Objectives
In the present study, we analyzed the clinical outcome of patients with multivessel coronary artery disease in whom at least one vessel was treated by percutaneous coronary intervention (PCI) and at least one other vessel was deferred on the basis of fractional flow reserve (FFR) measurements during the same session.

Background
Myocardial FFR is an established tool for assessing the severity of epicardial stenoses. It has been shown that it is safe to defer an intervention in single vessel disease patients when FFR > 0.75.

Methods
One hundred two patients (66 ± 10 years) with multivessel coronary artery disease were included in the study. In all patients, PCI of at least two vessels was contemplated. Yet in all of them at least one vessel was treated by PCI, whereas at least one other vessel was deferred based on an FFR > 0.75. Major adverse cardiac events (MACE) were recorded during an average follow-up of 29 ± 18 months.

Results
In 102 patients, 113 coronary arteries underwent PCI. In these arteries FFR was 0.57 ± 0.13 and mean diameter stenosis was 68 ± 14%. One hundred twenty-seven coronary arteries had an FFR > 0.75 and PCI was deferred. In these arteries FFR was 0.86 ± 0.06 and mean diameter stenosis was 47 ± 12%. No death occurred during the follow-up. A MACE occurred in 9% and 13% of patients after 12 and 36 months, respectively. These MACE were related to 22 (9.2%) arteries. Among them, 8 (6.3%) MACE were related to one of the initially deferred vessels, whereas 14 (12.3%) MACE were related to one of the initially treated coronary artery.

Conclusions
In patients with multivessel disease, PCI of hemodynamically non-significant stenoses can be safely deferred, even if initially planned on the basis of the angiogram. (J Am Coll Cardiol 2005;46:438–42) © 2005 by the American College of Cardiology Foundation

Inducible myocardial ischemia at non-invasive stress testing is a paramount prognostic factor (1,2) and its documentation remains essential prior to invasive evaluation. Nowadays, however, the majority of percutaneous coronary interventions (PCIs) are performed without prior non-invasive stress testing (3). In addition, in patients with multivessel coronary disease, the diagnostic accuracy of perfusion scans is poor in assessing which stenosis is hemodynamically significant (4). Fractional flow reserve (FFR) is an invasive index of the hemodynamic significance of stenosis severity with a diagnostic accuracy similar to myocardial perfusion scan but a better spatial resolution. It is derived from the ratio between coronary and aortic pressure measurements during maximal hyperemia. As this index is easy to measure and available in a few minutes in the catheterization laboratory, it can be used as a surrogate for non-invasive testing (5). The usefulness of FFR in patients referred for PCI with intermediate stenoses was demonstrated in single vessel diseased patients (6). In the present study we analyzed the clinical outcome of patients with multivessel coronary artery disease in whom at least one vessel was treated by PCI and at least one other vessel was deferred on the basis of FFR measurements during the same session.

Methods
Study patients. Patients with multivessel coronary artery disease at angiography were included in the study if at least one artery was treated by PCI and, during the same procedure, at least one stenosis was deferred from PCI on the basis of an FFR > 0.75. The study was performed in the Cardiovascular Center Aalst, Belgium, and in the Catharina Hospital in Eindhoven, the Netherlands.
May 2002. Fractional flow reserve and quantitative coronary arteriography were obtained in all patients. Moreover, all patients were informed beforehand that the therapeutic strategy would be guided by pressure measurements.

**Coronary pressure measurement and calculation of FFR.** The FFR was measured in all stenoses in which PCI was contemplated except stenoses with a Thrombolysis In Myocardial Infarction (TIMI) flow grade <3, and stenoses of which the significance had been demonstrated at perfusion scintigraphy. Intracoronary pressure measurements were performed with a 0.014-inch pressure guidewire (Radi Medical System, Uppsala, Sweden) introduced through a 6-F guiding catheter. The FFR was calculated from the ratio of mean hyperemic distal coronary pressure measured by the pressure-wire and the mean aortic pressure obtained by the guiding catheter (7,8). All patients received aspirin and either clopidogrel or ticlopidine for at least two months.

**Quantitative coronary arteriography.** Reference diameter (RD), minimum luminal diameter (MLD), and percent diameter stenosis (DS) were assessed in two views during the PCI procedure.

**Follow-up and clinical events.** All patients were evaluated at the outpatient clinic or by mail. Major adverse cardiac events (MACE) were defined as death, myocardial infarction (MI), and any repeat (target or non-target) vessel revascularization (TVR). Myocardial infarction was defined as the occurrence of new Q waves or a rise in creatinine phosphokinase of more than twice the upper limit (6). A repeat angiogram was not performed unless clinically indicated. The culprit artery vessel responsible for the recurrence of symptoms was defined by the operator’s judgment, based on the correlation of electrocardiographic changes, echocardiographic data (if available), and the diagnostic angiogram.

**Statistics.** Because of the design of the study, the unit of analysis became the coronary artery lesion rather than the patient. Therefore, potential correlations within patients could have been ignored. Continuous variables were expressed as mean ± standard deviation and discrete variables as counts and percentage. The chi-square test and the Fisher exact t test were used for categorical variables, and the Student t test was used for continuous variables. Clinical, angiographic variables, and FFR values were compared between the deferred- and the treated-vessels groups. Survival curves were constructed according to the Kaplan and Meier method and compared by the log-rank test. A p value >0.05 was considered statistically non-significant.

**RESULTS**

**Population.** One hundred two patients (240 arteries, mean age 66 ± 10 years, 71% men) were included. Eighteen percent of patients had diabetes, 34% hypertension, 29% were current smokers, 50% had dyslipidemia, and 43% had a positive familial history for ischemic heart disease. Most patients had stable angina (76%), and the remainder presented an acute coronary syndrome (ACS) (21 with unstable angina and 3 with non–ST-segment elevation MI). Angiographic and hemodynamic data of the treated and deferred arteries are shown in Table 1.

**Angiographic and hemodynamic results.** Thirty-five patients (34%) had three-vessel disease and 66 patients (66%) had two-vessel disease. The PCI procedure was performed in 113 coronary arteries: 1 artery was treated in 91 patients and 2 arteries in 11 patients. In patients admitted for an ACS, the “culprit” lesion was treated in all cases. Use of PCI was deferred based on an FFR ≥0.75 in 127 coronary arteries: in one artery in 77 patients and in two arteries in 25 patients. The individual values of FFR and of %DS for the treated and the deferred arteries are shown in Figure 1. By design, FFR was ≥0.75 in deferred arteries. In this group the mean value of FFR was 0.86 ± 0.06 (range 0.75 to 1.0). The FFR value in the treated arteries was 0.57 ± 0.13 (range 0.29 to 0.74). DS of the treated arteries (68 ± 14%, range 30% to 100%) was significantly higher than in the deferred arteries (47 ± 12%, range 15% to 74%, p < 0.001) but a large overlap of the values was observed. Among the 21 patients presenting with an ACS, a TIMI flow grade <3 was present in 6 culprit arteries. The FFR

![Table 1](image-url)
was measured in 15 culprit arteries in which flow was normal (0.53 ± 0.13, range 0.29 to 0.7) and in 28 non culprit arteries (0.85 ± 0.06, range 0.76 to 0.99).

**Follow-up.** Mean follow-up was 29 ± 18 months. No deaths occurred. A MACE occurred in 9 (9%) and in 13 (13%) patients after 12 and 36 months, respectively. These MACE were related to 22 (9.2%) vessels. Among them, 8 (6.3%) MACE were related to the initially deferred stenosis, whereas 14 (12.3%) MACE were due to the initially treated artery. Only one MACE was related to a stenosis with an FFR between 0.75 and 0.80.

At their last follow-up, 47% of patients received statins, 55% beta-blockers, and 25% angiotensin-converting enzyme inhibitors. Table 2 displays details of the MACE. The occurrence of events as a function of time is shown in Figure 2. There was no difference between treated and deferred arteries.

**Table 2.** Characteristics of Patients in Whom a MACE Was Observed During Follow-Up

<table>
<thead>
<tr>
<th>Gender/Age</th>
<th>Indication</th>
<th>Vessel</th>
<th>FFR</th>
<th>%DS</th>
<th>MLD (mm)</th>
<th>Type of MACE</th>
<th>Follow-Up (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/74</td>
<td>Stable</td>
<td>RCA</td>
<td>0.88</td>
<td>30</td>
<td>1.77</td>
<td>TVR</td>
<td>1</td>
</tr>
<tr>
<td>M/41</td>
<td>Stable</td>
<td>RCA</td>
<td>0.82</td>
<td>45</td>
<td>1.21</td>
<td>TVR</td>
<td>4</td>
</tr>
<tr>
<td>M/75</td>
<td>Stable</td>
<td>RCA</td>
<td>0.87</td>
<td>38</td>
<td>1.59</td>
<td>TVR</td>
<td>6</td>
</tr>
<tr>
<td>M/82</td>
<td>Stable</td>
<td>RCA</td>
<td>0.86</td>
<td>46</td>
<td>1.71</td>
<td>TVR</td>
<td>8</td>
</tr>
<tr>
<td>M/62</td>
<td>Stable</td>
<td>LAD</td>
<td>0.87</td>
<td>58</td>
<td>1.59</td>
<td>MI + TVR</td>
<td>9</td>
</tr>
<tr>
<td>M/69</td>
<td>Stable</td>
<td>LCx</td>
<td>0.91</td>
<td>54</td>
<td>1.02</td>
<td>TVR</td>
<td>13</td>
</tr>
<tr>
<td>M/54</td>
<td>ACS</td>
<td>LAD</td>
<td>0.76</td>
<td>62</td>
<td>0.64</td>
<td>TVR</td>
<td>19</td>
</tr>
<tr>
<td>F/56</td>
<td>ACS</td>
<td>LAD</td>
<td>0.9</td>
<td>50</td>
<td>1.5</td>
<td>TVR</td>
<td>26</td>
</tr>
<tr>
<td>M/74</td>
<td>Stable</td>
<td>RCA</td>
<td>0.57</td>
<td>75</td>
<td>0.8</td>
<td>TVR</td>
<td>3</td>
</tr>
<tr>
<td>M/70</td>
<td>Stable</td>
<td>LAD</td>
<td>0.33</td>
<td>79</td>
<td>0.6</td>
<td>TVR</td>
<td>3</td>
</tr>
<tr>
<td>M/70</td>
<td>Stable</td>
<td>LAD</td>
<td>0.55</td>
<td>67</td>
<td>0.67</td>
<td>TVR</td>
<td>4</td>
</tr>
<tr>
<td>M/70</td>
<td>Stable</td>
<td>LCx</td>
<td>0.73</td>
<td>50</td>
<td>1.0</td>
<td>TVR</td>
<td>6</td>
</tr>
<tr>
<td>F/58</td>
<td>Stable</td>
<td>LCx</td>
<td>0.73</td>
<td>50</td>
<td>1.0</td>
<td>TVR</td>
<td>6</td>
</tr>
<tr>
<td>F/80</td>
<td>ACS</td>
<td>RCA</td>
<td>0.65</td>
<td>57</td>
<td>1.38</td>
<td>TVR</td>
<td>8</td>
</tr>
<tr>
<td>M/55</td>
<td>ACS</td>
<td>LAD</td>
<td>0.65</td>
<td>57</td>
<td>1.38</td>
<td>TVR</td>
<td>17</td>
</tr>
<tr>
<td>F/67</td>
<td>Stable</td>
<td>RCA</td>
<td>0.63</td>
<td>76</td>
<td>1.08</td>
<td>TVR</td>
<td>22</td>
</tr>
<tr>
<td>F/57</td>
<td>Stable</td>
<td>RCA</td>
<td>0.72</td>
<td>63</td>
<td>1.0</td>
<td>TVR</td>
<td>25</td>
</tr>
<tr>
<td>F/56</td>
<td>ACS</td>
<td>LCx</td>
<td>0.51</td>
<td>46</td>
<td>0.82</td>
<td>TVR</td>
<td>26</td>
</tr>
<tr>
<td>F/44</td>
<td>ACS</td>
<td>LCx</td>
<td>0.29</td>
<td>61</td>
<td>0.8</td>
<td>MI + TVR</td>
<td>27</td>
</tr>
</tbody>
</table>

Shaded area shows deferred-vessel group; unshaded area shows treated vessels.

ACSn = acute coronary syndrome; MACE = major adverse cardiac events; MI = myocardial infarction; NM = not measured; TVR = target vessel revascularization; other abbreviations as in Table 1.
implantation after one year (9). Taken together these data MI and repeat revascularization was 85.6% after SESing coronary artery (LAD) involvement, the survival free of patients with multivessel coronary disease. Among the 99 registry RESEARCH of sirolimus-eluting stents (SES) for event rates reported after 12 months in the “real-world” deferred artery. These numbers are similar to the clinical myocardial infarction occurred in relation to the initially untreated required PCI in 5.9% of cases after one year and in 6.3% after three years. No deaths occurred and only one myocardial infarction occurred in relation to the initially deferred artery. These numbers are similar to the clinical event rates reported after 12 months in the “real-world” registry RESEARCH of sirolimus-eluting stents (SES) for patients with multivessel coronary disease. Among the 99 patients with multivessel disease and left anterior descending coronary artery (LAD) involvement, the survival free of MI and repeat revascularization was 85.6% after SES implantation after one year (9). Taken together these data suggest that, in patients with two- or three-vessel disease, it is at least as appropriate to defer a hemodynamically non-significant stenosis than to perform PCI.

FFR in patients with one-vessel disease and in left main disease. Studies have shown that in patients, scheduled for one-vessel PCI, it was safe to defer the intervention when the FFR was ≥0.75. A multicentric randomized trial included a total of 325 patients who were scheduled for single-vessel PCI but without any non-invasive stress testing (6). The FFR values ≥0.75 were measured in 181 patients. Among these patients, event-free survival after one year was 92% when PCI was deferred and 89% when PCI was actually performed. After two years the corresponding values were 89% and 83%, respectively. A large overlap existed in the values of %DS observed in vessels with an FFR <0.75 and in those with an FFR ≥0.75, indicating that angiography is not able to distinguish hemodynamically significant from non-significant stenoses. In addition, the percentage of patients free from angina after two years was similar in the two groups. These results indicated that there is no benefit in treating the stenoses with an FFR ≥0.75.

Two studies have extended these results to moderate left main disease (10,11). Both concluded that when FFR is ≥0.75, no revascularization of the left main stenosis should be proposed. Both studies, however, are based on small numbers of “deferred” patients, and the values of FFR should be applied with caution to individual patients. In addition, isolated left main stenoses are rare, and the value of FFR measured in a left main stenosis is often influenced by the presence of other stenoses in the LAD or in the left circumflex artery (LCx).

FFR for clinical decisions in multivessel disease. In patients with multivessel disease the spatial resolution of non-invasive testing is poor. Only a minority of patients with severe three-vessel disease exhibit a “multivessel pattern” at gated single-photon emission computed tomography myocardial perfusion imaging (5). In contrast, FFR performed in all three vessels provides the operator in the catheterization laboratory with precise functional information that cannot be obtained from non-invasive testing.

Chamuleau et al. (12,13) analyzed the clinical follow-up of patients with multivessel disease in whom the myocardial SPECT perfusion imaging showed no perfusion defect in a region supplied by an angiographically intermediate stenosis and in which FFR had been measured. The decision to perform PCI was based on the results of the perfusion scintigram. The investigators showed that the event rate was significantly higher (relative risk of 3.1) when, on the basis of a normal perfusion scan, no revascularization was performed despite an FFR <0.75. In other words, FFR is superior in detecting a hemodynamically significant stenosis in patients with multivessel disease at angiography.

In addition, Chamuleau’s data indicate that when FFR is <0.75, PCI is warranted even though the perfusion scan is normal in the region supplied by the PCI artery. Botman et al. (14) recently reported on a “tailored approach” based on FFR measurements in patients with multivessel disease. Patients were treated by coronary artery bypass grafting (n = 87) when the FFR is <0.75 in all three arteries or in two arteries including the proximal LAD. When only one or two stenoses (not including the proximal LAD) were physiologically significant, PCI (bare metal stent implantation) of these stenoses was performed (n = 63). After two years, there was no difference in death and MIs. More importantly, and in contrast to previous studies comparing surgery and PCI in patients with multivessel disease, the need for repeat revascularization, along with angina status, was similar in both groups. This “tailored approach” yielded similar results as the surgical group of the ARTS I study (15). In the present study, the retrospective character of the analysis might contribute to explain the particularly low number of events for patients with multivessel disease.

**Figure 2.** Cumulative major adverse cardiac events (combined end points of death, myocardial infarction, and target vessel revascularization) rate curves (Kaplan-Meier) for treated, deferred vessels, and for the entire patient population.

arteries (log rank test; p = 0.64). No differences existed in the MACE rate between stable and unstable patients (19% vs. 28%, p = 0.56).

**DISCUSSION**

The results of the present extend the usefulness of FFR in clinical decision making to patients with multivessel disease. The strategy of not performing PCI on stenoses associated with an FFR ≥0.75 while treating only stenoses that are hemodynamically significant appears safe. In these patients, arteries with an FFR ≥0.75 and that were initially left untreated required PCI in 5.9% of cases after one year and in 6.3% after three years. No deaths occurred and only one myocardial infarction occurred in relation to the initially deferred artery. These numbers are similar to the clinical event rates reported after 12 months in the “real-world” registry RESEARCH of sirolimus-eluting stents (SES) for patients with multivessel coronary disease. Among the 99 patients with multivessel disease and left anterior descending coronary artery (LAD) involvement, the survival free of MI and repeat revascularization was 85.6% after SES implantation after one year (9). Taken together these data suggest that, in patients with two- or three-vessel disease, it is at least as appropriate to defer a hemodynamically non-significant stenosis than to perform PCI.
CONCLUSIONS

In patients with multivessel disease at angiography, FFR allows distinction between functionally significant and non-significant stenoses. The PCI of the latter can be safely deferred, even when initially planned on the basis of the angiogram. In more general terms, these findings illustrate the difference between anatomical and functional multivessel disease, the therapeutic implications of this difference, and the safety and effectiveness of treatment of multi-vessel disease based on functional assessment.

Reprint requests and correspondence: Dr. Bernard De Bruyne, Cardiovascular Center Aalst, OLV Clinic, Moorselbaan, 164, B-9300 Aalst, Belgium. E-mail: bernard.de.bruyne@olvz-aalst.be.

REFERENCES