Acute Coronary Syndromes

Effects of Acute Hormone Therapy on Recurrent Ischemia in Postmenopausal Women With Unstable Angina

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OBJECTIVES	We tested whether acute hormone therapy reduces ambulatory electrocardiographic ischemia in postmenopausal (PMP) women with unstable angina (UA).
BACKGROUND	Endothelial dysfunction contributes to the pathophysiology of UA. Acute estrogen administration improves endothelial function in PMP women with coronary artery disease and increases coronary artery blood flow.
METHODS	Two hundred ninety-three PMP women with UA (mean age 69.7 years), treated with standard anti-ischemic therapy, were enrolled within 24 h of symptom onset. In a double-blind fashion, subjects were randomized to receive intravenous followed by oral conjugated estrogen for 21 days, intravenous estrogen followed by oral conjugated estrogen plus medroxyprogesterone for 21 days or placebo. The primary end point was the number of ambulatory electrocardiographic ischemic events over the first 48 h. Clinical events were also determined over six months of follow-up.
RESULTS	Electrocardiographic ischemia did not differ among the three randomized groups. The mean number of ischemic events per patient over 48 h was 0.74 for estrogen, 0.86 for estrogen plus progesterone and 0.74 for the placebo groups (p = 0.87). The percentage of patients with ischemic events and the mean duration of ischemia did not differ between hormone- and placebo-treated patients. In-hospital and six-month rates of adverse clinical events were also similar among the three randomized groups.
CONCLUSIONS	Acute hormone therapy does not reduce ischemia in PMP women with UA when added to standard anti-ischemic therapy. (J Am Coll Cardiol 2002;39:231–7) © 2002 by the American College of Cardiology

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in women over the age of 50 years (1). Acute coronary syndromes (ACS) present differently in men and women. Men more often present with ST-segment elevation myocardial infarction (MI) and suffer fewer infarct complications, including heart failure and cardiogenic shock (2,3). Women with ACS are older, have greater comorbidity and more often present with unstable

angina (UA) (2). Despite older age and greater number of risk factors compared with men, up to 30% of women compared with 14% of men presenting with UA have no

significant CAD on coronary angiography (2), suggesting that the pathophysiology of ischemic chest pain in women may be more diverse than it is in men (4).

In women without epicardial stenoses, small vessel CAD and endothelial dysfunction may cause coronary vasoconstriction, reduced coronary blood flow and ischemic chest pain (5). In the setting of atherosclerotic plaque rupture, coronary artery vasoconstriction occurs in response to serotonin and thromboxane A_2 released from activated platelets (6,7). Estrogen could, theoretically, reduce ischemia in both circumstances. Acute administration of estrogen causes coronary vasodilation and reverses endothelial dysfunction within minutes in postmenopausal (PMP) women with CAD (8–12). The addition of progesterone to estrogen, commonly utilized in many PMP women, may, however, attenuate the beneficial effects of estrogen on endothelial function and coronary vasodilation (13,14).

To assess the possible benefit of short-term estrogen therapy for PMP women with UA, we conducted a randomized, double-blind, placebo-controlled trial comparing the effects of conjugated equine estrogen (E) alone, E plus medroxyprogesterone (MPA) and placebo (PLBO) on am-

bulatory electrocardiogram (ECG) ischemia, a predictor of adverse outcomes in patients with ACS (15–17).

METHODS

Patient selection. Postmenopausal women presenting from July 1995 to September 1999 with an episode of UA within the prior 24 h were eligible. Postmenopausal status was defined as last menses >1 year before enrollment, previous bilateral oophorectomy or previous hysterectomy in women ≥55 years of age. Unstable angina was defined as ischemic pain lasting ≥10 min with reversible ECG ST-segment changes or ischemic chest pain in patients with CAD diagnosed by prior angiography or prior MI in whom an ECG was not available at the time of chest pain.

We excluded patients with uninterpretable ECG ST segments (e.g., ventricular paced rhythm, left bundle branch block), known MI within 24 h of enrollment, cardiogenic shock, estrogen replacement therapy within one year of admission or a history of hormone-dependent neoplasia, liver tumors or deep vein thrombosis. We also excluded patients with UA scheduled for percutaneous coronary intervention (PCI) within 24 h of admission to the hospital or who developed UA within 72 h after a PCI.

The investigational review board at each participating institution approved the study. Signed, informed consent was obtained from all patients.

Protocol. Patients received routine anti-ischemic therapy as determined by their attending physician, including aspirin, unfractionated heparin, beta-blockers and nitrates. Glycoprotein (GP) IIb/IIIa inhibitors were available for use when clinically indicated in the last 55 enrolled patients. The patient's attending physician made all decisions concerning cardiac catheterization and revascularization procedures.

Patients were randomized in a double-blind fashion to one of three 21-day courses of study drug. Each patient received a single intravenous infusion at study entry followed by two capsules for 21 days: 1) 1.25 mg of intravenous E infused over 30 min followed immediately by 1.25 mg/day of oral E plus 2.5 mg/day of oral MPA; 2) 1.25 mg of intravenous E followed immediately by 1.25 mg/day of oral E plus PLBO; and 3) intravenous PLBO followed immediately by oral PLBO capsules. This dose of E reversed cold pressor induced coronary vasoconstriction in 11 PMP women (preliminary data) as well as in men (18). Vital signs were monitored at 10-min intervals from 20 min before study drug infusion until 30 min after the end of study drug infusion.

During the first 48 h of the study, continuous ambulatory ECG monitoring (Oxford MR45 System, Oxford Medical Inc., Clearwater, Florida) was performed to measure ischemic episodes, defined as ST depression ≥1 mm lasting >1 min. During the hospital stay, investigators performed daily assessments for symptomatic ischemia, refractory ischemia (lasting >10 min despite standard therapy), MI (ischemic pain, ST changes and creatinine kinase >2× the upper limit of normal) and need for revascularization. Patients returned at 21 days for clinical assessment and 48-h ambulatory ECG monitoring. Pill counts for patient compliance was determined at this time. The study drug was discontinued at 21 days, and patients returned approximately 10 to 14 days later for clinical assessment and 48-h ambulatory ECG monitoring.

End points. The primary end point of the trial was the geometric mean number of ischemic episodes per patient for 48 h on the initial ambulatory ECG. Secondary outcomes included the percent of patients with ambulatory ECG ischemia and total duration of ischemia during the first 48 h. Secondary outcomes also included 21-day and 31-day ambulatory ECG ischemia, symptomatic ischemia, refractory ischemia, MI or death during the index hospitalization. Three-month and six-month outcomes of death, MI and need for coronary revascularization were determined by telephone interviews. Outcomes associated with inpatient admission were confirmed by hospital record review.

Statistical analysis. Patient characteristics are presented as counts and percentages and compared using the chi-square for categorical data and *t* tests for continuous data. Fisher exact test was used for characteristics with prevalence <5%. Outcomes were compared using tests of differences for two proportions for dichotomous data and *t* tests for continuous data for the two hormonal therapy groups (E + MPA and E + PLBO). When no difference between hormone therapy groups was found, the two groups were pooled and the same comparisons repeated for the pooled hormonal therapy groups and placebo group data. Analysis of the primary end point (number of ischemic episodes) was performed using the transformation log (48·[number of ischemic episodes + 0.5]/h recorded). Outcomes for clinical events were compared with survival analysis. Data are expressed as the geometric mean and the range because of the nonparametric distribution of the ambulatory ECG ischemic episodes.

The planned sample size was 117 patients per treatment group based on a two-sided alpha = 0.05 and power = 0.80, assuming a 40% reduction in the number of ischemic episodes in the hormone therapy group would be clinically significant. Interim analyses were planned setting the critical

Table 1. Patient Demographics

Characteristic (n)	E + MPA (n = 94)	E + PLBO (n = 100)	PLBO (n = 99)	p Value
Age (range, yrs)	69.9 (51–91)	69.7 (48–89)	69.6 (43–93)	0.99
African American	39.4%	31%	34.3%	0.25
ECG changes	64.9%	53.0%	57.6%	0.24
Prior CAD	75.5%	81.0%	80.8%	0.57
Hypertension	75.5%	81.0%	75.8%	0.78
Prior TIA/CVA	16.0%	17.0%	16.2%	0.98
Prior CHF	18.5%	16.0%	29.5%	0.05
Prior MI	47.3%	51.0%	53.5%	0.69
Prior CABG	21.3%	21.0%	27.3%	0.50
Prior PCI	22.8%	33.0%	24.2%	0.23
Diabetes	44.7%	42.0%	47.4%	0.75
Cigarettes (current)	12.9%	13.0%	19.2%	0.32

p value for any difference between the three groups.

CABG = coronary artery bypass grafting; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebral vascular accident; E = conjugated equine estrogen; ECG = electrocardiogram; MI = myocardial infarction; MPA = medroxyprogesterone; PCI = percutaneous coronary intervention; PLBO = placebo; TIA = transient ischemic attack.

values according to the method of Fleming et al. (19), adjusting the final, primary analysis critical value to p = 0.041. For secondary analyses p < 0.01 is required for some evidence of differences and p < 0.001 for strong evidence of differences. The Data and Safety Monitoring Committee advised terminating the study after a predetermined interim analysis when 293 patients were enrolled due to a lack of difference among the three randomized groups at that time and a decrease in the mean number of ischemic episodes in all of the groups.

RESULTS

Patient demographics. The study randomized 293 PMP women with UA: 94 patients received E + MPA, 100 patients received E + PLBO and 99 patients received PLBO only. Patient demographics are presented in Table 1, reflecting an older cohort of patients with UA with a high prevalence of prior CAD and risk factors. On admission ECG tracing, 3% to 5% of patients had reversible ST-segment elevation, one-third had new ST-segment depression and one-fifth had ischemic T-wave changes. Coronary risk factors and admission ECG patterns were similar among the three randomized groups. About one in four patients in each group had pulmonary vascular congestion on the admission chest radiograph.

The three groups received comparable anti-ischemic therapy (Table 2). The majority of patients in each randomized group received anticoagulation with intravenous hepa-

Table 2. Anti-Ischemic Medications

Medication	E + MPA	E + PLBO	PLBO	p Value
Heparin	85.1%	78.8%	76.8%	0.32
Aspirin	92.6%	92.0%	98.0%	0.14
Beta-blocker	76.6%	75.0%	79.6%	0.74
Nitroglycerin	72.3%	74.0%	76.5%	0.76

Abbreviations as in Table 1.

rin, aspirin, beta-blocker therapy and intravenous, topical or oral nitroglycerin. Nine patients, evenly distributed among the three randomized groups, received a GP IIb/IIIa inhibitor during the first 48 h of the study.

ECG ischemia during first 48 h. The study drug infusion was well tolerated. There were no differences in blood pressure or heart rate between those patients receiving intravenous estrogen and those receiving placebo. Table 3 shows results of the ambulatory ECGs performed during the 48 h after study enrollment. The mean number of ischemic events, the study's primary outcome variable, did not differ between patients treated with hormone therapy (E + MPA and E + PLBO) and with PLBO or between patients treated with E only compared with the combination of E and MPA. The percent of patients with ECG ischemia and the mean ischemic time per 48 h did not significantly differ between the two hormone therapy groups or between the patients who received hormone therapy and placebo. The median number of ischemic events and duration of ischemia over 48 h was zero in all three groups.

Recurrent symptomatic ischemia during the hospitalization did not vary among the three groups. In those patients who experienced ambulatory ECG ischemia, the majority had one to three ischemic events over the first 48 h, although five patients randomized to E + MPA, one patient randomized to E and three patients randomized to PLBO experienced ≥6 ischemic events.

Several predefined subgroups were evaluated for the effect of study drug on ECG ischemia. In subgroups comprising patients >70 years of age, African Americans and patients with diabetes, a prior MI or congestive heart failure, there were no differences between hormone therapy and placebo in the number of ischemic episodes, the duration of ischemia or percentage of patients with ECG ischemia over the first 48 h. Patients with transient ST-segment depression on the admission ECG experienced more ischemic episodes and represented a greater proportion of patients with ECG ischemia over the first 48 h than those without admission ECG ST-segment changes. However, there was no differ-

Table 3. First 48-H Ambulatory ECG and Symptomatic Ischemia

Ambulatory ECG	E + MPA	E + PLBO	PLBO	p Value
Mean #/48 h (range)	0.86 (0–14)	0.74 (0–7)	0.74 (0–29)	0.87
% with events	14.1	9.8	10.9	0.79
Mean ischemic time (min) (range)	23.5 (0–762)	4.2 (0–222)	8.0 (0–322)	0.81
Symptomatic ischemia	52.1%	39%	42.4%	0.16

p value is the comparison of (E + MPA) + (E + PLBO) vs. PLBO.
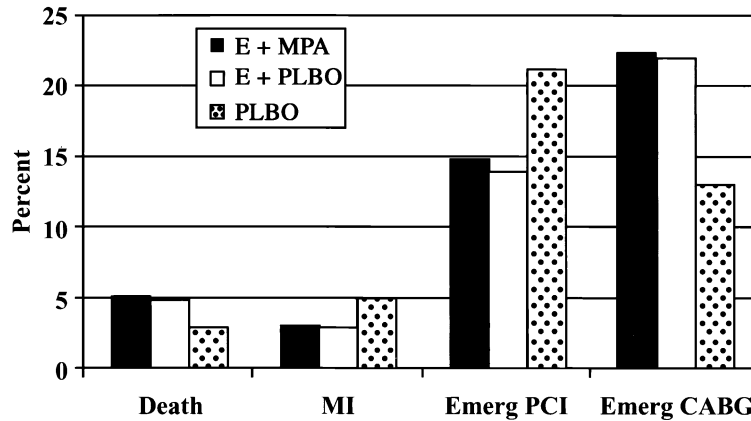
Abbreviations as in Table 1.

Figure 1. The rates of in-hospital death, myocardial infarction (MI), emergency percutaneous intervention (PCI) and emergency coronary artery bypass surgery (CABG) are shown for patients randomized to each group. Patients underwent revascularization for recurrent ischemic symptoms or high-risk presentation. There were no differences in hospital events among the three randomized groups, p = 0.91. E = conjugated equine estrogen; MPA = medroxyprogesterone; PLBO = placebo.

ence between hormone therapy and placebo in 48-h ECG ischemia in this subgroup. Similarly, hormone therapy did not reduce ECG ischemia in enrolled patients who did not receive therapy with nitroglycerin during their first 48 h of hospitalization.

Clinical outcomes during initial hospitalization. During the index hospitalization for UA, the incidences of death, MI and need for emergent PCI or coronary artery bypass grafting did not differ among the three randomized groups (Fig. 1). The incidences of refractory ischemia during hospitalization were also similar, 19.8%, 16.3% and 15.4% for those randomized to E + MPA, E + PLBO and PLBO only, respectively.

21-day and 31-day outcomes. A total of 20% of patients stopped the study drug before 21 days. These 58 patients were equally distributed across the three randomized groups. Eighteen of these 58 patients stopped the drug early due to side effects, and 29 patients stopped the drug early due to patient or family refusal. Among the 80% who completed the three weeks of study drug, compliance was 91% by pill count. After three weeks of the study drug, the mean number of ambulatory ECG ischemic episodes was small (Table 4), as was the percentage of patients with ECG ischemia and the mean duration of total ischemia. There were no differences among the three randomized groups in day 21 ambulatory ECG ischemia or the proportion of patients who developed symptomatic ischemia from hospital discharge to day 21.

Ten days after cessation of the study drug, patients underwent repeat ambulatory ECG monitoring. The number of ischemic episodes remained small and did not differ among the three randomized groups. There was no evidence of rebound ischemia in any group.

Side effects. Minor side effects were frequent in all groups during three weeks of the study drug (Table 5). Two patients in the combined hormone group and two in the E only group stopped the study drug early due to breast tenderness. One patient in the E only group stopped the study drug early due to vaginal bleeding. Additionally, one patient who received E alone developed a pulmonary embolism (day 2), and one patient who received PLBO developed a deep vein thrombosis (day 6). Two patients suffered strokes, one patient in the E + MPA arm (day 5) and one patient randomized to PLBO (day 9). Both strokes occurred after coronary artery bypass surgery.

Six-month clinical outcomes. Six-month clinical outcomes were available for 93% of patients in the entire study cohort. Kaplan-Meier survival curves for death or nonfatal MI (Fig. 2) and death, nonfatal MI or need for revascularization (Fig. 3) showed no six-month differences among the three randomized groups.

DISCUSSION

This randomized, placebo-controlled trial shows that adding E or E plus MPA to standard anti-ischemic therapy

Table 4. Day 21 ECG and Symptomatic Ischemia

Ambulatory ECG	E + MPA	E + PLBO	PLBO	p Value
Mean #/48 h (range)	0.71 (0–11)	0.69 (0–5)	0.78 (0–11)	0.27
% with events	8.1%	11.3%	11.9%	0.63
Mean ischemic time (min) (range)	7.5 (0–249)	4.7 (0–151)	10.0 (0–150)	0.40
Symptomatic ischemia	20.3%	26.7%	28.9%	0.43

p value is the comparison of (E + MPA) + (E + PLBO) vs. PLBO.
Abbreviations as in Table 1.

Table 5. Side Effects to Study Drug

Side Effect	E + MPA (n = 94)	E + PLBO (n = 100)	PLBO (n = 99)	p Value
Flushing	7.4%	7.0%	7.1%	0.99
Headache	12.8%	11.0%	10.1%	0.84
Edema	13.8%	11.0%	9.1%	0.58
Vaginal bleeding	17.0%	10.0%	1.0%	0.001
Breast tenderness	27.7%	23.0%	7.1%	0.001
Mood change	4.3%	5.0%	7.1%	0.67
Any side effect	53.2%	50.0%	44.4%	0.47

Abbreviations as in Table 1.

does not reduce ECG ischemia in PMP women with UA. Three weeks of hormone therapy did not affect any of the study's secondary end points, including in-hospital and six-month recurrent ischemia, MI, death and need for revascularization, although the study lacked sufficient power to determine with confidence these secondary clinical outcomes.

Estrogen and endothelial dysfunction. Our study was based on evidence that endothelial dysfunction with subsequent impairment in coronary blood flow has an important pathophysiologic role in ACS (20–22) and that acute estrogen administration reverses this abnormality (8). Intravenous estrogen increases Doppler measured coronary blood flow and coronary epicardial cross-sectional diameter and attenuates the vasoconstrictor response to acetylcholine in women with CAD (8–11). The coronary and brachial artery vasodilator response in PMP women to acetylcholine plus estrogen is obliterated with a concomitant infusion of N^G-monomethyl-L-arginine, an inhibitor of nitric oxide synthase (9,23). These findings suggest that the improvement in endothelial dysfunction with acute estrogen administration occurs via increased nitric oxide availability. Estrogen also causes vasodilation by stimulating the opening of calcium-activated potassium channels resulting in smooth muscle relaxation (24). Whether the addition of progester-

one decreases estrogen's endothelial-dependent vasodilator effect is controversial (25).

Failure of hormone replacement therapy to reduce ambulatory ECG ischemia. There are several potential explanations for the failure of acute hormone replacement therapy to reduce ambulatory ECG ischemia in our study. Although human endothelial cells and smooth muscle cells express estrogen receptors (12,26), Losordo et al. (27) reported that atherosclerotic coronary arteries expressed fewer estrogen receptors than coronary arteries without significant atherosclerosis. Furthermore, Post et al. (28) reported increased rates of estrogen receptor gene promoter methylation with increasing age, both in nondiseased vessels and even more so in areas with atherosclerotic plaque. Increased promoter methylation inactivates estrogen receptor gene transcription. Since women with UA are usually elderly with significant atherosclerosis, they may be unresponsive to hormone therapy due to lack of the estrogen receptor. It also is possible that the concurrent use of nitroglycerin in three-quarters of our patients resulted in maximal endothelial-independent coronary vasodilation, thus eliminating any possible benefit of acute estrogen therapy. These data contrast with the beneficial effects of acute estrogen therapy reported in small studies of PMP women with stable CAD on exercise treadmill-induced and pacing-induced ischemia (29,30). In contrast with the current cohort with UA, women in these studies were younger and, due to their stability, may have had less severe coronary atherosclerosis. Furthermore, the exercise treadmill tests and pacing studies were performed in the absence of any anti-ischemic therapies, which would have been unethical in our patients with UA.

Other explanations for the observed lack of benefit of acute hormone therapy are less likely. Although estrogen therapy induces many genes, these chronic effects are unlikely to influence 48-h outcomes (12). These more
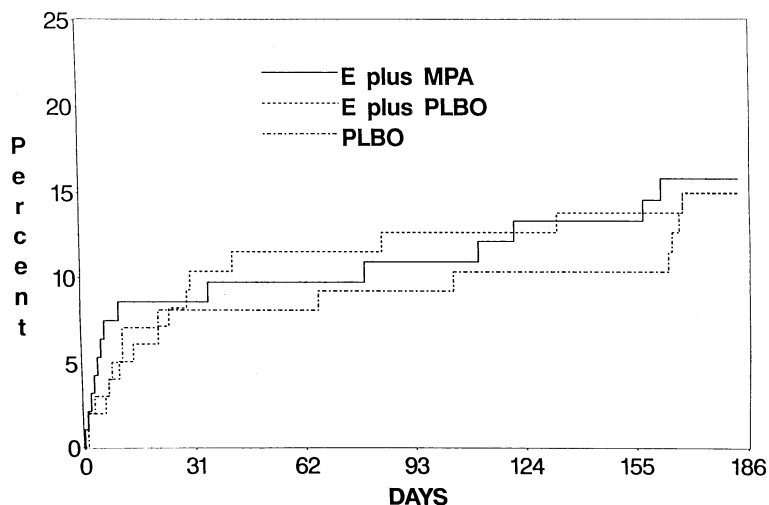

Figure 2. Six-month rates of death or nonfatal myocardial infarction among the three randomized groups. Event rates did not differ, p = 0.97. E = conjugated equine estrogen; MPA = medroxyprogesterone; PLBO = placebo.

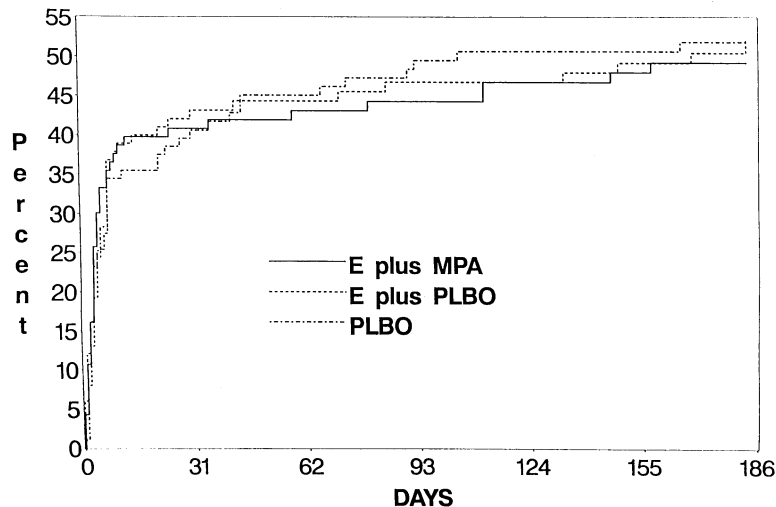**Figure 3.** Six-month rates of death, nonfatal myocardial infarction or need for revascularization (coronary artery bypass surgery or percutaneous intervention) among the three randomized groups. Most of the events occurred early, and hormone therapy did not reduce the adverse event rate, p = 0.98. E = conjugated equine estrogen; MPA = medroxyprogesterone; PLBO = placebo.

chronic effects include estrogen therapy's mixed effects on coagulation, increasing mediators of fibrinolysis but also having prothrombotic effects (31). Estrogen therapy also increases C-reactive protein (32), an inflammatory marker that is associated with coronary events in men and women (33,34).

This trial of acute hormone therapy use adds a previously unaddressed dimension to the study of estrogen therapy in ischemia. It also complements two recent randomized trials evaluating the role of longer-term hormone replacement therapy in PMP women with chronic stable CAD. The Heart and Estrogen/progestin Replacement Study (HERS) showed no difference in the primary end point of coronary heart disease death plus nonfatal MI in women randomized to E + MPA compared with PLBO after 4.1 years of follow-up (35). The Estrogen Replacement and Atherosclerosis trial showed no difference in coronary disease progression on quantitative angiography in women randomized to either E, E + MPA or PLBO after 3.2 years of follow-up (36).

Study limitations. Our power calculations, based on the existing literature, anticipated an average of one ischemic event per patient in the placebo group. In actuality, there were only 0.74 events per patient. The proportion of patients with any ECG ischemia decreased progressively during the study, from 16.1% in the first third of patients enrolled to 11.1% in the second third and 7.5% in the last third without any discernable change in the demographics of the population. Similarly, the mean number of ischemic events per patient for 48 h decreased from 0.86 for the first third to 0.77 for the second third and 0.71 for the last third of patients enrolled. These data suggest that aggressive anti-ischemic therapy has substantially reduced the frequency of ambulatory ECG ischemic events, making ambulatory ECG ischemia a less useful research end point. However, since there was no difference in the number of

ischemic events between patients randomized to hormone therapy or placebo at any point during the study, it is very unlikely that enrolling more patients would have yielded different results. Furthermore, we had a relatively high dropout rate, which did not affect the primary outcome variable but reduced our power to assess longer-term outcomes.

Finally, there was a nonsignificant trend for patients randomized to E + MPA to experience more ischemia and recurrent in-hospital angina than patients receiving E alone or PLBO. This trend supports concerns raised by HERS of an early increased risk of events in women with CAD treated with E + MPA (35).

Conclusions. Acute hormone therapy added to standard anti-ischemic therapy in PMP women with UA does not reduce the frequency of ECG ischemic events.

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