Transient myocardial ischemia in patients with coronary artery disease (CAD) occurs frequently during daily life and has been linked to increased morbidity and mortality (1). Only a proportion of ischemic episodes are accompanied by angina pectoris, and the activity, characteristics, and circadian distribution of ischemia can be determined using ST segment ambulatory electrocardiogram (ECG) monitoring (2).

Numerous studies have shown a complex pathophysiology responsible for transient myocardial ischemia during the patient’s daily activities.

The Circadian Anti-ischemia Program in Europe (CAPE) study demonstrated that amlodipine, a once-a-day dihydropyridine calcium channel blocking agent with an intrinsically long half-life, significantly reduced angina and ischemia over 24 h when added to background medication (5). These results contrasted with the earlier disappointing findings using first-generation short-acting dihydropyridine agents (6), but left several questions unanswered. In the CAPE study, approximately two-thirds of patients were receiving beta-blockers and, consequently, the impact of monotherapy with amlodipine could not adequately be assessed. Furthermore, the study was not designed to compare the efficacy of combination regimes widely used in clinical practice. It is well known that patients frequently do not comply with prescribing instructions, taking their medication at variable intervals or omitting doses completely. Irregular dosing in this way is known to affect blood pressure control and hypertension, but its impact on angina and transient myocardial ischemia in coronary patients has not been adequately evaluated (7,8). The CAPE II study was a multinational collaborative study in Europe, designed to address these issues in a large population of patients with
stable angina and CAD. The effect of an intrinsically long-acting dihydropyridine, amlodipine, was compared to diltiazem (Adizem XL), a benzothiazepine calcium channel blocker, which can be dosed once daily through an extended delivery system. The combination of amlodipine with a beta-blocker (atenolol) was then compared to diltiazem (Adizem XL) with isosorbide 5-mononitrate. These drug combinations are some of the most widely used treatments for patients with coronary disease and stable angina pectoris. For both monotherapy and combination phases, the anti-ischemic efficacy was assessed after regular dosing administration and following omission of a single dose, simulating the situation frequently encountered in clinical practice.

**METHODS**

**Patients.** Patients were recruited in 30 centers in 13 countries (see Appendix). Men and women age 21 to 80 years were screened if they had a history of stable angina (≥2 attacks per week, with no change in symptoms for ≥1 month, a positive exercise test together with at least one other objective indicator of coronary disease (thallium exercise test, coronary arteriogram demonstrating ≥70% stenosis of at least one major coronary artery, previous MI ≥2 months before screening based on history, ECG and/or enzyme changes, history of revascularization by coronary artery bypass surgery or angioplasty). Arteriography demonstrating occlusive coronary disease was an entry criterion for women because of the reduced specificity of ST segment changes during ambulatory ECG monitoring and exercise testing as markers of myocardial ischemia when compared to males.

Patients were excluded if they had congestive cardiac failure, uncontrolled arrhythmia or hypertension, standing systolic blood pressure (BP) <100 mm Hg, heart rate <50 beats/min, greater than first-degree atrioventricular block, or any ECG feature that would interfere with interpretation of ST segment changes. All patients gave written informed consent as approved by the institutional review boards of the individual study sites. Suitable patients on the basis of these clinical criteria underwent 72 h of continuous ambulatory ECG monitoring. If they had a total of ≥20 min of transient ST segment depression or ≥4 ischemic events they were randomized to the active phase of the study. The ST segment was measured 80 ms after the J point and an episode was recorded if there was ≥1 mm of horizontal or downsloping ST depression for ≥1 min with ≥1 min separating 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. Patients were maintained on stable doses of all concomitant cardiovascular medications (if any) throughout the study; only those who had received calcium channel blockers within the week before entry were excluded. Patients were instructed to take sublingual nitroglycerin for episodes of angina pectoris, but not for prophylaxis. In addition, open-labeled nitroglycerin tablets were provided to ensure nonexpired medication.

**Study design (Fig. 1).** During a two-week, single-blind placebo run-in, patients underwent ambulatory ECG monitoring and exercise testing. Suitable patients were then randomized to receive six weeks of treatment with either 5 mg amlodipine or 180 mg diltiazem (Adizem XL) (phase 2) once daily. The study medication was administered in a blinded manner using a double-dummy design. After two weeks of treatment, the doses of medication were adjusted to amlodipine 10 mg or diltiazem (Adizem XL) 300 mg unless this was deemed inappropriate by the clinician. At the end of phase 2, 72-h ambulatory ECG monitoring and exercise testing were repeated in an identical fashion to the initial evaluation. On the third day of ambulatory ECG monitoring, both study groups were given placebo medication to simulate the omission of a single drug dose against the background of previously stable active therapy. Exercise testing was performed both on and after omission of the drug.

A blinded, six-week active combination phase (phase 3) was then undertaken with 50 mg of atenolol once daily given to the patients receiving amlodipine and 50 mg of isosorbide 5-mononitrate once daily to those receiving diltiazem (Adizem XL). After two weeks, the doses of atenolol and 5-mononitrate were each increased to 100 mg unless clinically contraindicated. At the end of phase 3, 72-h ambulatory ECG monitoring and exercise testing were again repeated in a manner identical to the evaluation at the end of phase 2. Throughout the study, patients were instructed to record episodes of angina/sublingual nitroglycerin consumption and side effects in a structured diary.

**Ambulatory ECG monitoring.** Oxford Medilog 2 channel recorders (modified V3 lead for channel 1 and V5 or lead II for channel 2) were used for ST segment monitoring at all sites. Each tape was calibrated with a 0.1 MV signal and seven positional maneuvers were performed at the start of each 24-h period. Tapes were analyzed centrally at a core laboratory by a single technician, with each record overread in a blinded fashion by one experienced cardiologist (5). If the patients’ screening tapes fulfilled the ischemia criteria for inclusion, the investigators were informed within 48 h to enable timely randomization to phase 2. An alert system was also employed so that the treating physician could be made aware of findings that might require clinical intervention (such as arrhythmia).

Each 24-h recording was analyzed on an Oxford Medilog
Excel Analyzer for episodes of ST segment depression. ST segment elevation was very rare and was not included in the analysis. A minimum of 18 h of technically satisfactory signal per 24-h recording was required for inclusion in the final analysis. For each 24-h tape the number, duration, and peak depression of ST episodes and their time was noted. The presence or absence of chest pain was determined by a patient-activated event marker.

**Exercise testing.** Exercise testing was performed using a protocol of standard graded increase in workload (20-watt steps with 2-min increments) on a bicycle ergometer. Heart rate and blood pressure were monitored for each stage and the following measurements were made for each test: time to onset of 1-mm ST segment depression, double product at onset 1-mm ST segment depression, time to onset of angina, total workload, total exercise time, and reasons for stopping exercise. Testing was performed at the same time of day >2 h after the previous meal and >1 h after consumption of sublingual nitroglycerin. All exercise ECG records were analyzed by a core laboratory using standardized criteria by two experienced cardiologists (9).

**Angina diaries.** Patients completed standardized daily angina diaries during the whole trial period in which they recorded attacks of angina and consumption of sublingual nitroglycerin. The individual investigators recorded adverse events after nondirected patient enquiry throughout the trial. These were recorded in the study case records, and serious events were communicated to the sponsor within 24 h.

**Analysis.** The primary efficacy measurements were from the ambulatory ECG records and included: 1) total number of ST-segment episodes; 2) total duration of ST-segment episodes; and 3) peak ST segment depression during the 48-h monitoring on active therapy. The change from baseline at the end of monotherapy (week 8) and combination therapy (week 14) in each of these variables was analyzed using the Wilcoxon rank-sum test for between-treatment comparisons and the Wilcoxon signed-rank test for within-treatment comparisons. The mean change from baseline was analyzed for both on (first 48 h with active study medication) and off (last 24 h with placebo) study drug. The “drug holiday” (off) effect during monotherapy and combination therapy treatment periods was also analyzed over the entire 24 h and last 8 h of the Holter monitoring period, respectively.

Secondary efficacy measures were the 24-h ambulatory ECG records off medication, the exercise test measurements, and the daily diary data. Analysis of variance models were used to compare treatment groups across phases. These included main effects (such as treatment group and center) as well as interaction effects (such as treatment groups by center). This analysis was performed on the change from baseline for each exercise parameter. If the center-by-treatment interaction was not statistically signif-
Table 1. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Amlodipine</th>
<th>Diltiazem (Adizem XL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>128</td>
<td>122</td>
</tr>
<tr>
<td>Age distribution (yrs)</td>
<td>106</td>
<td>122</td>
</tr>
<tr>
<td>Race distribution</td>
<td>106</td>
<td>122</td>
</tr>
<tr>
<td>Mean body weight (kg)</td>
<td>80.7</td>
<td>80.3</td>
</tr>
<tr>
<td>Body weight range (kg)</td>
<td>58–109</td>
<td>59–106</td>
</tr>
</tbody>
</table>

Significant, a reduced model excluding the interaction term was to be used. Type III sum of squares was used for all hypotheses tested in each of the statistical models. Times to event variables (time to onset of angina and ST segment) were analyzed using paired *t* tests. Pearson’s chi-square test was used to compare treatment groups with respect to binary variables.

**RESULTS**

**Patient data (Table 1).** Of 513 patients screened, 250 (49%) were randomized to phase 2 and 128 received amlodipine and 122 diltiazem (Adizem XL). There were no significant differences in age, gender, angina history, incidence of previous MI or revascularization, heart rate, or blood pressure between the two groups. The majority of the patients were receiving aspirin and angiotensin-converting enzyme inhibitors. In addition, both groups commonly used lipid-lowering drugs.

One hundred twenty-two of 128 patients (98%) completed both the amlodipine monotherapy (phase 2) and amlodipine/ateno-lol combination (phase 3) stages, whereas 110 of 122 (90%) completed the diltiazem (Adizem XL) monotherapy and diltiazem (Adizem XL)/isosorbide 5-mononitrate combination stages. One patient died during phase 2 (in the diltiazem [Adizem XL] group), withdrawal because of adverse events (see later) occurred in five patients on amlodipine and two patients on diltiazem (Adizem XL) in phase 2, and in one patient on amlodipine/ateno-lol and two patients on diltiazem (Adizem XL)/5-mononitrate in phase 3. The remaining discontinuations were for reasons other than adverse events.

Titration of drug to the maximum specified dose was successfully achieved in the great majority of patients so that by the end of phase 2, the mean dose of amlodipine was 9.5 mg and diltiazem (Adizem XL) 292.9 mg. Similarly, in the combination phase, the mean dose of ateno-lol was 89.8 mg (with 9.3 mg of amlodipine) and 5-mononitrate 91.9 mg (with 292.5 mg of diltiazem [Adizem XL]).

**Monotherapy phase (phase 2). Ambulatory ECG monitoring.** Fully evaluable ambulatory ECG recordings were obtained in 236 of 250 (94%) of patients (120/128 for amlodipine and 116/122 for diltiazem [Adizem XL]).

There was no significant difference in baseline ischemia characteristics between the amlodipine and diltiazem (Adizem XL) patients. Both drugs as monotherapy resulted in significant reduction in episodes of transient ST segment depression with no significant difference in efficacy between the two treatments (Fig. 2). There was a marked difference, however, during the third day of ambulatory ECG monitoring, during which the patients received placebo (“drug holiday”). There was maintenance of anti-ischemic efficacy in the amlodipine-treated patients, whereas those in the diltiazem (Adizem XL) group showed significantly higher number (*p* < 0.0001), duration (*p* = 0.0002), and peak ST depression (*p* < 0.0001) (Fig. 2). The difference between these responses and “withdrawal” of a single dose of drug between amlodipine and diltiazem (Adizem XL) treated patients was highly significant for all ischemia parameters (*p’s* < 0.002).

At initial monitoring, the well-known circadian pattern in ischemic activity was present in both groups. Amlodipine and diltiazem (Adizem XL) monotherapy both reduced ischemic activity over 24 h with maintenance of the circadian variation. During the “drug holiday” third day of monitoring, there was a significant difference in circadian pattern between the two treatment groups. Those who had received amlodipine showed maintenance of ischemia reduction throughout the drug-free 24-h period (drug holiday effect *p* = 0.92), whereas those who had been receiving diltiazem (Adizem XL) showed loss of efficacy with levels of ischemia comparable to those found at baseline (drug holiday effect *p* < 0.0001) (Fig. 3A).
EXERCISE TESTING. The exercise testing results were consistent with those of ambulatory ST segment monitoring. Both amlodipine and diltiazem (Adizem XL) produced significant improvement in exercise-induced ischemia (time to 1 mm ST depression 430 to 477 s for amlodipine vs. 428 to 477 s for diltiazem (Adizem XL), p's < 0.01). However, on the drug holiday day there was significantly less effect with a lower ischemia threshold in the diltiazem (Adizem XL) group compared to those who had been receiving amlodipine (p = 0.03) for time to onset of 1 mm ST segment depression (474 s after amlodipine vs. 443 s after diltiazem).

Combination phase (phase 3). AMBULATORY ST SEGMENT MONITORING. Fully evaluable data for the combination phase was obtained in 121 patients receiving amlodipine and atenolol and 109 receiving diltiazem (Adizem XL) and isosorbide 5-mononitrate. The addition of atenolol to amlodipine produced a further significant reduction in all ambulatory ECG monitoring measures of ischemia (p's < 0.0001 for number, duration, and peak ST segment depression). The addition of isosorbide 5-mononitrate to diltiazem (Adizem XL) produced a small reduction in these ischemia measures, but none reached statistical significance.

Comparison between the two treatment groups revealed that the amlodipine/atenolol patients had the least ambulatory ischemia (p = 0.01).

During the drug holiday day, as in the monotherapy phase, the amlodipine/atenolol group had less ischemia than the diltiazem (Adizem XL)/isosorbide 5-mononitrate group, with significantly fewer ST segment depression episodes (p = 0.02) and peak ST segment depression (p = 0.02).

Addition of atenolol to amlodipine produced a reduction in ischemia over the 24-h period (p < 0.001). During the drug-free day the circadian pattern of ischemia was virtually identical to that seen during the drug-free day after the monotherapy phase (p = ns). In contrast, the diltiazem (Adizem XL) isosorbide 5-mononitrate combination showed a modest circadian benefit compared to the diltiazem (Adizem XL) monotherapy phase (p = ns), and there was rebound to baseline levels of ischemia during the drug-free day, particularly in the early morning hours and little benefit beyond (Fig. 3B).

EXERCISE TESTING. The differences between the two combination regimes on exercise testing measures of ischemia were significant and again consistent with the results of ambulatory monitoring. During active therapy, total exercise time, time to onset of angina, and 1 mm ST segment depression were significantly greater on amlodipine/atenolol (time to 1 mm ST segment depression 520 s on amlodipine/atenolol vs. 478 s on diltiazem (Adizem XL)/isosorbide 5-mononitrate, p < 0.05). During the drug-free day, these measures were again significantly greater in patients who had been on amlodipine/atenolol (502 s after amlodipine/...
Amlodipine vs. 434 s after diltiazem [Adizem XL]/isosorbide 5-mononitrate, p < 0.002).

ANGINA DIARIES. Both amlodipine and diltiazem (Adizem XL) monotherapy resulted in highly significant reduction in both angina attacks and nitroglycerin consumption (p < 0.0001). Both combination regimes were significantly better at reducing symptoms than monotherapy (p < 0.0001). The amlodipine/atenolol combination patients had lower nitroglycerin consumption than those receiving diltiazem (Adizem XL)/isosorbide 5-mononitrate (p < 0.03) with a nonsignificant reduction in angina (p = 0.10) (Figs. 4A and 4B).

HEART RATE AND BP. At the end of the monotherapy phase there was a modest reduction in systolic and diastolic BP for both amlodipine and diltiazem (Adizem XL) treatments. The reduction from baseline in systolic BP was −5.84 (p < 0.0001) and −2.00 (p = ns) mm Hg for amlodipine and diltiazem (Adizem XL) treatments, respectively. The corresponding diastolic BP changes in −3.01 (p = 0.0005) and −1.74 (p = ns) mm Hg. Addition of atenolol to amlodipine also produced a significant reduction, whereas addition of isosorbide 5-mononitrate to diltiazem (Adizem XL) resulted in a nonsignificant reduction in BP. The change from baseline in systolic BP was −11.32 (p < 0.0001) and +2.43 (p = ns) mm Hg for amlodipine and atenolol and diltiazem (Adizem XL) and isosorbide 5-mononitrate treatments, respectively. The corresponding diastolic BP changes are −8.07 (p < 0.0001) and −0.71 (p = ns) mm Hg. There was virtually no change in 24-h heart rate during amlodipine monotherapy (with no reflex tachycardia) and there was a modest reduction on diltiazem (Adizem XL) (−0.97 beats/min). Atenolol produced the anticipated marked reduction in 24-h heart rate (−11.04 beats/min), whereas addition of 5-mononitrate had a smaller effect (−1.16 beats/min).

ADVERSE EVENTS. During the monotherapy phase 22 (17%) amlodipine and 27 (21%) diltiazem (Adizem XL) patients reported adverse events. Two (1.64%) amlodipine-treated and four (3.3%) diltiazem (Adizem XL)-treated patients discontinued therapy because of treatment-emergent adverse events.

During the combination phase, 28 (23%) amlodipine/atenolol and 38 (31%) diltiazem (Adizem XL)/5-mononitrate patients reported adverse events, and one and three patients discontinued therapy for each group, respectively. The most frequent events were edema (12.5% in the
DISCUSSION

The CAPE II trial has shown the efficacy and tolerability of once-daily monotherapy with long-acting calcium channel blockers for the treatment of symptomatic and asymptomatic myocardial ischemia in patients with stable CAD. The anti-ischemic effects were demonstrated by both ambulatory monitoring and exercise testing and supported by reduction in angina and sublingual nitroglycerin consumption. There was an incremental benefit from addition of a second class of drug in combination therapy and the amlodipine/atenolol combination proved superior to diltiazem (Adizem XL)/isosorbide 5-mononitrate.

Amlodipine and diltiazem (Adizem XL) showed comparable efficacy in regular dosing, but the effect on myocardial ischemia of omission of even a single dose was very different. Amlodipine proved superior, with maintenance of its anti-ischemic active over 24 h after dose omission, whereas the benefits of diltiazem (Adizem XL) were markedly reduced within a few hours. This is likely to be relevant in the clinical setting, where patients often take their medication at irregular intervals or omit doses completely.

In CAPE II, subjective and objective measurements were used to evaluate treatment effects. Angina is known to underestimate myocardial ischemia and ambulatory ST segment monitoring permits the assessment of the pattern and activity of ischemia during normal daily life in patients with coronary disease (1, 2). The presence of transient myocardial ischemia during ambulatory monitoring confers an independent risk of subsequent cardiovascular events (10, 11). Exercise testing was also performed, permitting evaluation of therapy on ischemia provoked in a controlled environment. The exercise end points have been widely used both to detect ischemia and stratify risk (9). The pathophysiology of myocardial ischemia during exercise testing and during ambulatory monitoring is likely to differ, and the use of both objective measurements in CAPE II afforded

Figure 4. Angina attacks (A) and nitroglycerin consumption (B) during monotherapy and combination therapy. Both amlodipine and diltiazem (Adizem XL) reduced angina and nitroglycerin consumption (p < 0.0001). Nitroglycerin consumption was significantly lower in patients receiving amlodipine/atenolol. *p = 0.02.
the opportunity to examine systematically, the impact of widely used classes of anti-ischemic agents as monotherapy and in combination in these two settings. The response of ischemia during ambulatory monitoring and exercise testing proved very consistent in the two phases of the trial, both for efficacy and for the response to drug withdrawal.

The first CAPE trial had shown a benefit of addition of amlodipine to patients’ background medical therapy but did not examine the impact of monotherapy (5). In CAPE II, both amlodipine and diltiazem (Adizem XL) were very effective when given once daily, in contrast to the results of earlier studies using short acting first-generation dihydropyridine calcium channel blockers (6). Both agents achieve stable plasma levels over 24 h and are indicated for once-daily treatment of angina pectoris. They differ importantly, however, in the means by which this is achieved, and this is likely to be the explanation for the potentially important clinical difference demonstrated when the impact on ischemia control was examined after omission of a single dose of a drug. Amlodipine has long duration of action, with a plasma elimination half-life of 35 to 50 h. In contrast, diltiazem (Adizem XL) relies on a delivery system to maintain once-daily therapeutic effect for the intrinsically short-acting agent, and blood levels fall rapidly after dose omission. The benefits on ischemia/angina, both in ambulatory monitoring and exercise testing, were largely maintained in those who had been receiving amlodipine, whereas there was return to levels of ischemia seen at baseline within hours of omission of diltiazem (Adizem XL). It is widely recognized that patients’ compliance with prescribed medical regimes is often poor. The different response to omission of amlodipine to that of short-acting agents with extended delivery systems has been shown to affect control of blood pressure in hypertensive patients (12). Our findings in CAPE II suggest a similarly important benefit for amlodipine in the control of myocardial ischemia in patients with coronary disease. Effective therapy during the first few hours of the day may be particularly important in view of the peak incidence of ischemia and the increased risk of cardiovascular morbidity and mortality from MI, stroke, and sudden death during this period (13). The use of amlodipine, especially with a long-acting beta-blocker, is likely to provide the most consistent reduction of myocardial ischemia in clinical practice.

Patients in CAPE II were recruited from 30 centers in 13 countries. The entry criteria were not restrictive, and approximately half the screened patients were randomized, a higher proportion than in most previous studies using ambulatory ECG monitoring (5,14). As a result, the beneficial effects of the treatment regimes in CAPE II are likely to be widely applicable to the population of patients with angina and coronary disease. Both men and women were included. The trial was not designed to compare responses in the two genders, however, and no differences were noted.

Critique of study design. Each patient underwent 72 h of ambulatory monitoring on three occasions, a longer period than in most, if not all, previous trials. The purpose was not to improve detection or quantification of transient myocardial ischemia, but to study the effect of omission of therapy for a single day on the background of stable drug dosing regimes, using both monotherapy and combination of drugs. Thus, active therapy was evaluated over 48 h, as in the first CAPE trial. An excellent quality of ECG signal was obtained even on the third day of monitoring, and patients tolerated the extended period well. This has implications for the design of future trials using ambulatory ischemic end points. Both ambulatory ECG monitoring and exercise testing were read centrally. It is noteworthy that no problems were encountered in communication among clinical sites in 13 countries and the core laboratories both for eligibility and transmission of findings of potential clinical relevance.

Clinical implications. The CAPE II findings demonstrated excellent symptomatic improvement and ischemia reduction with medical therapy using single agents and, in particular, with combination therapy. The prognostic significance of ischemic activity of patients with coronary disease has been demonstrated (10,11), but the benefit of relief transient ischemia, both with medical therapy and angioplasty, remains controversial (15). Reduction in morbidity and mortality may require the use of agents that target the disturbed vascular biology of atherosclerotic arteries known to contribute to inflammation, vasoconstriction, thrombosis, and plaque instability (16,17). Angiotensin-converting enzyme inhibitors and amlodipine have been shown to affect favorably endothelial function (18), and clinical trials have indicated benefits on the arterial wall (19) and clinical events (18,19). Further studies are ongoing to examine the impact of such agents alone and in combination on the activity of ischemia, disease progression, and morbid events, and the results will be of great interest in determining optimal medical therapy in coronary disease. The CAPE II study provides firm evidence for the clinical benefit of medical therapy for angina and ischemia and supports the use of the intrinsically long-acting calcium channel blocker amlodipine, alone or with a beta-blocker. The maintained efficacy of amlodipine in irregular dosing confers an advantage in the clinical setting over short-acting drugs, even when they are used with extended-release delivery systems.

Reprint requests and correspondence: Prof. John E. Deanfield, Vascular Physiology Unit, Great Ormond Street Hospital for Children NHS Trust, Great Ormond Street, London WC1N 3JH, United Kingdom. E-mail: j.deanfield@ich.ucl.ac.uk.

REFERENCES


APPENDIX

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

Study Chairman: John E. Deanfield, FRCP. Steering Committee: Jean-Marie Detry, MD, Paul R. Lichtlen, MD, Eric Thaulow, MD, Jan Bultas, MD, Claudia Brennan MS, Bruce Beckerman, MD.

Participating Investigators