated a trend toward decreased CV event rates in those patients with a greater reduction of ischemic episodes during follow-up AECG (28). Therefore, it is not surprising that the secondary composite outcome of death, myocardial infarction, revascularization, or hospitalization for unstable angina at 1 year was lowest in the revascularization group (Fig. 4) (29). Decrease in CV event rates with revascularization was also evident at 2 years (3). However, there was no difference in event rates between either of the medical therapy groups. In conclusion, ACIP demonstrated increased suppression of ischemic episodes and decreased CV outcomes in patients treated with revascularization as compared with medical therapy.

The COURAGE trial. ACIP set the stage for the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial. This large study randomized 2,287 patients with stable angina to PCI plus optimal medical therapy versus optimal medical therapy alone (4). COURAGE did not specifically evaluate for silent ischemia; however, if examined, this likely would have been observed in a large proportion of participants (13). Moreover, 13% of participants were asymptomatic at baseline. Study protocol allowed liberal use of extended-release metoprolol (89% vs. 85%), amlodipine (49% vs. 40%), and isosorbide mononitrate (67% vs. 53%), for the medical versus PCI groups (percentages listed, respectively). Aspirin, statins, and angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers were also used in the majority of patients. This contrasts with medical therapy in ACIP where the use of these background medications was quite low; for example, in ACIP, only 42% of patients in the medical therapy groups and 20% of patients in the revascularization group were on a beta-blocker (atenolol) at 12 weeks (27). Additionally, statin medications were not recorded in ACIP and were presumably used in only a small minority of patients.

COURAGE documented similar outcomes, by intention to treat, between the medical therapy and PCI groups. At a median follow-up of 4.6 years, death or myocardial infarction had occurred in 18.5% of the medical therapy group versus 19.0% of the PCI group ($p = 0.62$). In the PCI group, 21% required repeat revascularization, whereas 33% of the medical therapy group crossed over to revascularization ($p < 0.001$). The findings of COURAGE do not apply to angina patients with high-risk coronary anatomy. Research published in the 1990s reported decreased adverse clinical outcomes in patients with left main trunk or multivessel CAD treated with CABG as compared to medical therapy (30). However, the recently published STICH (Surgical Treatment for Ischemic Heart Failure) trial suggested no difference in all-cause mortality between patients with CAD and left ventricular ejection fraction <35%, who received medical therapy plus CABG versus medical therapy alone, although CV mortality was reduced by CABG (31). At 1 year, the adherence to medical therapy was high and not different between the 2 treatment groups in STICH, with more than 80% of patients on aspirin, statin, beta-blockers, and ACE inhibitors. These findings along with those of COURAGE suggest that in certain

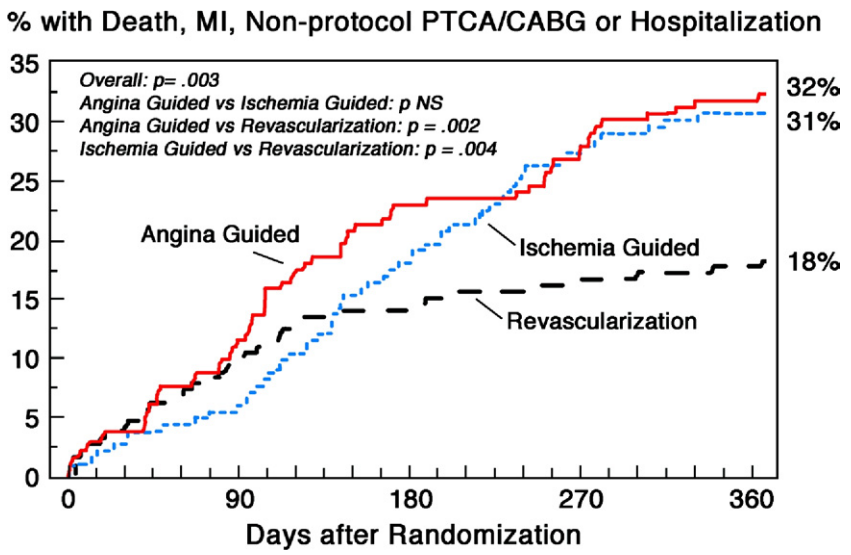

Figure 4 1-Year Cumulative Rates of Death, MI, or Cardiac Hospitalization in ACIP

Event rates were significantly different between the revascularization group and both the angina-guided and ischemia-guided groups. Event rates were not different between either of the medical therapy groups. Reprinted, with permission, from Rogers et al. (29). ACIP = Asymptomatic Cardiac Ischemia Pilot Study; CABG = coronary artery bypass graft; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

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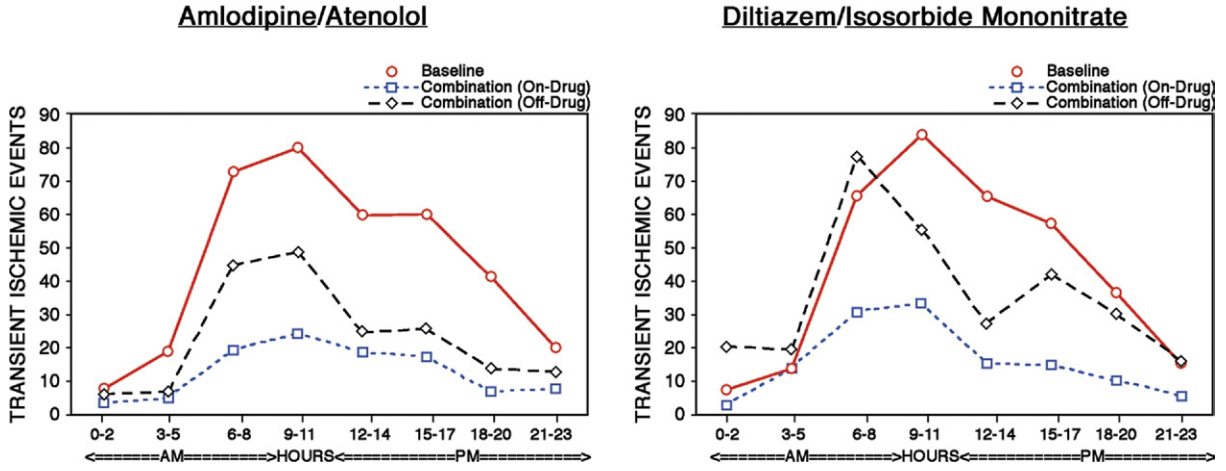

Figure 5 **Suppression of Ischemic Episodes With Various Medical Regimens**

Ischemic episodes are reduced with various medical regimens. Typical circadian pattern of ischemic episodes is also shown. Adapted, with permission, from Deanfield et al. (32).

patients optimal medical therapy may have a comparable impact on ischemia reduction to that of revascularization.

Optimal medical therapy beyond COURAGE. Because of the evolving importance of optimal medical therapy, it is important to discuss in more detail the various pharmaceutical agents that can be used to control angina and reduce frequency of silent ischemia. The CAPE (Circadian Anti-Ischemia Program in Europe) II trial found that amlodipine (10 mg daily) plus atenolol (100 mg daily) was associated with less ambulatory ischemia than extended release diltiazem (300 mg daily) plus isosorbide mononitrate (100 mg daily) (32). Also, during a drug-free period to mimic times when patients might forget to take their medications, the amlodipine plus atenolol regimen was superior at reducing ischemia, which is possibly related to the longer acting effects of amlodipine and atenolol (Fig. 5). The precise anti-ischemic regimen may be less important as long as the mean heart rate is sufficiently suppressed (33,34). Reduction of silent ischemia episodes has also been documented with aspirin, statins, and ACE inhibitors (35–37). This may be why medical therapy appears to have such an important role in management of silent ischemia patients.

Summary and Future Directions

Silent ischemia occurs often in patients with and without CAD. Initial studies documented that silent ischemia provided independent prediction of adverse outcomes. ACIP, which enrolled patients in the 1990s, found that revascularization was better than medical therapy in reducing silent ischemic episodes. Further, ACIP demonstrated a trend toward decreased CV event rates in those patients with a greater reduction in the number of ischemic episodes. The more recent COURAGE and STICH trials demonstrated similar outcomes between those patients with CAD who received revascularization and optimal medical therapy compared with optimal medical therapy alone. The medical therapy provided in COURAGE and STICH included aspirin, beta-blockers, statins, and ACE inhibitors, which was used at a much greater frequency than among ACIP patients. Separate studies have demonstrated the ability of all of these different medical therapies to suppress silent ischemic episodes, which may explain why medical therapy was as effective as revascularization in these more recent studies.

Consideration of silent ischemia may still be important for certain patients with CAD. The COURAGE and STICH trials did not evaluate for evidence of silent ischemia with AECG monitoring after treatment; therefore, it remains unclear if silent ischemia persists despite current era treatment. Presence of significant silent ischemia in the current era of optimal medical therapy might still identify a subset of patients with increased risk of CV events. Thus, silence may not always be golden. Also, silent ischemia is likely to occur with significant frequency in heart transplant patients with denervated hearts and coronary allograft vasculopathy, and future study aimed at improving the diagnosis and treatment of silent ischemia in this population is warranted. Additionally, future research is warranted to study the effect of newer medical therapies such as ranolazine or selected use of revascularization (for example, guided by fractional flow reserve) in those patients with persistent silent ischemia despite optimal current-era medical therapy.

Reprint requests and correspondence: Dr. John W. Petersen, University of Florida College of Medicine, 1600 SW Archer Road, PO Box 100277, Gainesville, Florida 32610. E-mail: john.petersen@medicine.ufl.edu.

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Key Words: asymptomatic ■ coronary artery disease ■ ischemia ■ myocardial ■ silent ischemia.