The Prognostic Significance of 50% Coronary Stenosis in Medically Treated Patients with Coronary Artery Disease

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SUMMARY In this study we determined the prognostic significance of 50% coronary stenosis in 1183 medically treated patients with coronary artery disease. Clinical outcome was measured by survival and event-free (freedom from death and infarction) rates. Significant disease was first defined as 75% or greater narrowing. In 225 patients with less than 75% narrowing of all vessels, including 68 patients with 50% stenosis of at least one vessel, the 3-year survival rate was 100%. Patients with one, two or three significantly (75% or greater) stenosed vessels had the same outcome as patients with one, two or three diseased vessels without additional 50% stenosed vessels. Significant disease was then defined as 50% or greater narrowing. Patients with significant (50% or greater) stenosis of one, two and three vessels and the left main coronary artery were divided into those in whom all diseased vessels were 75% or greater stenosed (group A) and those in whom at least one vessel was only 50% stenosed (group B). In every category, group B patients had a better outcome than group A patients. The largest differences were in three-vessel and left main coronary artery disease. Group B patients also had lower prevalences of previous infarction and abnormal left ventricular function than group A patients. In three-vessel disease, the differences in outcome between group A and group B patients remained significant in multivariable analyses with descriptors of left ventricular function. Thus, 50% coronary stenosis is associated with less risk than 75% or greater stenosis even after adjustment for left ventricular function. When 50% stenosis is defined as significant, subsets based on the number of diseased vessels may be heterogenous with respect to baseline characteristics and outcome.

THE EXTENT of coronary artery involvement is an important determinant of outcome in coronary artery disease.1-7 Survival is closely related to the presence or absence of left main coronary artery (LMCA) disease and the number of diseased vessels.1-7 To determine the extent of coronary involvement, the degree of stenosis considered significant must be defined. In clinical studies of coronary disease, some groups have defined 50% narrowing of the luminal diameter as significant,6,8,9 but others have required 70-80% stenosis.7,10-15 Evidence supporting these definitions has come from acute experiments in which coronary blood flow or myocardial perfusion has been examined under resting and high-flow conditions.16-18 There is little information available about the effect of the degree of stenosis on clinical outcome. In a recent study from this laboratory,20 Conley et al. concluded that the presence of 50% LMCA stenosis did not affect 3-year survival in patients with 75% or greater stenosis of the three other major vessels. Studies from the Cleveland Clinic4 have shown a relationship between the degree of stenosis and survival in single-vessel disease. In this study, we sought to determine the effect of 50% coronary stenosis on clinical outcome across all degrees of vessel involvement and the prognostic implications of defining 50% coronary stenosis as significant.

Methods

Population

From January 1973 to January 1978, 2389 patients underwent cardiac catheterization for suspected ischemic heart disease at Duke University Medical Center. This figure does not include patients who had prior revascularization procedures, congenital heart disease, hypertrophic cardiomyopathy or valvular heart disease other than mitral insufficiency thought to be secondary to ischemic heart disease. Of the 2389 patients, 658 had normal coronary arteries and 548 patients with coronary disease were treated surgically. The 1183 patients with coronary disease who were treated medically form the basis of this report.

Patient Selection

Decisions about catheterization and therapy were made by the individual physicians in conjunction with
Lesions in the anterolateral, posterior left ventricular and marginal branches of the three major coronary arteries were only defined as obstruction of their associated major vessels if the branches were large enough to accept a bypass graft and the narrowing exceeded the worst lesion in the associated major artery. In a left-dominant circulation in which the posterior surface of the heart was supplied by the LCA, significant obstruction of the proximal LCA was counted as two diseased vessels if the obstruction jeopardized blood supply to both the lateral and posterior surfaces of the heart. In this situation, RCA stenosis did not contribute to the count of diseased vessels. Patients with 50% or greater LMCA stenosis were analyzed separately.

Follow-up

All patients were followed 6 and 12 months after cardiac catheterization and annually thereafter. Follow-up information was obtained by a staff cardiologist during a clinic visit or by a research associate by telephone. Follow-up was 99% complete. At each interval, functional status was ascertained and new hospitalizations were documented. The patient's physician was contacted for further information when a patient had died or if there was any possibility that a hospitalization had been related to an ischemic event. The physician was asked to confirm his diagnosis for each event, and if relevant, to provide discharge summaries and documentation of each cardiac event. Fatal and nonfatal myocardial infarctions were documented by the standard electrocardiographic and enzyme criteria. A myocardial infarction was considered to be nonfatal if the patient was discharged from the hospital.

Data Analysis

Cumulative survival rates from the time of cardiac catheterization were calculated by standard life-table methods. The cumulative rate at which patients remained free from both death and nonfatal infarction (event-free rate) was calculated in the same manner as the survival rate by treating both death and nonfatal infarction as terminating events.

The significance of differences in outcome was tested by the Cox regression model. Chi-square statistics for the comparison of outcomes within each anatomic category were obtained by comparing the Cox regression parameters for two groups being compared. This approach produced a comparison of overall outcome rather than an interval-by-interval comparison. The time to the first event was used as the dependent variable in the Cox model analysis of event-free rates. The significance of differences in the prevalence of baseline characteristics was tested by chi-square analysis or Fisher's exact test if there were fewer than five patients in a cell.

To determine the effect of 50% stenosis on outcome, significant disease was first defined as 75% or greater stenosis. Patients with no, one, two or three significantly stenosed vessels were divided into those...
with no 50% lesions in other vessels, and those with one or more other vessels, including the LMCA, with 50% lesions. Survival and event-free rates were compared. Thus, in patients with no significant disease (no 75% or greater stenosed vessels), patients who had one or more 50% stenosed vessels were compared with those who had no 50% stenosed vessels. Patients who had one significantly diseased vessel and one or more 50% stenosed vessels were compared with those who had one-vessel disease and no additional 50% stenosed vessels. Patients who had two significantly diseased vessels and 50% stenosis of the third vessel were compared with those who had two-vessel disease and no 50% stenosis in the third vessel. Patients who had three-vessel disease and 50% LMCA disease were compared with those who had three-vessel disease and no 50% LMCA disease. The same comparisons were also made excluding patients who had 50% LMCA lesions. Patients with 75% or greater LMCA stenosis were not considered in this analysis.

To determine the prognostic implications of defining 50% coronary stenosis as significant, the same population was classified using 50% or greater stenosis to define significant disease. Patients with significant (50% or greater) stenosis of one, two and three vessels and the LMCA were divided into those in whom all significantly diseased vessels were 75% or more stenosed (group A) and those in whom one or more significantly stenosed vessels were only 50% stenosed (group B). Thus, group B patients with one-vessel disease had 50% stenosis of one vessel, group B patients with two- or three-vessel disease had various combinations of 50% and 75% or greater stenosed vessels and group B patients with LMCA disease had 50% stenosis of the LMCA. Within the one-, two- and three-vessel and LMCA disease categories, survival and event-free rates of group A and group B patients were compared.

The baseline comparability of group A and group B was determined by comparing the prevalences of 14 prognostically important characteristics within the one, two and three diseased vessel categories. To determine whether the differences in outcome between group A and group B patients with three-vessel disease could be entirely accounted for by differences in left ventricular function, a multivariable analysis was performed in which descriptors of coronary anatomy and left ventricular function were analyzed jointly using the Cox regression model.28

Results

One hundred seventy-one of 1183 patients died from cardiovascular causes and 83 suffered at least one nonfatal infarct. Eight noncardiovascular deaths were excluded from further analysis by withdrawing (censoring) the patients alive at the time of death.

Significant Stenosis Defined as
75% or Greater Narrowing

The distribution of patients with no, one-, two- and three-vessel and LMCA disease when significant stenosis was defined as 75% or greater narrowing is shown in table 1. Patients with no, one, two and three diseased vessels were divided into those with one or more additional vessels with 50% stenosis and those with no additional 50% stenoses (table 2). Of the 225 patients with no significant stenoses, 68 had one or more 50% stenosed vessels and the remaining 157 had no vessels with 50% (or greater) stenosis. Of the 265 patients with one-vessel disease, 93 had additional 50% stenosed vessels; of the 240 patients with two-vessel disease, 83 had additional 50% stenosed vessels, and of the 405 patients with three-vessel disease, 39 had additional 50% LMCA stenosis. The distribution of 50% stenosed vessels within the no, one-, two- and three-vessel disease categories is shown in table 3. There were no patients with three 50% stenosed vessels.

The cumulative survival rates for patients with one or more additional 50% stenosed vessels and for patients without additional 50% stenosed vessels are compared within the no, one-, two- and three-vessel disease categories in figure 1. Additional 50% stenosed vessels had no effect on cumulative survival rates (p > 0.2) in any category of significant disease. In the 225 patients who had no 75% or greater stenosed vessels, the 3-year survival rate was 100%, regardless of whether they had 50% stenosed vessels. The only death among these 225 patients occurred at 4 years in a patient with 50% stenosis of the LCA. In one-vessel disease, the 3-year survival rates were 95% in patients with additional 50% stenosed vessels and 94% in patients with no additional 50% stenosed vessels. In two-vessel disease, the 3-year survival rate was 85% in

| Table 1. The Distribution of 1183 Patients According to the Number of Diseased Vessels When Significant Stenosis Was Defined as 75% or Greater Narrowing |
|---|---|---|---|---|
| Number of vessels with significant (≥ 75%) stenosis | Left main coronary artery |
| Number of patients | 225 | 265 | 240 | 405 | 48 |

| Table 2. Patients with No, One, Two and Three Significantly Stenosed (≥ 75%) Vessels Divided into Those Without Additional 50% Stenosed Vessels and Those with Additional 50% Stenosed Vessels |
|---|---|---|---|
| Number of vessels with significant (≥ 75%) stenosis | 0 | 1 | 2 | 3 |
| Number of patients without additional 50% stenosed vessels | 157 | 172 | 157 | 366 |
| Number of patients with additional 50% stenosed vessels | 68 | 93 | 83 | 39* |

*The 39 patients with three-vessel disease and an additional 50% stenosed vessel all had 50% left main coronary artery stenosis.
patients with additional 50% stenosed vessels, including 11 patients with 50% LMCA stenosis, and 90% in patients with no additional 50% stenosed vessels. In three-vessel disease, the difference, still insignificant, was reversed: the 3-year survival rate was 81% in those with additional 50% LMCA stenosis and 75% in those without 50% LMCA stenosis.

Cumulative event-free rates are compared in figure 2. Again, there were no significant differences between those with and those without additional 50% stenosed vessels in the one-, two- or three-vessel disease categories. The maximum difference was in three-vessel disease, where the 3-year event-free rate was 71% in patients with additional 50% LMCA stenosis compared with 63% in those without additional 50% LMCA stenosis. In the 225 patients who had less than 75% stenosis of all vessels, there was one nonfatal infarct, which occurred in a patient with less than 50% stenosis of all coronary vessels.

Eleven of 57 patients who had 50% LMCA stenosis died. Of these 11, four had two other diseased vessels and seven had three other diseased vessels. When the patients with 50% LMCA stenosis were excluded from the no, one- and two-vessel disease categories, the differences in survival between those who did and did not have additional 50% stenosed vessels remained insignificant (fig. 3). The difference in event-free rates also remained insignificant. Because patients with 50% LMCA stenosis were excluded, patients with three-vessel disease are not shown in figure 3.

**Significant Stenosis Defined as 50% or Greater Narrowing**

The distribution of patients with significant stenosis of no, one, two and three vessels and the LMCA when significant stenosis was defined as 50% or greater...
FIGURE 3. The cumulative survival rates of patients with no, one and two significantly (75% or greater) stenosed vessels. Within each category, patients were divided into those with one or more additional 50% stenosed vessels and those with no additional 50% stenosed vessels, but patients with 50% left main coronary artery stenosis were excluded from the analysis.

Table 4. The Distribution of 1183 Patients According to the Number of Diseased Vessels When Significant Stenosis Was Defined as 50% or Greater Narrowing

<table>
<thead>
<tr>
<th>Number of vessels with significant (≥50%) stenosis</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>Left main coronary artery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>157</td>
<td>226</td>
<td>239</td>
<td>456</td>
<td>105</td>
</tr>
</tbody>
</table>

LMCA lesions (group B) and those with 75% or greater lesions (group A).

Survival

The cumulative survival rates of group A and group B patients with significant (50% or greater) stenosis of one, two and three vessels and the LMCA are shown in figure 4. The survival rate of group A patients with narrowing is shown in table 4. Patients with one-, two-, three-vessel and LMCA disease were divided into those in whom all diseased vessels were 75% or greater stenosed (group A) and those in whom one or more diseased vessels had only a 50% stenosis as the most severe lesion (group B). Table 5 shows the distribution of patients in group A and group B. Patients in group B who had one-vessel disease had 50% stenosis of one vessel, but patients with two- and three-vessel disease in group B had various combination of 50% stenosed vessels and 75% or greater stenosed vessels. For example, of the 90 patients with three significantly (50% or greater) stenosed vessels, 72 had one 50% stenosed vessel and two 75% or greater stenosed vessels, 18 had two 50% stenosed vessels and one 75% or greater stenosed vessel and none had three 50% stenosed vessels. Patients with LMCA disease were divided into those with 50%
Each category, group B patients had a lower prevalence of previous myocardial infarction, resting electrocardiographic abnormalities and abnormal ventricular function than group A patients. Many of the differences in prevalence were significant. The lower prevalence of abnormal ejection fraction in group B patients was significant ($p < 0.05$) in every anatomic category.

**Multivariable Analysis**

The results of the multivariable Cox model analysis of outcome in patients with three significantly (50% or greater) stenosed vessels are shown in Table 7. The presence of one or more 50% stenosed vessels remained a significant ($p < 0.05$) predictor of a better outcome (survival and events) after adjustment for differences in left ventricular ejection fraction. Because left ventricular ejection fractions were not measured in 67 of the patients with three-vessel disease, the multivariable analysis was repeated using descriptors of left ventricular function available in every patient: abnormal left ventricular contraction, diffusely abnormal left ventricular contraction, left ventricular end-diastolic pressure and arteriovenous oxygen difference. The presence of one or more 50% stenosed vessels remained a significant predictor of an improved outcome after adjustment for all of these descriptors of left ventricular function.

**Discussion**

The evidence that 50% coronary artery luminal diameter narrowing is hemodynamically significant comes largely from acute animal experiments in which coronary flow or myocardial perfusion was examined under high-flow conditions.\textsuperscript{16}–\textsuperscript{19}, \textsuperscript{29}–\textsuperscript{29} Under resting conditions, coronary flow is generally not affected until the degree of stenosis approaches 75%,\textsuperscript{16}–\textsuperscript{19}, \textsuperscript{27}–\textsuperscript{29} Parallel observations in man have yielded similar findings. In acute human experiments, myocardial perfusion defects have been shown by radionuclide imaging under high-flow conditions in patients with 60% or less coronary stenosis.\textsuperscript{31, 32} Studies during open heart surgery, however, failed to show that occlusion of a bypass graft decreased myocardial perfusion\textsuperscript{32} or produced reactive hyperemia\textsuperscript{33} unless the lesion in the bypassed vessel exceeded 75% stenosis.

In this study of clinical outcome in relation to the degree of coronary stenosis, 50% coronary artery stenosis alone was less likely to be associated with death and nonfatal infarction than 75% or greater stenosis. In fact, over the 4-year period of this study, 50% coronary stenosis was not shown to cause any increase in risk. For example, patients with 75% or greater stenosis of two vessels and 50% stenosis of the third vessel had survival and event-free rates comparable not to patients with three-vessel disease but to patients with two-vessel disease. Consequently, defining 50% coronary stenosis as significant distinguished groups that were heterogeneous with respect to clinically important baseline characteristics and outcome.
The fact that acute studies suggest the opposite conclusion about the importance of 50% lesions is not surprising. Many variables, not all of which are known, influence the relationship between the degree of stenosis and clinical outcome. Among those that have been considered are the length of the coronary lesion and the degree of collateralization.

The strongest argument that lesions causing less than 75% coronary narrowing are not prognostically significant over 3-4 years comes from the group of 225 patients who had coronary disease but no major vessels with 75% or greater stenosis. There was only one death (at 4 years) and one nonfatal infarct in this group, which included 68 patients with 50% stenosis of at least one artery. This group of 225 patients was virtually free from any bias introduced by the exclusion of surgical patients, because only four patients were excluded from it by selection for surgery.

Fifty percent coronary stenosis was also associated with a more benign history preceding cardiac catheterization. The important differences in baseline characteristics between group A and group B patients with the same number of 50% or greater stenosed vessels could be related to previous myocardial infarction and its consequences. Group B patients, those who had at least one 50% stenosed vessel, had lower prevalences of resting ECG changes and the clinical, chest x-ray, ventriculographic and hemodynamic manifestations of impaired left ventricular function. These differences in baseline ventricular function probably contributed to the differences in outcome. However, the multivariable analysis showed that when differences in baseline ventricular function were considered in patients with three 50% or greater stenosed vessels, the effect of 50% stenosed vessels on outcome remained significant.

The similar outcomes of group A and group B patients with two diseased (50% or greater) vessels can be explained by the finding that with the 75% definition, the outcomes of patients with one- and two-vessel disease were not different. The majority of group B patients with two-vessel disease did have one 75% or greater stenosed vessel.

The better survival of patients with 50% LMCA stenosis compared with 75% or greater LMCA

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**Table 6. Prevalence (%) of Baseline Characteristics in Group A and Group B Patients with One, Two and Three ≥ 50% Stenosed Vessels**

<table>
<thead>
<tr>
<th></th>
<th>One vessel</th>
<th>Two vessel</th>
<th>Three vessel</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>Group A</td>
</tr>
<tr>
<td>Age &gt; 50 years</td>
<td>40 (172 pts)</td>
<td>55 (54 pts)</td>
<td>48 (157 pts)</td>
</tr>
<tr>
<td>Duration of symptoms</td>
<td>&gt; 2 years</td>
<td>33 (26 pts)</td>
<td>41 (15 pts)</td>
</tr>
<tr>
<td>Typical angina</td>
<td>39 (25 pts)</td>
<td>39 (25 pts)</td>
<td>58 (35 pts)</td>
</tr>
<tr>
<td>Progressive chest pain</td>
<td>30 (20 pts)</td>
<td>40 (26 pts)</td>
<td>29 (15 pts)</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous myocardial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infarction</td>
<td>45 (25 pts)</td>
<td>11 (6 pts)</td>
<td>55 (35 pts)</td>
</tr>
<tr>
<td>Ventricular gallop</td>
<td>4 (2 pts)</td>
<td>0 (0 pts)</td>
<td>6 (4 pts)</td>
</tr>
<tr>
<td>Cardiomegaly on chest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x-ray</td>
<td>10 (6 pts)</td>
<td>9 (5 pts)</td>
<td>17 (10 pts)</td>
</tr>
<tr>
<td>Q waves on ECG</td>
<td>26 (16 pts)</td>
<td>15* (9 pts)</td>
<td>45 (28 pts)</td>
</tr>
<tr>
<td>Resting ST-T-wave</td>
<td>41 (24 pts)</td>
<td>24† (15 pts)</td>
<td>47 (28 pts)</td>
</tr>
<tr>
<td>Changes</td>
<td>13 (8 pts)</td>
<td>2† (1 pts)</td>
<td>29 (18 pts)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 40%</td>
<td>13 (8 pts)</td>
<td>11 (7 pts)</td>
<td>25 (16 pts)</td>
</tr>
<tr>
<td>Arteriovenous oxygen</td>
<td>15 (9 pts)</td>
<td>11 (7 pts)</td>
<td>15† (9 pts)</td>
</tr>
<tr>
<td>Differences &gt; 5 vol%</td>
<td>13 (8 pts)</td>
<td>11 (7 pts)</td>
<td>25 (16 pts)</td>
</tr>
<tr>
<td>LV end-diastolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pressure &gt; 17 mm Hg</td>
<td>4 (2 pts)</td>
<td>2 (1 pts)</td>
<td>14 (8 pts)</td>
</tr>
<tr>
<td>Diffusely abnormal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>contraction</td>
<td>2 (1 pts)</td>
<td>0 (0 pts)</td>
<td>10 (6 pts)</td>
</tr>
</tbody>
</table>

* p < 0.1.
†p < 0.05.

Abbreviations: NYHA = New York Heart Association; LV = left ventricular.

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**Table 7. Results of Multivariable Cox Model Analysis in Patients with Three Significantly Stenosed (≥ 50%) Vessels**

<table>
<thead>
<tr>
<th></th>
<th>Adjusted chi square for survival</th>
<th>Adjusted chi square for events</th>
</tr>
</thead>
<tbody>
<tr>
<td>One or more</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50% stenosed vessels</td>
<td>4.11</td>
<td>4.12</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>65.38</td>
<td>42.05</td>
</tr>
</tbody>
</table>

Chi square > 3.84, p < 0.05; chi square > 6.63, p < 0.01.
stenosis has been previously reported in a larger population. The present study shows that this difference is maintained when nonfatal myocardial infarction is included in the outcome. Although an association between 50% LMCA stenosis and increased risk in patients who had two vessels with 75% or greater stenosis could be inferred from our results, we believe this was a chance relationship. Four of 11 patients with this combination of lesions died. However, 50% LMCA stenosis did not affect the outcome in three-vessel disease in this study or in the larger series, and in the present study, there were no deaths among the seven patients who had 50% LMCA stenosis and fewer than two other diseased vessels.

Over a longer follow-up period, 50% lesions might progress to 75% or greater stenosis and have a significant effect on outcome. In longitudinal angiographic studies of coronary lesions, disease progression has been unpredictable. Thus, rather than counting 50% stenosis as significant when first documented, to allow for possible progression, we recommend classifying patients according to the number of 75% or greater stenosed vessels. Future studies of intermediate and long-term outcome in patients with 50% stenosed vessels may more clearly define the pattern of the progression of 50% stenosis over time.

General acceptance of the results of this study will depend on the accuracy and reproducibility of the coronary angiography. In a study published from this center involving patients catheterized in a period just before the commencement of this study, angiographic estimates of stenosis and autopsy measurements were compared. There was 79% agreement for lesions causing 75% or greater narrowing. The majority of errors was due to underestimation. The accuracy of estimating lesions causing less than 75% stenosis was not examined. In a later study, two angiographers estimated the presence of 75% or greater stenoses with 88% and 89% accuracy in comparison with autopsy findings and with agreement in 86% of 340 segments (unpublished results). These results are comparable to the accuracy and reproducibility of coronary angiography reported from other centers.

Patients with coronary disease are usually stratified by important prognostic variables. The results of this study indicate that if 50% stenosis is defined as significant, subsets based on the number of diseased vessels may be heterogenous with respect to baseline characteristics and outcome. Additional stratification by left ventricular function may reduce this heterogeneity. However, in this study, the differences in outcome in patients with three-vessel disease were not entirely accounted for by left ventricular function.

Despite varying definitions of significant stenosis, there has been reasonable agreement among the results of recently reported outcome studies. The effect on outcome of combining patients with 50% stenosis with patients with 75% or greater stenosis will obviously depend on the relative proportions of the two lesions. Until more information is available about the prevalence of 50% stenosis in other series, our interpretation of this investigation is that studies using different definitions of significant stenosis must be compared with caution. Further, the difference in definition is likely to most affect the comparison of individual subsets, particularly three-vessel disease and LMCA disease.

Acknowledgments

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