Do Major Cardiovascular Outcomes in Patients With Stable Ischemic Heart Disease in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation Trial Differ by Healthcare System?

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Background—The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial enrolled patients from 3 distinct healthcare systems (HCSs) in North America. The primary aim of this study was to determine whether there is a treatment difference in cardiovascular outcomes by HCS.

Methods and Results—The study population included 968 patients from the US Department of Veterans Affairs (VA), 386 from the US non-VA, and 931 from Canada with different comorbidities and prognoses. The primary outcome was all-cause mortality or nonfatal myocardial infarction (MI) during the median 4.6-year follow-up. Baseline demographics were similar between percutaneous coronary intervention and optimal medical therapy treatment groups within each HCS. After follow-up, the primary end point of total mortality and nonfatal MI was not statistically significant between percutaneous coronary intervention and optimal medical therapy, regardless of HCS: VA, 22.3% versus 21.9% (hazard ratio, 1.05; 95% CI, 0.80–1.38; \( P = 0.95 \)); US non-VA, 15.8% versus 21.8% (hazard ratio, 0.70; 95% CI, 0.43–1.12; \( P = 0.24 \)); Canadian HCS, 17.3% versus 13.5% (hazard ratio, 1.30; 95% CI, 0.93–1.83; \( P = 0.17 \)). The interaction between HCSs and treatment was not statistically significant. Long-term mortality was significantly higher in the VA system as a result of significantly greater comorbidity and worse left ventricular function.

Conclusions—In the COURAGE trial, addition of percutaneous coronary intervention to optimal medical therapy did not improve 5-year survival or reduce MI or other major adverse cardiovascular events regardless of whether patients were Canadian or American or US veterans or nonveterans. Outcome differences were largely explained by differences in baseline characteristics known to affect long-term prognosis.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00007657.

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Key Words: angina pectoris ■ angioplasty ■ coronary disease ■ prognosis ■ follow-up studies

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial reported that the addition of percutaneous coronary intervention (PCI) to optimal medical therapy (OMT) as an initial management strategy in patients with stable ischemic heart disease did not reduce the risk of death, myocardial infarction (MI), or other major adverse cardiac events compared with OMT alone, a finding confirmed in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial.1–4 The COURAGE trial enrolled 2287 patients with objective evidence of myocardial ischemia and significant coronary artery disease (CAD) from 3 healthcare systems (HCSs): 15 Department of Veterans Affairs (VA) sites, 19 US non-VA sites, and 16 Canadian sites.5,6 The VA HCS is one of the largest in the United States, funded by a global budget set by Congress and with medical care delivered by salaried physicians. In contrast, US non-VA med-
Clinical centers are funded through a complex system of indemnity or other types of private insurance, Medicare or Medicaid, or self-paying patients, and care is delivered by fee-for-service physicians. The Canadian system is a government-funded program that delivers universal health care provided by fee-for-service physicians. The Canadian system limits the number of specialists and family practitioners who can be trained through government funding during postgraduate education, and major hospital capital equipment requests are controlled and purchased by the Canadian government. The main objective of the present study was to examine treatment differences in the principal and major secondary cardiac outcomes across the 3 HCSs, a prespecified subgroup analysis in COURAGE. Additional analyses examined the 3 different practice environments, patient characteristics, and their impact on long-term cardiovascular event rates.

WHAT IS KNOWN

- The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation and the Bypass Angioplasty Revascularization Investigation 2 Diabetes trials show that in the absence of left main coronary disease or severe left ventricular dysfunction, percutaneous coronary intervention does not prevent myocardial infarction or cardiac death in patients with chronic angina and angiographic evidence of obstructive coronary disease over 5 years of follow-up.
- Percutaneous coronary intervention improves quality of life and reduces angina attack frequency and need for antianginal drug therapy.

WHAT THE STUDY ADDS

- Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation enrolled patients with chronic ischemic heart disease from 3 different healthcare systems. Baseline characteristics of the 3 populations were significantly different, resulting in significant differences in 5-year mortality rates.
- Percutaneous coronary intervention did not improve survival or prevent myocardial infarction regardless of which healthcare system patients were enrolled from. The findings along with the results from the Bypass Angioplasty Revascularization Investigation 2 Diabetes trial suggest that a routine strategy of prompt percutaneous coronary intervention to treat angiographic evidence of obstructive coronary disease in the absence of left main coronary disease compared to an initial strategy of optimal medical therapy is not required in most patients with chronic ischemic heart disease if the purpose or indication for doing the procedure is to prevent myocardial infarction or death. This indication is not supported by evidence-based data.

Methods

Study Design

The COURAGE trial design, baseline characteristics, and overall results were reported previously. Patients with stable ischemic heart disease were randomly assigned to receive PCI and OMT or OMT alone. Of the 2287 patients, 70% had either 1- or 2-vessel disease, and 83% had an ejection fraction ≥50%. Informed written consent was obtained from each patient, and the study protocol was approved by the institutional review board at each participating site. A permuted-block design was used to generate random assignments within each study site along with previous coronary artery bypass grafting (CABG) as a stratifying variable. The primary outcome measure was a composite of total mortality and nonfatal MI (time to first event). Secondary outcomes included the prespecified composite end point of total mortality, nonfatal MI, stroke, and hospitalization for unstable angina. Angina status was evaluated using the Seattle Angina Questionnaire.

Study Population

Table 1 presents the baseline characteristics of patients enrolled from each of the 3 HCSs between June 1999 and January 2004. OMT in both groups has been described previously. For patients randomized to PCI, target lesion revascularization was attempted in every case, with complete revascularization intended when technically feasible. A count of the number of comorbid conditions (a modification of the Charleson Comorbidity Index) was used to compare baseline demographics among HCSs, which included prior MI, diabetes mellitus, peptic ulcer disease, heart failure, cerebrovascular disease, pulmonary disease, renal disease, cancer, or liver disease. Each variable was assigned 1 point.

Statistical Analysis

Median follow-up was 4.6 years (range: 2.5 to 7 years) and was similar in both treatment groups and for all 3 HCSs. Analyses were performed according to the intention-to-treat principle. Categorical variables were compared by the use of the χ² test or the Wilcoxon rank sum test, and continuous variables were compared by use of the Student t test. Paired differences for medication use at baseline and 4 years after randomization were compared with McNemar test. Estimates of the cumulative event rate were calculated by the Kaplan-Meier method, and the primary efficacy measure of events among subjects randomized to PCI compared with OMT was assessed by the stratified log-rank statistic for each of the 3 HCSs. The treatment effect, as measured by the hazard ratio and its associated 95% CI, was estimated using the Cox proportional hazards model. For analytic purposes, missing baseline data were imputed using maximum likelihood imputation and then used in the logistic regressions and the Homer-Lemeshow tests. The treatment effect for each end point (primary and secondary) was adjusted using logistic regression by including all the baseline variables that were significantly different (P<0.01) among HCSs.

Results

The unadjusted all-cause death rates were 5.9% (50 deaths), 7.8% (30 deaths), and 10.0% (100 deaths) in the Canadian, US non-VA, and VA HCSs, respectively, after a median 4.6-year follow-up (P<0.001). Baseline demographic and angiographic variables (Table 1) were similar between treatment groups (PCI versus OMT) within each HCS. Comparison of the 3 HCSs revealed significant differences in baseline characteristics.

Medication use at baseline and after 4-years of follow-up and success in achieving treatment targets revealed significant differences among HCSs. At baseline, more VA patients were taking β-blockers, calcium antagonists, nitrates, and diuretics than patients in the other 2 HCSs, a difference that persisted during follow-up (Table 2) and supported the higher baseline comorbidity in this cohort. The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers increased in all HCSs from baseline to 4-year follow-up. At baseline, a greater percentage of Canadian patients achieved treatment targets for hypertension, American Heart Association step II...
Angiographic characteristics is reported elsewhere. In the OMT group, the rates of subsequent PCI or CABG were 32.6%, 34.8%, and 32.5% after a 4.6-year median follow-up in the VA, US non-VA, and Canadian HCSs, respectively (P=0.56). In the PCI group, the rates of repeat coronary revascularization were 28.1%, 23.4%, and 12.9% in the VA, US non-VA, and Canadian HCSs, respectively (P<0.001). CABG was performed during follow-up in 9%, 8.4%, and 4.7% patients in the OMT group, and 8.2%, 6.7%, and 5.4% patients in the PCI group for the VA, US non-VA, and Canadian HCSs, respectively (NS).

Angina Relief
The Seattle Angina Questionnaire angina frequency domain scores were not significantly different between the PCI and OMT groups at baseline regardless of HCS (VA patients, 64.9±26.1 versus 67.4±25; US non-VA patients, 72.9±24.6 versus 73.3±24.3; Canadian patients, 69.2±23.5 versus 69.9±27.4). At 1-year postrandomization, the Seattle Angina Questionnaire angina frequency domain scores were as follows: VA HCS, 84.0±21.3 versus 84.1±19.7 (P=0.96); US non-VA HCS, 90.6±16.2 versus 87.4±19.4 (P=0.14); and Canadian HCS, 88.8±18.4 versus 83.5±22.0 (P<0.001). After 3 years, the scores were as follows: VA HCS, 85.4±20.8 versus 87.4±17.8 (P=0.26); US non-VA HCS, 95.1±11.4 versus 91.1±17.8 (P=0.06); and Canadian HCS, 89.3±17.9 versus 86.9±18.3 (P=0.14). There were no

Table 1. Baseline Characteristics in the 3 HCSs

<table>
<thead>
<tr>
<th>Variable</th>
<th>VA (n=15)</th>
<th>US Non-VA (n=19)</th>
<th>Canadian (n=16)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>968</td>
<td>386</td>
<td>931</td>
<td></td>
</tr>
<tr>
<td>Mean age, y</td>
<td>63 (10)</td>
<td>63 (11)</td>
<td>61 (10)</td>
<td>0.006</td>
</tr>
<tr>
<td>Male sex</td>
<td>945 (98)</td>
<td>275 (71)</td>
<td>728 (78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White race</td>
<td>755 (78)</td>
<td>336 (87)</td>
<td>870 (93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>30 (5)</td>
<td>30 (6)</td>
<td>29 (5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Current smoking</td>
<td>264 (27)</td>
<td>70 (18)</td>
<td>185 (20)</td>
<td>0.008</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>396 (41)</td>
<td>121 (31)</td>
<td>249 (27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>768 (79)</td>
<td>256 (66)</td>
<td>497 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean LDL-C, mg/dL</td>
<td>104 (34)</td>
<td>111 (37)</td>
<td>104 (33)</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean HDL-C, mg/dL</td>
<td>38 (11)</td>
<td>43 (12)</td>
<td>43 (12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean triglycerides, mg/dL</td>
<td>175 (104)</td>
<td>170 (99)</td>
<td>169 (103)</td>
<td>0.21</td>
</tr>
<tr>
<td>Exercise &gt;30 min &gt;5 times/wk</td>
<td>203 (21)</td>
<td>100 (26)</td>
<td>266 (29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resting heart rate, bpm</td>
<td>66 (11)</td>
<td>69 (13)</td>
<td>64 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of cerebrovascular disease</td>
<td>125 (13)</td>
<td>32 (8)</td>
<td>45 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior MI</td>
<td>349 (36)</td>
<td>102 (28)</td>
<td>425 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior heart failure</td>
<td>47 (5)</td>
<td>16 (4)</td>
<td>45 (5)</td>
<td>0.84</td>
</tr>
<tr>
<td>Ejection fraction &lt;50%</td>
<td>210 (22)</td>
<td>60 (16)</td>
<td>129 (14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Single-vessel disease</td>
<td>283 (29)</td>
<td>114 (30)</td>
<td>306 (33)</td>
<td>0.08</td>
</tr>
<tr>
<td>Two-vessel disease</td>
<td>388 (40)</td>
<td>135 (35)</td>
<td>362 (39)</td>
<td></td>
</tr>
<tr>
<td>Three-vessel disease</td>
<td>297 (31)</td>
<td>136 (35)</td>
<td>263 (28)</td>
<td></td>
</tr>
<tr>
<td>Proximal LAD stenosis ≥70%</td>
<td>234 (24)</td>
<td>108 (28)</td>
<td>222 (24)</td>
<td>0.25</td>
</tr>
<tr>
<td>Any coronary revascularization</td>
<td>348 (37)</td>
<td>102 (28)</td>
<td>425 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR</td>
<td>79 (20)</td>
<td>73 (20)</td>
<td>81 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. comorbid conditions</td>
<td>1.2 (1)</td>
<td>0.9 (0.9)</td>
<td>1.0 (0.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Among HCSs.

Data are presented as no. (%), unless otherwise indicated. GFR indicates glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LAD, left anterior descending artery; and LDL, low-density lipoprotein cholesterol. Diet, and physical activity, whereas a greater proportion of VA patients were not at the secondary high-density lipoprotein cholesterol target (>40 mg/dL) compared with the other 2 HCSs. In general, the US non-VA patients were intermediate in risk between Canada and the VA except for a lower proportion of patients who were at systolic blood pressure target. After 4 years, a significantly greater percentage of patients were at treatment goal for each HCS except for smoking cessation, and hemoglobin A1c targets in patients with diabetes. For body mass index, a significantly greater percentage of patients were at the treatment target only in the US non-VA system. When differences among HCSs were compared after 4 years, a greater percentage of Canadian patients were at treatment goal for moderate physical activity and American Heart Association step II diet, whereas a lower percentage of patients in the VA HCS met the high-density lipoprotein cholesterol target goal.

PCI Results
The clinical success rate (all lesions successfully dilated and no in-hospital complications) were similar among HCSs (VA patients, 403 [86%]; US non-VA patients, 168 [88%]; Canadian patients, 394 [88%]). A more detailed description of HCS angiographic characteristics is reported elsewhere. In the OMT group, the rates of subsequent PCI or CABG were 32.6%, 34.8%, and 32.5% after a 4.6-year median follow-up in the VA, US non-VA, and Canadian HCSs, respectively (P=0.56). In the PCI group, the rates of repeat coronary revascularization were 28.1%, 23.4%, and 12.9% in the VA, US non-VA, and Canadian HCSs, respectively (P<0.001). CABG was performed during follow-up in 9%, 8.4%, and 4.7% patients in the OMT group, and 8.2%, 6.7%, and 5.4% patients in the PCI group for the VA, US non-VA, and Canadian HCSs, respectively (NS).
significant differences among HCSs for either treatment group (PCI, \( P = 0.62 \); OMT, \( P = 0.58 \)) at 3 years after adjusting for baseline Seattle Angina Questionnaire angina frequency domain.

**Primary Outcome**

No significant treatment differences were observed for the primary outcome of total mortality and nonfatal MI or major cardiovascular outcomes among the 3 HCSs after the median 4.6-year follow-up (Figures 1 and 2A, 2B). No treatment differences were observed after adjustment for baseline differences in sex, race, history of diabetes, fasting plasma glucose, resting heart rate, low-density lipoprotein cholesterol, history of cerebrovascular disease, MI, glomerular filtration rate, and comorbidity (\( P = 0.33 \)). The results were similar when periprocedural MI was censored from the analysis. \( P \) values for the interaction between treatment and the covariates were not statistically significant for any of the comparisons (data not shown).

**Secondary Outcomes**

No significant treatment differences were observed for the secondary outcomes of nonfatal MI or stroke within each of the 3 HCSs. Similarly, no significant treatment differences were observed for the outcome of total mortality (Figure 2B) or hospitalization for an acute coronary syndrome within each of the 3 HCSs (Figure 1).

**The Impact of Patient Demographics, HCS, Initial Treatment Assignment, and Death**

Logistic regression analyses were performed to examine the relationship among patient baseline characteristics, HCS, initial treatment assignment, and death (Table 3). Variables included in the analysis are those that are significantly different (\( P < 0.01 \)) among HCSs at baseline (Table 1). In the first model, HCS was an important determinant of death, particularly between the VA and Canadian HCSs. Initial treatment assignment was not significantly different and was not related to differences in mortality rates; neither was the interaction of HCS and treatment. After adjustment for baseline differences that were significantly different among HCSs (Table 3), the apparent relationship of HCS to death was no longer significant. The statistically significant independent predictors of long-term mortality in this analysis were age, number

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**Table 2. Medication Use at Baseline and 4 Years After Randomization**

<table>
<thead>
<tr>
<th></th>
<th>VA Baseline</th>
<th>4 Y</th>
<th>( P^* )</th>
<th>US Non-VA Baseline</th>
<th>4 Y</th>
<th>( P^* )</th>
<th>Canada Baseline</th>
<th>4 Y</th>
<th>( P^* )</th>
<th>( P^\dagger )</th>
<th>( P^\ddagger )</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>967</td>
<td>543</td>
<td></td>
<td>386</td>
<td>205</td>
<td></td>
<td>932</td>
<td>547</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \beta )-Blocker</td>
<td>90</td>
<td>88</td>
<td>0.42</td>
<td>81</td>
<td>81</td>
<td>0.64</td>
<td>86</td>
<td>81</td>
<td>0.008</td>
<td>&lt;0.001</td>
<td>0.002</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>47</td>
<td>51</td>
<td>0.4</td>
<td>26</td>
<td>31</td>
<td>0.28</td>
<td>42</td>
<td>47</td>
<td>0.03</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nitrates</td>
<td>80</td>
<td>73</td>
<td>&lt;0.001</td>
<td>44</td>
<td>48</td>
<td>0.05</td>
<td>64</td>
<td>32</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>61</td>
<td>65</td>
<td>0.004</td>
<td>43</td>
<td>46</td>
<td>0.08</td>
<td>64</td>
<td>67</td>
<td>0.008</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonist</td>
<td>2</td>
<td>12</td>
<td>&lt;0.001</td>
<td>8</td>
<td>22</td>
<td>&lt;0.001</td>
<td>6</td>
<td>14</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Antilipid therapy</td>
<td>93</td>
<td>97</td>
<td>0.048</td>
<td>87</td>
<td>94</td>
<td>0.04</td>
<td>88</td>
<td>98</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
<td>98</td>
<td>93</td>
<td>&lt;0.001</td>
<td>96</td>
<td>91</td>
<td>0.01</td>
<td>97</td>
<td>97</td>
<td>0.84</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diuretic</td>
<td>18</td>
<td>35</td>
<td>&lt;0.001</td>
<td>16</td>
<td>20</td>
<td>0.004</td>
<td>12</td>
<td>18</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment targets, % patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP &lt;130 mm Hg</td>
<td>39</td>
<td>61</td>
<td>&lt;0.001</td>
<td>31</td>
<td>60</td>
<td>&lt;0.001</td>
<td>52</td>
<td>65</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.31</td>
</tr>
<tr>
<td>DBP &lt;85 mm Hg</td>
<td>81</td>
<td>91</td>
<td>&lt;0.001</td>
<td>80</td>
<td>89</td>
<td>0.28</td>
<td>86</td>
<td>93</td>
<td>&lt;0.001</td>
<td>0.007</td>
<td>0.19</td>
</tr>
<tr>
<td>LDL-C (&lt;85 mg/dL)</td>
<td>29</td>
<td>66</td>
<td>&lt;0.001</td>
<td>24</td>
<td>69</td>
<td>&lt;0.001</td>
<td>28</td>
<td>72</td>
<td>&lt;0.001</td>
<td>0.19</td>
<td>0.1</td>
</tr>
<tr>
<td>LDL-C (&lt;70 mg/dL)</td>
<td>13</td>
<td>40</td>
<td>&lt;0.001</td>
<td>10</td>
<td>33</td>
<td>&lt;0.001</td>
<td>13</td>
<td>43</td>
<td>&lt;0.001</td>
<td>0.15</td>
<td>0.03</td>
</tr>
<tr>
<td>HDL-C (&lt;35 mg/dL)</td>
<td>54</td>
<td>63</td>
<td>&lt;0.001</td>
<td>70</td>
<td>76</td>
<td>0.06</td>
<td>73</td>
<td>84</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>48</td>
<td>63</td>
<td>&lt;0.001</td>
<td>48</td>
<td>66</td>
<td>&lt;0.001</td>
<td>53</td>
<td>61</td>
<td>0.004</td>
<td>0.08</td>
<td>0.32</td>
</tr>
<tr>
<td>AHA step II diet</td>
<td>48</td>
<td>77</td>
<td>&lt;0.001</td>
<td>49</td>
<td>73</td>
<td>&lt;0.001</td>
<td>62</td>
<td>84</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>16</td>
<td>16</td>
<td>0.62</td>
<td>17</td>
<td>22</td>
<td>0.004</td>
<td>18</td>
<td>17</td>
<td>0.9</td>
<td>0.9</td>
<td>0.31</td>
</tr>
<tr>
<td>Moderate activity (5 times/wk)</td>
<td>21</td>
<td>36</td>
<td>&lt;0.001</td>
<td>26</td>
<td>44</td>
<td>&lt;0.001</td>
<td>29</td>
<td>45</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>Smoking cessation</td>
<td>72</td>
<td>77</td>
<td>0.6</td>
<td>77</td>
<td>80</td>
<td>0.38</td>
<td>80</td>
<td>82</td>
<td>0.44</td>
<td>&lt;0.001</td>
<td>0.09</td>
</tr>
<tr>
<td>HbA1c among patients with diabetes (&lt;7.0)</td>
<td>49</td>
<td>50</td>
<td>0.42</td>
<td>52</td>
<td>60</td>
<td>0.98</td>
<td>49</td>
<td>51</td>
<td>0.28</td>
<td>0.89</td>
<td>0.48</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; AHA, American Heart Association; BMI, body mass index; DBP, diastolic blood pressure; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; and SBP, systolic blood pressure.

*Paired difference between baseline and 4 years.
†Difference among HCSs at baseline.
‡Difference among HCSs after 4 years.
of comorbid conditions, and baseline ejection fraction. None of the squares or interactions of baseline variables with treatment were significant.

**Discussion**

We explored 3 different practice environments (the VA, the US non-VA, and the Canada HCSs) to determine whether type of HCS might identify either a benefit or a lack of benefit for PCI in preventing death, MI, and other major cardiovascular outcomes compared with OMT alone in the COURAGE trial. Our main findings are that type of HCS did not influence the primary outcome of the composite of death or nonfatal MI; the secondary outcome of the composite of death, MI, stroke, and hospitalization for unstable angina; or the individual component end points when the initial treatment strategies were compared. A significant difference in mortality was observed after 4.6 years of follow-up among the different HCSs that was largely explained by age, comorbidity, conditions, and ventricular function.

**Differences in HCS Patient Characteristics**

In general, the Canadian patients who participated in COURAGE were younger, had a lower body mass index, were more likely to be white, performed regular moderate exercise, and were more likely to have had a prior MI and prior coronary revascularization but less likely to have a history of hyper-tension or stroke than the American patients. Significant differences in baseline characteristics, as well as process of care between patients enrolled in the United States and those enrolled in Canada have been described previously. The HCS analysis from COURAGE is unique in that it allows prospective examination of long-term randomized clinical trial data in a stable ischemic heart disease population between Canadian and American HCSs and within the American HCS. Earlier reports primarily examined randomized trial data from acute coronary syndrome studies or administrative databases. Further, the analysis offers the opportunity to assess treatment strategies within different HCSs that have different levels of prognostic risk.

After 4 years of follow-up in the COURAGE trial, pharmacological therapy was associated with improved attainment of risk factor goals in all 3 HCSs despite significant differences in baseline characteristics and comorbidity. In general, the more the baseline value approached treatment goals, the higher the percentage of patients who reached goal for any given risk factor. However, target goals for smoking cessation, body mass index, and hemoglobin A1c were less likely to be achieved, identifying a healthcare gap that warrants further study. In the BARI 2D trial that tested 2 intensive glycemic management strategies, only 48% of patients reached a target hemoglobin A1c after 3 years of follow-up. Smoking cessation programs recently

Figure 1. Forest plot of the primary and major secondary outcomes by HCS showing the number of events in each treatment group, the hazard ratio, 95% CI, and the 4.6-year event rate for each treatment group. ACS indicates acute coronary syndrome; CHF, congestive heart failure; no-peri, no perioperative MI included; $P_{adj}$, $P$ value adjusted for sex, race, diabetes, fasting plasma glucose, systolic blood pressure $>130$ mm Hg, pulse, low-density lipoprotein, cerebrovascular disease, prior MI, glomerular filtration rate, and comorbidity; $P_{(inter)}$, $P$ value for homogeneity and represents the $P$ value for the standard interaction before adjusting for any covariates.

**Figure 2.** A, Incidence of death and MI by HCS. B, Total mortality by HCS. CDN indicates Canadian HSC.
have been enhanced by the addition of nicotine-receptor partial agonists that may offer a greater potential to reduce smoking addiction. In the American system, increased comorbidity in VA patients was associated with increased rates of death or MI regardless of treatment assignment. The lowest rates of death or MI were seen in Canadian patients assigned to OMT.

Clinical Implications

COURAGE is the largest randomized controlled trial comparing PCI to medical therapy and confirms earlier, smaller, randomized controlled trials and metaanalyses that indicated that PCI does not prevent death or MI in patients with stable ischemic heart disease and angiography-documented CAD. The National Institutes of Health-sponsored BARI 2D trial reported a similar lack of benefit for PCI in 1605 mildly symptomatic patients with type II diabetes. A limitation of both trials is the relatively small number of patients with extensive angiographic CAD and impaired left ventricular function. In COURAGE, Mancini et al performed a post hoc analysis on 126 patients with 3-vessel CAD and an ejection fraction between 30% to 49%. After 3 years, patients in the PCI group showed a nonsignificant trend toward improved survival free of MI (P = 0.26). In the BARI 2D trial, 19% of patients had 3-vessel disease, and only 16% had an ejection fraction <50% in the PCI stratum. Thus, both large randomized trials had limited power to examine the role of coronary revascularization with PCI in patients with 3-vessel disease and impaired left ventricular function. COURAGE did not randomize patients to prompt CABG or OMT. In the BARI 2D trial, physicians were required to declare the intended revascularization procedure before randomization, resulting in patients with more extensive CAD, total occlusions, and proximal luminal narrowings selected for CABG as compared to PCI. In the CABG stratum, MI was significantly less frequent during follow-up than in patients who received initial OMT. Thus, additional studies should be considered to address the incremental role of coronary revascularization (PCI or CABG) in the prevention of death or MI compared to initial OMT in patients who have more extensive CAD and more-severe myocardial ischemia.

Study Limitations

A limitation of our post hoc analyses is the lack of power to test for interactions because each HCS is a subset of the entire COURAGE trial, and the number of patients in the US non-VA HCS was substantially less than in the other 2 HCSs. Because we have to test the comparisons at the 0.016 level to adjust for the number of comparisons, approximately double the number of events would be required to do a reliable test. A second limitation is the differences in baseline characteristics among HCS. This is off set in part by the fact that randomization was stratified by hospital, and baseline characteristics were similar between treatment groups within the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1 OR (95% Wald CI)</th>
<th>P</th>
<th>Model 2 OR (95% Wald CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>1.03 (0.88–1.21)</td>
<td>0.75</td>
<td>1.06 (0.90–1.23)</td>
<td>0.50</td>
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<tr>
<td>Strata</td>
<td>1.61 (1.06–2.45)</td>
<td>0.03</td>
<td>0.99 (0.56–1.75)</td>
<td>0.96</td>
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<tr>
<td>HCS</td>
<td></td>
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<tr>
<td>VA vs Canada</td>
<td>1.92 (1.34–2.75)</td>
<td>&lt;0.001</td>
<td>1.55 (1.02–2.35)</td>
<td>0.04</td>
</tr>
<tr>
<td>US vs Canada</td>
<td>1.45 (0.92–2.32)</td>
<td>0.20</td>
<td>1.25 (0.75–2.05)</td>
<td>0.38</td>
</tr>
<tr>
<td>Interaction Rx by HCS</td>
<td>1.18 (0.99–1.41)</td>
<td>0.07</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes</td>
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<td>Hypertension</td>
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<td>BMI</td>
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<td>Ejection fraction</td>
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<tr>
<td>Glomerular filtration rate</td>
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<tr>
<td>Prior MI</td>
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<tr>
<td>HDL-C</td>
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<tr>
<td>LDL-C</td>
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<tr>
<td>Smoker</td>
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<tr>
<td>Exercise &gt;30 min &gt;5 times/wk</td>
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<tr>
<td>Age</td>
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<tr>
<td>Sex</td>
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<td></td>
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<tr>
<td>Hosmer-Lemeshow goodness of fit</td>
<td></td>
<td>0.79</td>
<td></td>
<td>0.52</td>
</tr>
</tbody>
</table>

HDL-C indicates high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; and Rx, prescription.
HCs, thus allowing comparison of PCI to OMT across a
gradient of prognostic risk. Optimal medical therapy as
practiced in the COURAGE trial included free cardiovascular
medications and an aggressive approach to modification of
atherosclerotic risk profiles using individual case-based
management. Thus, the potential to observe overall outcome
differences among the HCs was likely minimized compared
to what might have been observed with a usual care approach;
thus, optimal medical therapy as practiced in COURAGE
provides a model demonstrating that it is possible to success-
fully implement life-saving therapies associated with reduced
major adverse outcomes across different HCs.

Conclusions
The COURAGE trial comparison of HCs provides a unique
opportunity to explore treatment differences over a gradient of
comorbidity and different processes of care in a large
cohort of patients with stable ischemic heart disease treated in
a contemporary fashion. The results amplify the overall
COURAGE findings and reveal that there are no significant
treatment differences between PCI and OMT for serious cardiovascular outcomes across different HCs. The data also
provide an important evidence base both for physicians and
for their patients with stable ischemic heart disease and
inducible ischemia who are similar to those enrolled in
COURAGE. In choosing between 2 effective initial treatment
strategies (PCI or OMT alone), there is no significant penalty
of increased exposure to cardiovascular events if an initial
approach of OMT as used in COURAGE is selected. Inten-
sive multifactorial intervention is an integral part of patient
management in stable ischemic heart disease and, as practiced
in COURAGE, resulted in a similar survival benefit free of
MI compared to an initial strategy of routine PCI.

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