unable to determine the proportion of AMI acute myocardial infarction (AMI) patients eligible for enrollment in the study.

Dr. Silverman questioned the safety of transfer of the AMI patient. Although his concerns are valid, all emergency medical systems that would be transferring AMI patients are trained in advanced cardiac life support. These systems should be able to resuscitate AMI patients, as well as the staff in the emergency department or intensive care units of small hospitals.

In fact, five randomized trials of transfer for primary angioplasty have shown that transfer is safe and is associated with better outcomes compared to on site thrombolitics (1–5) (Table 1).

Experienced angioplasty operators may safely perform primary angioplasty in diagnostic catheterization laboratories. However, the expense of training staff, both in the laboratory and in recovery units, in addition to stocking expensive angioplasty equipment, may not be feasible in small hospitals.

Finally, it would be far easier to instruct emergency medical staff drivers to head in the correct direction—toward a primary angioplasty facility.

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Possible Risks to Patients Receiving Statins Combined With Other Medications

The American College of Cardiology/American Heart Association/National Heart Lung, and Blood Institute (ACC/AHA/NHLBI) Clinical Advisory on Statins (1) was a timely review of an important issue, but I believe that additional information on the issue of drug interactions would be helpful to clinicians who manage patients receiving statins with other medications.

First, as for combining statins with CYP3A4 inhibitors, only lovastatin and simvastatin undergo extensive (90% or more) presystemic metabolism by CYP3A4 in the gut wall and liver (2). Hence, the risk of statin-induced myopathy due to CYP3A4 inhibitors appears to be considerably greater for lovastatin and simvastatin compared to the other statins. For example, potent CYP3A4 inhibitors such as itraconazole can produce 10- to 20-fold increases in the serum concentrations of lovastatin or simvastatin (3,4). Atorvastatin is also metabolized by CYP3A4, but it does not undergo extensive presystemic metabolism as lovastatin and simvastatin. Accordingly, potent CYP3A4 inhibitors tend to produce two- to four-fold increases in atorvastatin serum concentrations (5,6). Pravastatin is not metabolized by CYP3A4 or other cytochrome P450 isozymes, and inhibition of CYP3A4 has little effect on its pharmacokinetics (4,6). Fluvastatin is metabolized primarily by CYP2C9 and also is unlikely to interact with CYP3A4 inhibitors (2).

Second, as for macrolides and statins, erythromycin and clarithromycin are correctly listed as potentially increasing the risk of statin-associated myopathy. As described above, this caution results from the ability of these two macrolide antibiotics to inhibit the CYP3A4 metabolism of lovastatin, simvastatin, and to a lesser extent atorvastatin (7,8). But a separate bullet point lists “Macrolide antibiotics” (page 571 under “Prevention” heading). This might lead some readers to conclude that azithromycin and dirithromycin interact with statins, but substantial evidence suggests that these macrolides do not inhibit CYP3A4 (9).

Finally, as for the interaction of calcium-channel blockers and statins, verapamil—a known CYP3A4 inhibitor—is listed as increasing the risk of statin-associated myopathy, but diltiazem is not mentioned. Available evidence suggests that verapamil and diltiazem are roughly equivalent (moderate) inhibitors of CYP3A4. Indeed, diltiazem has been shown in pharmacokinetic studies to increase serum concentrations of both lovastatin and simvastatin (10,11), and isolated cases of myopathy have been reported in patients receiving simvastatin plus diltiazem (12,13).

Table 1. Pooled Outcomes From Five Studies of Transfer for Primary PTCA Versus On Site: Lytics

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>Lytic</th>
<th>p Value</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>103/1,468 (7.0%)</td>
<td>129/1,443 (8.9%)</td>
<td>0.055</td>
<td>1.3</td>
<td>0.99–1.70</td>
</tr>
<tr>
<td>Nonfatal reMI</td>
<td>19/1,037 (1.8%)</td>
<td>68/1,022 (6.7%)</td>
<td>&lt;0.0001</td>
<td>3.82</td>
<td>2.28–6.40</td>
</tr>
<tr>
<td>Total stroke</td>
<td>11/1,037 (1.1%)</td>
<td>22/1,022 (2.2%)</td>
<td>0.049</td>
<td>2.05</td>
<td>0.99–4.25</td>
</tr>
<tr>
<td>Death/stroke/MI</td>
<td>121/1,468 (8.2%)</td>
<td>217/1,443 (15.0%)</td>
<td>&lt;0.0001</td>
<td>1.97</td>
<td>1.56–2.49</td>
</tr>
</tbody>
</table>

CI = confidence interval; MI = myocardial infarction; PCI = percutaneous coronary intervention.
The available evidence would thus suggest that the risk of adding verapamil or diltiazem to simvastatin or lovastatin is roughly equivalent. Conversely, calcium-channel blockers such as amlodipine, felodipine, and nifedipine have not been shown to inhibit CYP3A4 significantly.

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