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Editorial Comment

Is There Evidence in Support of the Ischemia Suppression Hypothesis?*

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Myocardial ischemia, regardless of the presence or absence of anginal symptoms, predicts an increased risk of future coronary events and cardiac death in patients with coronary artery disease (1). Although in the past angina pectoris has been considered the cardinal manifestation of myocardial ischemia, numerous studies during the past decade have demonstrated that asymptomatic (silent) ischemia is the most common form of ischemia in patients with coronary artery disease (2). Technologic advances in ambulatory electrocardiographic (ECG) monitoring techniques have made it possible to accurately detect ischemic ST segment depression during daily life. Studies in patients with coronary artery disease have documented that between 25% and 45% of patients with a variety of acute and chronic ischemic syndromes show evidence of myocardial ischemia, most of which is silent and occurs largely during routine daily activities (2–5). Furthermore, it has been shown that silent ischemic episodes frequently occur despite medical therapy effective in controlling anginal symptoms (3). Because of the obvious lack of any patient discomfort, the clinical importance of silent ischemic episodes has been questioned. However, several recent studies have shown that the presence of silent ischemic episodes detected during daily activities by ambulatory ECG monitoring is predictive of an adverse clinical outcome and increased cardiac mortality in patients with an established diagnosis of coronary artery disease (2–5). On the basis of these results, clinicians have begun prescribing various therapies, including myocardial revascularization, with the hope that suppression of myocardial ischemia would be associated with improvement in survival and clinical outcome (6). Although conceptually such a therapeutic strategy might sound attractive, there has been no large-scale, well controlled clinical trial to support the notion that suppression of asymptomatic cardiac ischemia is of benefit in improving the associated poor prognosis. Two reports in this issue of the Journal provide seminal information in this area from the Asymptomatic Cardiac Ischemia Pilot (ACIP) study, which was organized and funded by the National Heart, Lung, and Blood Institute (7,8).

The ACIP study. There were two primary objectives of the ACIP study. It was designed to assess the feasibility of recruiting patients with well defined coronary artery disease and evidence of myocardial ischemia on both exercise testing and ambulatory ECG monitoring (7). The second main objective of the study was to evaluate the effectiveness of prespecified treatment strategy in suppressing myocardial ischemia during daily life (8). The results described in the report by Pepine et al. (7) in this issue of the Journal is the first published report of this study and illustrates several important findings. First, it is evident from the enrollment of 618 patients, within the time allotted for the study, that it is quite feasible to enroll patients according to the strictly specified criteria in which all patients have evidence of proved coronary artery disease as well as evidence of inducible and spontaneous ischemia (9). The patients were enrolled from 11 different centers from the United States, Canada and England and, as shown in Table 4, although the distribution of patients screened and randomized from these centers was quite comparable, the percent of screened patients who were eligible on ambulatory ECG monitoring varied considerably (38% to 67%). Also, contrary to the common belief that patients with coronary artery disease and silent ischemia are a low risk group, a careful examination of patient characteristics in the ACIP study, as described in Table 5, clearly illustrates that most patients with silent ischemia are elderly, have evidence of multivessel coronary artery disease, have ischemia on exercise testing and ambulatory ECG monitoring, and many have additional cardiac risk factors. The clinical characteristics of patients enrolled in the ACIP study emphasize the point that patients with coronary artery disease and evidence of ischemia during daily life are not a low risk group but indeed represent a high risk subset, a point emphasized by the findings of another recent study (10).

The other important finding described by Pepine et al. (7) is that with proper selection it is quite feasible to identify patients with evidence of asymptomatic ischemia during ambulatory ECG monitoring with a high degree of success. Of the 1,959 patients who qualified for ambulatory ECG monitoring, 952 (49%) were found to have one or more episode of ischemic ST segment changes on ambulatory ECG monitoring. The 49% prevalence rate of asymptomatic ischemia detected by ambulatory ECG monitoring in the ACIP study is comparable to that previously described in other studies (2–5) that have evaluated patients with similar characteristics and emphasizes the point that patient selection and enrollment of low risk subjects might indeed have accounted for a lower prevalence of ischemia during ambulatory ECG monitoring in another recently published study (11).

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The report by Knatterud et al. (8) describes the comparative safety and efficacy of three different treatment strategies used in the ACIP study for suppression of myocardial ischemia. In this report of the largest prospective and randomized trial published to date in patients with coronary artery disease and asymptomatic ischemia, the investigators evaluated the benefits of ischemia-guided drug therapy versus treatment with drugs titrated for control of symptoms (angina-guided strategy) and compared the efficacy of anti-ischemic drugs with that achieved with the revascularization strategy in eliminating ischemia during ambulatory ECG monitoring.

The drug combinations chosen for the study consisted of anti-ischemic agents previously proved to have a high degree of efficacy in suppressing myocardial ischemia. Although there are some legitimate concerns about the randomization procedure used in the study, the available results do provide interesting information. The percent of patients who were free of ischemia on ambulatory ECG monitoring during randomized treatment was comparable in the group assigned to the angina-guided strategy versus those assigned to the ischemia-guided strategy, despite the obvious attempt to titrate drug therapy for suppression of all ischemic episodes on repeat ambulatory ECG monitoring at 4- and 8-week follow-up visits in the ischemia-guided strategy. Whereas the persistence of ischemia in the group assigned to angina-guided strategy is in line with previous observations (2,3), the high rate of persistent ischemia on ambulatory ECG monitoring in the ischemia-guided strategy is clearly disappointing and could be a result of some design flaws that deserve attention. It is clear that the titration of drugs and their combination was not aggressive enough, as evidenced by only a modest reduction in mean heart rates recorded on ambulatory ECG monitoring during therapy. More than half of the patients assigned to drug therapy strategies were either receiving one drug or no anti-ischemic drug therapy at the 12-week visit (8). It is not clear why 16% of the patients assigned to the ischemia-guided strategy were not given any drug therapy at all. The dosages of anti-ischemic drugs used in both groups were also relatively modest and not large enough for ischemia suppression. Although the average daily dose of atenolol in the ischemia-guided group was higher than the small dose (61 mg/day) used in the group assigned to angina-guided strategy, several previous studies have indicated that significantly larger doses of beta adrenergic-blocking agents are needed to achieve maximal success in eliminating ischemic episodes during daily life (12,13). As pointed out by Knatterud et al., the titration period allowed in the study was quite short, and the schema selected did not allow an option for higher dosages. Also, it is conceivable that some patients would have required all three classes of anti-ischemic drugs given in maximally tolerated dosages to suppress all ischemic episodes. Another important finding from the ACIP study is that treatment with atenolol and nifedipine-XL in combination was significantly more effective in totally suppressing ischemia when compared with the diltiazem and isordil combination (47% vs. 32% ischemia free, $p = 0.03$) (8). The superiority of the atenolol/nifedipine-XL combination could be largely attributed to the beta-blocking effects of atenolol (8). Indeed, several other recent studies have demonstrated that beta-blockers are the most effective anti-ischemic drugs for suppression of myocardial ischemia (12,13). An additional important finding of practical importance in the ACIP study is that 90% of patients completed all follow-up visits, and the majority (96%) of patients in all treatment strategies had good compliance for taking study medications.

Whereas it is not entirely surprising that when compared with the drug therapy groups, patients assigned to the revascularization strategy were more likely to be free of ischemia at the 12-week evaluation, it is disturbing to note that 45% of patients assigned to the revascularization strategy continued to have ischemia at the 12-week evaluation. This is particularly bothersome because many of these patients (35%) were also given antianginal drugs to control symptoms. This high rate of failure of revascularization procedures in eliminating ischemia is most likely due to incomplete revascularization, as evidenced by failure of angioplasty procedures in 24% of the patients and dilation of only one vessel in 54 (81%) of the 65 patients with multivessel coronary artery disease. It is also likely that some patients may have developed restenosis by 12 weeks, also contributing to the high rate of ischemia detected in the angioplasty group on 12-week ambulatory ECG monitoring. Of the 82 patients who underwent bypass surgery and had 12-week ambulatory ECG monitoring evaluations, 58 (71%) were ischemia free, suggesting that bypass surgery may indeed be superior to angioplasty if the primary goal of therapy is to suppress all ischemic episodes.

Limitations of the ACIP study. Although the results of the ACIP study provide clinically relevant and useful information, there are some limitations that deserve attention. First, most of the patients enrolled were older white men, and thus the data obtained may not necessarily be applicable to all patients with asymptomatic cardiac ischemia. Also, because only 15% of the patients enrolled were women, the study does not allow comparison of clinical characteristics based on gender differences. Although the investigators have provided reasons for exclusion of nearly one-third of patients eligible for ambulatory ECG monitoring, this could introduce a selection bias and should have been avoided by more careful attention at screening before the qualifying ambulatory ECG monitoring was done. There could also be a selection bias toward a specific drug combination because a large number ($n = 255$) of patients randomized to drug therapy were assigned to specific treatment based on physician preference and not the randomization sequence. Whereas it might be necessary to avoid certain drugs (e.g., beta-blockers in patients with chronic obstructive pulmonary disease), the value of the randomization procedure is diminished if a large number of patients receive nonrandomized therapy. Similar limitations exist for those randomized to receive the revascu-

larization strategy, where the choice of revascularization procedure was left up to an individual physician on the basis of local practices. This resulted in obvious selection bias and led to a referral of a greater number of patients for angioplasty, which was unfortunately not as successful in eliminating myocardial ischemia on ambulatory ECG monitoring as bypass surgery.

It is well known that some of these limitations might be unavoidable in a large clinical trial, but they should have been kept to a minimum because when a significant proportion of patients fall out of the randomization scheme, it is difficult to accurately interpret the findings described. The other major limitation of the ACIP study is that the results described do not give any data for the long-term outcome of patients and thus do not really provide an answer to the critical question about the effectiveness of ischemia suppression in altering the associated adverse prognosis. Longer follow-up data from the ACIP study should be available soon and will shed some light on this clinically meaningful issue.

Lessons learned from the ACIP study. Despite some limitations, the results of the ACIP study provide clinically relevant and important findings and confirm that patients with coronary artery disease and exercise-induced ischemia do indeed have frequent episodes of spontaneous ischemia (mostly silent) during daily life. Assessment of various therapeutic strategies in the ACIP study revealed that although it is possible to suppress ischemia by antianginal drugs, significantly larger dosages than those used in the ACIP study titrated over a longer period, using multiple drugs in combination, might be necessary to achieve greater success in suppressing ischemic episodes. The results of the ACIP study also confirmed that beta-blockers are most effective in eliminating ischemia. The results of the revascularization strategy, although somewhat better than drug therapy, did not show a statistically significant difference. These findings suggest that in the full-scale trial it might be prudent to first randomize patients to angina-guided and ischemia-guided strategies, and only those failing to respond after 4 to 6 months of adequate drug therapy should be considered for randomization to the revascularization strategy, which should preferably consist of bypass surgery because of its superiority in eliminating ischemia, as demonstrated in the ACIP study (8). On the basis of the results of the ACIP study, such a scheme would not only appear to be logical but would constitute the most effective treatment strategy, which is essential to test the ischemia suppression hypothesis.

Comparison with other studies. Although at present there is no published report available from other studies similar to the ACIP, there are three major randomized trials in this area that have been recently completed. The Atenolol Silent Ischemia Trial (ASIST) (14) was conducted to evaluate the effects of atenolol versus placebo on ischemia suppression and clinical outcome in asymptomatic or minimally symptomatic patients with proved coronary artery disease, exercise-induced ischemia and evidence of asymptomatic ischemia during a 48-h ambulatory ECG monitoring. Although originally it was planned to enroll 350 patients, the study was prematurely terminated by the Data and Safety Monitoring Board because of a significant benefit with atenolol therapy in reducing the risk of coronary events. Although not yet published, the preliminary findings of the ASIST study indicated that treatment with atenolol was highly effective in eliminating ischemia in a majority of patients and that the benefit in clinical outcome was related to the effect of atenolol on myocardial ischemia. The results of the ASIST study, however, cannot be extrapolated to patients participating in the ACIP study because unlike most patients in the ACIP study who had a history of angina, the majority of patients in the ASIST study were either asymptomatic or had minimal symptoms that did not require prophylactic antianginal therapy. The other major clinical trial that has also been recently completed is the Total Ischaemic Burden European Trial (TIBET) (15). In the TIBET study, 682 patients with a history of stable angina were randomly assigned to receive atenolol or nifedipine or their combination, and evaluation consisted of exercise testing and ambulatory ECG monitoring before randomization and during active therapy. Although the preliminary data from the TIBET study suggest that all three treatments had a favorable effect on ischemia and that combination therapy was more effective than monotherapy, the results with respect to clinical outcome have not yet been reported (15). There are also significant differences between patients participating in the TIBET study versus those enrolled in the ACIP study. Unlike the ACIP study, the patients in the TIBET study did not always have a confirmed diagnosis of coronary artery disease. Ten percent of patients in the TIBET study did not even have exercise-induced ischemia, and only one-third had ischemia during ambulatory ECG monitoring. These differences in clinical characteristics of patients will certainly make it difficult to compare the results of the TIBET and ACIP studies. The third study in this area is the Canadian Amlodipine Silent Ischemia Study (CASIS) (16) in which 120 patients with coronary artery disease and stable angina were randomized to receive either amlodipine or atenolol or their combination. Although completed, the results of CASIS have not yet been reported. An important message from the successful enrollment of the target population in these studies, including the ACIP study, is that it is indeed feasible to identify and enroll patients with coronary artery disease asymptomatic cardiac ischemia.

Is the ischemia suppression hypothesis proved? The ischemia suppression hypothesis has emerged largely on the basis of logical thinking that if the presence of myocardial ischemia is predictive of an increased risk of coronary events and cardiac death, then suppression of ischemia should be associated with an improved clinical outcome. Although an attractive concept, the ischemia suppression hypothesis needs to be proved before popularizing it because the experience from the Cardiac Arrhythmia Suppression Trials has certainly taught us an important lesson by showing that some remedies

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are worse than the disease. To date, the only evidence available in support of the ischemia suppression hypothesis is the finding in the ASIST study that demonstrated that the suppression of ischemia was indeed the most powerful predictor of event-free survival at 1 year in that study. The data from studies like ASIST do suggest that suppression of ischemia is beneficial and results in improved outcome. More data, however, are needed before the ischemia suppression hypothesis can be proved.

Future implications. The results of the ACIP study (7,8) and preliminary findings from other clinical trials (14,15) have confirmed that asymptomatic cardiac ischemia does indeed occur frequently during daily life in patients with coronary artery disease. Furthermore, these studies have documented that the currently available treatment strategies can effectively eliminate ischemia during daily life. It is likely that lessons learned from these trials, as well as the introduction of newer therapeutic agents, such as platelet receptor antagonists and new anticoagulants, will improve the future success rate in eliminating myocardial ischemia. The critical question, however, is whether total suppression of asymptomatic ischemia is essential and beneficial in improving the clinical outcome. Because >6 million Americans have chronic coronary artery disease, and many of them have evidence of asymptomatic ischemia, it is crucial to find an accurate answer to this critical question in a timely manner. Clearly, the only way to prove or disprove the ischemia suppression hypothesis is to conduct a full-scale clinical trial planned by the National Heart, Lung, and Blood Institute.

References

1. Chatterjee K. Ischemia—silent or manifest: Does it matter? [editorial]. J Am Coll Cardiol 1989;13:1503.
2. Deedwania PC, Carbajal EV. Silent myocardial ischemia—a clinical perspective. Arch Intern Med 1991;151:2373–82.
3. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. N Engl J Med 1986;314:1214–9.
4. Deedwania P, Carbajal EV. Silent ischemia during daily life is an independent predictor of mortality in stable angina. Circulation 1990;81: 748–56.
5. Deedwania PC. Asymptomatic ischemia during pre-discharge Holter monitoring predicts poor prognosis in the postinfarction period [editorial]. Am J Cardiol 1993;71:859.
6. Cohn PF. Silent myocardial ischemia. Ann Intern Med 1988;109:312.
7. Pepine CJ, Geller NL, Knatterud GL, et al. The Asymptomatic Cardiac Ischemia Pilot (ACIP) Study: Design of a randomized clinical trial, baseline data and implications for a long-term outcome trial. J Am Coll Cardiol 1994;24:1–10.
8. Knatterud GL, Bourassa MG, Pepine CJ, et al. Effects of treatment strategies to suppress ischemia in coronary artery disease patients. J Am Coll Cardiol 1994;24:11–20.
9. Deedwania PC. Does myocardial ischemia portend poor prognosis? J Am Coll Cardiol 1994;23:229–32.
10. Deedwania PC, Carbajal EV, Oakley J. Silent ischemia during ambulatory ECG monitoring identifies multi-vessel CAD patients who are at increased risk of cardiac death [abstract]. J Am Coll Cardiol 1994;23:443A.
11. Moss AJ, Goldstein RE, Hall J, et al. Detection and significance of myocardial ischemia in stable patients after recovery from an acute coronary event. JAMA 1993;269:2379–85.
12. Pepine CJ. Beta-blockers or calcium antagonists in silent ischemia? Eur Heart J 1993;14 Suppl F:7–14.
13. Deedwania PC, Carbajal EV. Anti-ischemic effects of atenolol versus nifedipine in patients with coronary artery disease and ambulatory silent ischemia. J Am Coll Cardiol 1991;17:963–9.
14. Pepine CJ, Cohn PF, Deedwania PC, et al. Effects of treatment on outcome in asymptomatic and mildly symptomatic patients with ischemia during daily life: the Atenolol Silent Ischemia Study (ASIST). Circulation. In press.
15. TIBET Study Group: Total Ischaemic Burden European Trial (TIBET). Effect of treatment on exercise and Holter ECG in angina. Circulation 1992;86 Suppl I:I-713.
16. Davies RF, Herbert M, Habibi H, et al. Beta-blockers lower the heart rate threshold for ischemia during ambulatory monitoring (abstract). J Am Coll Cardiol 1993;21:20A.