Effects of Once-Daily Angiotensin-Converting Enzyme Inhibition and Calcium Channel Blockade–Based Antihypertensive Treatment Regimens on Left Ventricular Hypertrophy and Diastolic Filling in Hypertension

The Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement (PRESERVE) Trial

Richard B. Devereux, MD; Vittorio Palmieri, MD; Norman Sharpe, MD; Vincent De Quattro, MD; Jonathan N. Bella, MD; Giovanni de Simone, MD; J. Findlay Walker, MD; Rebecca T. Hahn, MD; Björn Dahlöf, MD, PhD

Background—The Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement (PRESERVE) study was designed to test whether enalapril achieves greater left ventricular (LV) mass reduction than does a nifedipine gastrointestinal treatment system by a prognostically meaningful degree on a population basis (10 g/m²).

Methods and Results—An ethnically diverse population of 303 men and women with essential hypertension and increased LV mass at screening echocardiography were enrolled at clinical centers on 4 continents and studied by echocardiography at baseline and after 6- and 12-month randomized therapy. Clinical examination and blinded echocardiogram readings 48 weeks after study entry in an intention-to-treat analysis of 113 enalapril-treated and 122 nifedipine-treated patients revealed similar reductions in systolic/diastolic pressure (−22/12 versus −21/13 mm Hg) and LV mass index (−15 versus −17 g/m², both P>0.20). No significant between-treatment difference was detected in population subsets defined by monotherapy treatment, sex, age, race, or severity of baseline hypertrophy. Similarly, there was no between-treatment difference in change in velocities of early diastolic or atrial phase transmitral blood flow. More enalapril-treated than nifedipine-treated patients required supplemental treatment with hydrochlorothiazide (59% versus 34%, P<0.001) but not atenolol (27% versus 22%, NS).

Conclusions—Once-daily antihypertensive treatment with enalapril or long-acting nifedipine, plus adjunctive hydrochlorothiazide and atenolol when needed to control blood pressure, both had moderately beneficial and statistically indistinguishable effects on regression of LV hypertrophy. (Circulation. 2001;104:1248-1254.)

Key Words: angiotensin ■ calcium ■ trials ■ echocardiography ■ hypertension ■ hypertrophy

Left ventricular (LV) hypertrophy is a cardinal manifestation of preclinical cardiovascular disease1 that strongly predicts cardiovascular events and death in hypertensive patients,2,3 the general population,4,5 and patients with coronary disease.6,7 Rates of death or nonfatal complications are 2- to 4-fold higher in the presence of LV hypertrophy independent of age, sex, and other risk factors.2–5 Several studies suggest that hypertrophy regression is associated with improved prognosis in hypertensive patients.8–10 As a result, prevention or reversal of hypertensive LV hypertrophy is widely accepted as a desirable treatment goal. However, despite numerous trials of pharmacologic and nonpharmacologic therapy, uncertainty persists about how best to regress hypertensive LV hypertrophy. Most published studies have been relatively small and have had additional limitations, including short duration, lack of comparative agents, unblinded echocardiogram readings, and study populations without sexual and ethnic diversity.11–13 Available large-scale trials have been confounded by concomitant non-drug therapy, high subject dropout or absence of LV hypertrophy before therapy.14,15

Methods

Study Design

The Prospective Randomized Enalapril Study Evaluating Reversal of Ventricular Enlargement (PRESERVE) trial was designed to test 2
primary hypotheses: (1) antihypertensive treatment with enalapril induces greater regression of LV hypertrophy than treatment with nifedipine by a prognostically meaningful amount on a population basis (10 g/m²) despite equivalent blood pressure (BP) reduction; and (2) enalapril produces greater normalization of the Doppler early/late diastolic LV filling velocity ratio.16

Study Outline
PRESERVE used a randomized, double-blind, parallel-group design, with sequential stages of screening and randomization followed by baseline echocardiography (Figure 1). Blinded study medication was titrated and then maintained for 1 year, with echocardiograms performed after 6 and 12 months, after which double-blinded therapy was continued during “clean-up” of measurements and clinical event ascertainment to prevent knowledge of treatment assignment from influencing data adjudication. A planned 3-year extended follow-up was not undertaken because the enrollment target of 480 patients was not attained.

Subjects
To enter echocardiographic screening, patients needed to have seated BP during the previous 4 weeks ≥140 mm Hg systolic and/or 90 mm Hg diastolic (Korotkoff phase 5) if taking antihypertensive medications or ≥150 and/or 90 mm Hg if unmedicated and to give written informed consent. Patients received placebo tablets for ≤1 week and needed 80% to 120% compliance by pill count to enroll. Patients with LV ejection fraction <40%, severe valvular disease, or coexisting cardiomyopathy on screening echocardiogram were excluded. Initially, patients receiving treatment with ACE inhibitors or calcium channel blockers were excluded, but when the frequent use of these agents by patients with LV hypertrophy became evident, they were enrolled with stratified randomization to assure balanced representation in both treatment arms.

If measurements of screening echocardiograms at clinical centers documented LV hypertrophy, studies were sent to the echocardiography Reading Center to confirm technical quality and determine the presence of LV hypertrophy. Recruitment of subjects on 4 continents assured ethnic diversity. To ensure applicability of study findings to hypertensive patients at high risk because of LV hypertrophy, studies were sent to the echocardiography Reading Center and repeated readings of 22 echocardiograms in 183 PRESERVE patients showed excellent reliability (intraclass correlation coefficient, 0.93; P<0.001) without significant regression to the mean (mean difference, 1.1±1.2 g/m²; P=NS). Outlines of Doppler flow patterns at the mitral annulus were traced electronically to measure early and late diastolic LV filling. After verification readings to determine the accuracy of extreme values, data were exported electronically to the Merck Statistical Coordinating Center in Brussels. Baseline echocardiographic results were combined with limited identifying information to generate clinical reports for patients.

Analysis Plan
Because the study had two primary objectives, it was to be considered positive only if enalapril was more effective than nifedipine for both LV mass reduction and normalization of LV diastolic filling at a value of P<0.05 or if one comparison had a value of P<0.025. All analyses were by intention to treat, with site and BP change as covariates in ANOVA.

Study Power
The planned sample of 480 patients was chosen to have >90% power to detect postulated differences between enalapril and nifedipine treatment arms in both primary end points. The numbers of participants with satisfactory baseline and 1-year studies needed for this power were 133 per treatment group, for a between-treatment difference of 10 g/m² for change in LV mass and 191 per group for 0.04 m/s difference for change in peak E velocity, assuming standard deviations of changes to be 25 g/m² and 0.12 m/s. Based on the short-term between-study standard deviation of 11.2 g/m² for LV mass index in PRESERVE and that of 20 g/m² with a similar protocol over a 1-year period of blinded therapy with losartan or atenolol in LIFE (B. Dahlöf, personal communication, March 2000), power to detect a between-group difference of 10 g/m² in PRESERVE was >90% with <100 patients per arm.
Results

Patients
A total of 303 hypertensive patients with echocardiographic LV hypertrophy enrolled in PRESERVE in 28 centers in 10 countries (see Appendix). Baseline clinical and echocardiographic characteristics of enalapril or nifedipine groups were virtually identical (Table 1). Prior antihypertensive therapies were taken by similar percentages of enalapril- or nifedipine-treated patients, including atenolol (16/15%), metoprolol (13/12%), amlodipine (8/11%), captopril (12/6%), diltiazem (6/4%), enalapril (11/15%), indapamide (8/10%), lisinopril (6/6%), nifedipine (22/15%), verapamil (3/6%), and hydrochlorothiazide (9/14%).

A total of 222 patients completed the study. Of 148 patients randomly assigned to enalapril, 104 (70%) completed the study, 7 (5%) discontinued because of insufficient therapeutic response, 22 (15%) because of patient noncooperation, 4 (3%) because of patient noncooperation, 4 (3%) because of loss to follow-up, and 6 (4%) because of protocol deviations. Among 155 patients randomly assigned to nifedipine, 118 (76%) completed the study, 5 (3%) discontinued because of inadequate therapeutic response, 10 (6%) because of clinical adverse experiences (predominantly cough), 5 (3%) because of patient noncooperation, 4 (3%) because of loss to follow-up, and 6 (4%) because of protocol deviations. Among 155 patients randomly assigned to nifedipine, 118 (76%) completed the protocol (P=0.299 versus enalapril): 5 (3%) discontinued because of inadequate therapeutic response, 10 (6%) because of clinical adverse experiences, 12 (8%) because of patient noncooperation, 4 (3%) because of loss to follow-up, 5 (3%) because of protocol deviations, and 1 (1%) for other causes. An attempt was made to obtain echocardiograms on all patients at each scheduled interval whether or not they continued to receive blinded study medication. Baseline-48 week echocardiographic comparison data for primary intention-to-treat analyses were obtained in 113 and 122, 76% and 79%, respectively, of the total enrolled in enalapril- and nifedipine-treated groups, including 9 and 4, respectively, who had withdrawn from study therapy; 105 and 117 patients in enalapril- and nifedipine-treated groups provided baseline-24 week echocardiographic comparisons.

Hemodynamic Effects of Study Treatment
After 48 weeks of treatment, BP was reduced by 21.8±23.9/11.9±10.6 mm Hg in the enalapril arm and by 21.1±23.3/13.4±11.4 mm Hg in the nifedipine arm (P=NS). Both systolic and diastolic BP fell more rapidly during drug titration by nifedipine than by enalapril (Figure 2) because of greater pressure reduction (by 6/5 mm Hg) by nifedipine monotherapy titration. By 48 weeks, BP levels and changes from baseline were similar in the two groups. The BP goal of PRESERVE, to reduce BP to <140/90 mm Hg or to reduce sitting systolic BP by ≥30 mm Hg and diastolic BP by ≥15 mm Hg, was attained in 38% of patients in each treatment arm. BP control was achieved less consistently by monotherapy with enalapril than nifedipine (43% versus 61% of patients, P<0.005), with similar BP reductions of 21.6/11.0 and 20.4/13.6 mm Hg on monotherapy. Hydrochlorothiazide was added in more enalapril- than nifedipine-treated patients (59% versus 34%, P<0.001), without between-group difference in atenolol use (27% versus 22%, P=NS).

Heart rate fell from baseline by 2.6±14.7 and 1.3±10.3 beats/min in enalapril- and nifedipine treated groups at 24 weeks and 3.5±13.9 and 3.7±10.5 beats/min at 48 weeks (P=NS). Body weight and body surface area showed no significant change.

Change in LV Dimensions and Mass During Blinded Treatment
Both septal and posterior wall thickness decreased similarly in both treatment groups during 48 weeks of blinded treatment (Figure 3 and Table 2) without significant change in LV diameter (Table 2 and Figure 4, upper panel). Relative wall thickness decreased similarly during study treatment in both groups but differed from primary LV dimensions in showing additional decrease between 24 and 48 weeks of treatment (Figure 4, lower panel). As a result of changes in primary LV dimensions, mean LV mass decreased similarly by 26 g versus 32 g (P=0.36) in patients in enalapril or nifedipine treatment arms (Table 2). There were similar changes over 48 weeks in the primary predesignated end point of LV mass/body surface area of -14.7±20.6 g/m² in enalapril and -16.9±18.4 g/m² in nifedipine-treated patients (Table 2). Indexation of LV mass for height², to identify potential effects of weight change, revealed similar mean decreases in

| TABLE 1. Characteristics of Patients Randomly Assigned to Enalapril or Nifedipine Treatment |
|---------------------------------|---------------------------------|
| Sex (male/female) | Enalapril (n=148) | Nifedipine (n=155) |
| Race, white/black/Asian/Hispanic/other | 72/12/57/6/1 | 84/10/54/6/0 |
| Age, y | 63.5±9.0 | 63.0±8.6 |
| Height, cm | 165.2±9.7 | 165.8±10.5 |
| Weight, kg | 73.0±14.8 | 73.3±14.7 |
| Systolic pressure, mm Hg | 172.0±21.1 | 171.0±20.7 |
| Diastolic pressure, mm Hg | 97.7±10.1 | 98.2±10.2 |
| Heartbeat, beats/min | 73.3±13.1 | 73.3±11.2 |
| LV mass index, g/m²² | 130.9±25.1 | 133.3±25.2 |
| Mitral E velocity, cm/s | 49.2±14.9 (n=50) | 51.3±23.0 (n=59) |
| Mitral A velocity, cm/s | 68.2±23.9 (n=49) | 69.1±21.7 (n=59) |
| Values are mean±SD. All P>0.5. |

Indexation of LV mass for height², to identify potential effects of weight change, revealed similar mean decreases in.
LV mass of \(-6.8 \text{ g/m}^2\) with enalapril and \(-7.4 \text{ g/m}^2\) with nifedipine \((P=\text{NS})\). Most reduction in LV mass occurred by 24 weeks of study treatment (Figure 5). Changes in LV mass index during treatment were positively but weakly related to systolic and diastolic BP changes in both treatment groups \((r=0.08 \text{ to } 0.29)\). Adjustment of baseline to 48-week change in LV mass index for change in mean BP confirmed lack of difference between treatments \((P=0.225)\).

LV Mass Change in Population Subsets

Patients receiving enalapril and nifedipine monotherapy had similar mean decreases in LV mass \((-13.9 \text{ versus } -17.7 \text{ g/m}^2, P=\text{NS})\). Women had similar reductions in LV mass index during treatment were positively but weakly related to systolic and diastolic BP changes in both treatment groups \((r=0.08 \text{ to } 0.29)\). Adjustment of baseline to 48-week change in LV mass index for change in mean BP confirmed lack of difference between treatments \((P=0.225)\).

nifedipine were similar in whites \((-13.2 \text{ versus } -17.2 \text{ g/m}^2)\), Asians \((-14.8 \text{ versus } -16.8 \text{ g/m}^2)\), and others (including blacks, \(-20.1 \text{ versus } -14.6 \text{ g/m}^2\)). LV mass index decreased less while receiving enalapril or nifedipine in patients with milder LV hypertrophy \((\leq125 \text{ g/m}^2 \text{ in women and } \leq134 \text{ g/m}^2 \text{ in men}) \((-10.7 \text{ versus } -10.5 \text{ g/m}^2)\) than with severe hypertrophy \((-21.2 \text{ versus } -24.8 \text{ g/m}^2)\).

Change in Diastolic Filling Parameters During Blinded Treatment

There were parallel reductions of both “E” and “A” velocities at the mitral annulus in the two treatment arms (Table 3). As a result, there was no significant between-treatment difference in the change in the “E/A” ratio from baseline to either 24- or 48-week echocardiograms (Table 3).

Discussion

The PRESERVE trial provides the largest prospective, randomized, double-blind study to date comparing cardiac ef-
effects of ACE inhibition and calcium channel blockade in patients with hypertensive LV hypertrophy. The most important result of the study is that regimens based on once-daily administration of enalapril or long-acting nifedipine significantly reduced LV mass index and relative wall thickness during 1 year of treatment: LV mass index was reduced to the normal range in 56% of enalapril-treated patients and 48% of nifedipine-treated patients. The primary outcome measure of LV mass index was reduced similarly by the two treatment regimens, both in primary intention-to-treat analyses and in the subset of patients treated per protocol (data not shown), on monotherapy or in various population subsets. Similarly, the two treatment groups did not differ with regard to the transmitral diastolic flow E/A ratio, the second a priori outcome measure of the study.

Comparison With Previous Studies
An early meta-analysis of antihypertensive treatment trials reported that ACE inhibitors reduced LV more than calcium channel blockers or other treatments when induced BP reduction and baseline LV mass were taken into account. That meta-analysis and another study suggested that dihydropyridine calcium channel blockers had little effect on LV hypertrophy. However, more recent analyses of better quality trials found no difference between LV effects of ACE inhibitors and newer, long-acting calcium channel blockers. The results of the present study suggest that disappointing results in early studies with dihydropyridine calcium channel blockers may have been caused by actions that are not

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enalapril Baseline</th>
<th>Enalapril 48 wk</th>
<th>Nifedipine Baseline</th>
<th>Nifedipine 48 wk</th>
<th>Between Arms Change, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST, cm</td>
<td>1.15±0.15</td>
<td>1.05±0.16</td>
<td>1.15±0.18</td>
<td>1.02±0.16</td>
<td>0.314</td>
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<td>LVID, cm</td>
<td>5.35±0.44</td>
<td>5.38±0.53</td>
<td>5.51±0.52</td>
<td>5.49±0.53</td>
<td>0.308</td>
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<tr>
<td>PWT, cm</td>
<td>1.04±0.12</td>
<td>0.94±0.11</td>
<td>1.03±0.131</td>
<td>0.95±0.11</td>
<td>0.149</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>232.1±47.6</td>
<td>206.0±49.5</td>
<td>240.8±55.0</td>
<td>209.6±45.1</td>
<td>0.360</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>129.9±22.6</td>
<td>115.2±24.3</td>
<td>132.8±24.5</td>
<td>115.9±23.0</td>
<td>0.403</td>
</tr>
<tr>
<td>RWT</td>
<td>0.39±0.05</td>
<td>0.35±0.05</td>
<td>0.38±0.07</td>
<td>0.35±0.06</td>
<td>0.100</td>
</tr>
</tbody>
</table>

Values are mean±SD.
ST indicates septal thickness; LVID, LV internal diameter; LVMI, LV mass index; PWT, posterior wall thickness; and RWT, relative wall thickness.

Figure 4. Change from baseline (vertical axes) of LV internal dimension (A) and relative wall thickness (B).

Figure 5. Change of LV mass index (vertical axis) during blinded study treatment.
characteristic of subsequently introduced longer-acting preparations, including induction of volume overload and sympathetic activation. In the Treatment of Mild Hypertension Study (TOMHS), treatment was observed between ACE inhibitor and calcium blocker arms. The Veterans’ Administration Study provided suggestive evidence of greater LV hypertrophy regression by a diuretic or ACE inhibitor but had high participant dropout (61%) by 1 year.

Hemodynamic Correlates of LV Mass Change
In keeping with previous studies, LV mass changes were positively but weakly related to induced BP reduction. Previous studies have revealed that LV mass change during treatment is more closely related to change in 24-hour BP than clinical BP. Thus, the impact of intrapatient variability in BP reduction on LV mass change may be underestimated in the present study.

An interesting observation is that in the currently studied patients with relatively severe hypertension (by both BP levels and uniform presence of hypertrophy), enalapril controlled BP less consistently than did nifedipine as once-daily monotherapy, requiring more frequent supplementation with hydrochlorothiazide to equalize BP in the treatment arms. This may have been partially related to BP measurement 20 to 26 hours after the last dose, at a time when blockade of angiotensin II production by enalapril may have been incomplete. An exploratory retrospective analysis of covariance with LV mass change between enalapril or nifedipine treatment arms in the ratio of early diastolic to atrial phase transmitral flow velocities during study therapy.

### Table 3. Change in LV Diastolic Filling Parameters in Enalapril- and Nifedipine-Treated Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Enalapril Baseline</th>
<th>Enalapril 48 wk</th>
<th>Nifedipine Baseline</th>
<th>Nifedipine 48 wk</th>
<th>Between Arms Change, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>E velocity, cm/s</td>
<td>48.2±13.9</td>
<td>45.2±13.2</td>
<td>50.9±28.3</td>
<td>45.4±14.8</td>
<td>0.948</td>
</tr>
<tr>
<td>A velocity, cm/s</td>
<td>68.5±30.0</td>
<td>60.2±26.5</td>
<td>69.3±21.8</td>
<td>65.5±18.0</td>
<td>0.397</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>0.80±0.43</td>
<td>0.84±0.37</td>
<td>0.74±0.27</td>
<td>0.73±0.27</td>
<td>0.470</td>
</tr>
</tbody>
</table>

Values are mean±SD.

Time Course of LV Geometric Changes
In contrast to earlier trials of 6 months’ duration, PRESERVE performed on-treatment echocardiograms after 6 and 12 months of blinded study medication. Between 6- and 12-months studies, there were small further reductions in LV wall thicknesses with slight increase in chamber diameter, as a result of which there was no further change in LV mass additional reduction in relative wall thickness over the second 6 months of study treatment. This suggests that the benefit of antihypertensive treatment on LV remodeling cannot be appreciated unless treatment trials last ≥1 year.

Effect of ACE Inhibition and Calcium Channel Blockade on LV Diastolic Filling
The present study showed no significant difference between treatment arms in the ratio of early diastolic to atrial phase transmitral flow velocities during study therapy.

Limitations of the Study
PRESERVE compares effects on LV geometry and filling of treatment regimens based on ACE inhibition or calcium channel blockade with no placebo group and hence could overestimate or underestimate beneficial cardiac effects of study treatments. Although it was unethical to randomize hypertensive patients with moderately elevated BP and documented LV hypertrophy to placebo, precautions were taken to minimize measurement bias. In-study echocardiograms were not identified to the Reading Center as being performed at baseline or after 6 or 12 months of therapy; nearly 75% of studies used in primary analyses were batch-read at the end of the study; and final measurements on 98% of studies were made by one highly-experienced investigator. In addition, primary intention-to-treat results reflect LV effects of regimens based on ACE inhibition and calcium channel blockade rather than pure monotherapy. However, in view of the known difficulty of controlling BP in patients with moderate hypertension complicated by target organ damage, this emulates actual clinical practice.

Clinical Implications
PRESERVE revealed similarly beneficial effects of antihypertensive treatment regimens on the basis of ACE inhibition or calcium channel blockade on LV structure, with no effect on diastolic filling, thus not supporting the hypothesis that ACE inhibition has special cardiac benefits beyond those obtained by BP lowering. However, it is possible that hypertensive patients with LV hypertrophy may resemble patients with heart failure in requiring maximal ACE inhibitor doses to suppress angiotensin II production completely and thereby normalize LV mass out of proportion to pressure reduction.

Appendix

Steering Committee
Richard Devereux, MD, New York, NY (Chairman), Bjorn Dahlof, MD, Goteborg, Sweden; Vincent de Quattro, MD, Los Angeles, Calif; Daniel Levy, MD, Framingham, Mass; Marc Pfeffer, MD, PhD, Boston, Mass (until initiation of study treatment); Norman Sharpe, MD, Auk-
land, New Zealand; William Grossman, MD, West Point, PA (nonvoting); and Munir Gabriel, PhD, Whitehouse Station, NJ (nonvoting).

Clinical Centers and Investigators
Aukland, New Zealand (Drs Norman Sharpe and Fiona Stewart); Beersheba, Israel (Dr Esther Paran); Berlin, Germany (Prof Hermann Eichstaedt); Bonn, Germany (Dr Killan Glazerz); Brescia, Italy (Drs Enrico Agitibi-Rosei and M. Lorenza Muiesan); Göteborg, Sweden (Dr Björn Dahlöf and Dr Filip Jacobson); Haifa, Israel (Dr A. Lorber); Hong Kong (Dr Yuk-Kong Lau); Lisbon, Portugal (Dr Mario Lopes); Los Angeles, Calif (Drs Anthony Chandraratana, Vincent de Quattro, Willa Hseuh, and Deborah Lee); Milwaukee, Wis (Dr Donald Schmidt); Naples, Italy (Drs Maurizio Galdarisi and Oreste De Divitis); New York City (Drs Michael Alderman and Richard Devereux); Oslo, Norway (Drs John Kjekhus and Halfdan Ihlen); Perugia, Italy (Dr Paolo Verdeccchia and Dr Carlo Porcellati); Pisa, Italy (Dr Eugenio Picano); Rapallo, Italy (Dr Guido Gigli); and Shanghai, China (Dr Wan-Chun Chen).

Echocardiography Reading Center
Echocardiography Laboratory, Division of Cardiology, Cornell Medical Center, New York, NY (Drs Richard Devereux, Rebecca Hahn, Jonathan Bella, Vittorio Palmieri, and Giovanni de Simone; Michael O’Grady, Mary Paranicas).

Statistical Coordinating Center
Merck Statistical Coordinating Center, Brussels, Belgium (Roger Hill).

Data and Safety Monitoring Board
Marc Pleffer, MD, PhD, and Charles Hennekens, MD, Brigham and Women’s Hospital, Boston, Mass; James Ware, PhD, Harvard School of Public Health, Boston, Mass.

End Point Committee

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