Transdermal Nitroglycerin Patch Therapy Improves Left Ventricular Function and Prevents Remodeling After Acute Myocardial Infarction

Results of a Multicenter Prospective Randomized, Double-Blind, Placebo-Controlled Trial

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Background—Nitrates are widely used in the treatment of angina in patients with acute myocardial infarction (AMI). Short-term administration prevents left ventricular (LV) dilation and infarct expansion. However, little information is available regarding their long-term effects on LV remodeling in patients surviving Q-wave AMI.

Methods and Results—This was a randomized, double-blind, placebo-controlled trial designed to investigate the long-term (6-month) efficacy of intermittent transdermal nitroglycerin (NTG) patches on LV remodeling in 291 survivors of AMI. Patients meeting entry criteria had baseline gated radionuclide angiography (RNA) followed by randomization to placebo or active NTG patches delivering 0.4-, 0.8-, or 1.6-mg/h. RNA was repeated at 6 months and 6.5 days after withdrawal of double-blind medication. The primary study end point was the change in end-systolic volume index (ESVI). Both ESVI and end-diastolic volume index (EDVI) were significantly reduced with 0.4-mg/h NTG patches (ΔESVI, −11.4 and −11.6 mL/m², respectively, P < .03). This beneficial effect was observed primarily in patients with a baseline LV ejection fraction ≤40% (ΔESVI, −31 mL/m²; ΔEDVI, −33 mL/m²; both P < .05) and only at the 0.4-mg/h dose. After NTG patch withdrawal, ESVI significantly increased but did not reach pretreatment values.

Conclusions—Transdermal NTG patches prevent LV dilation in patients surviving AMI. The beneficial effects are limited to patients with depressed LV function and only at the lowest (0.4-mg/h) dose. Continued administration is necessary to maintain efficacy. Whether these remodeling effects confer a clinical or survival advantage will need to be addressed in an adequately powered cardiac event trial. (Circulation. 1998;97:2017-2024.)

Key Words: remodeling ■ myocardial infarction ■ nitroglycerin

Event-free survival after acute myocardial infarction is most influenced by the extent of residual myocardial ischemia and the global left ventricular (LV) ejection fraction (EF). Patients with LV dysfunction are more likely to have progressive LV dilation, which is an independent determinant of long-term survival. Recent studies demonstrate that ACE inhibitors improve survival in patients with chronic LV dysfunction and in those after acute myocardial infarction. This benefit is thought to be at least partially due to prevention of LV dilatation.

Nitrates reduce infarct size, prevent acute LV dilation, and limit infarct zone expansion. Prolonged nitrate use in animal models of infarction also limits LV dilation and improves EF; however, there is limited information regarding their long-term effects on remodeling in humans. This study was designed to investigate the effects of transdermal nitroglycerin patches on LV remodeling over a 6-month period in patients surviving acute Q-wave myocardial infarction.

Methods

Details of the study design are reported elsewhere by Pratt et al (Fig 1). Briefly, this was a randomized, double-blind, placebo-controlled, multicenter trial designed to investigate the efficacy of...
intermittent nitroglycerin patch therapy delivering 0.4, 0.8, and 1.6 mg/h over a 6-month period in patients surviving an acute Q-wave myocardial infarction. The study was conducted between July 6, 1992, and December 29, 1994.

Patients eligible for enrollment were identified between the third hospital day until hospital discharge. Exclusion criteria included (1) severe congestive heart failure, (2) persistent hypotension (systolic blood pressure <90 mm Hg), (3) sustained ventricular tachycardia or high-degree AV block, (4) unstable angina pectoris, (5) a significant noncardiac illness that would contribute to 6-month morbidity or mortality, or (6) either a requirement for or a known intolerance to nitrates.

Patients meeting all entry criteria had baseline gated radionuclide angiography to measure LVEF and cardiac volumes. Long-acting nitrates were discontinued a minimum of 48 hours before angiography. All other cardiovascular medications were allowed, but every attempt was made to maintain constant dosing throughout the 6-month study period.

After radionuclide angiography, patients were randomized to double-blind medication, which was increased at 5- to 7-day intervals until the randomly assigned dosage (placebo or 0.4, 0.8, or 1.6 mg nitroglycerin) was achieved. Medication was allowed to be deescalated to the previously tolerated dosage if side effects developed. Patients were then maintained on this final dosage for the 6-month study period and evaluated monthly for clinical stability.

Gated radionuclide angiography was used to assess sequential changes in LVEF and cardiac volumes. The description of this method and its reproducibility were given previously. Hemodynamic parameters measured were the LV EDV, ESV, stroke volume, and EF. All cardiac volumes were indexed to body surface area.

Gated radionuclide angiography was performed at baseline, after 6 months of double-blind medication (end-point visit 1), and 1 week later after withdrawal of study medication (end-point visit 2). The radionuclide angiograms were interpreted blinded to treatment allocation by one experienced investigator (J.J.M.) at the core laboratory at Baylor College of Medicine.

**Statistical Analysis**

This study was not powered to detect a difference in 6-month cumulative cardiac event rates among the four treatment groups. Rather, the prospectively defined primary end-point variable was the change in ESVI as assessed by sequential gated radionuclide angiography. Other variables assessed were (1) temporal changes in LVEF, EDVI, and stroke volume index and (2) subsequent cardiac event rates over the 6-month time interval. Prospectively defined subgroup analyses were performed based on baseline LVEF dichotomized at 40% and ACE inhibitor use. This study had 90% power to detect an 11-mL/m² absolute change in ESVI between treatment groups assuming 50 to 60 patients per group. All data analyses were performed as intention to treat. Unless otherwise specified, all data are reported as mean±SD. A value of P <.05 was considered significant.

**Results**

**Patient Population**

Two hundred ninety-one patients were randomized to one of four treatment limbs (77 to placebo and 75 to 0.4-mg/h, 71 to 0.8-mg/h, and 68 to 1.6-mg/h nitroglycerin patches), and 282 had a baseline gated radionuclide angiogram (Fig 2). Of these latter patients, 245 had a repeat study at end-point visit 1, and 243 had one at end-point visit 2.

The baseline patient characteristics of the study population are shown in Table 1. No significant differences between the

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**SELECTED ABBREVIATIONS AND ACRONYMS**

EDV = end-diastolic volume
EDVI = end-diastolic volume index
EF = ejection fraction
ESV = end-systolic volume
ESVI = end-systolic volume index
LV = left ventricular
LVEF = left ventricular ejection fraction

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**STUDY DESIGN**

**PHASE I:** Patient Identification (3 days post MI)

Rest Gated Radionuclide Angiography

Randomization

Placebo

0.4 mg/hr NTG patch

0.8 mg/hr NTG patch

1.6 mg/hr NTG patch

**PHASE II:** Double-Blind Dose Escalation (2-4 wks)

Double blind medication increased at 6 to 7 days intervals until assigned dosage achieved. Patients unable to tolerate medication were de-escalated to the previously tolerated dosage which was then continued for the trial duration.

**PHASE III:** Maintenance (5 months)

Gated RNA performed 1 to 4 hours after patch application at 6 month visit (Endpoint Visit 1).

**PHASE IV:** Medication Withdrawal

Gated RNA performed 3 to 7 days following medication withdrawal (Endpoint Visit 2).

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**Table 1.** Summary of study population characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=77)</th>
<th>0.4 mg/hr NTG patch (n=75)</th>
<th>0.8 mg/hr NTG patch (n=71)</th>
<th>1.6 mg/hr NTG patch (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 1.** Study design. MI indicates myocardial infarction; NTG, nitroglycerin; and RNA, radionuclide angiography.

**Figure 2.** Sequence of gated radionuclide angiography among randomized patients in the four treatment limbs. Abbreviations as in Fig 1, and CHF indicates congestive heart failure; Pt, patient.
four randomized groups were observed in any of the demographic variables. Approximately 50% of the patients had anterior infarction and most patients were in New York Heart Association class I. Most patients were on aspirin and β-blockers at the time of randomization, and approximately one third were taking calcium antagonists and ACE inhibitors. The mean LVEF was not statistically different among the four treatment groups, and 35% of patients had an EF #40%. The four groups were well balanced at baseline as to the primary end-point variable (ie, ESVI) (Table 2). Other volume measurements were likewise similar in the randomized patients.

### Nitroglycerin Patch Doses and Therapy Duration

All patients randomized to placebo and 0.4-mg nitroglycerin patches continued on this regimen throughout the trial. Protocol design allowed downtitration if side effects occurred at higher doses (Table 3). Accordingly, 60 of 71 patients randomized to 0.8-mg/h patches (85%) were maintained on the assigned dosage, whereas 11 patients had their dose decreased to 0.4-mg/h. Forty-nine of 68 patients (72%) randomized to 1.6-mg/h patches continued on this dosage throughout the study, but 11 patients were downtitrated to the 0.4-mg/h dose and 8 to the 0.8-mg/h dosage. Despite downtitration of study medication in certain patients, the mean

### TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Nitroglycerin Patch, mg/h</th>
<th>Placebo (n=77)</th>
<th>0.4 (n=75)</th>
<th>0.8 (n=71)</th>
<th>1.6 (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>58±11</td>
<td>56±10</td>
<td>55±10</td>
<td>57±11</td>
</tr>
<tr>
<td><strong>Men, n (%)</strong></td>
<td>62 (81)</td>
<td>60 (80)</td>
<td>59 (83)</td>
<td>55 (81)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus, %</strong></td>
<td>10</td>
<td>17</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td><strong>Smoking, n (%)</strong></td>
<td>30 (39)</td>
<td>25 (33)</td>
<td>23 (32)</td>
<td>25 (37)</td>
</tr>
<tr>
<td><strong>Time to randomization, d</strong></td>
<td>7.8±4.8</td>
<td>7.1±3.5</td>
<td>7.7±4.8</td>
<td>6.9±4.5</td>
</tr>
<tr>
<td><strong>Thrombolytic therapy, n (%)</strong></td>
<td>29 (38)</td>
<td>32 (43)</td>
<td>21 (30)</td>
<td>29 (43)</td>
</tr>
<tr>
<td><strong>Intravenous nitroglycerin, n (%)</strong></td>
<td>50 (65)</td>
<td>52 (69)</td>
<td>45 (63)</td>
<td>47 (69)</td>
</tr>
<tr>
<td><strong>PTCA before randomization, n (%)</strong></td>
<td>28 (36)</td>
<td>33 (44)</td>
<td>31 (44)</td>
<td>29 (43)</td>
</tr>
<tr>
<td><strong>CABG before randomization, n (%)</strong></td>
<td>7 (9)</td>
<td>7 (9)</td>
<td>4 (6)</td>
<td>7 (10)</td>
</tr>
<tr>
<td><strong>MI location, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>48</td>
<td>49</td>
<td>51</td>
<td>50</td>
</tr>
<tr>
<td>Inferior/posterior</td>
<td>47</td>
<td>40</td>
<td>38</td>
<td>42</td>
</tr>
<tr>
<td>Lateral</td>
<td>5</td>
<td>11</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td><strong>Q-Wave MI, n (%)</strong></td>
<td>74 (96)</td>
<td>73 (97)</td>
<td>67 (94)</td>
<td>66 (97)</td>
</tr>
<tr>
<td><strong>NYHA class I, n (%)</strong></td>
<td>74 (96)</td>
<td>69 (92)</td>
<td>64 (91)</td>
<td>63 (93)</td>
</tr>
<tr>
<td>class II</td>
<td>3 (4)</td>
<td>6 (8)</td>
<td>6 (9)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>class III</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Medications at randomization, n (%)</strong></td>
<td>75 (97)</td>
<td>73 (97)</td>
<td>71 (100)</td>
<td>67 (99)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>64 (83)</td>
<td>61 (81)</td>
<td>58 (82)</td>
<td>56 (82)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>24 (31)</td>
<td>25 (33)</td>
<td>22 (31)</td>
<td>22 (32)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>24 (31)</td>
<td>30 (40)</td>
<td>27 (38)</td>
<td>21 (31)</td>
</tr>
</tbody>
</table>

PTCA indicates percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft surgery; MI, myocardial infarction; and NYHA, New York Heart Association.

### TABLE 2. Baseline Hemodynamic Results in the Four Treatment Groups

<table>
<thead>
<tr>
<th>Nitroglycerin Patch, mg/h</th>
<th>Placebo (n=76)</th>
<th>0.4 (n=74)</th>
<th>0.8 (n=65)</th>
<th>1.6 (n=67)</th>
<th><strong>P</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>EDVI</td>
<td>105±27</td>
<td>109±31</td>
<td>107±29</td>
<td>109±28</td>
<td>NS</td>
</tr>
<tr>
<td>ESVI</td>
<td>58±25</td>
<td>63±28</td>
<td>60±25</td>
<td>61±26</td>
<td>NS</td>
</tr>
<tr>
<td>SVI</td>
<td>47±13</td>
<td>46±14</td>
<td>47±14</td>
<td>48±15</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF</td>
<td>47±12</td>
<td>44±13</td>
<td>45±12</td>
<td>45±13</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (≤40), n (%)</td>
<td>24 (31)</td>
<td>26 (35)</td>
<td>25 (38)</td>
<td>25 (37)</td>
<td>NS</td>
</tr>
</tbody>
</table>

SVI indicates stroke volume index.

*Placebo vs all active treatment groups.
doses of nitroglycerin administered were still significantly higher in patients randomized to 0.8- and 1.6-mg/h patches (0.74 and 1.31, respectively) compared to those given 0.4-mg/h patches. The major reasons for downtitration of study medication in these 30 patients were as follows: severe headache (40%), dizziness (27%), hypotension (20%), and skin reactions to the patch (13%). Compliance with study medication was comparably high (>90%) in all four treatment groups. Randomized drug therapy was continued for at least 5 months in 91% of patients on placebo and for 81% of patients on 0.4-mg/h, 77% on 0.8-mg/h, and 72% on 1.6-mg/h patches.

**LV Volume Changes**

The primary end point of this study was the LV ESVI. During the 6-month study period, the mean LV EDVI and ESVI both increased in patients assigned to placebo. Conversely, EDVI and ESVI were significantly reduced on active therapy, but a statistically significant effect was limited to patients assigned to the 0.4-mg/h nitroglycerin patch dosage ($P<0.05$). Likewise, the EDVI increased by 17 mL/m$^2$ on 0.4-mg/h active patch therapy ($P<0.05$). Patients assigned to 0.8- and 1.6-mg/h nitroglycerin patches had a smaller increase in cardiac volumes after the study drug withdrawal. Although the salutary effects of nitroglycerin patches were partially reversed after study drug withdrawal, there remained a significant reduction in ESVI compared with placebo at the 0.4-mg/h dose ($P=0.038$).

**Cardiac Volumes After Nitroglycerin Withdrawal**

After study medication was discontinued for a mean of 6.5 days, gated radionuclide angiography was repeated. No significant changes in EDVI or ESVI occurred in patients randomized to placebo (Table 4). In contrast, patients assigned to 0.4-mg/h nitroglycerin patches had a significant increase in both EDVI and ESVI (5.7±12.1 and 4.2±7.7, respectively; $P<0.05$). Patients assigned to 0.8- and 1.6-mg/h patches had a smaller increase in cardiac volumes after the study medication was discontinued. Although the salutary effects of nitroglycerin patches were partially reversed after study drug withdrawal, there remained a significant reduction in ESVI compared with placebo at the 0.4-mg/h dose ($P=0.038$).

**LVEF**

The baseline LVEF was similar among all four treatment groups (Table 2). The mean LVEF on placebo did not significantly change from baseline (47±12%) to end-point visit 1 (47±12%) or 2 (47±13%). However, compared with placebo, there was a significant overall increase in LVEF on active patch therapy from 45±13% to 48±13% ($P=0.031$). Likewise, the LVEF significantly increased from baseline to end-point visit 1 at both the 0.4- and 1.6-mg/h doses (Fig 5). We have previously demonstrated that a ≥7% change in LVEF defines the 95% confidence limit for describing a real change beyond the intrinsic variability associated with gated radionuclide angiography. Significantly more patients randomized to nitroglycerin patch therapy had a ≥7% increase in LVEF compared with those administered placebo (23% versus 11%, $P<0.01$).

**TABLE 3. Nitroglycerin Patch Dosage by Treatment Group**

<table>
<thead>
<tr>
<th>Randomization Group</th>
<th>No Medication</th>
<th>0.4</th>
<th>0.8</th>
<th>1.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=77)</td>
<td>77</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.4-mg/h patch (n=75)</td>
<td>0</td>
<td>75</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>0.8-mg/h patch (n=71)</td>
<td>0</td>
<td>11</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>1.6-mg/h patch (n=68)</td>
<td>0</td>
<td>11</td>
<td>8</td>
<td>49</td>
</tr>
<tr>
<td>Total (n=291)</td>
<td>77</td>
<td>97</td>
<td>68</td>
<td>49</td>
</tr>
</tbody>
</table>
Effect of Nitroglycerin Patches on LV Volumes on the Basis of Concomitant ACE Inhibitor Therapy

A prospectively defined analysis was to evaluate the interaction of nitroglycerin patch therapy and ACE inhibitors on ESVI. Of the 245 randomized patients who had a repeat radionuclide angiogram, 79 (32%) were taking an ACE inhibitor at study entry (Table 5). Of the 79 patients with an LVEF \( \leq 40\% \), 42 (53\%) were on an ACE inhibitor compared with 37 of 166 patients (22\%) with an LVEF >40\%. The distribution of ACE inhibitor use was not significantly different among the four treatment groups.

In patients not taking an ACE inhibitor at study entry, the ESVI was significantly reduced among those randomized to 0.4-mg/h nitroglycerin patches (Table 5). This occurred regardless of initial LVEF. In patients with an LVEF \( \leq 40\% \), the ESVI increased by \( \approx 34 \text{ mL/m}^2 \) in patients on placebo but decreased by 22 \( \text{ mL/m}^2 \) in those assigned to 0.4-mg/h patches.

In patients taking an ACE inhibitor at study entry, nitroglycerin patch therapy did not significantly reduce ESVI beyond that observed with placebo. This negative result was due in part to the minimal change in ESVI over the course of the study in patients assigned to placebo, thereby limiting the detection of a nitrate effect. However, in the subgroup of patients with an LVEF \( \leq 40\% \), a 10-\( \text{ mL/m}^2 \) difference in ESVI was observed between those assigned to placebo versus 0.4-mg/h patches. Although this analysis was underpowered to detect a statistically significant difference because of small sample sizes (24 patients), the magnitude of the change in ESVI closely paralleled that observed in the main trial.

Cardiac Events

Cardiac event rates over the 6-month period were not significantly different between the placebo and active treatment groups (Table 6).

Discussion

The results of this study provide the first evidence of a long-term pharmacodynamic effect on LV remodeling with intermittent (12 hours on and off) nitroglycerin patch therapy initiated within 1 week after acute myocardial infarction and continued for 6 months. The prevention of LV dilatation by nitroglycerin patches in this study is most likely due to an acute pharmacological effect rather than a permanent structural alteration, as evidenced by the observed diminution in the magnitude of LV volume reduction following study drug withdrawal after only 1 week. As might be expected, the remodeling effects of nitroglycerin patches were seen primarily in patients with poor LV systolic function (LVEF \( \leq 40\% \)) and large volumes at baseline. Of interest is the fact that although the 0.4-mg/h dose resulted in a statistically significant reduction in LV volumes compared with placebo, higher nitroglycerin doses (up to a fourfold-higher dose range) prevented remodeling to a lesser degree. A reasonable inference is that nitroglycerin tolerance may have limited efficacy at the higher doses of patch therapy used in this study.

Selection of LV ESVI as the Primary End Point

Previous studies have demonstrated the prognostic importance of the LV ESV, particularly when myocardial dysfunction is present after acute infarction.\(^{1,9}\) LV dilatation may develop within the initial 24 hours of acute infarction presumably as a compensatory mechanism for maintaining stroke volume.\(^{21}\) This is particularly true in patients with anterior wall infarcts who generally have the largest extent of initial LV dysfunction and therefore are most likely to develop early infarct zone expansion.\(^{21,22}\) Over the ensuing months, structural and geometric changes occur that entail scar formation and thinning of the infarct zone, as well as hypertrophy and dilatation of noninfarcted regions.\(^{23,25}\) The initial loss of myocardium, if large enough, leads to progres-

![Figure 5. Changes in LVEF from baseline to end-point visits 1 and 2 in the four randomized treatment groups. Patients on placebo had no significant change in LVEF over the course of the study. The improvement in LVEF observed in the 0.4- and 1.6-mg/h nitroglycerin (NTG) patch groups was maintained even after withdrawal of double-blind medication. Data are presented as mean±SEM.](image-url)
Nitrates in the early postinfarction period reduce infarct size\textsuperscript{11–13} and limit LV expansion and thinning within the infarct zone.\textsuperscript{12,14} These beneficial effects may result from a reduction in LV preload/afterload,\textsuperscript{26} improvement in myocardial blood flow to the infarct and noninfarct border zones,\textsuperscript{11} and sustained integrity of the myocardial collagen matrix.\textsuperscript{27} Prolonged nitrate therapy during infarct healing may be more efficacious than short-term treatment. In a recent trial of acute infarction in dogs, 2 weeks of either transdermal or oral dinitrate preparations significantly reduced LV volumes, LV cavity expansion, and aneurysm formation compared with placebo.\textsuperscript{14} However, animals that received nitrates over a 6-week period had less LV dilation than those treated for only 2 weeks, with a significant improvement in LVEF. The results of the present trial closely reflect these animal data in that at least one dose of intermittent long-term nitrate patch therapy significantly reduced LV volumetric indexes and improved LVEF compared with placebo.

**Comparison With the Remodeling Effects of ACE Inhibitors**

The results we report are directionally similar to those found in trials assessing the effects of ACE inhibitors.\textsuperscript{9,10} In the SOLVD study, a cohort of 56 patients with chronic symptomatic LV dysfunction (EF <35%) underwent serial gated radionuclide angiography at baseline and again at 1 year.\textsuperscript{10} Patients in the placebo group had progressive LV dilation over the ensuing year, with significant increases in EDV and ESV. However, in those treated with enalapril, both volumetric indexes significantly decreased over time, with a shift in the pressure volume curve to the left and an improvement in LVEF. Of note, after withdrawal of enalapril for only 2 weeks, LV volumes increased to pretherapy levels but were still significantly less than those observed with placebo.

A substudy from the SAVE trial examined the effects of captopril in 512 patients with an LVEF <40% who had sequential two-dimensional echocardiography.\textsuperscript{9} At a 1-year follow-up, LV EDV and ESV were significantly larger in patients who received placebo compared with those given active therapy. Importantly, 1-year survivors had a significantly smaller increase in LV dimensions compared with those patients who died.

In the present trial, significant reductions in both EDVI and ESVI were observed but were almost exclusively limited to patients with an LVEF ≤40%. The nitrate effect was most pronounced in patients not taking ACE inhibitors, presumably because patients receiving ACE inhibitors had only minimal subsequent LV dilation. Nonetheless, even in patients taking an ACE inhibitor, the ESVI was reduced by 10 mL/m\textsuperscript{2} in those with an LVEF ≤40% who were assigned to 0.4-mg/h nitroglycerin patches. This difference did not reach

### TABLE 5. Changes in ESVI From Baseline to End-Point Visit 1 on the Basis of ACE Inhibitor Therapy

<table>
<thead>
<tr>
<th>Nitroglycerin Patch, mg/h</th>
<th>Placebo (n = 166)</th>
<th>0.4 (n = 37)</th>
<th>0.8 (n = 129)</th>
<th>1.6 (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF ≤40%</td>
<td>LVEF &gt;40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>8.9 ± 5.32</td>
<td>33.8 ± 110.8</td>
<td>1.7 ± 10.6</td>
<td>0.1 ± 12.7</td>
</tr>
<tr>
<td>0.4-mg/h NTG patch</td>
<td>−7.5 ± 16.3 ň</td>
<td>−21.9 ± 12.0 ň†</td>
<td>−4.4 ± 15.5 ř</td>
<td>−1.1 ± 18.5</td>
</tr>
<tr>
<td>0.8-mg/h NTG patch</td>
<td>−1.4 ± 15.3</td>
<td>3.7 ± 20.5</td>
<td>−3.2 ± 13.0</td>
<td>6.8 ± 21.5</td>
</tr>
<tr>
<td>1.6-mg/h NTG patch</td>
<td>−3.4 ± 9.0 ř†</td>
<td>−3.3 ± 14.8</td>
<td>−3.5 ± 6.8 ř†</td>
<td>−1.1 ± 15.6</td>
</tr>
</tbody>
</table>

NTG indicates nitroglycerin.

*P <.05 vs baseline.

### TABLE 6. Clinical End Points by Therapy Group

<table>
<thead>
<tr>
<th>Cardiac Event</th>
<th>Placebo (n = 77)</th>
<th>0.4 (n = 75)</th>
<th>0.8 (n = 71)</th>
<th>1.6 (n = 68)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, n (%)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>0</td>
<td>1.000</td>
</tr>
<tr>
<td>Recurrent MI, n (%)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>0</td>
<td>1 (1.5)</td>
<td>.899</td>
</tr>
<tr>
<td>CHF, n (%)</td>
<td>4 (5)</td>
<td>3 (4)</td>
<td>7 (10)</td>
<td>6 (9)</td>
<td>.477</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>31 (40)</td>
<td>23 (31)</td>
<td>34 (48)</td>
<td>26 (38)</td>
<td>.205</td>
</tr>
<tr>
<td>Any event, n (%)</td>
<td>33 (43)</td>
<td>27 (36)</td>
<td>38 (53)</td>
<td>29 (43)</td>
<td>.202</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; CHF, congestive heart failure.

*Compares incidence rates among the three treatment groups and placebo.
statistical significance because of the small sample size (24 patients). However, the magnitude of the reduction in ESVI within this subgroup was consistent with the reduction observed in the main trial at the 0.4-mg/h dose. These results imply that nitrates may further reduce LV dilation beyond that achieved with ACE inhibitors alone.26 The ACE inhibitor trials clearly support the concept that preventing LV enlargement improves clinical outcome. Our trial was not powered to evaluate whether preventing LV dilation with nitrates might also confer such a survival benefit.

Previous Long-term Trials of Nitrates After Acute Myocardial Infarction

Two large multicenter trials involving almost 80,000 patients have recently addressed whether transdermal nitroglycerin therapy over 6 weeks29 or isosorbide mononitrate treatment over 4 weeks30 can reduce cardiac events in patients surviving acute myocardial infarction. In GISSI-3, there was a trend toward an overall reduction in cardiac events with nitrate therapy (relative risk, 0.94; 95% confidence interval, 0.87 to 1.02; P = .12), which reached statistical significance among the elderly and women.29 Likewise, ISIS-4 showed no significant difference in overall mortality with isosorbide mononitrate but did demonstrate an early survival benefit.30 Although these results are not as impressive as those reported for ACE inhibitors, several comments about study design are noteworthy. First, in both ISIS-4 and GISSI-3, some 50% to 60% of patients in the placebo group were on open-label nitrate preparations, which invariably limited their ability to detect a survival advantage with double-blind medication. Second, only 5% of patients in GISSI-3 and an unknown percentage in ISIS-4 had a depressed LVEF. This is an important limitation because the beneficial effects of nitrates on LV remodeling in our study were almost exclusively observed in patients with depressed LV function.

Study Limitations

This study assessed the long-term effects of intermittent nitroglycerin patch therapy on LV remodeling in survivors of acute myocardial infarction. Thrombolytic therapy17,31 and intravenous nitroglycerin12 administered during acute infarction are also reported to limit subsequent LV remodeling. These medications were evenly distributed among the four treatment groups at the time of randomization. Whether other medications, such as β-blockers or calcium antagonists, interact with nitroglycerin to alter remodeling cannot be determined from this study; however, these medications were also evenly distributed across all treatment groups.

The effect of nitroglycerin patch therapy on LV remodeling in patients with anterior and inferior infarction was not specifically addressed in this study. Rather, we prospectively chose to analyze our data on the basis of initial LVEF. As expected, most of the patients with an LVEF ≤40% (78%) had an anterior infarction. Because the beneficial effects of nitroglycerin patches were almost exclusively limited to patients with an LVEF ≤40%, it seems reasonable to surmise that patients with anterior infarction would benefit most from this form of therapy. However, nitroglycerin patch therapy may also be beneficial in patients with inferior infarction who have an LVEF <40%.

Finally, gated radionuclide angiography was chosen to assess changes in LVEF and cardiac volumes because it is a precise and reproducible count-based technique that, unlike two-dimensional echocardiography, is not dependent on geometric assumptions.19,20 However, two-dimensional echocardiography does address other aspects of LV remodeling, such as regional changes in wall thickness and infarct expansion, that could not be assessed in this study with nuclear imaging.

Conclusions

Intermittent transdermal nitroglycerin patch therapy at a dose of 0.4-mg/h prevents LV dilation and improves LVEF in patients surviving acute myocardial infarction. These hemodynamic effects are predominantly observed in patients with depressed LV function who are most prone to progressive cardiac dilation, if untreated. Whether improvement in LV function and geometry with nitrates will ultimately confer a clinical or survival advantage in patients with LV dysfunction will need to be addressed in an adequately powered cardiac event trial.

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References


Transdermal Nitroglycerin Patch Therapy Improves Left Ventricular Function and Prevents Remodeling After Acute Myocardial Infarction: Results of a Multicenter Prospective Randomized, Double-Blind, Placebo-Controlled Trial

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