Patients with significant coronary artery stenoses are at increased risk of future cardiac events. However, in the absence of acute coronary syndrome or recent myocardial infarction and residual ischemia, elective percutaneous coronary intervention has not been shown to improve prognosis. Possible explanations for this might be the limited follow-up time adopted by most randomized trials comparing percutaneous coronary intervention with medical therapy, limited number of patients with proven ischemia enrolled in these trials, and adoption of complex, elaborate techniques that have not proved their usefulness. Published evidence identifies certain indications for percutaneous coronary intervention in patients with stable coronary lesions: demonstration of significant inducible ischemia, particularly in the context of a recent myocardial infarction; detection of unequivocally reduced fractional flow reserve; and specific angiographic features of coronary stenoses. Operators should take into account long-term consequences of adopted techniques rather than immediate angiographic results. We review existing evidence and provide our recommendations in this setting. (J Am Coll Cardiol 2008;52: 889–93) © 2008 by the American College of Cardiology Foundation

Recent randomized trials (1,2) and meta-analyses (3–5) have argued against the clinical usefulness of percutaneous coronary intervention (PCI) in patients with stable coronary artery disease. Although PCI undoubtedly relieves angina and reduces the need of medication, thus improving the quality of life, there is no proof of effect on hard clinical outcomes such as cardiac or total mortality. Indeed, in the absence of acute coronary syndrome (6) or recent myocardial infarction (MI) and residual ischemia (7), elective PCI has not been shown to improve prognosis and might even be harmful (3). However, patients with significant coronary artery stenoses are at increased risk of future cardiac events. In longitudinal studies in patients with known or suspected coronary artery disease, detection of ischemia predicts a significantly higher overall mortality, cardiac death, or MI (8–10), even in the absence of angina (11), whereas normal scintigraphy studies identify patients with a good prognosis at a low risk for future cardiac events (10,12). Myocardial ischemia is an established cause of polymorphic ventricular tachycardia or fibrillation and sudden cardiac death (13–15). The majority of sudden deaths due to ischemic heart disease are not associated with an acute MI (16–18), but transient acute ischemia is an important trigger, preceding 35% to 80% of deaths due to a ventricular tachyarrhythmia (19–21). Not unexpectedly, therefore, the extent of significant lesions (i.e., >50% diameter stenosis) on the coronary arteries has been correlated with long-term mortality (22), and revascularization, either by PCI or surgery, usually (23,24), although not invariably (25), confers a greater survival benefit than medical therapy in patients with significant inducible ischemia.

Why then can we not document a reduction of cardiac risks in the presence of stable but angiographically significant coronary artery stenoses for PCI? Several plausible explanations can be offered.

Follow-Up Time

If we consider the randomized trials that have been studied in the 2 most recent meta-analyses (3,4), the median follow-up was only 2 years. With the exemption of the SWISSI II (Swiss Interventional Study on Silent Ischemia Type II) trial (10.2 years) (26), and the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial (4.6 years) (1), patients were followed up for just a few years. This time is probably inadequate to show any significant effect on the natural history of coronary artery disease, an insidious condition that may take more than 10 years to demonstrate its harmful consequences. Hence, in light of the inadequate duration of follow-up, the lack of proof of efficacy is likely not the proof of lack of efficacy.
Patients enrolled in studies comparing medical therapy with PCI did not represent a homogeneous cohort. For example, of the 2,950 patients who were involved in a recent meta-analysis, only 455 patients enrolled in 4 out of 10 studies had objectively detectable ischemia (3). Subgroup analyses in this study produced no evidence that trials with definitive documentation of ischemia by exercise test or scintigraphy had different risk ratios compared with trials where functional ischemia was not as thoroughly documented. However, a possible survival benefit was seen for PCI in trials of patients who had a relatively recent MI (risk ratio: 0.40, 95% confidence interval: 0.17 to 0.95) (3). In the COURAGE trial (1), 95% of patients had documented ischemia total and cardiac mortality was not statistically different between medical therapy and PCI groups. Yet in the COURAGE nuclear substudy (27), more PCI patients exhibited significant ischemia reduction and had lower risk for death or MI, particularly if baseline ischemia was moderate to severe. In the SWISSI II trial (26), a clear benefit of PCI was also demonstrated with an unequivocal reduction of cardiac and total mortality in patients with proven silent ischemia. The ACIP (Asymptomatic Cardiac Ischemia Pilot) study (24) found improvements in ischemia and improved clinical outcomes with revascularization, primarily with coronary artery bypass grafting, although the numbers of major clinical events were limited. The DANAMI (Danish trial in Acute Myocardial Infarction) trial (28) 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, and the benefit pertained to patients with documented ischemia. If we consider randomized comparisons of PCI versus medical therapy in patients with clearly detected ischemia, there is also a clear trend for improved outcomes with PCI by means of both total and cardiac mortality (Table 1) (1,7,29–32). Notably, the trend seems to be driven by studies with the longer follow-up time. The symptomatic status of the patient is also important, particularly in the context of relative uncertainty and lack of convergence between various tests for the detection of ischemia. Imaging tests such as exercise scintigraphy results do not correlate well with angiographic findings, both in patients with (33) and without angina (34) and they may not identify the culprit lesion(s) with certainty in the presence of multivessel disease (35). Fractional flow reserve shows modest concordance with imaging tests such as perfusion scintigraphy and dobutamine stress echocardiography (36). Thus, no single test is a valid substitute for clinical judgment and individualized care for each of our patients.

### Table 1: Randomized Studies of MT Versus PCI in Patients With Documented Ischemia

<table>
<thead>
<tr>
<th>Study</th>
<th>MT/PCI, n</th>
<th>No Angina, (%)</th>
<th>Ischemia Follow-Up, yrs</th>
<th>MT Death, n</th>
<th>PCI Death, n</th>
<th>MT NFMI, n</th>
<th>PCI NFMI, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACME (1 vessel), Hartwig et al. (29)</td>
<td>107/105</td>
<td>31</td>
<td>9</td>
<td>3</td>
<td>16</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>ACME (2 vessels), Folland et al. (30)</td>
<td>50/51</td>
<td>41</td>
<td>18</td>
<td>5</td>
<td>10</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Dakik et al. (31)</td>
<td>22/19</td>
<td>100</td>
<td>ND</td>
<td>1</td>
<td>14%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hambrecht et al. (32)</td>
<td>51/50</td>
<td>100</td>
<td>0</td>
<td>1</td>
<td>1%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>COURAGE, Boden et al. (1)</td>
<td>1,138/1,149</td>
<td>31</td>
<td>9</td>
<td>1</td>
<td>14%</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>SWISSI II, Kastrati (7)</td>
<td>105/96</td>
<td>100</td>
<td>13</td>
<td>39</td>
<td>6%</td>
<td>68</td>
<td>25</td>
</tr>
</tbody>
</table>

*Exercise- or vasodilator stress-induced ischemia.

**Abbreviations and Acronyms**

- **MI** = myocardial infarction
- **PCI** = percutaneous coronary intervention
- **MT** = medical therapy
- **ND** = no data
- **NFMI** = nonfatal myocardial infarction
- **RN** = radionuclide angiography
- **SC** = stress echocardiography
- **SE** = stress echocardiography
- **ETT** = exercise treadmill test
- **SE** = stress echocardiography
- **SPECT** = single-photon emission computed tomography
Angiographic Characteristics of Stenoses

Evidence of ischemia sought before intervention in stable patients is the ideal background of ad hoc angioplasty. Short of it, several angiographic features are to be considered by the interventionist for sensible decisions. Significant discordance between quantitative coronary angiography and fractional flow reserve has been demonstrated for lesions with 30% to 70% diameter stenoses (35). Thus, there is always uncertainty about borderline stenoses that generally do well with medical therapy alone. Subtotal occlusions of vessels supplying the noninfarcted myocardium; stenoses greater than 90% that by definition represent vulnerable plaques (37); significant, complex lesions that are prone to develop total occlusions (38); and stenoses with unequivocally reduced fractional flow reserve (<0.75%) (39,40), undoubtedly, represent optimal targets for PCI. Although MIs often occur at sites of mild-to-moderate stenoses (41,42), postmortem examinations have demonstrated that ruptured plaques leading to acute coronary syndrome more likely occur within the segment of significant stenoses (43–45). There are good arguments that these cases should not receive medical therapy alone. We also believe that less severe lesions (i.e., <90% diameter stenosis) should not be automatically excluded from PCI, particularly when offered ad hoc during the session of diagnostic angiography, judiciously assessing the global situation of the patient. Randomized data to support our view are still lacking. The 5-year follow-up of a respective trial failed to show a benefit in hard end points of PCI over medical treatment (46). Indirectly, this signifies that having performed PCI when it was handy (during the diagnostic coronary angiogram) was not harmful. Although both groups were doing well during this limited follow-up, the problem can only be considered solved in the group with PCI.

Notwithstanding, the adoption of strict indications for PCI as opposed to the subjectivity of nonscientific approaches such as the so-called oculostenotic reflex applied to every identified lesion is the basis of optimal clinical outcome following PCI.

PCI Techniques

Current PCI techniques and approaches in general may also be inappropriate at times. If anything, there is a trend for more cardiac deaths or MIs, in particular nonfatal MIs, in patients who undergo PCI, with the point estimate suggesting approximately a 30% increase in the relative risk of nonfatal MI with PCI (3). Thus, it might be that we negate a benefit offered by alleviation of ischemia through stenosis dilation by an avoidably increased iatrogenic risk of intra-procedural or late MI. We tend to downplay procedure-related MIs by a threshold enzyme rise of at least 3 times the upper normal limit. There has been evidence that myocardial necrosis has prognostic significance regardless of its extent (48,49). The
use of stents (particularly the drug-eluting types) is associated with an increased risk of late thrombosis, particularly when very long, overlapping, or side-branch stents are used (50). In the 3 randomized comparisons published so far, side-branch stenting, regardless of the deployed technique adopted, was associated with an increased incidence of MI, stent thrombosis, and target lesion revascularization (51–53), not to mention irradiation doses and costs (Table 2). Nevertheless, various techniques for both main vessel and side-branch stenting are routinely used by most in an effort to achieve an ideal angiographic result. Brophy et al. (54) have elegantly shown that beyond a 20% to 40% rate of stenting, there is no additional benefit to be expected over plain balloon angioplasty.

Thus, published evidence identifies certain indications for PCI, and revascularization in general, in patients with stable coronary lesions. A history of recent MI (<3 months), demonstration of significant inducible ischemia, detection of unequivocally reduced fractional flow reserve, or the presence of specific angiographic features of coronary stenoses are necessary to indicate PCI. Operators should take into account long-term consequences of adopted techniques rather than immediate angiographic results. The art of keeping things as simple as possible with the whole picture and the long-term outcome in the focus could not be more called for than in this setting.

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Key Words: angioplasty • ischemic heart disease • coronary intervention.