JACC Vol. 27, No. 7
June 1996:1586–91

Persistent Transient Myocardial Ischemia Despite Beta-Adrenergic Blockade Predicts a Higher Risk of Adverse Cardiac Events in Patients With Coronary Artery Disease

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Objectives. **We evaluated the prevalence and prognostic significance of transient myocardial ischemia despite beta-adrenergic blockade in patients with coronary artery disease.**

Background. **Persistence of transient ischemia despite therapy may correspond to a subset of high risk patients with coronary disease. The impact of beta-blocker withdrawal in these patients remains unknown.**

Methods. **Patients (n = 313) with documented coronary artery disease and beta-blocker therapy, with (group I, n = 84) or without (group II, n = 229) transient ischemia on ambulatory electrocardiographic monitoring, were followed up during 21 ± 9 months for cardiac events (death, myocardial infarction, percutaneous transluminal coronary angioplasty, coronary artery bypass surgery and worsening angina). Occurrence of events was compared by log-rank test.**

Results. **The number of coronary stenoses did not differ significantly between groups I and II. Beta-blocker therapy was discontinued more frequently during follow-up in group II (25% vs. 14% in group I, p = 0.04). Cumulative percentage of death or myocardial infarction, or both, tended to be higher in group I at 30 months (17% vs. 5% in group II, p = 0.09). Coronary angioplasty and bypass surgery were significantly more frequent in group I (p = 0.01 and 0.0008, respectively). Transient ischemia was associated with a higher cumulative probability of adverse events (p = 0.004). The number of coronary stenoses, presence of transient ischemia and beta-blocker withdrawal were the only significant prognostic factors of cardiac events in the Cox model. In group I patients, the relative hazard of cardiac events was increased threefold when beta-blocker therapy was interrupted.**

Conclusions. **These data suggest that 1) the occurrence of transient ischemia despite beta-blocker therapy identifies a subset of high risk patients with coronary artery disease, and 2) the interruption of beta-blocker therapy increases the risk of adverse cardiac events.**

(J Am Coll Cardiol 1996;27:1586–91)

Several studies (1–4) have demonstrated that the presence of transient episodes of myocardial ischemia, mostly silent, detected by ambulatory electrocardiographic (ECG) monitoring was related to an increased risk of adverse cardiac outcome. However, the relation between survival and the detection of transient ischemia on monitoring in patients with stable angina is not yet established (5).

Standard antianginal regimens, directed toward symptom control, have been shown (6) to reduce the frequency and duration of transient ischemic episodes on ambulatory ECG monitoring. Among these regimens, beta-blocker therapy prevents the greatest proportion of transient ischemic episodes and is therefore the most effective monotherapy (7). Although a recent study (8) has suggested a link between improved outcome and beta-blocker treatment of transient myocardial ischemia, the clinical long-term benefit of reducing transient ischemia on ambulatory monitoring is unknown. Furthermore, the reported persistence of transient myocardial ischemia despite continuous beta-blocker therapy among 40% of patients with stable coronary disease (9,10) may point to a subset of high risk patients with coronary artery disease, but no morbidity or mortality study has yet addressed this question. Moreover, the impact of withdrawal of beta-blocker therapy in these patients remains unknown. The purposes of this study were to evaluate the prevalence of transient ischemia detected by ambulatory ECG monitoring despite beta-blocker therapy, its long-term prognosis and the impact of withdrawal of beta-blocker therapy in patients with stable angina due to coronary artery disease.

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Manuscript received October 11, 1995; revised manuscript received January 22, 1996, accepted January 30, 1996.

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0735-1097/96/$15.00
PII S0735-1097(96)00050-2

Methods

Patient selection. The study patients were drawn from the subjects of a 2-week double-blind randomized placebo-controlled trial carried out at 39 cardiology centers between January 1990 and April 1993. That trial evaluated the short-term efficacy of combined therapy with a beta-blocker and a calcium channel blocker (amlodipine) in reducing transient ischemia (11).

Patients were eligible for the present study if they met the following criteria: 1) coronary artery disease documented either by coronary angiograms showing ≥50% diameter stenosis in at least one major coronary artery or by previously documented myocardial infarction; 2) pretreatment with a beta-blocker for ≥2 weeks; 3) stable angina, defined as stable exercise angina without angina at rest; 4) exercise-induced ischemia within 6 months before study entry, defined as the presence of ≥1-mm horizontal or downsloping ST segment depression persisting 80 ms after the J point during an exercise ECG (standard Bruce protocol or treadmill); and 5) age 18 to 75 years.

Patients who had any of the following criteria were excluded: 1) myocardial infarction within 1 month of study entry or cardiac surgery in the preceding 2 months; 2) unstable angina; 3) atrial arrhythmias, bundle branch block, sinus bradycardia, atrioventricular node block, sick sinus syndrome, Wolff-Parkinson-White syndrome or presence of a pacemaker; 4) ST segment depression ≥1 mm due to left ventricular hypertrophy or conduction defects or any other condition that might interfere with interpretation of ST segment depression; 5) concomitant therapy with digitalis or antiarrhythmic drugs with the exception of amiodarone; 6) uncontrolled hypertension or hypotension (supine systolic blood pressure <90 mm Hg); and 7) renal or hepatic failure.

The protocol was approved by the Pitié Salpétrière University Hospital Ethic Committee. All the patients gave informed written consent for participation before enrollment in the study. Among the 313 eligible patients who underwent 48-h ambulatory ECG monitoring, 84 patients with ischemic ambulatory monitoring criteria were randomized in the 2-week trial. Because only patients with ischemic ambulatory monitoring criteria entered the short-term study, physicians were not blinded to patient data. All 313 patients entered the long-term follow-up study including the 84 patients who completed the short-term combined beta-blocker–calcium antagonist trial.

Ambulatory ECG monitoring. Continuous 48-h two-channel ambulatory ECG recordings were obtained by using 1-mm/s analog AM tape recorders (ELA medical model 2448) with a frequency bandpass between 0.05 and 50 Hz ± 3 dB. All tapes (C 120) were sent to a core ECG analysis laboratory, where they were scanned at 120 times real speed on a computerized Elatec system (ELA medical, Montrouge, France) under continuous visual inspection of an experienced physician unaware of treatment assignment. Real-time printouts showing ST segment abnormalities were also blindly reviewed by two physicians. To ensure uniform quality of recordings among different investigation centers, reference tapes were sent to the core ECG analysis laboratory before starting the study and were found compatible. Ambulatory Holter recordings were obtained from pre-jelled electrodes, positioned after careful skin preparation to record bipolar leads (V_1 to V_2 and V_5). Baseline ECG recordings were performed on each patient before and after hyperventilation and postural maneuvers were carried out to ensure the absence of artifactual ST segment depression. Patients were instructed to press an event button on the record if they had an episode of angina and to note the time and duration of any symptom in a provided diary. Because of the great variability of transient ischemia in ambulatory patients with coronary artery disease (12) and to increase the specificity of the detection (13,14), patients were required to have either four or more ischemic episodes or a total duration of ischemia ≥20 min, or both, or 48-h ambulatory ECG recordings in order to be qualified in the group with transient ischemia. An ischemic episode was defined as ≥1-mm horizontal or downsloping ST depression persisting 80 ms from the J point and lasting ≥1 min in consecutive beats and separated from other episodes by ≥1 min (12). The maximal heart rate during the ischemic episode had to be <120 beats/min. An episode was labeled silent or symptomatic on the basis of details recorded in the patient's diary.

Follow-up. The physicians in charge of the 313 patients were twice contacted to complete a questionnaire (once between December 1992 and April 1993 and again between January and April 1994). They had to determine the occurrence of death or a coronary event, or both. A coronary event was defined as myocardial infarction, need for revascularization by percutaneous transluminal coronary angioplasty or coronary artery bypass surgery, or worsening angina. The decision to perform a revascularization procedure or to change medication, or both, was determined by the physicians on the basis of their own medical practices independently of the Coordination Committee of the study. Death was classified as cardiac or noncardiac. Death was classified as cardiac if it was due to a documented cardiac cause such as fatal myocardial infarction, arrhythmias, cardiac failure or sudden cardiac arrest that occurred within 1 h of the onset of symptoms. Death due to any other cause was classified as noncardiac. Myocardial infarction was defined by chest pain with associated ECG changes and creatine kinase patterns.

Statistical analysis. Statistical analysis was performed with use of SAS (Statistical Analysis System) computer software. Results are expressed as frequency for categoric variables, mean ± SD for continuous variables. Comparisons between groups were performed by using the Student unpaired *t* test of significance for continuous variables and two-tailed chi-square test for categoric variables. Nonnormally distributed data were compared with the nonparametric Wilcoxon rank-sum test. Kaplan-Meier survival estimates of the cumulative probabilities of the outcomes at a given time were compared with the log-rank test (15). Multivariate Cox proportional hazards model was used to assess the relative prognostic values of

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Table 1. Baseline Demographic and Clinical Characteristics of Patients

	Group I: With Ischemia (n = 84)	Group II: Without Ischemia (n = 229)	p Value
Age (yr)	60 ± 10	60 ± 9	0.82
Male	91%	93%	0.46
Duration of angina (mo)	50 ± 53	54 ± 57	0.66
Asymptomatic patients	43%	47%	0.54
Previous myocardial infarction	63%	64%	0.86
Previous PTCA	31%	28%	0.52
Previous CABG	24%	25%	0.78
Cigarette smoker	60%	46%	0.03
Hypertension	44%	30%	0.02
Diabetes	13%	11%	0.67
Heart rate at rest (beats/min)	63 ± 10	66 ± 11	0.13
Medications used			
Antiaggregating agent	71%	60%	0.06
ACE inhibitor	14%	11%	0.42
Nitrate	42%	26%	0.009
Diuretic drug	19%	8%	0.005
Amiodarone	1%	3%	0.69
Oral anticoagulating agent	5%	14%	0.02

Values are expressed as mean value ± SD or percent of patients in group. ACE = angiotensin-converting enzyme; CABG = coronary artery bypass surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

different variables considered likely to have a clinically important association with outcome during follow-up. These variables were age, gender, hypertension, diabetes, history of cigarette smoking, history of previous myocardial infarction, number of anginal episodes, number of coronary artery stenoses, occurrence of transient ischemia on ambulatory ECG monitoring and beta-blocker withdrawal during follow-up. Because the exact date of interruption of beta-blocker therapy was unknown, this interruption was entered in the Cox model as a fixed covariate and not as a time-dependent covariate. In addition, the interactions between factors found significantly linked to the occurrence of cardiac outcomes were tested.

Results

Clinical characteristics. Table 1 shows the baseline characteristics of the 313 study patients. With the exception of hypertension and cigarette smoking history, all the clinical characteristics including age, gender, prevalence and mean duration of angina, previous myocardial infarction history, previous revascularization procedures, prevalence of diabetes and heart rate at rest were similar in the patients with (group I) or without (group II) ambulatory ECG monitoring criteria for transient ischemia. Coronary angiography was performed in 276 patients (88%) with 178 angiographies within 1 year before inclusion. The mean number of coronary stenoses was 2 ± 0.9 in both group I and group II, with a similar distribution of stenoses in the two groups: one-vessel disease in 31%, two-vessel disease in 35% and three-vessel disease in 34% of

Table 2. Findings During 48-h Ambulatory Electrocardiographic Monitoring

	Group I: With Ischemia (n = 84)	Group II: Without Ischemia (n = 229)	p Value
Episodes of ST ↓/48 h (no.)	7.0 ± 5.4	0.3 ± 1.2	0.0001
Mean duration of ST ↓/episode (min)	25 ± 26	9 ± 13	0.0001
Heart rate during ischemia (beats/min)	78 ± 15	90 ± 15	0.0007
Silent ischemic episodes	89%	91%	0.7000

Data are presented as mean value ± SD or percent of ischemic episodes. ST ↓ = ST segment depression.

patients. Comparison of the mean left ventricular ejection fraction evaluated by ventriculography revealed no significant difference between the two groups (62% ± 12% in group I vs. 59% ± 13% in group II). Nitrates and diuretic drugs were prescribed more often in group I patients, whereas the prescription of an oral anticoagulant agent was more frequent in group II.

Ambulatory ECG monitoring results. The results of 48-h ambulatory monitoring among the 313 patients are summarized in Table 2. Eighty-four patients (27%) had the required ECG recording criteria for myocardial ischemia (group I). In these patients, the mean number of episodes of transient ischemia/48 h was 7 ± 5, of which 89% were silent. Heart rate at onset of ischemia was significantly lower in group I patients (78 ± 15 vs. 90 ± 15 beats/min in patients without ischemia [group II] p = 0.0007).

Clinical outcome. The mean duration of follow-up was 21 ± 9 months (range 1 to 37, median 22). Of the 313 patients, 27 patients (3 of 84 in group I and 24 of 229 in group II) were lost to follow-up. This proportion (8.6%) was not significantly different between groups. During follow-up, 5 of the 84 patients in group I died (including 4 who died of cardiac causes), 3 had a myocardial infarction, 11 had worsening angina and 25 underwent coronary angioplasty or bypass surgery; a total of 28 patients in this group had one or more of these events during follow-up. Of the 229 patients in group II, 6 died during follow-up (4 from cardiac causes), 9 had a myocardial infarction, 24 had worsening angina and 19 required coronary angioplasty or bypass surgery; a total of 40 patients in this group had one or more events during follow-up. The addition of amlodipine to beta-blocker therapy did not significantly decrease the number or duration of transient ischemic episodes on ambulatory ECG monitoring during the 2-week treatment period (13) and did not influence the long-term outcome of the patients.

Revascularization procedures (coronary angioplasty, bypass surgery) were required significantly more often in group I (with ischemia). At the 30-month follow-up date, the need for bypass surgery was 18% in group I versus 6% in group II (p = 0.0008), whereas coronary angioplasty was performed in 13% of patients in group I versus 9.0% in group II (p = 0.018). These differences were already significant after 1 year (p = 0.002 and

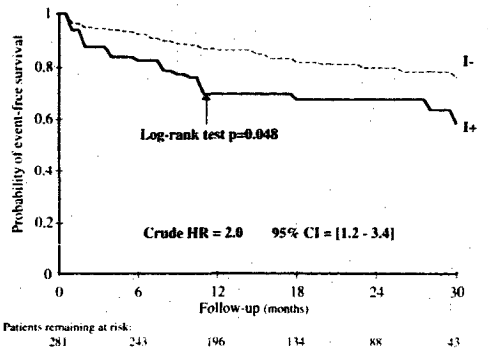


Figure 1. Kaplan-Meier estimates of the probability of event-free survival during follow-up in the 84 patients in group I with transient ischemia (I+) and the 229 patients in group II without ischemia (I−) as detected by ambulatory ECG monitoring. Arrow shows the results of the first questionnaire at the 10-month follow-up date. CI = confidence interval; HR = hazard ratio.

0.016, respectively). No significant differences between groups were observed with regard to mortality or clinical morbidity outcome (myocardial infarction or worsening angina). However, a trend toward increased probability of death was observed in group I. The rate of death, infrequent until 1 year in both groups, reached 14.6% in group I patients versus 2.9% in group II patients at the 30-month follow-up date ($p = 0.093$).

Figure 1 shows the probability of event-free survival when all coronary events are combined. The prognosis was clearly worse in group I at all follow-up times, with a relative hazard of 2.0 (95% confidence interval [CI] 1.2 to 3.4, $p = 0.004$). This difference was already significant on the first questionnaire, corresponding to a follow-up date of 10 months ($p = 0.048$). The cumulative event-free survival rate in group I versus group II patients was 70 ± 5% versus 87 ± 2% at 1 year, 67 ± 5% versus 80 ± 3% at 2 years and 58 ± 8% versus 76 ± 4% at 30 months.

Multivariate analysis showed that among all the variates entered in the Cox model, three were prognostic factors of a worse coronary outcome; these were (in decreasing importance) beta-blocker withdrawal during follow-up, presence of transient ischemia on ambulatory ECG monitoring and number of coronary artery stenoses on angiography (Table 3). Beta-blocker treatment was withdrawn among 25% of the patients in group II in contrast to 14% in group I ($p = 0.04$). None of the tested interactions were found statistically significant. The trend toward greater mortality observed in patients with ischemia was not related to a greater frequency of bypass surgery. Hazard ratio of ambulatory ischemia was not changed with the introduction of the bypass surgery variable in the Cox model (hazard ratio 2.9, 95% CI 0.8 to 10.9 and hazard ratio 3.0, 95% CI 0.8 to 11.1 before and after, respectively, introduction of this variable. Moreover, no significant interaction was observed; therefore, mortality determined according to the presence or absence of ambulatory ischemia was similar with or without revascularization.

Table 3. Multivariate Cox Proportional Hazards Regression Model of Time to Cardiac Events or Death

	Relative Hazard	95% Confidence Interval	p Value
Hypertension*	0.96	0.53–1.74	0.8884
Male gender	1.14	0.40–3.34	0.8066
Age	0.99	0.96–1.06	0.6302
Diabetes*	0.70	0.26–1.88	0.4604
Cigarette smoking history*	1.27	0.70–2.31	0.4240
Previous myocardial infarction*	0.68	0.39–1.17	0.1686
Number of anginal episodes	1.05	0.99–1.11	0.1045
Number of coronary artery stenoses	1.41	1.02–1.96	0.0356
Transient ischemia on AEM*	1.91	1.09–3.36	0.0270
Beta-blocker withdrawal*	3.09	1.65–5.79	0.0012

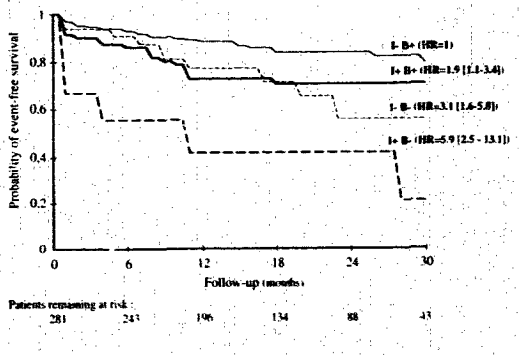
*Relative hazard of cardiac events or death in patients who had the factor as opposed to those who did not. AEM = ambulatory ECG monitoring.

Figure 2 shows the probability of coronary event-free survival among patients classified by the presence or absence of transient ischemia and the interruption or continuation of beta-blocker treatment. The group with the best prognosis, chosen as reference (HR in Fig. 1), comprised patients without transient ischemia who continued beta-blocker treatment during follow-up. The group with the worst prognosis (sixfold increase in risk of a coronary event) comprised patients with transient ischemia in whom beta-blocker therapy was discontinued.

Discussion

The prognostic significance of transient myocardial ischemia has already been demonstrated, but whether the treatment of transient ischemia can affect the long-term morbidity and mortality of patients with stable coronary artery disease remains questionable. In this study over a median follow-up

Figure 2. Kaplan-Meier estimates of the probability of event-free survival among patients in group I with ischemia (I+) and patients in group II without ischemia (I−) who had continued (B+) or interrupted (B−) beta-blocker treatment during follow-up. HR = hazard ratio; numbers in brackets indicate 95% confidence interval.



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period of 22 months, cardiac events including death, myocardial infarction, worsening angina and coronary angioplasty and bypass surgery procedures were recorded in 313 patients. The results show that persistence of a myocardial ischemia on ambulatory ECG recordings, in patients with stable angina receiving beta-blockers therapy, is a powerful predictor of cardiac events. Considering all the noninvasive and invasive data, the multivariate analysis showed two other factors with an independent prognostic value: 1) withdrawal of beta-blocker therapy during follow-up, and 2) the number of coronary artery stenoses.

Number of coronary artery stenoses. That the number of coronary artery stenoses on angiography could be a predictor of cardiac outcome is not surprising (16–20). This result is in agreement with studies (17,19) showing that after myocardial infarction, the prognosis of patients is related to the patency of coronary arteries and is impaired when arteries remain occluded. More interesting were the results of the angiographic data. In this study, the mean number of coronary stenoses was not significantly different between the groups with or without ischemia. Thus, the presence of ambulant myocardial ischemia is not dependent on the extent of coronary lesions but can be associated with a poorer cardiac prognosis.

Occurrence of transient ischemia. Numerous studies have demonstrated that in patients who have unstable angina or have had an acute myocardial infarction, coronary angioplasty or bypass surgery, the presence of transient myocardial ischemia on ambulatory ECG monitoring significantly alters the prognosis from that of patients without ischemia (1,21–23). The prognostic significance of transient ischemia on ambulatory monitoring in patients with stable coronary artery disease has also been evaluated in three important studies (2,3,24), which showed that the occurrence of transient ischemia on monitoring was a significant predictor of unfavorable coronary outcome. The results of our study are consistent with these previous reports. However, no long-term follow-up study has been performed in a large group of patients initially screened for presence or absence of transient myocardial ischemia while receiving beta-blocker therapy.

Recently the ASIST study (9) suggested that the reduction of transient ischemia with atenolol in patients with mildly symptomatic coronary artery disease was associated with a reduced risk of adverse outcome. Among the 154 patients treated with atenolol, 42% continued to have transient ischemia on ambulatory monitoring after 52 weeks of treatment. The most powerful predictor of event-free survival was the absence of ischemia on monitoring after 4 weeks of beta-blocker treatment.

To test the hypothesis that the suppression of transient ischemia would reduce the risk of adverse outcome among patients with coronary artery disease, the ACIP study (25) evaluated the benefit of a prespecified treatment strategy (ischemia-guided, angina-guided and revascularization procedures) in improving the event-free survival at 1 year. Revascularization seemed to have a significant advantage over drug therapy in improving prognosis. Surprisingly, no death occurred in the group assigned to a revascularization procedure, and the mortality rate in this group was significantly less than that in the angina-guided strategy group but similar to that in patients assigned to an ischemia-guided strategy. The results of combined incidence of myocardial infarction and death were similar. Nevertheless, the ischemia-guided therapy did not seem to improve the clinical outcomes over that of angina-guided therapy. The follow-up period of that study was relatively short. Patients in the ischemia-guided arm did not receive the drugs at a large enough dosage to suppress ischemia, and some of the patients were not given any drug at all. Each of the three strategies was only partially effective in suppressing ischemia as >40% of patients had persistent evidence of transient ischemia. No statistical outcome subgroup analysis was performed in the ACIP study, grouping patients assigned to the ischemia-guided strategy on the basis of persistence or absence of transient ischemia on ambulatory ECG monitoring. The results of our study addressed this question and identified a subset of high risk patients with coronary artery disease.

Beta-blocker withdrawal. One major finding of the present study is that the relative hazard of having a cardiac event was increased threefold in patients with transient ischemia whose beta-blocker therapy was interrupted during follow-up as over that in patients with ischemia and continuous beta-blocker therapy. This difference was even greater (sixfold) when the outcome of patients with transient ischemia and interrupted beta-blocker treatment was compared with that of patients without ischemia and continuous beta-blocker therapy. Several studies have demonstrated the existence of a possible rebound phenomenon with an increased incidence of angina, myocardial infarction, arrhythmias and death in patients with angina after abrupt interruption of beta-blocker therapy (26,27). Several mechanisms for this phenomenon have been suggested, including the presence of unmasked up-regulated myocardial beta-receptors after abrupt beta-blocker withdrawal (28). Recommendations for gradual interruption of beta-blocker treatment have been established. However, the problem of the duration of a long-term beta-blocker therapy in patients with coronary artery disease remains unsolved. Because the highest rate of death after hospital discharge of patients after myocardial infarction occurred during the 1st year in controlled randomized clinical trials (29), many investigators suggested that beta-blocker treatment needed not to be continued after 1 or 2 years. Previous myocardial infarction occurred, on average, 5 years before the study entry of our patients. Therefore, although our patients were not at the highest risk period, interruption of beta-blocker therapy during follow-up increased threefold the risk of a coronary event. No long-term study has yet evaluated the effect on prognosis of the interruption of a beta-blocker therapy in patients with stable coronary artery disease after 1 or 2 years of treatment. Such a large prospective clinical trial would require ≥20,000 patients followed up for some years and remains to be undertaken (30).

Limitations of the study. The significant increase in the event rate of coronary angioplasty and bypass surgery in

patients with transient ischemia in our study might have been in part influenced by the possible tendency of physicians to recommend invasive therapy in light of the results of the ambulatory ECG monitoring. However, a trend, although not significant, toward increased risk of death was evident in the group with transient ischemia and was not related to the greater frequency of revascularization procedures. Gill et al. (22) recently showed the significance of myocardial ischemia detected by ambulatory monitoring in 400 patients early after acute myocardial infarction. The difference between the mortality rates at 1 year—11.6% among patients with ischemia and 3.9% among those without ischemia—was highly significant ($p = 0.009$). These percentages were similar in our study over a median follow-up interval of 22 months (15% vs. 3%). Our study is also limited by a lack of precise information on the time of and reason for beta-blocker withdrawal. However, we assume that this bias does not significantly modify the interpretation of the results because, although beta-blocker withdrawal was significantly more frequent in the low-risk group II patients (without ischemia), it remained the most significant predictor of unfavorable outcome. This observation reinforces the possible impact of beta-blocker interruption.

Conclusions. Our results suggest that 1) the occurrence of transient myocardial ischemia despite beta-blockade is associated with an unfavorable outcome in patients with stable coronary artery disease, and 2) interruption of beta-blocker therapy during follow-up is the most powerful predictor of coronary events. No large scale long-term study has yet demonstrated the impact of suppression of ambulant ischemia on benefit and improved prognosis. Although this hypothesis is conceptually attractive, it remains to be proved. Further clinical studies such as ACIP II study will probably determine the role of the suppression of transient ischemia on ambulatory ECG monitoring in preventing death in patients with coronary artery disease. The question of the impact of interruption of beta-blocker therapy should be specifically addressed in these clinical trials.

We are indebted to Dominique Costagliola, PhD for statistical consultation. We are also grateful to Sandrine Maquenhem for excellent secretarial work and to Annick Guillardeau for assistance throughout the study.

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