

# Principal Results of the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) Trial

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**T**HE BACKGROUND AND SCIENTIFIC rationale, inclusion and exclusion criteria, baseline characteristics, and early blood pressure control data regarding the participants for the Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) Trial have been previously published.<sup>1,2</sup> CONVINCE was planned in 1994 as a large, simple trial<sup>3</sup> to assess the equivalence of controlled-onset extended-release (COER) verapamil and standard therapy in preventing cardio-

**For editorial comment see p 2128.**

**Context** Hypertensive patients are often given a calcium antagonist to reduce cardiovascular disease risk, but the benefit compared with other drug classes is controversial.

**Objective** To determine whether initial therapy with controlled-onset extended-release (COER) verapamil is equivalent to a physician's choice of atenolol or hydrochlorothiazide in preventing cardiovascular disease.

**Design, Setting, and Participants** Double-blind, randomized clinical trial conducted at 661 centers in 15 countries. A total of 16602 participants diagnosed as having hypertension and who had 1 or more additional risk factors for cardiovascular disease were enrolled between September 1996 and December 1998 and followed up until December 31, 2000. After a mean of 3 years of follow-up, the sponsor closed the study before unblinding the results.

**Intervention** Initially, 8241 participants received 180 mg of COER verapamil and 8361 received either 50 mg of atenolol or 12.5 mg of hydrochlorothiazide. Other drugs (eg, diuretic,  $\beta$ -blocker, or an angiotensin-converting enzyme inhibitor) could be added in specified sequence if needed.

**Main Outcome Measures** First occurrence of stroke, myocardial infarction, or cardiovascular disease-related death.

**Results** Systolic and diastolic blood pressure were reduced by 13.6 mm Hg and 7.8 mm Hg for participants assigned to the COER verapamil group and by 13.5 and 7.1 mm Hg for participants assigned to the atenolol or hydrochlorothiazide group. There were 364 primary cardiovascular disease-related events that occurred in the COER verapamil group vs 365 in atenolol or hydrochlorothiazide group (hazard ratio [HR], 1.02; 95% confidence interval [CI], 0.88-1.18;  $P=.77$ ). For fatal or nonfatal stroke, the HR was 1.15 (95% CI, 0.90-1.48); for fatal or nonfatal myocardial infarction, 0.82 (95% CI, 0.65-1.03); and for cardiovascular disease-related death, 1.09 (95% CI, 0.87-1.37). The HR was 1.05 (95% CI, 0.95-1.16) for any prespecified cardiovascular disease-related event and 1.08 (95% CI, 0.93-1.26) for all-cause mortality. Non-stroke hemorrhage was more common with participants in the COER-verapamil group ( $n=118$ ) compared with the atenolol or hydrochlorothiazide group ( $n=79$ ) (HR, 1.54 [95% CI, 1.16-2.04];  $P=.003$ ). More cardiovascular disease-related events occurred between 6 AM and noon in both the COER verapamil (99/277) and atenolol or hydrochlorothiazide (88/274) groups; HR, 1.15 (95% CI, 0.86-1.53).

**Conclusions** The CONVINCE trial did not demonstrate equivalence of a COER verapamil-based antihypertensive regimen compared with a regimen beginning with a diuretic or  $\beta$ -blocker. When considered in the context of other trials of calcium antagonists, these data indicate that the effectiveness of calcium-channel therapy in reducing cardiovascular disease is similar but not better than diuretic or  $\beta$ -blocker treatment.

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vascular disease–related events. It was also the first prospective study of the timing of acute myocardial infarction (MI), cardiovascular event–related death, and stroke—all of which have their highest incidence during the early morning hours (6 AM to noon).<sup>4,5</sup> Planned mean follow-up was 5 years; however the trial was stopped 2 years early by the sponsor for commercial reasons.

**METHODS**

**Study Participants**

Participants were randomized from 661 clinical sites in 15 countries.<sup>2</sup> All had signed informed consent, were 55 years or older, and had at least 1 other established risk factor (eg, diabetes or cigarette smoker) for cardiovascular disease, in addition to hypertension.<sup>1</sup>

**Study Design**

CONVINCE was a randomized, double-blind, active-controlled, multicenter, international clinical trial (FIGURE 1). One group initially received COER verapamil (Covera-HS in the United States, Chronovera in other countries; Pharmacia Corp, Peapack, NJ), which exerts its major antihypertensive effect 6 to 12 hours after administration.<sup>6,7</sup> The active-control group began with either hydrochlorothiazide or atenolol.

The choice was made by the investigator prior to randomization, based on which treatment the investigator thought would be more suitable for the individual participant, should the participant be randomized to the atenolol or hydrochlorothiazide group.

The primary objective was to compare the 2 regimens in preventing acute MI, stroke, or cardiovascular disease–related death.<sup>1</sup> Major secondary outcomes included (1) an expanded cardiovascular disease end point, which included hospitalization for angina, cardiac revascularization or transplant, heart failure, transient ischemic attack or carotid endarterectomy, accelerated or malignant hypertension, or renal failure in addition to the primary outcome; (2) all-cause mortality; (3) cancer; (4) hospitalization for bleeding (excluding hemorrhagic stroke); and (5) incidence of primary end points occurring between 6 AM and noon.<sup>1</sup>

The design of CONVINCE assumed 2024 participants would develop a primary end point, which provided 84% power for detecting a 14% difference between regimens at a 2-sided significance level of .05. Estimates of non-compliance to COER verapamil (7.5 in first year; 3% each subsequent year) and lost to follow-up rates (1% per year)

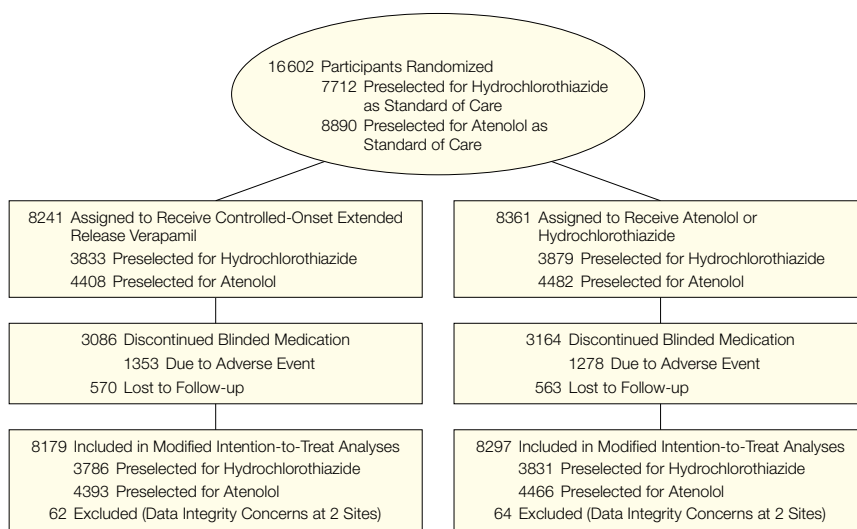
were incorporated in the sample size and power calculations. It was estimated that 15000 participants would have to be enrolled to obtain the 2024 events over a 5-year mean follow-up. The sample size was increased to 16600 (with a target of 2246 events) when it became apparent early in the study that the withdrawal rate from study medication was greater than initially assumed. Equivalence bounds for the hazard ratio (HR) were prespecified as 0.86 to 1.16.<sup>1</sup>

The randomization schedule was stratified by site and atenolol or hydrochlorothiazide choice in successive permuted blocks of 2, 4, or 6, selected randomly. Schedules were prepared by the statistical center at the Division of Biostatistics at the University of Minnesota, Minneapolis, and provided only to a contract research organization (Parexel International, Waltham, Mass), which used them to implement a transtelephonic interactive voice response system, whereby participants could be randomized by calling a toll-free number.<sup>1</sup>

**Treatments**

Participants received 2 bottles for initial treatment (step 1). One bottle contained tablets, 1 to be taken at bedtime, of either placebo or 180 mg of COER verapamil, which provides plasma levels of verapamil that peak<sup>8</sup> at about the same time as the early morning increase in blood pressure, pulse rate, and risk of cardiovascular disease–related events.<sup>4,5</sup> The other bottle contained tablets, 1 to be taken each morning, of placebo or 50 mg of atenolol, or 12.5 mg of hydrochlorothiazide. The dose of step 1 medication was doubled if systolic blood pressure remained at or above 140 mm Hg and/or diastolic blood pressure remained at or above 90 mm Hg. If blood pressure still was not controlled after increasing the dose, 12.5 mg of hydrochlorothiazide could be added to either the initial dose of either atenolol or COER verapamil. Or 50 mg of atenolol could be added to the initial dose of hydrochlorothiazide (step 2 treatment). The added drug could also be doubled in dose if needed. All step 1 and 2 drugs

**Figure 1.** Controlled Onset Verapamil Investigation of Cardiovascular End Points (CONVINCE) Trial



were blinded. Any additional antihypertensive agent (except a nondihydropyridine calcium antagonist, thiazide diuretic, or  $\beta$ -blocker) could be added as a step 3 medication (nonblinded) if needed. An angiotensin-converting enzyme inhibitor was recommended (but not mandated). The study physician could change doses or medications at any time during follow-up.

All study medication for a participant was obtained by using the interactive voice response system, which provided the appropriate bottles of medication based on the step and dose of treatment the participant was currently taking. Each bottle used in the study was assigned a unique number to maintain blinding.

### Data Collection and Monitoring

Participants were seen at least semiannually for blood pressure measurements, treatment dispensing, and end point surveillance. On-site data verification was performed at least annually by the contract research organization. An independent data and safety monitoring board met semiannually to review accumulating data. Confidence intervals (CIs) based on the Lan-DeMets version<sup>9</sup> of the O'Brien-Fleming group sequential boundaries were used as guidelines for early termination.<sup>10</sup> The data and safety monitoring board met 8 times and recommended continuation of the trial after each meeting. All analyses were performed independently of the sponsor by the statistical center at the Division of Biostatistics at the University of Minnesota. All study investigators and the study sponsor were blinded to all between-treatment comparisons until completion of end point data collection and review.

The sponsor closed the study 2 years earlier than originally planned for commercial reasons. A common calendar date of December 31, 2000, was chosen through which all participants would be followed up. Clinical sites were asked to verify the end point status (primary end point and survival status) of each participant as of this date. In addition, in the United States, vital

status was determined through the National Death Index for 263 participants whose vital status was unknown through other sources at the end of the trial. Four previously unknown decedents and 15 individuals with previously unknown cause of death were identified as having died from cardiovascular disease.

### Primary End Point Review and Adjudication

All possible primary end points were reviewed by an end points committee that was blinded to treatment assignment. This committee consisted of 7 experts in cardiovascular medicine. Two members of the committee independently reviewed documentation provided by the clinical sites for each event to assess whether the event met prespecified criteria. When the 2 reviewers did not agree, the full committee reviewed and adjudicated the case. If documentation was insufficient to confirm (or reject) the event, the site clinician's diagnosis was used. For deaths found only through the National Death Index, the coded cause of death provided was used. Of the 729 participants with a primary event included in the analysis, the end point committee confirmed 651 (89%).

Acute MI required 2 of the following 3 conditions (1) symptoms compatible with acute MI (eg, chest pain) lasting longer than 15 minutes; (2) electrocardiographic changes (new persistent ST-segment elevation or pathological Q waves in 2 contiguous leads); or (3) increased cardiac enzymes (more than twice the upper limit of normal). A diagnosis of stroke required the presence of focal neurological deficit lasting longer than 24 hours. Imaging studies were not required to document a stroke. Any death thought to be compatible with coronary heart disease (eg, heart failure, sudden death) or cardiovascular disease was counted as a cardiovascular disease-related death.

### Statistical Methods

Time to event methods (Cox proportional hazards model and Kaplan-Meier curves) were used to compare

outcomes for participants randomly assigned COER verapamil with those assigned atenolol or hydrochlorothiazide. Analyses were by modified intent to treat (modified by the exclusion of 2 sites with data integrity concerns), unless otherwise specified, and were stratified by the choice of standard of care and geographic region (United States, Canada, Western Europe, and other [Eastern Europe, Mexico, Israel, or Brazil]) in which the participant's clinical site was located. Analyses of primary and secondary events considered censoring due to losses to follow-up (ie, participants for whom the primary event status was unknown on the closing date), noncardiovascular disease-related deaths (as appropriate), and the closing date of the study. Losses were censored at the date the primary event status was last known (either the date provided by the site during the closeout process; or the date of the last follow-up visit). The HR for COER verapamil vs atenolol or hydrochlorothiazide was estimated from a stratified Cox model with a binary indicator (COER verapamil vs atenolol or hydrochlorothiazide) as the sole covariate. The proportional hazards assumption was tested by including an interaction term between the randomized treatment indicator and log-transformed follow-up time. Heterogeneity of HR for selected prespecified baseline subgroups was assessed by inclusion of an interaction term (randomized treatment by subgroup variable) in the Cox model. To determine whether HRs for the primary end point varied according to time of day of the event, a competing risk analysis was performed for 4 time intervals: midnight to 6 AM; 6 AM to noon; noon to 6 PM; and 6 PM to midnight.<sup>11</sup> This analysis allows simultaneous estimation of the HRs for each time interval. The homogeneity of HRs across intervals was tested using a  $\chi^2_3$  statistic. For the secondary outcome of primary events that occurred between 6 AM and noon, events with other times or unknown times were censored at the date of the event. *P* values are 2-tailed.

Blood pressure changes from baseline were compared between the 2 treat-

ment groups using the *t* test. All analyses were performed using SAS statistical software (Version 8.0, SAS Institute Inc, Cary, NC).

## RESULTS

### Enrollment

Between September 1996 and December 1998, 16 602 participants were randomized. Participants from 2 sites ( $n=126$ ; 62 randomized to COER ver-

apamil) were excluded because of data integrity concerns. Thus, our report is based on 16 476 randomized participants (Figure 1). The mean age was 66 years; 56% of participants were women.<sup>2</sup> Most participants (84%) had previously been prescribed antihypertensive drugs; hydrochlorothiazide was chosen over atenolol for 7617 (46.2%) participants; 49% had 2 or more risk factors (TABLE 1).<sup>2</sup>

### Visit Attendance and Lost to Follow-up Rates

Participants were followed up for at least 2 years and a maximum of 4.25 years; the median follow-up was 3 years. Among the participants who were alive at the time of each visit, attendance was 92% for the COER verapamil group compared with 93% for the atenolol or hydrochlorothiazide group at 12 months; 86% for both groups at 24 months; and 79% for the COER verapamil group compared with 80% for the atenolol or hydrochlorothiazide group at 36 months. On the closing date of the trial, the primary end point status was unknown for 570 participants assigned to the COER verapamil group compared with 563 assigned to atenolol or hydrochlorothiazide ( $P=.52$  by log-rank test for time to lost to follow-up). Corresponding percentages for unknown vital status were 1.5% for COER verapamil and 1.6% for the atenolol or hydrochlorothiazide group ( $P=.67$ ). In both treatment groups, those lost to follow-up were older; had higher baseline blood pressure levels; were more likely to smoke cigarettes; and have a history of MI, stroke, or transient ischemic attacks compared with participants followed up through the closing date.

### Adherence to Study Medication

Median time receiving blinded treatment was 2.2 years for both the COER verapamil group and the atenolol or hydrochlorothiazide group. By the close of the trial, 39.4% of COER verapamil group and 39.7% of the atenolol or hydrochlorothiazide group had discontinued blinded study medication. The proportion was identical for both groups at 1 year (27%). Reasons for withdrawal were available for 78% of those withdrawing in each treatment group. Participants assigned COER verapamil withdrew more often due to adverse signs or symptoms compared with those assigned atenolol or hydrochlorothiazide ( $P=.02$ ); the most common reason was constipation (216 in the COER verapamil group compared with 28 in the atenolol or hydrochlorothiazide group). However, fewer partici-

**Table 1.** Baseline Characteristics of Randomized Groups

| Characteristic                                    | No. (%) of Participants*     |  |
|---|------------------------------|--|
|   | COER Verapamil<br>(n = 8179) | Atenolol or<br>Hydrochlorothiazide<br>(n = 8297) |
| Choice of diuretic as standard of care            | 3786 (46.3)                  | 3831 (46.2)                                      |
| Sex   |                              |  |
| Men   | 3583 (43.8)                  | 3669 (44.2)                                      |
| Women   | 4596 (56.2)                  | 4528 (55.8)                                      |
| Age, mean (SD), y                                 | 65.6 (7.4)                   | 65.6 (7.4)                                       |
| 55-64   | 3984 (48.7)                  | 4045 (48.8)                                      |
| 65-74   | 3098 (37.9)                  | 3155 (38.0)                                      |
| ≥75   | 1097 (13.4)                  | 1097 (13.2)                                      |
| Race/ethnicity                                    |                              |  |
| White   | 6864 (84.2)                  | 6981 (84.5)                                      |
| Black   | 559 (6.9)                    | 563 (6.8)  |
| Asian   | 99 (1.2)                     | 100 (1.2)  |
| Hispanic  | 592 (7.3)                    | 579 (7.0)  |
| Other   | 36 (0.4)                     | 41 (0.5)   |
| Geographic area                                   |                              |  |
| United States                                     | 4020 (49.2)                  | 4124 (49.7)                                      |
| Canada  | 1692 (20.7)                  | 1713 (20.6)                                      |
| Western Europe                                    | 1023 (12.5)                  | 1025 (12.4)                                      |
| Eastern Europe, Israel, Brazil, or Mexico         | 1444 (17.7)                  | 1435 (17.3)                                      |
| Previous use of antihypertensive drugs            | 6815 (83.7)                  | 6890 (83.5)                                      |
| Blood pressure at randomization, mean (SD), mm Hg |                              |  |
| Systolic  | 150.1 (15.8)                 | 150.1 (16.0)                                     |
| Diastolic   | 86.8 (9.8)                   | 86.8 (9.8)                                       |
| Cardiovascular risk factor                        |                              |  |
| Obesity†  | 4150 (51.0)                  | 4096 (49.6)                                      |
| Dyslipidemia‡                                     | 2540 (31.2)                  | 2575 (31.2)                                      |
| Cigarette use in past 3 y                         | 1912 (23.5)                  | 1883 (22.8)                                      |
| Type 2 diabetes mellitus                          | 1616 (19.9)                  | 1623 (19.7)                                      |
| Established vascular disease                      | 1362 (16.7)                  | 1387 (16.8)                                      |
| Left ventricular hypertrophy§                     | 1000 (12.3)                  | 1019 (12.4)                                      |
| Myocardial infarction                             | 607 (7.5)                    | 652 (7.9)  |
| Vascular bruit                                    | 403 (5.0)                    | 409 (5.0)  |
| Stroke  | 370 (4.5)                    | 393 (4.8)  |
| Transient ischemic attack                         | 184 (2.3)                    | 162 (2.0)  |
| ≥2 Risk factors                                   | 4060 (49.9)                  | 4038 (48.9)                                      |

Abbreviation: COER, controlled-onset extended-release.

\*Values expressed as number (percentage) unless otherwise indicated.

†Body mass index higher than 28.5 or compared with 1977 Metropolitan Life Tables.

‡Elevated total cholesterol level higher than 250 mg/dL (>6.46 mmol/L) or low-density lipoprotein cholesterol level higher than 159 mg/dL (>4.11 mmol/L), or high-density lipoprotein cholesterol level lower than 35 mg/dL (<0.9 mmol/L).

§Determined by electrocardiogram or echocardiogram.

pants assigned COER verapamil (n=115) withdrew because of poor blood pressure control (treatment failures) compared with those assigned atenolol or hydrochlorothiazide (n=207) ( $P<.001$  by log-rank).

### Blood Pressure Control and Step of Medication

Both regimens lowered blood pressure significantly.<sup>2</sup> Averaged over the entire follow-up period, systolic blood pressure was reduced by 13.6 mm Hg and diastolic blood pressure by 7.8 mm Hg from baseline in the COER verapamil group. In the atenolol or hydrochlorothiazide group, systolic blood pressure was reduced by 13.5 mm Hg and diastolic by 7.1 mm Hg. The mean differences in blood pressure change (COER verapamil minus atenolol or hydrochlorothiazide) were small for systolic blood pressure (0.06 mm Hg; 95% CI, -0.44 to 0.56 mm Hg) and diastolic blood pressure (0.67 mm Hg; 95% CI, 0.38-0.95 mm Hg). At the last follow-up visit attended, a systolic blood pressure of less than 140 mm Hg and diastolic blood pressure of less than 90 mm Hg was achieved in 65.5% of the COER verapamil group and 65.9% of the atenolol or hydrochlorothiazide group.

During follow-up, the prescribed antihypertensive regimen was similar across randomized groups (FIGURE 2). In both groups, the proportion of participants prescribed more than 1 antihypertensive medication increased with longer follow-up.

At the last visit, 28.4% of the COER verapamil group and 26.1% of the atenolol or hydrochlorothiazide group were taking only the initially assigned medication. The percentages of participants taking step 2 or step 3 treatment or nonblinded medication only were similar between treatment groups. For step 2, 15.5% of the COER verapamil group were receiving treatment compared with 16.1% of the atenolol or hydrochlorothiazide group; step 3, 16.7 vs 18.2%; and no blinded medication, 39.4% vs 39.7%, respectively. Since  $\beta$ -blockers, by design, were not used with COER verapamil, the 2 treat-

ment groups differed more with respect to blinded  $\beta$ -blocker use (0% of the COER verapamil group vs 43% of the atenolol or hydrochlorothiazide group) than with diuretic use (26% vs 44%, respectively).

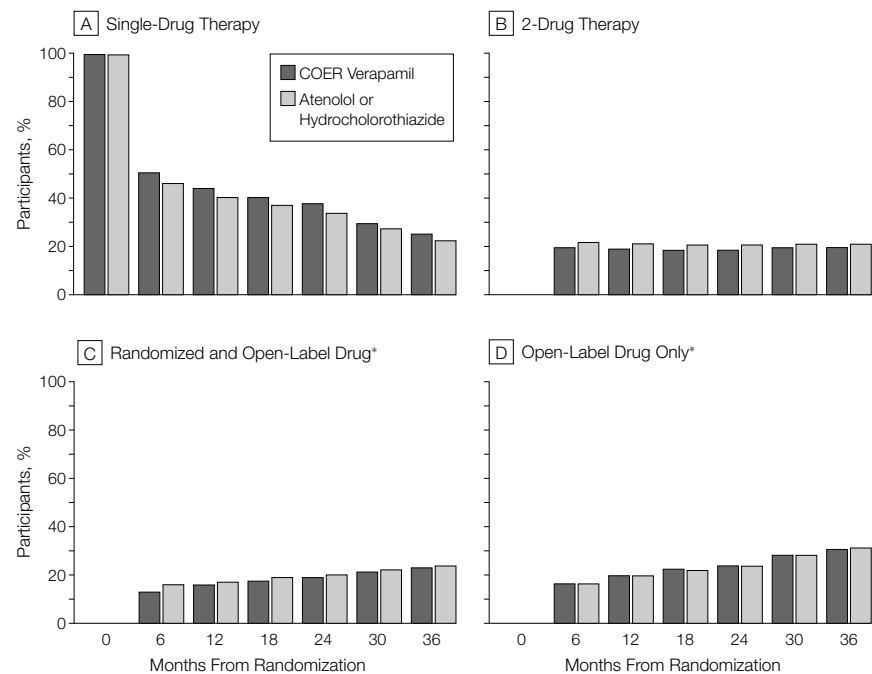
### Primary End Point and Its Components

There were 364 first primary events in the group randomized to COER verapamil compared with 365 among the atenolol or hydrochlorothiazide group (TABLE 2). FIGURE 3 shows the Kaplan-Meier curves for the primary end point. Among those assigned COER verapamil, 1.51% of participants had an event after 12 months of follow-up, 3.12% after 24 months, and 4.94% after 36 months. Among those assigned atenolol or hydrochlorothiazide, 1.69% of participants had an event after 12 months of follow-up, 3.10% after 24 months, and 4.73% after 36 months. The HR for COER verapamil group compared with the atenolol or hydro-

chlorothiazide group was 1.02 (95% CI, 0.88-1.18;  $P=.77$ ). There was no evidence that this HR varied over follow-up (proportional hazards  $P=.36$ ).

Two supplemental on-treatment analyses were performed. In 1 analysis, follow-up was censored 30 days after blinded study medication was discontinued (220 events among participants in the COER verapamil group compared with 217 events in the atenolol or hydrochlorothiazide group; HR, 1.05 [95% CI, 0.87-1.26];  $P=.63$ ). A second analysis included only those participants who were still taking blinded study medication 1 year after randomization. The result of this analysis, which only included events after the first year (171 events among participants in the COER verapamil group compared with 157 in the atenolol or hydrochlorothiazide group), yielded a HR of 1.14 (95% CI, 0.91-1.41;  $P=.25$ ). After adjusting for age, sex, and risk factors at entry, the HRs were 1.06 (95% CI, 0.88-1.28) using the first

**Figure 2.** Participants Taking Determined Level of Therapy



Asterisk indicates angiotensin-converting enzyme inhibitor primarily; COER, controlled-onset extended-release. During 6 to 36 months of follow-up, 41 (0.8%) to 105 (1.7%) of participants in either randomized group reported taking no antihypertensive medications.

**Table 2.** Primary and Secondary Events by Treatment Assignment

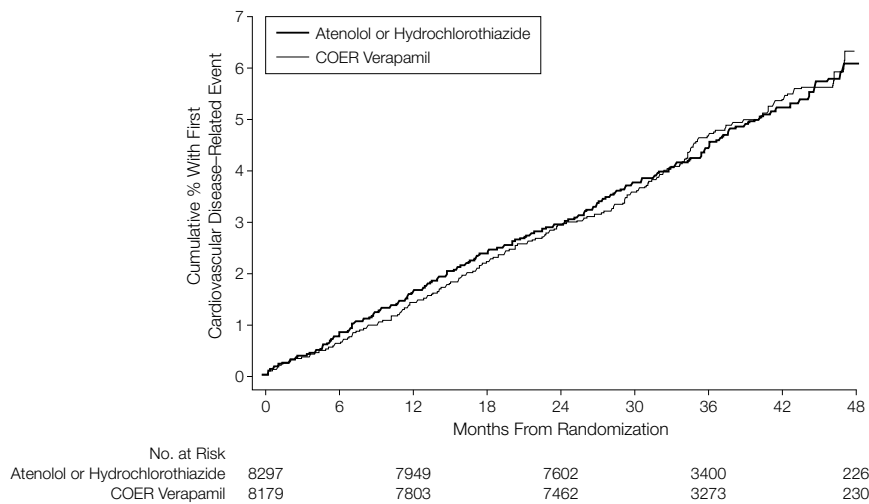
|   | No. (%) of Participants With Event |                                    | Hazard Ratio<br>(95% Confidence Interval) | P Value |
|---|------------------------------------|------------------------------------|---|---------|
|   | COER<br>Verapamil                  | Atenolol or<br>Hydrochlorothiazide |   |         |
| Primary (composite) outcome*                            | 364 (4.5)                          | 365 (4.4)                          | 1.02 (0.88-1.18)                          | .77     |
| Fatal or nonfatal myocardial infarction                 | 133 (1.6)                          | 166 (2.0)                          | 0.82 (0.65-1.03)                          | .09     |
| Fatal or nonfatal stroke                                | 133 (1.6)                          | 118 (1.4)                          | 1.15 (0.90-1.48)                          | .26     |
| Cardiovascular disease–related death                    | 152 (1.9)                          | 143 (1.7)                          | 1.09 (0.87-1.37)                          | .47     |
| Primary event or cardiovascular hospitalization         | 793 (9.7)                          | 775 (9.3)                          | 1.05 (0.95-1.16)                          | .31     |
| Angina pectoris   | 202 (2.5)                          | 190 (2.3)                          | 1.09 (0.89-1.33)                          | .39     |
| Cardiac revascularization/cardiac transplant            | 163 (2.0)                          | 166 (2.0)                          | 1.01 (0.82-1.26)                          | .91     |
| Heart failure   | 126 (1.5)                          | 100 (1.2)                          | 1.30 (1.00-1.69)                          | .05     |
| Transient ischemic attack and/or carotid endarterectomy | 89 (1.1)                           | 105 (1.3)                          | 0.87 (0.66-1.15)                          | .33     |
| Accelerated/malignant hypertension                      | 22 (0.3)                           | 18 (0.2)                           | 1.26 (0.67-2.34)                          | .47     |
| Renal failure (acute/chronic)                           | 27 (0.3)                           | 34 (0.4)                           | 0.81 (0.49-1.35)                          | .43     |
| Death   | 337 (4.1)                          | 319 (3.8)                          | 1.08 (0.93-1.26)                          | .32     |
| New cancer (excluding nonmelanoma skin cancer)          | 310 (3.8)                          | 299 (3.6)                          | 1.06 (0.91-1.24)                          | .46     |
| Death   | 95 (1.2)                           | 93 (1.1)                           | 1.04 (0.79-1.39)                          | .76     |
| Death or hospitalization due to bleeding†               | 118 (1.4)                          | 79 (1.0)                           | 1.54 (1.15-2.04)                          | .003    |
| Deaths from bleeding                                    | 6 (0.1)                            | 6 (0.1)                            | 1.02 (0.33-3.17)                          | .97     |
| Death or hospitalization due to serious adverse event   | 1381 (16.9)                        | 1363 (16.4)                        | 1.04 (0.97-1.12)                          | .29     |
| Hospitalization for serious adverse event               | 1150 (14.1)                        | 1143 (13.8)                        | 1.03 (0.95-1.12)                          | .44     |

Abbreviation: COER, controlled-onset extended-release.

\*First occurrence of stroke, myocardial infarction, or cardiovascular disease–related death.

†Does not include intracerebral bleeding, which was counted as a primary end point (stroke).

**Figure 3.** Incidence of Primary Outcome Measure Over Time



COER indicates controlled-onset extended-release. The COER verapamil group experienced 364 cardiovascular disease–related events and the atenolol or hydrochlorothiazide group experienced 365 (hazard ratio, 1.02; 95% confidence interval, 0.88-1.18).

on-treatment analysis method and 1.12 (95% CI, 0.90-1.40) using the second on-treatment analysis method.

For fatal or nonfatal MI, the HR was 0.82 (95% CI, 0.65-1.03;  $P = .09$ ); fatal or nonfatal stroke, 1.15 (95% CI, 0.90-

1.48;  $P = .26$ ); and cardiovascular disease–related death, 1.09 (95% CI, 0.87-1.37;  $P = .47$ ). Among participants in the COER verapamil group, there were 152 cardiovascular disease–related deaths (24 MIs, 18 strokes, and 110 had other

cardiovascular disease). There were 143 cardiovascular disease–related deaths among participants in the atenolol or hydrochlorothiazide group (22 MIs, 21 strokes, and 100 had other cardiovascular disease).

**Secondary End Points**

The HR for the primary end point or cardiovascular-related hospitalization was 1.05 (95% CI, 0.95-1.16;  $P = .31$ ) and 1.08 (95% CI, 0.93-1.26;  $P = .32$ ) for death. Hospitalization for heart failure, a component of the secondary cardiovascular disease end point, was 30% higher with COER verapamil compared with atenolol or hydrochlorothiazide (HR, 1.30; 95% CI, 1.00-1.69;  $P = .05$ ). More participants assigned COER verapamil ( $n = 118$ ; 1.4%) than atenolol or hydrochlorothiazide ( $n = 79$ ; 1.0%) died or were hospitalized for bleeding unrelated to stroke (HR, 1.54; 95% CI, 1.15-2.04;  $P = .003$ ). Six participants in each group died of hemorrhage not related to stroke (HR, 1.02 [95% CI, 0.33-3.17];  $P = .97$ ). Cancer incidence did not vary by treatment group (310 participants

reported cancer in the COER verapamil group vs 299 in the atenolol or hydrochlorothiazide group; HR, 1.06 [95% CI, 0.91-1.24];  $P = .46$ ). About 14% of participants in each treatment group were hospitalized at least once during follow-up ( $P = .62$ ).

For the primary end point, treatment HRs did not vary significantly by time of day of the event ( $P = .43$ ). In each treatment group, more participants had primary events between 6 AM and noon than any other 6-hour period (FIGURE 4). The HR for the 6 AM to noon events was 1.15 (95% CI, 0.86-1.53;  $P = .34$ ). For an additional analysis that censored participant follow-up 30 days after blinded medication was discontinued, the HR for events occurring between 6 AM and noon was 1.19 (95% CI, 0.84-1.70).

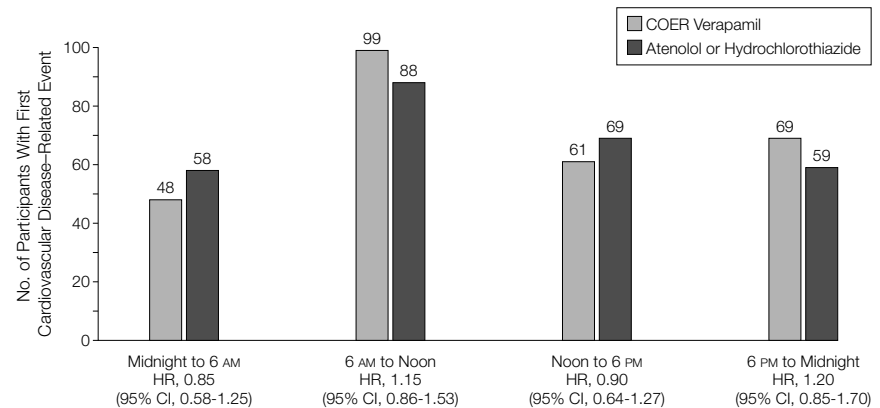
### Baseline-Defined Subgroup Results

When participants were grouped according to baseline characteristics, there was no evidence of a treatment by subgroup interaction for any of the predefined baseline subgroups (TABLE 3).

### COMMENT

The results of this study indicate that COER verapamil is not equivalent to atenolol or hydrochlorothiazide in preventing cardiovascular disease–related events. The upper bound of the 95% CI for the primary end point (1.18) slightly exceeded the prespecified boundary (1.16) for equivalence of COER verapamil and atenolol or hydrochlorothiazide.<sup>1,12</sup> All HRs involving efficacy were close to 1.0, including the primary end point (1.02), the major secondary combined cardiovascular disease end point (1.05), and mortality (1.08). Similarly, although the HRs increased slightly in the on-treatment analyses for the primary end point, they remained close to 1.0 (1.06 and 1.12). The relative risks for the primary end point did not differ significantly across multiple subgroups (Table 3), including choice of atenolol or hydrochlorothiazide, suggesting that there was no particular baseline characteristic associated with a different outcome overall. Further analyses

**Figure 4.** Incidence of Primary End Points by Treatment Assignment and Time of Day



Time of onset of first cardiovascular disease–related event was determined for 277 participants in the controlled-onset extended-release (COER) verapamil group and 274 participants in the atenolol or hydrochlorothiazide group. There were 178 (24%) events for which time of onset could not be determined (87 among those randomized to COER verapamil and 91 among those randomized to atenolol or hydrochlorothiazide; hazard ratio [HR], 0.98; 95% confidence interval [CI], 0.73-1.32).

**Table 3.** Primary Composite End Point by Treatment Assignment

|                  | No. (%) of Participants |                                 | Relative Risk (95% Confidence Interval) | P Value for Interaction |
|------------------|-------------------------|---------------------------------|---|-------------------------|
|                  | COER Verapamil          | Atenolol or Hydrochlorothiazide |   |                         |
| Overall          | 364 (4.5)               | 365 (4.4)                       | 1.02 (0.88-1.18)                        |                         |
| Standard of care |                         |                                 |   |                         |
| Diuretic         | 181 (2.2)               | 165 (2.0)                       | 1.12 (0.91-1.38)                        | .24                     |
| β-Blocker        | 183 (2.2)               | 200 (2.4)                       | 0.94 (0.77-1.15)                        |                         |
| Geographic area  |                         |                                 |   |                         |
| United States    | 204 (2.5)               | 212 (2.6)                       | 1.00 (0.82-1.21)                        | .82                     |
| Canada           | 93 (1.1)                | 86 (1.0)                        | 1.10 (0.82-1.48)                        |                         |
| Western Europe   | 39 (0.5)                | 35 (0.4)                        | 1.13 (0.72-1.79)                        |                         |
| Other            | 28 (0.3)                | 32 (0.4)                        | 0.87 (0.52-1.44)                        |                         |
| Sex              |                         |                                 |   |                         |
| Men              | 203 (2.5)               | 192 (2.3)                       | 1.08 (0.89-1.31)                        | .42                     |
| Women            | 161 (2.0)               | 173 (2.1)                       | 0.96 (0.77-1.18)                        |                         |
| Age, y           |                         |                                 |   |                         |
| <65              | 102 (1.2)               | 124 (1.5)                       | 0.85 (0.65-1.10)                        | .09                     |
| ≥65              | 262 (3.2)               | 241 (1.9)                       | 1.11 (0.93-1.32)                        |                         |
| Diabetes         |                         |                                 |   |                         |
| Present          | 101 (1.2)               | 116 (1.4)                       | 0.86 (0.66-1.12)                        | .16                     |
| Absent           | 261 (3.2)               | 244 (2.9)                       | 1.10 (0.92-1.31)                        |                         |
| Risk factor      |                         |                                 |   |                         |
| 1                | 131 (1.6)               | 121 (1.4)                       | 1.14 (0.89-1.46)                        | .29                     |
| >1               | 231 (2.8)               | 239 (2.9)                       | 0.97 (0.81-1.16)                        |                         |

Abbreviation: COER, controlled-onset extended-release.

by choice of atenolol or hydrochlorothiazide that take into account use of treatment steps 2 and 3 are planned. The HR was also close to unity for all of the prespecified secondary cardiovascular disease–related events, with the exception of heart failure. This was expected because both diuretics and β-blockers

are usually recommended for heart failure,<sup>13</sup> whereas verapamil has been associated with an increased risk of heart failure in previous studies.<sup>14,15</sup>

The treatment regimens showed some minor and statistically nonsignificant differences in the incidence of each component of the primary end

point. The incidence of acute MI was about 18% lower with COER verapamil ( $P=.09$ ) than with the atenolol or hydrochlorothiazide group; this benefit was offset by a 15% higher risk of stroke ( $P=.26$ ). Although quite possibly due to chance, these trends are consistent with COER verapamil's ability to inhibit platelet aggregation,<sup>16-18</sup> leading to both reduced MI incidence and more bleeding. Such a mechanism has been postulated to explain aspirin's tendency to increase hemorrhagic stroke, which is outweighed by a protective effect on MI.<sup>19</sup> These trends are opposite to those seen in the Nordic Diltiazem (NORDIL) study, which used the nondihydropyridine calcium antagonist diltiazem.<sup>20</sup> A similar contrast is observed when comparing the results of CONVINCENCE and a recent meta-analysis.<sup>21</sup>

The prospectively gathered data of Figure 4 confirm previous epidemiological observations concerning the increased risk of cardiovascular events in the early morning hours,<sup>4,5</sup> but do not support the concept of chronotherapeutics.<sup>22</sup> However, our analyses of this secondary outcome were limited by the smaller than expected number of events, and may be further confounded by non-adherence and use of multiple drugs in each treatment group to control blood pressure.

The findings of CONVINCENCE are subject to many limitations. The decision to terminate CONVINCENCE prematurely did not derive from a recommendation of the data and safety monitoring board,<sup>23-26</sup> nor from review of external data from other clinical trials.<sup>27,28</sup> In this respect, the study is flawed. When stopped, the results were still inconclusive with respect to the prespecified equivalence bounds. Less than a third of the planned number of events were observed, which affects the width of the 95% CIs, and limits the ability to make conclusions about any results (which may not be similar) with longer follow-up. More participants than expected discontinued blinded medication, which pushes the overall result toward the null. Approximately 7% of participants were

lost to follow-up for the primary end point. In both treatment groups, participants who were lost to follow-up had baseline risk factors that placed them at a higher risk of cardiovascular disease-related events than participants who continued follow-up. Finally, the effectiveness of atenolol or hydrochlorothiazide in the population studied might differ from that in previous clinical trials establishing the efficacy of atenolol or hydrochlorothiazide, which is a common problem in interpreting the results of equivalence trials.

In summary, CONVINCENCE was unable to demonstrate equivalence of a COER verapamil-based antihypertensive regimen and a regimen beginning with a diuretic or  $\beta$ -blocker. When considered in the context of other trials of calcium antagonists, including the larger Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),<sup>29</sup> which found that the calcium channel blocker amlodipine was not superior to the diuretic chlorthalidone, in reducing the rate of coronary heart disease or stroke and was associated with a higher rate of heart failure, these data indicate that the effectiveness of calcium channel blocker therapy in reducing cardiovascular disease-related morbidity and mortality is similar but not better than diuretic or  $\beta$ -blocker treatment. These data support the recommendation of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure<sup>30</sup> for low-dose diuretic (or possibly  $\beta$ -blocker) therapy for hypertensive patients who have no specific indication for another antihypertensive drug.

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## REFERENCES

- Black HR, Elliott WJ, Neaton JD, et al, for the CONVINCE Research Group. Rationale and design for the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) Trial. *Controlled Clinical Trials*. 1998;19:370-390.
- Black HR, Elliott WJ, Neaton JD, et al. Baseline characteristics and early blood pressure control in the CONVINCE trial. *Hypertension*. 2001;37:12-18.
- Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. *J Clin Epidemiol*. 1995;48:23-40.
- Cohen MC, Rohtla KM, Lavery CE, Muller JE, Mittleman MA. Meta-analysis of the morning excess of acute myocardial infarction and sudden cardiac death. *Am J Cardiol*. 1997;79:1512-1516.
- Elliott WJ. Circadian variation in the timing of stroke onset: a meta-analysis. *Stroke*. 1998;29:992-996.
- White WB, Anders RJ, MacIntyre JM, et al. Nocturnal dosing of a novel delivery system of verapamil for systemic hypertension. *Am J Cardiol*. 1995;76:375-380.
- White WB, Black HR, Weber MA, Elliott WJ, Bryzinski B, Fakhouri TD. Comparison of effects of COER-verapamil at bedtime and nifedipine GITS on arising on early morning blood pressure, heart rate and the heart rate blood pressure product. *Am J Cardiol*. 1998;81:424-431.
- Gupta SK, Yih MY, Atkinson L, Longstreth J. The effect of food, time of dosing, and body position on the pharmacokinetics and pharmacodynamics of verapamil and norverapamil. *J Clin Pharmacol*. 1995;35:1083-1093.
- Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*. 1983;70:659-663.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics*. 1979;35:549-556.
- Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York, NY: Springer; 2000:170-179.
- Ellenberg SS, Temple R. Placebo-controlled trials and active-control trials in the evaluation of new treatments, part 2: practical issues and specific cases. *Ann Intern Med*. 2000;133:464-470.
- Gomberg-Maitland M, Baran DA, Fuster V. Treatment of congestive heart failure: guidelines for the primary care physician and the heart failure specialist. *Arch Intern Med*. 2001;161:342-352.
- Danish Study Group on Verapamil in Myocardial Infarction (DAVIT-I). Verapamil in acute myocardial infarction. *Eur Heart J*. 1984;5:516-528.
- Danish Study Group on Verapamil in Myocardial Infarction. Effect of verapamil on mortality and major events after acute myocardial infarction: the Danish Verapamil Infarction Trial II (DAVIT-II). *Am J Cardiol*. 1990;66:779-785.
- Addonizio VP Jr, Fisher CA, Strauss JF 3rd, Wachtfogel YT, Colman RW, Josephson ME. Effects of verapamil and diltiazem on human platelet function. *Am J Physiol*. 1986;250:H366-H371.
- Lacoste L, Lam JY, Hung J, Waters D. Oral verapamil inhibits platelet thrombus formation in humans. *Circulation*. 1994;89:630-634.
- Ding YA, Chou TC, Lin KC. Effects of long-acting propranolol and verapamil on blood pressure, platelet function, metabolic and rheological properties in hypertension. *J Hum Hypertens*. 1994;8:273-278.
- He J, Whelton PK, Vu B, Klag MJ. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized clinical trials. *JAMA*. 1998;280:1930-1935.
- Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and  $\beta$ -blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) Study. *Lancet*. 2000;356:359-365.
- Blood Pressure Lowering Treatment Trialists' Collaborative. Effects of ACE-inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet*. 2000;356:1955-1964.
- Smolensky MH, Portaluppi F. Chronopharmacology and chronotherapeutics of cardiovascular medications: relevance to prevention and treatment of coronary heart disease. *Am Heart J*. 1999;137:S14-S24.
- The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on death from cardiovascular causes, myocardial infarction, and stroke in high-risk patients. *N Engl J Med*. 2000;342:145-153.
- ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT). *JAMA*. 2000;283:1967-1975.
- Staessen JA, Fagard R, Thijs L, et al, for the Systolic Hypertension Europe (Syst-EUR) Trial Investigators. Morbidity and mortality in the placebo-controlled European Trial on Isolated Systolic Hypertension in the Elderly. *Lancet*. 1997;350:757-764.
- Agodoa LY, Appel L, Bakris GL, et al, for the African American Study of Kidney Disease and Hypertension (AASK) Study Group. Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. *JAMA*. 2001;285:2719-2728.
- Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851-860.
- Brenner BM, Cooper ME, de Zeeuw D, et al, for the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) Study Group. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-869.
- ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-2997.
- The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med*. 1997;157:2413-2446.