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Amlodipine Reduces Transient Myocardial Ischemia in Patients With Coronary Artery Disease: Double-Blind Circadian Anti-Ischemia Program in Europe (CAPE Trial)

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Objectives. **This study was carried out to determine the effect of the once-daily calcium channel blocking agent amlodipine (half-life 35 to 50 h) on the circadian pattern of myocardial ischemia in patients with chronic stable angina.**

Background. **Myocardial ischemia during normal daily life, both symptomatic and asymptomatic, has been associated with increased risk of cardiovascular morbidity and mortality, and the circadian pattern parallels that for myocardial infarction and sudden death.**

Methods. **The Circadian Anti-Ischemia Program in Europe (CAPE) was a large, 10-week international (63 sites), double-blind, parallel study. After a 2-week, single-blind placebo phase, during which stable doses of antianginal treatment were maintained (beta-adrenergic blocking agents in 65% of patients), patients with chronic stable angina with at least three attacks of angina per week, with at least four ischemic episodes or ≥20 min of ST segment depression in 48 h of Holter monitoring, were randomized to receive treatment with either 5 mg/day of amlodipine or placebo (2:1 randomization). The dose was increased to 10 mg/day after 4 weeks. During week 7 of treatment, 48-h ambulatory ECG monitoring was repeated.**

Results. **Three hundred fifteen of 1,160 patients screened were eligible, and 250 had complete evaluable data. Compared with placebo, amlodipine significantly reduced both the frequency of ST segment depression episodes (60% for amlodipine vs. 44% for placebo, $p = 0.025$) and total integrated ST ischemic area (62% mm-min vs. 50% mm-min, $p = 0.042$). Amlodipine reduced ischemia over the 24 h with the intrinsic circadian pattern maintained. In addition, diary data showed a significant reduction in angina (70% for amlodipine vs. 44% for placebo, $p = 0.0001$) and in nitroglycerin consumption (67% vs. 22%, respectively, $p = 0.0006$). Amlodipine and placebo demonstrated similar safety profiles (adverse events 17.3% for amlodipine and 13.3% for placebo; discontinuation rates due to adverse events were 2% vs. 4.4%, respectively).**

Conclusions. **Once-daily amlodipine, when added to background treatment, significantly reduced both symptomatic and asymptomatic ischemic events over 24 h in patients with chronic stable angina.**

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It is now appreciated that the activity of transient myocardial ischemia in patients with chronic stable angina is considerably underestimated by the complaint of chest pain (1–3). Ischemic activity can be documented objectively during normal daily activities using ST segment Holter monitoring; the presence of asymptomatic myocardial ischemia has been related to increased morbidity and mortality (4,5). There is a pronounced circadian variation in ischemia characterized by a peak incidence of episodes in the early morning hours and a lower incidence at night (6). This parallels the risk of nonfatal myocardial infarction and sudden cardiac death (7,8). Increasingly, therefore, treatment regimes are being developed that target this 24-h pattern of ischemia, both symptomatic and asymptomatic (9). Once-daily beta-adrenergic blocking agents have been shown to be effective (10,11), but dihydropyridine calcium-channel blocking agents with a short plasma half-life, such as nifedipine capsules, have been disappointing because their pharmacokinetic and pharmacodynamic properties lead to uneven drug levels throughout the day and to an unpredictable dose response in individual patients (9,11). Recently, a multicenter trial (12) using a delivery system for nifedipine that results in more stable plasma levels demonstrated benefit on symptomatic and silent ischemic episodes over

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24 h, especially when combined with a beta-blocker, indicating that sustained plasma levels of calcium channel blocker are associated with improved efficacy.

Amlodipine is a novel dihydropyridine calcium channel blocker with a gradual onset of action and a long elimination half-life (35 to 50 h). These favorable pharmacokinetic and pharmacodynamic characteristics provide steady plasma levels with once-daily administration (13). Several clinical studies have (14,15) shown efficacy in patients with angina and hypertension, with a low incidence of side effects. The Circadian Anti-Ischemia Program in Europe (CAPE) was designed to test the effect of amlodipine alone or combined with background medical therapy on the circadian pattern of ischemic episodes, angina attack rate and nitroglycerin utilization in patients with chronic stable angina during normal daily life.

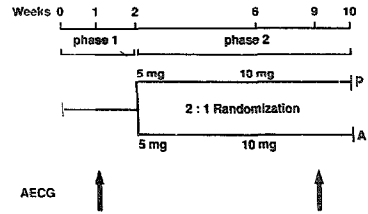

Figure 1. CAPE study design. After a 2-week screening period (phase I), suitable patients (see text) were randomized (2:1 in favor of active therapy) to amlodipine (A) or placebo (P) (5 mg/day) in addition to background therapy (if any). This dose was doubled after 4 weeks. AECG = ambulatory electrocardiographic monitoring.

Methods

Patients. Patients were recruited at 63 sites in 10 European countries between July 1989 and January 1992 (see Appendix). Male outpatients between 35 and 80 years of age were enrolled if they had stable angina pectoris with at least three attacks of angina per week with no change in symptoms for at least 1 month and coronary artery disease on the basis of the presence of one or more of the following: 1. coronary angiography demonstrating ≥70% stenosis of one or more major coronary artery; 2. previous myocardial infarction ≥2 months before screening on the basis of typical history, ECG or enzymatic changes; 3. previous coronary artery bypass graft surgery or coronary angioplasty, or both; 4. a positive exercise tolerance test within 12 months.

Patients were excluded if they had congestive cardiac failure, uncontrolled arrhythmia or hypertension, standing systolic blood pressure <90 mm Hg, heart rate <50 beats/min, more than first-degree atrioventricular block or any ECG feature that would interfere with interpretation of ST segment changes. All patients gave written consent, as approved by the institutional review boards for the individual study sites. Suitable patients, on the basis of these clinical criteria, then underwent 48-h ST segment Holter monitoring (see later). If they had four or more ischemic episodes or ≥20 min of ST segment depression in 48 h, or both, they were randomized to the active phase of the study. Patients were to be maintained on stable doses of all concomitant cardiovascular medications (if any) throughout the study, and only those who had been receiving calcium channel blockers within 1 week before entry were excluded. Patients were instructed to take sublingual nitroglycerin for episodes of angina pectoris but not for prophylaxis, and open label nitroglycerin tablets were provided to ensure nonexpired medication.

Study design. This placebo-controlled study (Fig. 1) consisted of an initial 2-week, single-blind placebo run-in period (phase I) followed by randomized allocation to treatment in a 2:1 amlodipine/placebo ratio. Patients then entered an 8-week, double-blind treatment period (phase II). The study medication was administered in blinded manner using a double-dummy design, with patients starting on 5 mg once daily of either amlodipine or placebo and increasing to 10 mg after 4 weeks of treatment. At the end of the seventh week of phase II, 48-h ambulatory ECG monitoring was repeated in an identical fashion to the initial evaluation. Throughout the study, patients were instructed to record episodes of angina and sublingual nitroglycerin tablet consumption and side effects in a structured diary.

Ambulatory ECG monitoring. Ambulatory ECG monitoring for ST segment analysis was performed using ACS 8500 two-channel recorders with a modified V_5 lead for channel 1 and V_5 or II lead for channel 2. Each tape was calibrated with a 0.1-mV signal. At the screening visit, recordings were made during seven positional maneuvers, and patients without artifactitious ST segment shifts were then monitored for two consecutive 24-h periods (48 h). The tapes were analyzed at a central analysis facility (Medifacts) using a Marquette 8000 Holter XP analyzer by three experienced analysts for the number, magnitude and duration of ischemic episodes to a 15-s temporal resolution as well as the presence of potentially serious arrhythmia. The investigator was notified of the results by telephone or facsimile, followed by a hard-copy report. If the patients fulfilled the entry criteria for myocardial ischemic episodes, they were allocated a randomization number and entered into the active treatment phase. All recordings of both qualifying and nonqualifying patients were then sent for blinded overreading to the Ischemia Monitoring Laboratory at Duke University, Durham, North Carolina. The final reports generated were used for determination of the study results. Analysis of the second 48-h period of ambulatory ECG monitoring was performed in the same way, and data obtained were used for comparison with the baseline measurements. A minimum of 18 h of technically satisfactory signal for ST segment analysis per 24-h recording was required for inclusion in the final analysis.

The ST segment was measured 80 ms after the J point; an episode was recorded if there was ≥1 mm of horizontal or downsloping ST depression for ≥1 min, with ≥1-min separat-

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ing episodes. The duration of each episode was defined as the interval between the initial 1-mm ST segment depression at the start of the episode and the time at which the ST segment depression became <1 mm for >60 s at the end of the episode. Episodes of ST segment elevation were rare and thus not included in any analysis of ST segment changes. The use of a centralized laboratory facility with a single physician overread provided consistency for interpretation of data.

Statistical analysis. The primary efficacy measurements from the ambulatory ECG data were as follows: 1) total frequency of episodes of ST segment depression; 2) total duration of ST segment depression; 3) total integrated ST ischemic area (*ST segment integral*); and 4) total peak ST segment depression, that is, the maximal ST segment depression per episode averaged for each patient over 48 h. The median of the distribution for each group was then evaluated. The ambulatory ECG data obtained during phase I served as baseline, and the data at week 9 served as the final measurement. Baseline primary efficacy measurements were assessed with analysis of variance models that included main effects (i.e., treatment group and center) and interaction effects (i.e., treatment group by center). Although the center main effects were significant, no consistent pattern emerged across variables, and the interaction effects were not statistically significant.

Secondary measures of efficacy included angina attack rates and nitroglycerin tablet consumption obtained from the daily diary data and the patients' self-assessments of angina control and ability to perform usual physical activities derived from questionnaire data. The within-group daily diary changes compared the weekly baseline (week 2) angina attack rate and nitroglycerin consumption with the data from the final week of treatment. Distribution-free statistics were used to evaluate the data; within-group and between-group significance was determined with the Wilcoxon signed-rank and Wilcoxon rank-sum tests, respectively.

Descriptive statistics, including mean values and standard deviations for normally distributed variables and median values and percentiles otherwise, were provided for baseline demographic and disease characteristics. Pearson chi-square tests were computed, and groups were examined for homogeneity at baseline. Between-group comparisons were made with unpaired *t* tests. All continuous data were examined for normality and formally tested with a Kolmogorov-Smirnov goodness-of-fit test. All 48-h Holter ECG data were expressed on a 24-h scale.

The effect of treatment was evaluated by comparison of changes from baseline in primary and secondary efficacy measurements. Changes from baseline for continuous data were found not to be normally distributed, but both square-root and logarithmic transformations of the data failed to provide satisfactory distribution. Nonparametric techniques were used for the formal data analysis, and medians were used to represent measures of central tendency. Wilcoxon signed-rank tests were used for within-group changes and Wilcoxon rank-sum tests (kappa = 2 treatments), consisting of chi-square tests with respect to the ranks and expected values, were used for between-group differences in the change from baseline. Analysis of diurnal distribution of ischemia was performed using repeated measures analysis of variance for the data in 3-h intervals; the models included treatment main effects and their interaction. The pattern of differences in the change from baseline was explored using Duncan's new multiple-range test. Patients' self-assessments were obtained at weeks 1 and 2 of phase I and weeks 6 and 10 of phase II. Consistency during pretreatment (weeks 1 and 2) was tested with paired *t* tests. Because none of these comparisons was significantly different ($p > 0.1$), the values at the end of week 2 were used as baseline for comparison with follow-up data. Analysis of covariance models, with baseline as covariate, were used to evaluate the significance of between-group differences in the change from baseline. Responder analyses were performed on angina diary data, patient self-assessments and the investigator global assessments of efficacy and toleration. These variables were dichotomized into improvement and no improvement. The significance of the between-group responder rates was determined with Pearson chi-square tests. All adverse events were compiled regardless of cause, and between-group differences were tested with Fisher exact tests. Mean changes in blood pressure and heart rate were calculated, and within-group changes were tested with paired *t* tests. Statistical analyses were performed with two-tailed tests using statistical analysis software programs, and an alpha level of 0.05 was assumed throughout the analysis.

Table 1. Clinical Characteristics of 315 Randomized Patients

	Amlodipine (n = 202)	Placebo (n = 113)
Mean [±SD] age (yr)	58.5 ± 0.7	59.6 ± 0.8
Mean duration (range) of AP (yr)	4.1 (0.13–26)	4.9 (0.08–25)
Previous MI/PTCA/CABG	73%	72%
Concomitant medication		
Beta-blockers	63%	67%
Aspirin	56%	56%
Baseline BP (mm Hg)	133/83	137/83
Baseline HR (beats/min)	70	69

None of the baseline comparisons between amlodipine- and placebo-treated patients reached statistical significance. AP = angina pectoris; BP = blood pressure; CABG = coronary artery bypass graft surgery; HR = heart rate; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Results

Patient data. Of 1,160 patients who were screened, 315 were randomized (Table 1). Of these, 24 did not meet all protocol requirements but were nevertheless included by the investigators (11 had important concomitant illnesses; 11 had insufficient ischemia during ambulatory monitoring; 1 was female; 1 was receiving a calcium channel blocker).

Of the 315 patients entering the active treatment phase (phase II), 202 received amlodipine and 113 placebo. There were no significant differences in age, angina history, incidence

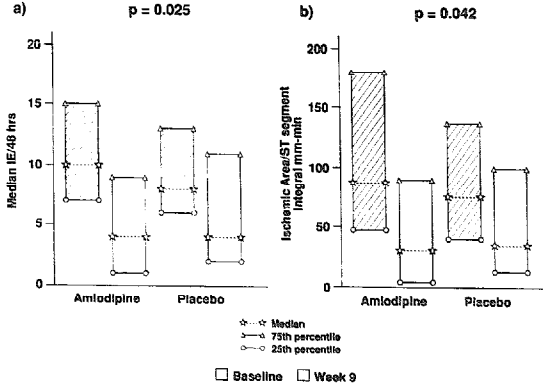

Figure 2. Comparison of frequency of transient myocardial ischemia during initial and final monitoring. Amlodipine produced a significantly greater reduction than placebo in (a) ischemic events (IE) (p = 0.025) and (b) ischemic area/ST segment integral (p = 0.042).

of previous myocardial infarction or revascularization, heart rate or blood pressure between patients who received amlodipine and placebo. The majority of the patients in both groups were receiving more than one concomitant cardiovascular medication, including beta-blockers in 63% of amlodipine- and 67% of placebo-treated patients and aspirin in 56% of both treatment groups.

One hundred ninety-one (95%) of amlodipine- and 100 (88%) of placebo-treated patients completed the full course of treatment. One patient died in each group, and four (2.0%) of amlodipine- and five (4.4%) of placebo-treated patients discontinued the study because of adverse events (see later). Most other patients were discontinued because of protocol violations or elective operation. During phase II, 93% of amlodipine- and 89% of placebo-treated patients had their dose adjusted to 10 mg/day as per protocol.

Ambulatory ECG monitoring. Of 315 patients randomized to phase II, 250 patients (n = 167 for amlodipine; n = 83 for placebo) were fully evaluable for ambulatory ECG analysis. The most common problems were uninterpretable ECG data or insufficient baseline ischemia. Of those patients with evaluable ECG data, 96% of amlodipine- and 100% of placebo-treated patients received 10 mg/day.

There was no significant difference between the baseline ischemia characteristics in the 167 patients who received amlodipine and the 83 who received placebo. Before phase II, amlodipine-treated patients had a median number of 10 ischemic episodes in 48 h versus 8 in placebo-treated patients, median ischemic time of 60 min versus 53 min, median peak ST segment depression of 1.84 versus 1.89 mm and median ischemic ST segment integral of 87 versus 76 mm-min, respectively (p > 0.05).

Episodes of transient myocardial ischemia were less frequent at the end of phase II in both amlopidine- and placebo-treated patients. The reduction in the frequency of ischemic events (median reduction 60% vs. 43.8%, p = 0.025) and ST segment integral (median reduction 61.6% vs. 49.5%, p = 0.042) was significantly greater during amlodipine than placebo treatment (Fig. 2). Amlodipine reduced the total duration of ST segment depression by 56% compared with 49.5% for placebo (p = 0.066). Total peak ST segment depression was reduced by 14.3% with amlodipine compared with 7.1% for placebo (p = 0.07).

Circadian variation. At initial monitoring, the well known circadian pattern in ischemic activity was present, with peaks in the morning and afternoon (Fig. 3). Amlodipine significantly reduced ischemia throughout the day compared with placebo but did not abolish the underlying circadian variation; attenuated peaks in the morning and afternoon were still present. Similar effects were seen for the duration of ST segment depression, ST integral and peak ST segment depression.

Objective improvement in ischemia on ambulatory monitoring was accompanied by improvement in subjective measures. During week 10, amlodipine-treated patients experienced a 70% reduction in episodes of angina pectoris (median attack rate 5 vs. 1.5/week) compared with 44% in placebo-treated patients (4 vs. 2.8/week, p = 0.0001) (Fig. 4). Seventy-nine percent of amlodipine-treated patients, compared with 59% of placebo-treated patients (p = 0.0001), reported fewer angina attacks during week 10. In addition, weekly nitroglycerin consumption with amlodipine was significantly reduced (by 67%, from median 2.9 to 0.6 tablets) compared with placebo (by 22%, from median 2.5 to 1.0 tablets) (p = 0.0006). In patient self-assessment questionnaires, 75.3% of amlodipine-treated patients reported improvement in their

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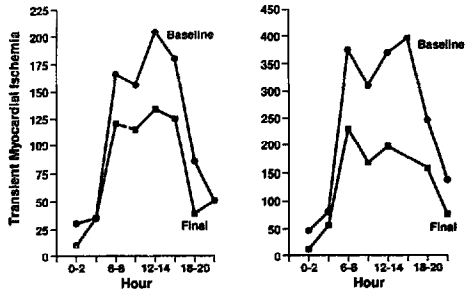


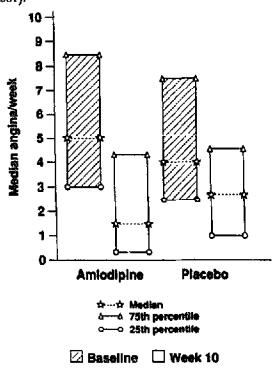
Figure 3. Circadian pattern of transient ischemic episodes during baseline and final monitoring in placebo-treated (**left**) and amlodipine-treated (**right**) patients. There was no increase in heart rate associated with amlodipine treatment.

ability to perform usual physical activities compared with 58.5% placebo-treated patients ($p = 0.003$).

Heart rate and blood pressure. After 8 weeks of active treatment, the patients who received amlodipine had a modest reduction in systolic and diastolic blood pressures (133/83 to 126/79 mm Hg vs. 137/83 to 136/83 mm Hg for placebo-treated patients). There was virtually no change in heart rate in either group throughout the 24 h (Fig. 5).

Adverse effects. After randomization, 35 (17.3%) amlodipine-treated and 15 (13.3%) placebo-treated patients reported adverse events (Table 2). Four (2%) amlodipine-treated and five (4.4%) placebo-treated patients discontinued treatment, and four (2%) amlodipine-treated patients had a dose reduction from 10 to 5 mg/day. The most frequent events were edema (5.4% with amlodipine, 1.8% with placebo), increased angina (2% with amlodipine, 3.5% with placebo) and headache (2.5% with amlodipine, 0.9% with placebo), none of the between-group comparisons reached statistical significance. One patient in each group died (one had insulin-dependent diabetes; one had had disseminated carcinoma).

Figure 4. Effect on angina frequency. Amlodipine produced a significantly greater reduction in median angina attack rate than placebo ($p = 0.0001$).



Discussion

This study showed that a new once-daily calcium channel blocker, amlodipine, when added to background medical therapy, reduced transient myocardial ischemia in patients with chronic stable angina. The anti-ischemic effect was demonstrated by objective measurement of ST segment changes during ambulatory ECG monitoring and supported by improvement in angina pectoris and nitroglycerin tablet consumption. The beneficial effect was sustained over 24 h, and amlodipine was well tolerated even at the higher dose used (10 mg).

There has been great interest in measuring ischemic activity during normal daily life in patients with coronary artery disease because it has become clear that ambulatory monitoring of ST segment changes can be used to document transient myocardial ischemia and identify high risk subgroups of patients (16). Studies in patients with unstable angina (4), after myocardial infarction (17), chronic stable angina (5,18) and peripheral vascular disease (19) have shown that the presence of myocardial ischemia defined in this way is an independent marker of morbid events. Furthermore, the pattern of ischemic events over 24 h in patients with chronic stable angina has been linked to that for major cardiovascular complications, such as myo-

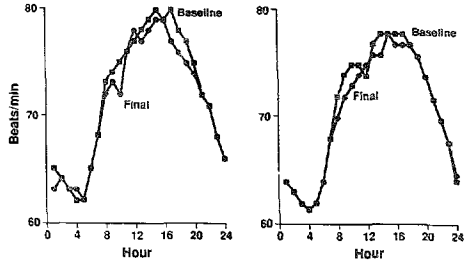


Figure 5. Circadian pattern of heart rate at baseline and final monitoring in placebo-treated (**left**) and amlodipine-treated (**right**) patients; there was no increase in heart rate associated with amlodipine treatment.

cardial infarction and sudden death (6–8). Attempts have therefore been made to develop and test treatment regimes for ischemia that target this pattern throughout the 24 h.

Medical treatment of myocardial ischemia. Once-daily beta-blockers have proved effective in reducing ischemic activity over 24 h but characteristically exert their greatest effect on ischemic episodes that are preceded by an increase in heart rate (20). In the remainder, which are not preceded by evidence of increased myocardial oxygen demand, dihydropyridine calcium channel blockers have been shown to be effective (20). However, the data for the first-generation agents, such as nifedipine, have been conflicting (21,22). When tested over 24 h, the effect of nifedipine capsules on the circadian pattern of ischemia has been disappointing, and this very likely relates to its rapid absorption and short plasma half-life (9). These pharmacokinetic characteristics result in variable plasma levels of the drug throughout the day, with reflex tachycardia and vasodilator side effects at peak levels as well as subtherapeutic levels at other times. In contrast, efficacy has been demonstrated when the drug is given with a novel delivery system (gastrointestinal therapeutic system [GITS]) that results in more even plasma levels (12). Amlodipine is a recently developed dihydropyridine calcium channel blocker that has a distinctive pharmacokinetic and pharmacodynamic profile, including gradual onset, intrinsically long duration of action and a plasma elimination half-life of 35 to 50 h. When given once a day it produces very stable plasma levels over 24 h and thus avoids the need for a slow-release preparation or a delivery system (13). This has a number of advantages, particularly when dosing intervals are variable, as is often the case in clinical practice (23). In this study, amlodipine was given in addition to background medical therapy, which included beta-blockers in ~65% of patients. The observed benefit from amlodipine is consistent with the theoretic advantages of this combination of dihydropyridine calcium channel blockers and beta-blockers (20) and with previous observations using ambulatory measures of ischemia (12,24). The findings of this large trial support reports of smaller studies (25) showing improvement in exercise testing measures of ischemia with amlodipine.

A major advantage of amlodipine over short-acting dihydropyridines, such as nifedipine capsules, is the lack of reflex tachycardia. There was no significant increase in heart rate found at any time of the day, and this presumably is one factor contributing to both the efficacy noted over the whole 24 h and the low incidence of adverse effects with amlodipine. In addition, there were no adverse electrophysiologic effects noted when the drug was used alone or in combination with a beta-blocker.

Ambulatory ECG monitoring. ST segment changes in ambulatory ECG monitoring was the primary end point of the study (26). To maximize specificity as a marker of ischemia, we confined inclusion to men in whom the reliability of this ECG signal is greatest. Because there has been considerable variability in reporting of ambulatory ECG ST segment findings, we used a single, experienced core laboratory for analysis, with review of all reports by one physician. In this trial, patients with sufficient ischemia were entered while continuing their usual medical therapy (if any) to which active amlodipine or placebo was added in a double-blind fashion. Approximately 65% of the patients were receiving beta-blockers, and this, together with the 2:1 randomization, resulted in too small a subgroup of patients receiving active amlodipine or placebo monotherapy for separate analysis. Entry into the study required the presence of both angina and at least four episodes of ambulatory ischemia. As a result of these rigorous criteria, patients were in an active phase of their disease at the start of the study. This may at least partially explain the considerable improvement in objective and subjective measures of ischemia also seen in the patients treated with placebo, as a result of "regression to the mean." Nevertheless, despite the placebo group's improvement, the patients treated with active medication showed significantly more benefit in both ambulatory ECG ischemia and angina pectoris. The recruitment rate of 30% achieved in this study is higher than that of previously published studies using ambulatory ECG monitoring inclusion criteria (16% of 409 patients screened for the Regionally Organized Cardiac Key European Trial (ROCKET) [27] and 18% in the Nifedip-

Table 2. All-Causality Adverse Events in the 315 Randomized Patients

	Amlodipine (n = 202) No. of Pts (%)	Placebo (n = 113) No. of Pts (%)	Between-Group p Value*
AE	35 (17.3)	15 (13.3)	0.422
Severe AE	7 (3.5)	7 (6.0)	0.268
Discontinued because of AE	4 (2.0)	5 (4.4)	0.291
Dose reduced	4 (2.0)	0 (0)	0.301
Cardiovascular AE	21 (10.4)	10 (8.8)	0.699
Increased AP	4 (2.0)	4 (3.5)	0.464
Dizziness	4 (2.0)	2 (1.8)	1.000
Edema	11 (5.4)	2 (1.8)	0.146
Headache	5 (2.5)	1 (0.9)	0.426
Hypotension	1 (0.5)	0 (0)	1.000
MI	1 (0.5)	1 (0.9)	1.000
Palpitation	1 (0.5)	0 (0)	1.000
Syncope	0 (0)	1 (0.9)	0.359
Tachycardia	1 (0.5)	0 (0)	1.000

*Probability based on Fisher two-sided exact test; none of the between-group comparisons was statistically significant.
AE = adverse events; Pts = patients; other abbreviations as in Table 1.

ine GITS Circadian Anti-Ischemia Program (N-CAP) studies [12]).

Clinical implications. The true "once-daily" calcium channel blocker amlodipine provides effective treatment of transient myocardial ischemia over 24 h in patients with chronic stable angina, particularly when combined with a beta-blocker. In view of the known high incidence of ischemia in the early morning hours and the higher risk of serious cardiovascular events during this period, the long duration of effect of amlodipine with a low incidence of side effects may provide important clinical benefit. The availability of effective medical regimes that target ischemia over the whole 24 h will enable prospective clinical trials to test whether this approach to treatment of patients with chronic stable angina will result in improved morbidity and mortality (28).

Appendix

Circadian Anti-Ischemia Program in Europe (CAPE) Study Group

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