JACC Vol. 29, No. 7
June 1997:1483–9

Relation Between Clinical, Angiographic and Ischemic Findings at Baseline and Ischemia-Related Adverse Outcomes at 1 Year in the Asymptomatic Cardiac Ischemia Pilot Study

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Objectives. **We attempted to investigate the relation between patient characteristics and adverse outcome in patients with ischemia and clinically stable coronary artery disease (CAD).**

Background. **Evidence suggests that cardiac ischemia, detected by exercise stress testing (ETT) and ambulatory electrocardiographic (AECG) monitoring during daily living, identifies a subgroup of patients at increased risk for adverse outcome, but the relation between these ischemia findings and clinical and angiographic characteristics is largely unknown.**

Methods. **We examined the relation between clinical, angiographic and ischemia characteristics at entry with adverse outcome observed at 1 year in the 558 patients enrolled in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study.**

Results. **By the 12-month visit 13.1% of patients had an ischemia-related adverse clinical outcome that included death, nonfatal myocardial infarction or an ischemia-related hospital admission. Multivariate analysis identified only the number of AECG ischemic episodes at entry (odds ratio [OR] 1.06, 99% confidence interval [CI] 1.01 to 1.12, p = 0.002) as an independent predictor of outcome. Assignment to revascularization (as opposed to an initial medical treatment strategy) showed a trend (OR 0.56, 99% CI 0.26 to 1.2, p = 0.05). None of the other baseline clinical, exercise or angiographic variables examined provided additional information relative to adverse outcome.**

Conclusions. **Determinants of adverse outcome, among clinically stable patients with CAD and ischemia induced by stress and daily life were magnitude of AECG ischemia before treatment and, possibly, initial treatment assignment. Among the many other characteristics examined, including age, symptom status and angiographic and exercise variables, none contributed additional independent prognostic information. These two simple variables, which may be modifiable, need further study in a larger trial.**

(J Am Coll Cardiol 1997;29:1483–9)

Management of clinically stable patients with coronary artery disease (CAD) remains an important challenge. This is, in part, related to the relatively low rate of adverse outcome in this patient group and the, at best, relatively modest potential benefit from specific therapies. Thus, clinicians search for predictors of adverse outcome to enhance the possibility of improving outcome in patients judged to be at highest risk. Although ischemia during stress testing has long been linked with prognosis, considerable recent evidence (1–20) suggests that cardiac ischemia during daily living, detected by ambulatory electrocardiographic (AECG) monitoring, identifies increased risk for adverse outcome. However, the precise relation between clinical, coronary angiographic, exercise treadmill test (ETT) and AECG ischemic findings and subsequent ischemia-related adverse outcome has not been clearly defined. Published data are limited by small sample size, lack of prospective protocol design, selection biases associated with

From the University of Florida, College of Medicine, Division of Cardiology, Gainesville, Florida. This study was funded by the National Heart, Lung, and Blood Institute, Cardiac Diseases Branch, Division of Heart and Vascular Diseases, National Institutes of Health, Bethesda, Maryland, by Research Contracts HV-90-07, HV90-08, HV-91-05 to HV-91-14. Study medications and placebo were donated by Zeneca Pharmaceuticals Group, Wilmington, Delaware; Marion-Merrell Dow, Kansas City, Missouri; and Pfizer, New York, New York. Support for electrocardiographic data collection was provided in part by Applied Cardiac Systems, Laguna Hills, California; Marquette Electronics, Milwaukee, Wisconsin; Mortara Instrument, Milwaukee, Wisconsin; and Quinton Instruments, Seattle, Washington. Some centers had partial support from grants from the General Clinical Research Center, National Institutes of Health.
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Manuscript received November 27, 1996; revised manuscript received February 10, 1997, accepted February 26, 1997.

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0735-1097/97/$17.00
PII S0735-1097(97)00083-1

Abbreviations and Acronyms

ACIP = Asymptomatic Cardiac Ischemia Pilot study
AECG = ambulatory electrocardiogram, ambulatory electrocardiographic
CAD = coronary artery disease
CI = confidence interval
ECG = electrocardiogram, electrocardiographic
ETT = exercise treadmill + exercise stress test
MMCC = Mortality and Morbidity Classification Committee
OR = odds ratio
QV = qualifying visit

heterogenous clinical presentations and physician-assigned rather than randomly assigned treatment and lack of core laboratory readings of tests for ischemia and angiograms.

We hypothesized that ischemia findings would interact with clinical and angiographic findings to determine outcome. Accordingly, we investigated the relation of clinical, coronary angiographic and cardiac ischemia findings at entry with ischemia-related adverse outcome during follow-up in patients enrolled in the Asymptomatic Cardiac Ischemia Pilot (ACIP) study.

Methods

Overview of ACIP project. The ACIP study design, patient characteristics and treatment outcomes are reported in detail elsewhere (21–23). Briefly, this trial, sponsored by the National Heart, Lung, and Blood Institute, investigated three different randomly assigned initial treatment strategies in clinically stable patients with CAD amenable to revascularization and stress-induced and daily life ischemia as assessed by AECG. The treatment strategies were angina-guided medical therapy, AECG ischemia–guided medical therapy and revascularization. Medical therapy consisted of two drug combinations (i.e., atenolol and nifedipine or diltiazem and isosorbide dinitrate), which were randomly assigned except when prohibited by the clinical condition (e.g., postmyocardial infarction prophylaxis). Revascularization consisted of either percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery, as determined by the site investigator. A total of 558 patients were entered into the study at 10 sites and evaluated for treatment-related effects on ischemia-related adverse outcome at predetermined time periods after study entry. Standardized forms were used to collect information about clinical characteristics, coronary anatomy and ischemia at study entry (qualifying visit [QV]) and outcome at follow-up visits. These forms were completed by a site study nurse or physician-investigator at scheduled visits or clinically indicated interim visits throughout the follow-up period. Coronary angiograms, AECGs, electrocardiograms (ECGs) and ETT ECGs were each read at three respective core laboratories. Investigators did not know the AECG or core laboratory findings. Core laboratory personnel did not know the clinical outcome or other core laboratory findings as each core laboratory had access only to the results that they generated in each case.

Outcomes of analyses. Analyses were conducted to investigate the hypothesis that patient characteristics at entry would interact to determine the presence of an ischemia-related adverse outcome during follow-up. The analyses conducted used ACIP secondary outcome variables consisting of ischemia-related clinical events that occurred by 1 year. The events included in this definition were death, nonfatal myocardial infarction and ischemia-related hospital admissions. These ischemia-related events were defined by the independent Mortality and Morbidity Classification Committee (MMCC) after review of all available patient-related documents (e.g., hospital records, ECGs, cardiac enzyme levels). The adjudicated ischemia-related hospital admissions were used to express clinically important ischemia-related events, in addition to cardiac death and nonfatal myocardial infarction, and to eliminate physician-directed nonprotocol revascularization procedures and hospital admissions that may have occurred without an antecedent exacerbation in ischemia. In these analyses, patients experiencing multiple events were tabulated according to a hierarchy so that only the most serious event was tabulated. The following order was used: death > nonfatal myocardial infarction > ischemia-related hospital admission.

Statistical analyses. The demographic and other information on patient characteristics obtained at entry were analyzed for associations with ischemia-related adverse outcome as defined before with the use of univariate Cox regression analysis. All characteristics found by univariate analysis at $p < 0.1$ were then included in the stepwise multivariate Cox regression analysis. Odds ratios (OR) and 99% confidence intervals (CI) were calculated for both the univariate and multivariate models. The p values were calculated by using chi-square, Mantel-Haenszel or Student *t* tests as appropriate. A priori, for all multigroup comparisons, a p value of < 0.01 was taken to indicate statistical significance for all the ACIP analyses (23,24).

Results

Baseline characteristics and adverse outcomes. *Entry characteristics (at QV).* As previously reported (21–23), the ACIP patients were clinically stable, and principally elderly (mean age 61.4 years), male (85.8%) and white (85.7%). Although 70.1% had reported angina either within 6 weeks of entry or induced during a study ETT or AECG, most (75.6%) had multivessel CAD, proximal coronary artery stenosis ≥50% (63.6%) and angiographic evidence for complex plaque (53.9%). These coronary angiographic findings were recently published in detail (25). An ejection fraction ≥50% was present in 88.9%. The majority had a normal 12-lead rest ECG and, although patients with ≥1-mm ST segment depression at entry were excluded by protocol, 23.7% had negligible or minor (≤0.09-mm) ST segment changes on the entry ECG. The mean number of ischemic episodes for the 48-h AECG monitoring period was 4.9 ± 5.3 (median 3) and the mean

Table 1. Frequency of Ischemia-Related Adverse Clinical Events

	Angina-Guided Strategy (n = 183)		Ischemia-Guided Strategy (n = 183)		Revascularization Strategy (n = 192)		All Patients (n = 558)	
	No.	%	No.	%	No.	%	No.	%
By 1 year								
Any ischemic event	29	15.9	25	13.7	19	9.9	73	13.1
Death	8		3		0		11	
Nonfatal MI	8		8		5		21	
Ischemia-related hospital admission*	13		14		14		41	
Details of clinical events and combinations								
Death, MI, CABG	0		1		0		1	
Death, MI	2		0		0		2	
Death, CABG	1		0		0		1	
Death, PTCA	1		0		0		1	
Death	4		2		0		6	
MI, CABG, PTCA	1		0		0		1	
MI, CABG	5		7		2		14	
MI, PTCA	1		1		1		3	
MI	1		0		2		3	
Ischemic event,* PTCA, CABG	1		3		0		4	
Ischemic event,* CABG	3		7		3		13	
Ischemic event,* PTCA	4		3		4		11	
Ischemic event*	5		1		7		13	

*Ischemia-related hospital admission classified by the Mortality and Morbidity Classification Committee as due to exacerbation of ischemia and tabulated as an ischemic event. CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

duration of these episodes was 42.9 ± 57.9 (median 22) min. The mean total exercise time using the ACIP study ETT protocol was 6.8 ± 3.2 min, and 83.1 ± 11.8% of patients achieved their age-predicted heart rate. The mean maximal ST segment depression during exercise was 2.4 ± 1.0 mm. The protocol permitted an alternate stress test that documented ischemia in the 10 patients who could not exercise.

Clinical outcomes. The frequencies (by number and percent) of ischemia-related adverse events observed by 1 year are summarized in Table 1 according to treatment strategy and for all patients. The adverse events included only death, nonfatal myocardial infarction and MMCC-adjudicated ischemia-related hospital admissions, and a total of 73 patients (13.1%) had at least one event by 1 year. Eleven patients died from cardiac causes, 21 had a nonfatal myocardial infarction and 41 were admitted to the hospital for other ischemia-related events.

Relation between baseline characteristics and adverse outcome. *Univariate analysis.* The patient entry characteristics associated with the presence (73 patients) or absence (485 patients) of adverse outcome events by 1 year are summarized in Table 2. Among ischemia characteristics, total exercise time at entry on the QV ETT (OR 0.88, 99% CI 0.78 to 0.99, p = 0.006) was associated with adverse outcome, and trends were noted for proximal left anterior descending coronary artery stenosis >50% (OR 1.79, 99% CI 0.93 to 3.45, p = 0.02), number of ischemic episodes (OR 1.03, 99% CI 1.00 to 1.07, p = 0.02) and duration of ischemic episodes (OR 1.03, 99% CI 1.03 to 1.07, p = 0.03) on the QV AECG. None of the other clinical or angiographic findings at entry that we examined were associated with adverse outcome in this univariate analysis.

Multivariate analysis. Stepwise multivariate Cox regression analysis identified only the number of ischemic episodes at entry on the QV AECG (OR 1.06, 99% CI 1.01 to 1.12, p = 0.002) as a significant independent predictor of adverse outcome (Table 3). A trend (p = 0.05) was noted for initial revascularization strategy treatment assignment as compared with the angina-guided medical treatment strategy. No other variables examined contributed additional information relative to outcome. The risks for adverse outcome by 1 year associated with increasing AECG ischemia at entry are illustrated in Figure 1.

Discussion

Our findings confirm that ischemia during daily life, as assessed by AECG, can be used to identify a group of patients with CAD who are at relatively high risk for adverse ischemia-related outcome among those who appear to be otherwise clinically stable. By 1 year, among the patients assigned to all three treatment strategies (Table 1), 13% had died, had a nonfatal myocardial infarction or had been admitted to the hospital because of an ischemic event. Among patients assigned an initial medical treatment strategy, the adverse outcome rates were even higher: 15% for death, nonfatal myocardial infarction or hospital admission for an ischemic event and 7.9% for only death or nonfatal myocardial infarction. Al-

Table 2. Baseline Characteristics and Clinical Outcome: Univariate Analysis

	Death, MI or Ischemia-Related Hospital Admission by 365 Days						
	No (n = 485)		Yes (n = 73)		Univariate Cox Regression		
	No.	%	No.	%	Odds Ratio	99% CI	p Value
Age (yr) (mean ± SD)	61.5 ± 8.2		61.2 ± 9.3		0.96	0.67–1.38	0.76
≥60 yr	299	61.7	44	60.3	0.95	0.52–1.77	0.84
Men	417	86.0	62	84.9	0.93	0.40–2.16	0.83
White	418	86.2	60	82.2	0.76	0.34–1.66	0.36
Symptoms: angina (within 6 wk of entry or on QV ETT or other stress test or with EPI on QV AECG)	331	68.3	60	82.2	2.06	0.94–4.54	0.08
Drug regimen							
Atenolol/nifedipine	242	49.9	42	57.5			
Diltiazem/isosorbide dinitrate	243	50.1	31	42.5	0.75	0.41–1.39	0.22
History							
Previous MI	202	41.7	24	32.9	0.71	0.37–1.34	0.16
Diabetes	76	15.7	14	19.2	1.26	0.59–2.71	0.44
Heart failure	15	3.1	1	1.4	0.44	0.03–5.94	0.42
Peripheral vascular disease	33	6.8	5	6.9	0.98	0.30–3.24	0.97
Hypertension	184	37.9	25	34.3	0.88	0.46–1.66	0.59
Current smoker	78	16.3	12	16.4	1.00	0.44–2.26	0.99
Ever smoked	317	65.4	49	67.1	1.07	0.57–2.04	0.78
Previous PTCA	85	17.5	15	20.6	1.21	0.58–2.56	0.51
Previous CABG	27	5.6	4	5.5	0.98	0.26–3.72	0.98
Previous PTCA or CABG, or both	107	22.1	19	26.0	1.24	0.62–2.46	0.43
Family history of CAD <55 yr	195	40.2	36	49.3	1.39	0.76–2.54	0.16
Physical examination (mean ± SD)							
SBP (mm Hg)	138.4 ± 19.1		142.2 ± 21.5		1.10	0.94–1.29	0.11
DBP (mm Hg)	79.5 ± 9.9		79.1 ± 10.7		0.97	0.71–1.32	0.78
HR (beats/min)	69.3 ± 11.8		69.3 ± 11.3		1.00	0.77–1.29	0.99
Coronary angiography (stenosis ≥50%)					1.13	0.76–1.67	0.43
1 vessel	120	24.7	16	21.9	1.00		
2 vessel	185	38.1	26	35.6	1.05	0.47–2.39	0.87
3 vessel	180	37.1	31	42.5	1.26	0.57–2.77	0.46
Proximal stenosis ≥50%	301	62.3	52	72.2	1.51	0.77–2.97	0.12
Proximal LAD stenosis ≥50%	155	32.1	33	458	1.79	0.93–3.45	0.02
Proximal stenosis ≥70%	192	39.8	35	48.6	1.41	0.77–2.60	0.14
Definite complex plaque	166	36.9	26	37.7	1.04	0.55–1.99	0.88
Definite or probable complex plaque	245	54.5	35	50.7	0.88	0.47–1.63	0.59
Ejection fraction							
<35%	7	1.5	1	1.5	0.83	0.06–11.28	0.85
35% to 49%	45	9.8	6	8.7	0.87	0.28–2.70	0.75
50% to 64%	204	44.3	27	39.1	0.84	0.43–1.63	0.50
≥65%	205	44.5	35	50.7	1.00		
Not available	24		4				
by 10% unit					1.05	0.76–1.44	0.70
QV rest 12-lead ECG							
Abnormal	229	47.2	42	57.5	1.46	0.80–2.69	0.11
Q waves	58	12.0	10	13.7	1.15	0.48–2.79	0.66
ST depression <0.1 mm	108	22.3	24	32.9	1.66	0.87–3.15	0.04
T wave abnormalities	145	29.9	25	34.3	1.20	0.63–2.26	0.47
QV AECG (mean ± SD)							
No. of EPIs	4.7 ± 5.0		6.2 ± 6.6		1.03	1.00–1.07	0.02
Duration of EPIs	40.8 ± 50.5		56.4 ± 92.7		1.03	1.00–1.07	0.03
HR change (max − mean)	56.4 ± 14.8		54.5 ± 15.3		0.92	0.74–1.14	0.30
QV ETT (mean ± SD)							
Total exercise time	7.0 ± 3.2		5.8 ± 2.8		0.88	0.78–0.99	0.006
Final HR	132.0 ± 18.8		130.3 ± 19.3		0.96	0.82–1.13	0.51
% age-predicted HR	83.3 ± 11.9		82.0 ± 11.6		0.92	0.72–1.19	0.43
Max ST depression	2.4 ± 1.0		2.5 ± 1.1		1.08	0.81–1.45	0.48

For the continuous variables ischemic episode (EPI) on qualifying visit ambulatory electrocardiogram (QV AECG) and total exercise time, the odds ratio corresponds to a 1-unit increase; for all other continuous variables (age, systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate [HR], ejection fraction, duration of ischemia, heart rate change, final heart rate, % age-predicted heart rate) the odds ratio corresponds to a 10-unit increase. CAD = coronary artery disease; CI = confidence interval; ETT = Asymptomatic Cardiac Ischemia Pilot study protocol exercise treadmill + stress test; LAD = left anterior descending coronary artery; other abbreviations as in Table 1.

Table 3. Factors Associated With Ischemia-Related Adverse Outcomes: Multivariate Analysis*

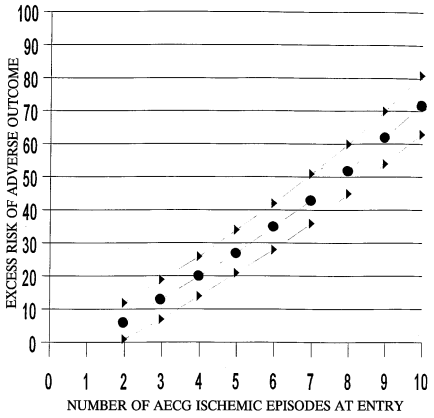
Adverse Outcome/Factor	Odds Ratio	99% CI	p Value
Death, myocardial infarction or hospital admission†			
Ischemia-guided medical strategy‡	0.80	0.39–1.61	0.41
Revascularization strategy‡	0.56	0.26–1.2	0.05
AECG ischemia (QV EPI§)	1.06	1.01–1.12	0.002

*Multivariate stepwise Cox regression odds ratios, 99% confidence interval (CI) and p values. †Ischemia-related hospital admission classified by Mortality and Morbidity Classification Committee. ‡Odds ratio as compared with the angina-guided medical treatment strategy. §Odds ratio for increase of one episode of ischemia (EPI) per 48 h of monitoring at entry on the qualifying visit ambulatory electrocardiogram (QV AECG).

though most previous reports (1–20) have suggested that AECG ischemia predicts a higher rate of adverse outcome than that of patients without AECG ischemia, some reports (24,26,27) have not. However, the three latter reports are limited by relatively small sample size, single-center and retrospective design selection bias, very low risk subjects and different inclusion criteria. None used ACIP entry criteria or addressed the relative predictive value and potential confounding of the historical, ischemic (both ETT and AECG) and angiographic data by using multiple centers, common protocols and core laboratory readings.

Clinical implications. Results of this analysis suggest that the magnitude of AECG ischemia before treatment and, perhaps, initial medical treatment (as opposed to initial revascularization) are independent predictors of subsequent increased risk for ischemia-related adverse outcome. This conclusion is limited to clinically stable patients with revascularizable CAD and ischemia during both stress testing and daily life as assessed by AECG. These findings imply that, given two patients assigned to the same medical therapy, an increase of one AECG episode of ischemia at entry will be associated with an increase in risk for clinical adverse outcome (i.e., cardiac death, myocardial infarction or hospital admission for an ischemic event) at 1 year of ~5% to ~10% with a remarkably narrow 99% CI (Fig. 1). Conversely, in similar patients with AECG ischemia at entry, initial revascularization (as opposed to initial medical therapy) is likely to be associated with an ~45% reduction in risk for clinical adverse outcome (Table 3).

Figure 1. Relation between risk of adverse outcome at 1-year follow-up and magnitude of ischemia at entry. Plot of excess risk (**circles**) (OR − 1 × 100%) and 99% CI (**triangles**) for clinical outcome by number of AECG ischemic episodes recorded at entry.



Link between ischemia and adverse outcome. These results advance our understanding of the link between the magnitude of risk and AECG-detected ischemia occurring during daily life that has been suggested elsewhere (1–20). The precise amount of AECG ischemia at which an increased risk for adverse outcome may begin (i.e., threshold) has not yet been defined. In the ACIP study we used an arbitrary definition of abnormality based on ST segment deviation of 1.0 mm with a duration ≥1.0 min. This definition was chosen in earlier studies (28,29) of AECG monitoring for ischemia, largely to circumvent various artifactual and biologic variations in the ST segment level that may occur throughout the day and may not be of ischemic origin. When studying patients with well defined CAD and stress-induced ischemia such as those in the ACIP study, where other variations of ST segments have been excluded or minimized, it seems appropriate to explore other definitions of ST segment depression (e.g., <1.0-min duration and <1.0 mm-deviation). Such an analysis could identify the threshold value at which the ST segment depression level or duration reached during daily life is associated with increased risk for adverse outcome. This could be important to better define those CAD patients at increased risk and, perhaps, those with a suggested reduction in risk imparted by appropriate therapy (8–10,13,20,23). Little attention has been given to this low cost, simple and easily obtained marker of increased risk in relation to clinical findings. The current results provide compelling data to confirm that a greater number of ischemic episodes is directly related to greater risk for adverse outcome (Fig. 1).

The precise mechanism by which daily life ischemia detected by AECG monitoring is linked to adverse outcome is unknown, but this ischemia probably represents a marker for patients with functionally more severe and unstable CAD (e.g., endothelial dysfunction, microthrombi, plaque fissuring). Previous reports (14,20) have indicated that the association between AECG ischemia and adverse outcome appears strongest in patients presenting with clinical findings of an acute ischemic syndrome such as unstable angina or postinfarction ischemia. Such patients often have unstable, complex coronary lesions, and such pathologic findings have a direct relation to recurrent ischemia on AECG monitoring and to adverse outcome (19,20). The ACIP study of patients with clinically stable CAD and daily life ischemia detected on AECG monitoring and abnormal ETT findings also revealed a high risk for adverse outcome that was related to AECG ischemia. Angiographic data from the ACIP core laboratory also indicate that the majority of these patients with daily life ischemia had definite or possible complex coronary plaques, as well as proximal coronary lesions at angiography (25). However, even

proximal stenosis ≥70% did not achieve statistical significance in the univariate analysis. Of all ACIP patients, ~30% were asymptomatic and the remainder had mild, stable angina during the 6 weeks before study entry. Although the presence of symptoms, as assessed by the ACIP definition, showed a slight trend suggesting an association with outcome in the univariate analysis, it was not predictive of adverse clinical outcome in the multivariate analysis. These findings support the view that the clinical distinction between patients with biologically stable CAD and those with unstable disease is often unreliable when based on symptoms alone. It seems that a subgroup of patients who appear to be clinically stable are at relatively high risk for an adverse outcome because they have "biologically unstable CAD," as characterized by ulcerated coronary plaques, acute thrombus formation and endothelial dysfunction. Thus, ischemia detected by AECG monitoring may be a simple, readily obtainable marker for patients with more severe, complex and active CAD (30).

Traditional clinical risk factors. In this analysis the AECG ischemic findings overwhelmed traditional risk factors for CAD adverse outcome, such as age, hypertension, smoking, prior myocardial infarction and family history. Even the extent of CAD by angiography and ejection fraction was not predictive of adverse outcome in this group with predominantly multivessel CAD. Of the various angiographic and ETT variables examined, some were predictive in the univariate model, but none were predictive in the multivariate model, supporting the suggestion that most of the useful predictive information was contained in the AECG data. These findings, along with those recently reported by Gill et al. (16) and the ease of use and low cost of AECG, add support for further studies assessing AECG ischemia in patients with CAD. If our findings can be confirmed in a larger trial over a longer period of time, using only death and myocardial infarction as outcomes, they could have an important impact on the utilization of more expensive tests in the evaluation of patients with known CAD and ischemia.

The lack of association of coronary angiographic variables with ischemia-related adverse outcome deserves additional comments. This observation emphasizes the limitations of coronary angiograms used alone to assess the overall functional and prognostic importance of the atherosclerotic disease process. However, our results should not necessarily lead to the conclusion that coronary angiographic variables are not related to adverse outcome in other patient cohorts. Although the ACIP patient inclusion criteria were broad, the need for both abnormal ETT and AECG findings selected a group in which the overall burden of ischemia resulted in a relatively high risk for adverse clinical outcome. The current findings suggest that in such a group, the presence of single-vessel disease (defined by >50% coronary artery obstruction at angiography) identified patients just as likely to have an adverse outcome as those with double- or triple-vessel disease (defined by >50% stenosis in two or three vessels). Thus, in patients with ischemia during ETT and daily living, the CAD is functionally severe and likely to be important in terms of adverse outcome. Attempts to further quantify risk for adverse outcome based on conventional angiographic criteria do not contribute additional information related to this already high risk.

Study limitations. This study has some limitations worthy of discussion. First, these results are from a pilot study with a relatively small sample size and only 1 year of follow-up. Nevertheless, it is the largest study yet reported on ischemia detected during daily life in clinically stable patients. Second, we were able to adjust for only a specific number of patient factors present at study entry. Some clinical factors not included in these analyses may be important, specifically those providing additional anatomic or physiologic information. Although our analysis included many clinical, ECG and angiographic variables, further analysis of symptoms or other measurements, such as minimal lumen diameter, jeopardy scores and territory at risk, intracoronary ultrasound or angioscopy-derived intimal plaque characteristics, heart rate variability or time of ST segment recovery, might be useful. Third, the medical therapy was not used at maximal doses and was limited to only two drug combinations (23). It is possible that additional doses or other combinations would provide greater suppression of AECG ischemia and ischemia-related events. Nevertheless, we believe that the doses used in the ACIP study are similar to the doses used in current clinical practice.

Conclusions. The determinants of adverse outcome in the patient with clinically stable CAD and cardiac ischemia are multiple. Our analysis demonstrates that a few simple baseline variables, which may be readily obtainable and modifiable, seem to contain most of the prognostic information. These include the magnitude of ischemia detected by AECG at entry and, possibly, initial treatment.

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