The possible benefits of percutaneous coronary intervention (PCI) in the management of stable patients with coronary artery disease (CAD) in nonacute settings have been debated for more than a decade. A meta-analysis of early data from 6 randomized controlled trials1–6 showed convincingly that PCI improves anginal symptoms compared with conservative management7; however, early data were very limited in their ability to address conclusively hard end points such as mortality and the risk of myocardial infarction (MI), because there were only 26 deaths and only 70 patients had MI. Early data also suggested a significant increase in the need for CABG surgery with PCI.7 Most of the early published trials have accumulated and published long-term follow-up information in the interim.8–11 and several new randomized trials (including some pilot studies) have been conducted in the last 5 years12–16 to address the comparison of PCI and conservative medical interventions in patients with nonacute CAD. A quantitative appraisal and synthesis of this information would be essential in understanding whether PCI affects long-term hard clinical outcomes in these patients and in providing an evidence frame for choosing PCI indications in this patient population. We report the results of a meta-analysis including data from 11 studies in patients with angiographically documented coronary stenoses in nonacute CAD settings.

Methods

Eligibility and Search Strategy
The meta-analysis considered randomized trials comparing coronary revascularization by PCI versus conservative medical therapy for the treatment of patients with CAD documented by angiographic evidence of stenosis in 1 or more coronary vessels. We included trials regardless of the extent of additional documentation for the functional impact of the stenoses (angina, positive exercise test, or positive scintigraphy). We excluded studies involving patients who had an acute coronary syndrome within 1 week of entering the study but included patients who had MI or unstable angina in the more distant past. For 3-arm trials in which conservative treatment was compared against separate arms of PCI and CABG, we considered the comparison of conservative treatment against PCI. We excluded 2-arm trials in which conservative treatment was compared against any type of revascularization, including both PCI and CABG,
because the comparison of PCI versus medical treatment would no longer be protected by randomization.

We identified eligible trials by searching PubMed and the Cochrane Controlled Trials Registry (last search updated October 2004) using keywords that pertained to the characterization of PCIs (including balloon angioplasty, athectomy, and stent placement) combined with a keyword algorithm suggested for identification of randomized controlled trials (available at www.cochrane.org). The full search strategy is available on request. Abstracts and data from trials reported in major meetings of the American College of Cardiology and American Heart Association were also screened. Finally, we perused the bibliographies of retrieved articles and relevant reviews.

Outcomes

We considered the following hard clinical outcomes: death, cardiac death or MI (fatal or nonfatal), nonfatal MI, CABG, and PCI during follow-up (in the target vessel or other vessel/segment). For each outcome, we used the data that pertained to the longest follow-up available for that outcome from each eligible study. Death included mortality due to all causes, unless only cardiac deaths were reported. MI was diagnosed on the basis of standard ECG and enzyme criteria.

Data

We systematically extracted information on patient and disease characteristics, study design, quality characteristics (blinding, mode of generation of the randomization sequence, allocation concealment, and description of withdrawals), and outcomes (as above). Two investigators extracted data independently, discussed discrepancies, and eventually reached consensus on all items.

Statistical Analysis

We used the risk ratio as the metric of choice for all outcomes. Between-study heterogeneity was evaluated with the χ²-based Q statistic and considered significant at P<0.10.17 We also used the I² statistic that is independent of the number of studies and quantifies heterogeneity on a scale of 0% to 100%. Very large heterogeneity could not be explained by chance. For each analysis, we considered the presence of heterogeneity using a χ²-based Q statistic and considered significant at P<0.10 to determine whether random or fixed effects models were more appropriate. We used fixed effects models for all outcomes except PCI, because the comparison of PCI versus medical treatment would no longer be protected by randomization.

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53 and 61 years, and men were predominantly or exclusively enrolled. The proportion of patients with diabetes ranged between 0% and 30% across trials. There was large variability in the proportion of patients who had a history of MI, and 2 trials included exclusively patients with a relatively recent history of MI (in the last 3 months but not in the past week). Patients with single-vessel or 2-vessel disease were included primarily, but a considerable proportion of patients in MASS II had 3-vessel disease. The large majority of patients had at least some anginal symptoms, but some trials also included a few patients without symptoms (Table 1). The reported average left ventricular ejection fraction was <60% in only 1 trial that lowered the eligibility threshold for ejection fraction to 35% (mean 46%). Moreover, 7% of RITA-2 patients did not have excellent or very good wall motion, and 3% of ALKK patients were classified as class 2 New York Heart Association, with no data on ejection fraction. Five trials with 1790 patients had a mean follow-up that exceeded 2 years, whereas the other 6 trials (1160 patients) had more limited follow-up data available.

All patients had angiographically documented disease, but there was considerable variability with regard to whether exercise testing or scintigraphy was also performed. Exercise testing was generally performed in the ACME trials and in the study by Hambrecht et al, whereas the study by Dakik et al and MASS also demonstrated positive scintigraphy in 100% and 84% of their patients, respectively. Conversely, a positive exercise test was documented in only 13% and 40% of the ALKK and MASS II trials, respectively; RITA-2 provided no data on ischemia assessment; all patients in AVERT had to be able to exercise for at least 4 minutes without ischemia according to the Bruce protocol; and all analyzed patients who had noninvasive ischemia testing in the trial by Bech et al had either negative or inconclusive testing, and the fractional flow reserve was at least 0.75.

No trial used drug-eluting stents. Bare-metal stents were used in all PCI patients in the study by Hambrecht et al and in 72% and 40% of the PCI patients in the ALKK and Bech et al trials, respectively, although they were used less extensively in 3 other trials (AVERT, Dakik et al, and MASS). There were also some differences in the primary defining characteristics of management in the conservative treatment arms. Hambrecht et al placed emphasis on an intensive exercise intervention, and AVERT was based on statin treatment with atorvastatin. All trials typically used antianginal and antischemic treatment in the conservative treatment arm, whereas statins were used to various extents in trials conducted in the last decade.

Blinding would be impossible for the patients and treating physicians but might have been considered in assessment of the outcomes. The RITA-2, ACME, and AVERT trials and the study by Bech et al specifically mentioned the use of independent assessors for some or all of the outcomes. Inadequate or no information was provided in all trial reports about the mode of generation of the randomization sequence and how allocation concealment was ensured, although at least 1 trial presented design details in a separate publication. All analyzed trials provided some information on withdrawals from the study during follow-up.

### Data Synthesis

Table 2 provides the number of events, and Table 3 summarizes the effect sizes for the main outcomes of the meta-analysis. There were a total of 196 deaths (PCI arm n=95 versus conservative arm n=101), 235 patients had cardiac death or MI, 101 had an MI (PCI arm n=87 versus conservative arm n=109), and 153 patients had nonfatal MIs (PCI arm n=87 versus conservative arm n=66), whereas 215 patients underwent EPIC.

#### Table 2. Number of Patients With Major Clinical Outcomes per Arm

<table>
<thead>
<tr>
<th>Study</th>
<th>RITA-2</th>
<th>ACME-1</th>
<th>ACME-2</th>
<th>AVERT</th>
<th>Dakik et al</th>
<th>MASS</th>
<th>MASS II</th>
<th>ALKK</th>
<th>Sievers et al</th>
<th>Hambrecht et al</th>
<th>Bech et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT/PCI</td>
<td>43/43</td>
<td>15/16</td>
<td>10/9</td>
<td>1/1</td>
<td>1/1</td>
<td>6/6</td>
<td>3/11</td>
<td>17/6</td>
<td>1/0</td>
<td>0/0</td>
<td>4/2</td>
</tr>
<tr>
<td>Death</td>
<td>42/44</td>
<td>14/7</td>
<td>6/6</td>
<td>5/4</td>
<td>3/0</td>
<td>5/3</td>
<td>23/13</td>
<td>12/10</td>
<td>2/0</td>
<td>1/0</td>
<td>4/0</td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td>23/32</td>
<td>7/12</td>
<td>6/6</td>
<td>4/5</td>
<td>0/2</td>
<td>4/3</td>
<td>63/64</td>
<td>13/20</td>
<td>0/1</td>
<td>0/1</td>
<td>8/6</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>63/64</td>
<td>13/34</td>
<td>3/8</td>
<td>2/9</td>
<td>0/0</td>
<td>8/4</td>
<td>139/86</td>
<td>1/18</td>
<td>1/1</td>
<td>3/9</td>
<td>6/9</td>
</tr>
<tr>
<td>CABG</td>
<td>139/86</td>
<td>34/31</td>
<td>11/8</td>
<td>18/21</td>
<td>0/0</td>
<td>4/2</td>
<td>86/66</td>
<td>21/21</td>
<td>8</td>
<td>9</td>
<td>9/9</td>
</tr>
<tr>
<td>PCI</td>
<td>86/66</td>
<td>31/21</td>
<td>8/21</td>
<td>21/21</td>
<td>0/0</td>
<td>6/2</td>
<td>66/86</td>
<td>9/9</td>
<td>6</td>
<td>9</td>
<td>9/9</td>
</tr>
</tbody>
</table>

MT indicates medical (conservative) treatment.
In ACME-1, for data on nonfatal MI, CABG, and PCI, there was information on 107 patients treated conservatively and 105 treated with PCI. For ALKK, separate data for CABG and PCI pertain to 6 months of follow-up. Otherwise, patient denominators and follow-up for all trial outcomes are as shown in Table 1.

#### Table 3. Summary Risk Ratios for Major Outcomes with PCI vs Conservative Medical Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RE Risk Ratio (95% CI)</th>
<th>P</th>
<th>Q (I²)</th>
<th>RE Risk Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.94 (0.72–1.24)</td>
<td>0.68</td>
<td>10.05 (0%)</td>
<td>0.95 (0.72–1.23)</td>
<td>0.68</td>
</tr>
<tr>
<td>Cardiac death or MI</td>
<td>1.17 (0.88–1.57)</td>
<td>0.28</td>
<td>11.3 (13%)</td>
<td>1.16 (0.91–1.48)</td>
<td>0.24</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>1.28 (0.94–1.75)</td>
<td>0.12</td>
<td>4.93 (0%)</td>
<td>1.32 (0.97–1.79)</td>
<td>0.077</td>
</tr>
<tr>
<td>CABG</td>
<td>1.03 (0.80–1.33)</td>
<td>0.82</td>
<td>9.16 (0%)</td>
<td>1.04 (0.81–1.34)</td>
<td>0.76</td>
</tr>
<tr>
<td>PCI</td>
<td>1.23 (0.80–1.90)</td>
<td>0.34</td>
<td>38.4 (74%)</td>
<td>0.91 (0.77–1.07)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

RE indicates random effects; FE, fixed effects.
CABG (PCI arm n = 109 versus conservative arm n = 106) and
462 had PCI during follow-up (PCI arm n = 219 versus
conservative arm n = 243).

Overall, despite some differences, particularly between
the results of the MASS and ALKK trials, there was no statistically
significant between-study heterogeneity for death, car-
diac death or MI, nonfatal MI, and need for CABG; thus,
random and fixed effects estimates were very similar for these
outcomes. There was large between-study heterogeneity in
the risk ratios for PCI during follow-up.

The summary estimates showed no difference between PCI
and conservative treatment in the mortality risk, and the 95% CIs
clearly excluded relative risk differences of 28% (Figure, A).
If anything, there was a trend for more cardiac deaths or
MIs (Figure, B), particularly nonfatal MIs (Figure, C), in
patients who underwent PCI, with the point estimate suggest-
ing approximately a 30% increase in the relative risk of
nonfatal MI with PCI.

There was no difference in need for CABG between the 2
compared treatment strategies (Figure, D). The 95% CIs also
excluded differences in the relative risk exceeding 20% in
favor of PCI and 33% in favor of conservative treatment.
There was no overall difference in the risk for PCI during
follow-up (Figure, E); however, given the considerable
between-study heterogeneity, the random effects 95% CIs were
more substantial. Bayesian models gave very similar point
estimates: 0.90 for death (95% credibility interval 0.62 to 1.33),
1.16 for cardiac death or MI (95% credibility interval 0.84 to
1.60), 1.28 for nonfatal MI (95% credibility interval 0.91 to
1.87), 1.04 for CABG (95% credibility interval 0.71 to 1.40),
and 1.15 for PCI (95% credibility interval 0.68 to 1.96).

Bias and Subgroup Analyses
For 2 outcomes (cardiac deaths and MI; and nonfatal MI),
smaller trials with fewer events showed a more unfavorable
risk ratio with PCI versus conservative treatment than larger
trials with more events (Kendall $\tau$ correlation coefficient
between variance and logarithm of the risk ratio 0.53 [$P=0.024$]
for both outcomes). Correlations between vari-
ance and effect sizes were nonsignificant for the other
outcomes.

Subgroup analyses (Table 4) showed that availability of
stents did not make a substantial difference for any of the 5
end points considered. Trials with follow-up exceeding 2
years showed no differences between PCI and conservative
treatments, with risk ratio estimates very close to 1.00 for all
outcomes. Trials with more limited follow-up suggested an
increase in deaths, MI, and nonfatal MI in PCI-treated
patients, and the difference reached formal statistical signifi-
cance for cardiac death or MI, with almost a doubling of risk
conferred by PCI; however, the CIs overlapped with the
results from longer-term trials. The 2 trials that exclusively
enrolled patients with relatively recent MIs showed a statisti-
cally significant reduction in the risk of death ($P=0.037$)
and risk for subsequent PCI ($P=0.029$) and possibly also
CABG ($P=0.12$) in the PCI arms. Data were driven by the
ALKK trial.14 This subgroup significantly differed from the
remaining trials with regard to death and PCI risk ratios.
Finally, there was no evidence that trials with definitive
documentation of ischemia by exercise test or scintigraphy
had different risk ratios than trials in which functional
ischemia was not documented as thoroughly (Table 4).

Discussion
The present meta-analysis shows that compared with conser-
ervative medical treatment, PCI does not decrease mortality or
the risk of MI during follow-up in patients with chronic CAD
except in the context of a recent MI. By extending the number
of deaths >7-fold compared with a previous meta-analysis,7
CIs in the present study exclude differences exceeding 28%
in the relative risk of death between the 2 treatment strategies.

We observed a trend for increased risk of MI in patients
undergoing PCI. This may reflect the risk inherent in the
invasive procedure itself. Data were not available consistently
across these trials to separate procedure-related infarctions
from subsequent MI. Additionally, microinfarcts caused in a
considerable proportion of patients undergoing PCI may have
adverse prognostic importance in the long term.22 It is
unlikely that myocardial enzymes were checked routinely
after PCI in these trials. Minor procedure-related infarctions
without definitive ECG changes may have been largely
underreported in the PCI arms.

The early literature suggested that PCI may cause an
increased need for CABG.7 We found no evidence for any
increased need of CABG in the PCI strategy compared with
the conservative strategy. The present meta-analysis includes
more data and much longer follow-up data, with a several-
fold larger number of events, and thus, the CIs are quite
narrow. Similarly, we found no difference in the risk of
requiring PCI during follow-up with interventional versus
conservative therapy, although there was considerable vari-
ability in this outcome across trials. The reason for this
heterogeneity is not immediately clear. One possibility is
that although indications for CABG are relatively clear-cut, indi-
cations for PCI are more subjective.23 Thus, different inves-
tigators and centers might have had different biases toward
the use of PCI during follow-up depending on whether PCI
had been used previously.

Some caveats must be discussed. First, several of these
trials were conducted in the time period before the routine use
of stents in clinical practice. Although both this meta-analysis
and simulations of a cost-effectiveness analysis24 suggest that
PCI is probably not indicated in patients with chronic CAD,
by extrapolating from the results of trials in acute settings,25
it may be speculated that stents could offer superior outcomes
compared with simple balloon angioplasty. Some interven-
tional cardiologists may be tempted to discard the results of
trials that did not use stents as being obsolete. Nevertheless,
importantly, our meta-analysis found no evidence of superi-
ority for the PCI strategy, even when analyses were limited to
trials that used stents. Furthermore, even in acute settings, a
recent meta-analysis26 suggested that the advantages of stents
have probably been overestimated. Finally, the impact of
drug-eluting stents cannot be predicted, but the available data
suggest that they may not offer any benefit other than to
reduce the need for revascularization, whereas the risk of
death and MI is not affected.27,28
Second, the disease background of the patients included was different across trials. We found some evidence that PCI may actually be more effective in reducing the risk of death, especially in trials in which all patients had a relatively recent MI. These patients may also have a reduced need for subsequent revascularization if revascularization is performed at first. Longer follow-up and additional data would be useful before a strong recommendation is made to use PCI in this setting, because the data are driven largely by a single trial.14

Patient populations also differed across trials with regard to intensity of angina symptoms, functional demonstration of
ischemia, and angiographic extent of CAD. Individual-level data are required to fully assess whether these parameters make a difference in the relative outcomes of the interventional versus conservative strategies. Nevertheless, all trials included patients with generally unimpaired left ventricular function regardless of the extent and manifestations of CAD. Moreover, we found no evidence of a benefit in the subgroup of trials with strictly documented ischemia. Some additional evidence may be generated from the ongoing adenosine technetium-99m Sestamibi single-photon emission computed tomography post-infarction evaluation (INSPIRE) trial.

Third, the included trials did not routinely use the full spectrum of conservative interventions currently available for CAD management. Interestingly, excellent results for the conservative arm were obtained in a trial in which special emphasis was placed on exercise, although it should be acknowledged that weekly counseling was also provided to patients in the exercise group. Exercise may be unjustifiably acknowledged that emphasis was placed on exercise, although it should be acknowledged that exercise was underutilized in current clinical practice. Moreover, the advent of statins has improved the treatment and outcomes of patients with chronic CAD with or without significant hypercholesterolemia. This potential benefit was not available in any of the early trials. In view of current recommendations, the angioplasty-treated group in AVERT had inadequate control of their lipids. Overall, the different and potentially suboptimal medical management across trials is a limitation of the meta-analysis; however, one would expect even better outcomes if medical management were optimized. Maximized medical treatment compared with the combination of PCI and maximized medical treatment is being tested in the ongoing COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive drUG Evaluations) trial.

Finally, the present meta-analysis did not consider the option of CABG in patients with stable chronic CAD and preserved left ventricular function, yet these patients typically were excluded from the trials considered here. The MASS and MASS II trials also included separate randomized arms in which patients were allocated to CABG; surgical treatment offered excellent relief from anginal symptoms and decreased the need for further revascularization, but there was no clear benefit in terms of survival or the risk of subsequent MI. Three other trials have compared medical treatment versus invasive treatment that could include either PCI or CABG, with the choice being performed in a nonrandomized fashion. The TIME trial (Trial of Invasive versus Medical therapy in the Elderly) found a large benefit in angina and quality of life with revascularization, but there was a trend for more deaths in the invasive treatment arm. The Asymptomatic Cardiac Ischemia Pilot (ACIP) study found improvements in ischemia and improved clinical outcomes with revascularization, primarily with CABG, but the number of major clinical events was limited. Finally, the Danish trial in Acute Myocardial Infarction (DANAMI) found similar mortality rates in the 2 arms and a modest reduction in MI with revascularization over 2.4 years of follow-up in survivors of acute MI. The benefit pertained to patients with documented ischemia. More data and longer follow-up are needed to understand the potential benefits of major surgery in low-risk patient populations.

Acknowledging these caveats, we conclude that for patients with chronic CAD and good left ventricular function, PCI does not confer any clear benefit in terms of long-term hard clinical outcomes compared with conservative medical treatment. At the same time, the early fear of an increased risk of bleeding after PCI probably also is not warranted. PCI may be indicated in special circumstances, eg, relatively early after MI. By comparing the benefits, if any, against cost considerations, we believe that many percutaneous interventions that currently are performed in patients with nonacute CAD probably are not justified.

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Death (95% CIs)</th>
<th>Cardiac Death or MI (95% CIs)</th>
<th>Nonfatal MI (95% CIs)</th>
<th>CABG (95% CIs)</th>
<th>PCI (95% CIs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent availability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.89 (0.33–2.36)</td>
<td>1.28 (0.66–2.48)§</td>
<td>1.32 (0.81–2.15)</td>
<td>0.99 (0.35–2.77)</td>
<td>1.42 (0.67–3.00)¶</td>
</tr>
<tr>
<td>No</td>
<td>0.99 (0.71–1.39)</td>
<td>1.18 (0.85–1.63)</td>
<td>1.26 (0.84–1.89)</td>
<td>1.06 (0.80–1.40)</td>
<td>1.11 (0.64–1.94)¶</td>
</tr>
<tr>
<td>Mean follow-up &gt;2 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.88 (0.64–1.22)</td>
<td>0.99 (0.68–1.46)</td>
<td>1.15 (0.80–1.65)</td>
<td>1.06 (0.80–1.40)</td>
<td>1.22 (0.64–2.31)¶</td>
</tr>
<tr>
<td>No</td>
<td>1.39 (0.60–3.22)</td>
<td>1.82 (1.10–2.99)</td>
<td>1.72 (0.95–3.13)</td>
<td>0.97 (0.42–2.25)</td>
<td>1.27 (0.66–2.42)¶</td>
</tr>
<tr>
<td>All patients with recent MI*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>0.40 (0.17–0.95)§</td>
<td>1.01 (0.18–5.60)</td>
<td>1.26 (0.27–5.83)</td>
<td>0.24 (0.04–1.42)</td>
<td>0.42 (0.20–0.91)¶</td>
</tr>
<tr>
<td>No</td>
<td>1.04 (0.78–1.39)§</td>
<td>1.31 (1.00–1.73)</td>
<td>1.35 (0.96–1.90)</td>
<td>1.06 (0.82–1.38)</td>
<td>1.41 (0.88–2.24)¶§</td>
</tr>
<tr>
<td>Ischemia documented in &gt;80%†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.98 (0.63–1.55)</td>
<td>1.50 (0.88–2.56)</td>
<td>1.13 (0.60–2.14)</td>
<td>1.11 (0.64–1.90)</td>
<td>1.85 (0.87–3.91)¶</td>
</tr>
<tr>
<td>No</td>
<td>0.86 (0.42–1.74)¶</td>
<td>1.10 (0.71–1.72)</td>
<td>1.33 (0.93–1.91)</td>
<td>1.00 (0.58–1.72)</td>
<td>0.96 (0.56–1.65)¶</td>
</tr>
</tbody>
</table>

*Eight days to 3 months before entry into the trial. ¶Based on exercise test with or without scintigraphy. §Statistically significant heterogeneity between the 2 subgroups of studies (P<0.05 for comparison of subgroups).
References


