Prognosis of 1000 Young Women Studied by Coronary Angiography

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SUMMARY One thousand women younger than age 50 years suspected of having coronary disease were followed for at least 5 years (average 8.4 years) to determine their course after coronary arteriography. Three patients were lost to follow-up; all had normal arteriograms. The survival rate was 96.9% at 5 years for 761 patients who had less than 50% narrowing of any artery. One patient who had coronary ectasia died within 5 years, and one woman who had minimal lesions suffered sudden death. Seven of 727 women who had normal arteries or less than 30% narrowing of any artery had coronary events (death, myocardial infarction, bypass operation for progressive disease), and six of 34 women who had 30 to almost 50% obstruction of at least one artery had coronary events. Calculations of survival for 236 women who had severe coronary lesions were affected by withdrawal for operation. Five-year survival was 74%.

SYMPTOMATIC OBSTRUCTIVE DISEASE of the coronary arteries is less common in premenopausal women than in men of comparable age.1 A report of 1000 women younger than 50 years who had coronary arteriography indicated that the clinical diagnosis is often difficult to establish.2 Most of the patients in this report had no serious obstructive disease. If severe coronary obstruction was frequently missed arteriographically, there should have been appreciable cardiac mortality in those women thought to be free from severe organic lesions. This study was designed to provide a 5-year minimum follow-up of 1000 patients, recognizing that a number of those with severe lesions would drop out during the 5-year period because of surgical intervention.

Methods

The clinical characteristics of 1000 women younger than age 50 years who were studied by selective coronary arteriography between 1961 and 1968 have been reported.2 All had been suspected of having coronary disease, although only 222 had typical angina, defined as pain or a pain variant in the upper half of the body induced by walking and relieved promptly (within 15 minutes) by rest. Nine hundred seventy-six were studied because of chest pain and the others for other indications, usually electrocardiographic abnormalities.

Patients who had congenital heart disease, valvular abnormalities, or subaortic stenosis were excluded, but hypertension and cardiomyopathy were not grounds for exclusion if coronary disease was suspected. The data were reviewed specifically for the study. Computers were used only for analysis.

Disagreements in arteriographic interpretations were resolved among arteriographers before data entry. An attempt was made to follow each patient for at least 5 years or until death and to determine the course after arteriography. The objective was achieved in 997 patients and in all 236 who had at least 50% decrease in the diameter of one or more major coronary arteries. Three patients thought to have entirely normal coronary arteries could not be traced. The average follow-up period was 8.4 years; the maximum was 173 months.

Clinical records were reviewed or physicians, patients or patients’ families were contacted in writing or by telephone, without knowledge of the catheterization findings. Inquiry was made relative to chest pain, the occurrence of myocardial infarction, subsequent coronary arteriography or cardiac operation, and, in appropriate cases, the cause of death. Pain induced by walking was of specific interest. An attempt was made to document myocardial infarction; only transmural myocardial infarction, manifested by development of new abnormal Q waves or QS deflections, was considered typical. The criteria for nontransmural infarction are less rigid and not universally accepted. Death thought to be due to coronary disease, myocardial infarction and arteriographically proved development or progression of coronary obstruction to at least 50% luminal diameter and at least 20% more narrowing than in the original arteriogram were considered coronary events. The cause of death was determined as accurately as possible and supporting evidence for the certified cause was sought. Sudden death was considered to be death within 1 hour after the onset of the terminal illness in the absence of recent striking change of symptoms, or unwitnessed death of a patient whose health had been considered stable. These two categories were kept separate, but both were coded as sudden death. The survival curves were constructed by the method of Cutler and Ederer.3 Patients were considered dropouts at the date of any cardiac operation; 98 of 110 patients were operated on in the first year, usually soon after catheterization. Comparison of subsets was done by the chi-square method with Yates' correction formula.

All clinical records of patients who had severe cor-
Coronary disease were reviewed to determine if the patient had been a candidate for coronary bypass surgery according to the following criteria: at least 60% narrowing, in an area sufficiently proximal to permit bypassing, of a major coronary artery that was without severe distal disease and supplied contractile myocardium. Classification was done without knowledge of the patient’s clinical outcome.

The original coding of angina pectoris was based on the history of discomfort of some type other than dyspnea, the distress being located in the upper half of the body or arms and being induced by walking and relieved within 15 minutes by enforced rest. This restrictive definition was thought to be a relatively specific but an insensitive one. For correlative purposes, specificity was considered preferable.

Results

Normal or Mild Coronary Lesions

A 5-year minimum and 8.4-year average for survivor follow-up was accomplished in 761 of 764 women who had less than 50% narrowing of the diameter of any major artery. Thirty-four of the 761 had moderate (30% to almost 50%) narrowing of the diameter, 644 had normal arteries and 83 had minimal irregularities. The 5-year gross survival after catheterization of the 761 women without severe obstructive disease was 96.9 ± 1.1% (± sem) and the 10-year survival was 94.2 ± 1.3%. Forty of the 761 women died during follow-up, 15 of heart disease, although only five deaths were attributed to coronary artery disease (table 1). Myocardial disease was considered to be the cause of death in nine patients and mitral prolapse in one patient.

Three cases require special comment. A percutaneous myocardial biopsy was done 3 days after catheterization in case 1; cardiac tamponade resulted and death followed operation for relief of tamponade. Postmortem examination showed severe myocardio- pathy. Case 4 had a routine ECG at age 27 years that showed evidence of a remote anterior myocardial infarction. Catheterization 8 years later revealed a large ventricular aneurysm but no evidence of coronary disease. Resection of the aneurysm was uneventful, but high-grade atrioventricular block developed several months later and a pacemaker was inserted transvenously elsewhere. The pacemaker failed, and she died. Postmortem examination in her community hospital showed no coronary disease and only an area of scarring in the region of the operative ventricular closure. Case 12 died from ventricular fibrillation 65 months after catheterization. She had atypical chest pain thought to be possibly of cardiac origin. Coronary arteriography showed only minimal irregularities and a percutaneous myocardial biopsy was not diagnostically helpful. The cause of the terminal arrhythmia was not determined.

Table 1. Cardiac Deaths in 761 Women Without Severe Coronary Obstruction

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age* (years)</th>
<th>Pain</th>
<th>ECG</th>
<th>FH</th>
<th>Tob</th>
<th>H</th>
<th>DiabChol</th>
<th>Catheterization</th>
<th>Ventriculogram</th>
<th>Dead (mos)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>Angina</td>
<td>LBBB</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>2</td>
<td>SD</td>
<td>0</td>
<td>See text</td>
</tr>
<tr>
<td>2</td>
<td>48</td>
<td>Not angina</td>
<td>LBBB</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>SD</td>
<td>4</td>
<td>Sudden</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>Not angina</td>
<td>Rep</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>Mitral prolapse</td>
<td>5</td>
<td>Sudden</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>Not angina</td>
<td>Anterior</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>VA</td>
<td>14</td>
<td>See text</td>
</tr>
<tr>
<td>5</td>
<td>46</td>
<td>Not angina</td>
<td>Normal</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>1</td>
<td>Normal</td>
<td>21†</td>
<td>Sudden</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>None</td>
<td>Rep</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td></td>
<td>2</td>
<td>SD</td>
<td>31</td>
<td>Congestive failure</td>
</tr>
<tr>
<td>7</td>
<td>43</td>
<td>Atypical</td>
<td>Inferior</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>2</td>
<td>Inferior akinesis</td>
<td>45†</td>
<td>Sudden</td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>Not angina</td>
<td>Rep</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>1</td>
<td>SD</td>
<td>49†</td>
<td>Sudden</td>
</tr>
<tr>
<td>9</td>
<td>40</td>
<td>Not angina</td>
<td>Rep</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>E</td>
<td>E</td>
<td>1</td>
<td>Normal</td>
</tr>
<tr>
<td>10</td>
<td>44</td>
<td>Atypical</td>
<td>LBBB</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>ND</td>
<td>60</td>
<td>Congestive failure</td>
</tr>
<tr>
<td>11</td>
<td>47</td>
<td>Not angina</td>
<td>Normal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1</td>
<td>Normal</td>
<td>64†</td>
<td>Postop (bypass)</td>
</tr>
<tr>
<td>12</td>
<td>47</td>
<td>Not angina</td>
<td>Rep</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td>1</td>
<td>Normal</td>
<td>65</td>
<td>Ventricular fibrillation</td>
</tr>
<tr>
<td>13</td>
<td>47</td>
<td>Not angina</td>
<td>Rep</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td>SD</td>
<td>73</td>
<td>Congestive failure</td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>Not angina</td>
<td>Rep</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>LVH</td>
<td>116</td>
<td>? cardiac</td>
</tr>
<tr>
<td>15</td>
<td>42</td>
<td>None</td>
<td>Rep</td>
<td>+</td>
<td>+</td>
<td>S</td>
<td></td>
<td></td>
<td>LVH</td>
<td>120</td>
<td>Sudden</td>
</tr>
</tbody>
</table>

*Patients are listed in order of date after catheterization.

*Age at catheterization.

†Death attributed to coronary disease.

Abbreviations: AD = anterior descending artery; anterior = anterior myocardial infarct; Chol = cholesterol level > 250 mg/dl; CX = circumflex; Diab = diabetes mellitus; E = ectasia; FH = family history of coronary disease; H = hypertension (> 150/98 mm Hg); Inferior = inferior infarction; LBBB = left bundle branch block; LVH = left ventricular hypertrophy; ND = not done; Rep = repolarization defect; RT = right coronary artery; S = systolic hypertension (> 150 mm Hg); SD = severe diffuse impairment; Tob = cigarette smoking; VA = ventricular aneurysm; 1 = less than 30% decrease in diameter; 2 = 30% to almost 50% decrease in diameter; AD = left anterior descending coronary artery.
Five women are known to have had myocardial infarction. Case 1 (table 2) had moderate obstruction of all three arteries and inferior infarction at 9 months. Case 2, who had 40% narrowing of the anterior descending artery and a similar degree of narrowing in the right coronary artery, had inferior infarction at 52 months. Case 3 had 30% narrowing of the right coronary artery and an inferior infarction at 66 months. Case 4 survived anterior myocardial infarction at 87 months, but died of Kimmelstiel-Wilson syndrome at 119 months. Case 5 had high lateral myocardial infarction at 119 months; arteriography had shown mild disease in the right coronary artery.

Seven of the 761 patients showed arteriographic progression in a second arteriogram, and each had bypass surgery. Nine women had undergone coronary operations during the period of follow-up, four within 5 years after catheterization (table 3). One woman had normal coronary arteriograms and another had mild one-vessel disease and both had internal mammary artery implantation operations elsewhere more than 1 year after catheterization, without coronary arteriography being repeated (cases 1 and 2). Two who had operation within 5 years, cases 3 and 4, had bypass surgery for arteriographically proved progressive coronary disease. After 5 years, five other women had bypass operation for progressive disease, 64–123 months after the original arteriography. All seven who had undergone bypass operations had abnormal coronary arteriograms when studied originally; three had mild irregularities and four showed moderate obstruction, and all had progressive disease before operation. Case 5 died postoperatively elsewhere and the other six were living at most recent follow-up.

No deaths thought to be due to coronary disease occurred in the 644 women who had normal arteriograms and none had a coronary event (death due to coronary disease, myocardial infarction, or arteriographically proved development or progression of coronary disease) during follow-up. Total survival on an actuarial basis was 97.1% at 8 years, the last year for which follow-up was available for more than half of the patients.

Table 3 lists patients in order of date after catheterization.

The initial ventriculogram was normal in all patients who had bypass operation and all showed preoperative progression to at least 70% obstruction in one or more arteries. Case 4 is case 1 in table 2; case 5 is case 11 in table 1; case 7 is case 3 in table 2; case 9 is case 5 in table 2.

Abbreviations: CF = coronary failure (prolonged pain thought to be of coronary origin); Chol = cholesterol level > 250 mg/dl; CX = circumflex artery; Diab = diabetes mellitus; FH = family history of coronary disease; H = hypertension (> 150/98 mm Hg); MI = myocardial infarction; Rep = repolarization defect; RT = right coronary artery; Tob = cigarette smoking; = less than 50% decrease in diameter; ≥ = 50% decrease in diameter.
ties (narrowing of less than 30%) had nine coronary events during the follow-up; two patients died within 5 years after catheterization. Seven events occurred after 5 years; two were deaths attributed to coronary disease, two were myocardial infarction, and three were arteriographically demonstrated progressive disease. On an actuarial basis, 89.8% were free from events at 8 years, after which only 31 patients were followed (one event in the tenth year).

Of the 34 women who had moderate (30% to almost 50%) narrowing of a major artery, three died of cardiac causes: case 7 died suddenly and cases 1 and 6 died of cardiomyopathy (table 1). One woman who had moderate obstruction died of cancer at 117 months and one died of unknown cause at 26 months. Actuarial survival was 91.1% at 8 years (one additional death in the tenth year, but only about one-third followed up). Cases 3, 4, 7 and 8, who had moderate obstructions, had arteriographically demonstrated progressive disease and all had bypass operation for progressive coronary disease (table 3); two of these had inferior myocardial infarction 9 and 66 months after arteriography. Case 2 had a myocardial infarction at 52 months (table 2).

Six of the 34 women had eight coronary events; one died suddenly, three had transmural myocardial infarction, and four had arteriographically proved progression of disease, and all underwent operation; four had five events within 5 years. Actuarially, freedom from events was 84.5% at 8 years (one event in tenth year, but only 13 patients were eligible). The difference in the incidence of these events from that of the combined group that had less than 30% narrowing or normal arteries (seven of 727) was significant (p < 0.001). The difference in the incidence of events in the mild and moderate subsets was not significant. The numbers of cardiac deaths were so small that further statistical analysis was meaningless.

Table 4 is a summary of the data relative to survival and coronary events at 5 years. The difference in survival between the normal subset and the two abnormal subsets combined is significant (p < 0.001). There were no deaths due to coronary disease in the normal subset and there were three in the two abnormal subsets of minor coronary disease. Patients in the normal subset had no coronary events, but six patients who had events in the mildly or moderately abnormal subset did have coronary events. Noncoronary deaths were more common in the abnormal subsets (nine deaths; 7.9%) than in those who had normal coronary arteriograms (12 deaths; 1.9%).

Eleven patients in whom no seriously obstructive arterial disease was demonstrated had electrocardiographic evidence of myocardial infarction. In one case, the original diagnosis was changed subsequently to atypical Wolff-Parkinson-White syndrome. Only one of the remaining 10 had a history somewhat suggestive of myocardial infarction, and she was the only patient who had an akinetic segment in the left ventricle. This patient, case 7, died suddenly at 45 months (table 1). One patient did not have a ventriculogram. Case 4 died and is discussed above. The other eight patients were living at last follow-up (80 months minimum), and none had a history of myocardial infarction.

The ECG was abnormal in 330 of 761 patients (43%) who had no severely obstructive lesions. Of 15 cardiac or probable cardiac deaths, 13 patients had abnormal ECGs, although only three of five deaths suspected of being of coronary origin occurred in patients whose ECG was abnormal.

Of 761 patients who had normal or nearly normal coronary arteriograms, 397 (52%) had chest pain at last follow-up. Ninety-four women had no severe coronary lesions and normal ventriculograms and had what was considered to be typical angina pectoris. There were no cardiac deaths and three noncardiac deaths. None had experienced myocardial infarction when last checked, but 57 (61%) still had chest pain.

**Severely Obstructive Coronary Disease**

Two hundred thirty-six women had 50% or more narrowing of the diameter of at least one major coronary artery. Average follow-up for nonsurgical survivors was 8.1 years. In survival curves, patients were considered dropouts at the time of any subsequent operation for coronary disease. Five-year survival was 74.1 ± 3.7% and the 10-year survival was 62.6 ± 4.3% (fig. 1).

All patients were classified by candidacy for bypass operation by modern criteria on the basis of the original catheterization findings; 163 qualified and 95 of these had some type of operation within 5 years, most (89%) within 1 year after catheterization: 60 had internal mammary artery implants, 21 had bypass operations, and 13 had other operations. Sixteen others thought not to be surgical candidates for bypass surgery actually underwent operations. Two women who had no significant coronary lesions had implants elsewhere without coronary arteriography being repeated. Sixty-nine of the surgical candidates had no operations within 5 years. The 5-year survival of surgical candidates was 87.4 ± 3.5%; patients who had operations were dropped at the date of operation (fig. 1). However, 31 of the surgical candidates who did not undergo operation had one-vessel disease. Five-year
survival for women with single-artery obstruction was 92.5 ± 5.2% and it was 80.9 ± 5.2% for obstruction of multiple arteries.

Only one serious complication of cardiac catheterization occurred in the 1000 women. A 26-year-old woman who had an atypical history died during coronary arteriography, which showed more than 90% narrowing of the orifice of the left main coronary artery and severe obstructions in the anterior descending and circumflex coronary arteries. No patient had a myocardial infarction as a result of cardiac catheterization.

Discussion

The 1000 women studied represented 6.8% of patients catheterized during the specified 8-year period. All had been thought by at least one referring physician to have coronary artery disease. A new clinical diagnosis was made for this study without knowledge of the arteriographic findings. Only 222 women had typical angina pectoris as defined above. More than 50% obstruction of at least one coronary artery was found in 128 patients (58%) who had angina. Using the same criteria for diagnosis of angina pectoris, the correlation rate was 90% for New York Heart Association functional classes I-III in young men and 94% for patients unselected by age. Atypical angina was diagnosed in 149 women and 27% had significant coronary obstruction as defined. Eighty of the 1000 women were thought not to have coronary disease and only one had severe coronary obstruction. Ten percent of the 501 patients who were believed to have normal hearts actually had severe coronary disease. These figures illustrate the difficulty in making a clinical diagnosis that correlates well with arteriographic findings in young women. During the study, coronary arteriography was advised in patients who had a clinical diagnosis of typical or atypical angina. Coronary arteriography was advised on the basis of these diagnoses in 371 patients. Ninety women had experienced prolonged pain that was thought to be of coronary origin and a small group had no pain but strong suspicion of coronary disease on some other basis. The remaining patients had a previous diagnosis of coronary disease, but review of the clinical findings suggested that coronary disease was not or was probably not present. If the patient did not accept reassurance because of the conflict with previous diagnosis, coronary arteriography was advised. Selection of patients would not necessarily be the same at this time as in the 1961-1968 period, because additional studies, such as graded stress tests and radionuclide studies, have altered some attitudes. Physicians are now more reluctant to make a clinical diagnosis of coronary disease without strong evidence than they were 12 or more years ago. This is reflected by a change in referral patterns in our institution for men as well as women.

Waters et al. studied 239 women younger than 45 years of age arteriographically between 1972 and 1976, about a decade later than our study period. The precise indications for arteriographic study cannot be compared, but myocardial infarction was diagnosed electrocardiographically in about 19% of the group studied by Waters and 5% in the present study. This suggests a difference in patient selection. Women younger than 45 years of age constituted 3% of patients catheterized in the Waters' study and 4% in the present report. Waters et al. found no severe coronary lesions in 56%, compared with 76% in this report. These differences are not great, considering the difference of about a decade between the two periods of study. Problems in clinical diagnosis remain and coronary arteriography may be required for precise evaluation.

High survival rates for at least 2 years have been reported for patients who had no significant coronary obstructions, but most studies have not clearly separated the sexes and ages. Waxler et al. reported the early survival of women demonstrated arteriographically to be free from severe obstructive lesions. Of 100 patients, 86 had no apparent basis for pain, though eight were thought to have typical angina. None died or had myocardial infarction during a follow-up of 6–30 months. The average age was 44 years (range 21–60 years). It was concluded that the symptoms of these patients were probably due to neurocirculatory asthenia. Bemiller et al. reported similarly favorable prognosis for 37 patients who had normal coronary arteriograms. The average age of their patients was 42.7 years and the

![Figure 1](http://circ.ahajournals.org/)

**SURVIVAL IN YOUNG WOMEN**

FIGURE 1. Survival curves of women who had normal coronary arteriograms or mild or moderate narrowing (normal or <50%), severe obstructive disease, and severe disease and surgical candidacy. Numbers of living, nonoperated patients at 5 and 10 years were 735 and 317, respectively, for normal, mild and moderate cases, 99 and 24 for severe obstruction, and 61 and 14 for surgical candidates. All deaths, not just cardiac, are included. Dropouts at the date of operation affect the lower two survival curves (see text).
average duration of follow-up was 4.1 years. Twenty were thought to have typical angina pectoris. Sixteen were women. One patient died suddenly during the follow-up period and postmortem examination showed normal coronary arteries. Bruschke et al.\textsuperscript{12} reported no deaths within 5 years in the 79 women younger than 45 years who had no severe coronary lesions.

The present study confirms a favorable prognosis for young women without severe coronary obstruction and expands the reported experience of patients followed up for a long period. No deaths due to coronary disease occurred in patients who were arteriographically and ventriculographically normal, and there were four deaths attributed to coronary disease in women who had mild lesions, one in a patient who also had coronary ectasia. One of 34 women with moderate obstruction died from coronary disease.

Coronary events occurred in no patient whose arteriograms were thought to be normal, in seven of 83 who had mild disease, and in six of 34 who had moderate lesions. Combination of the normal and mild obstructive subsets and comparison of event rate with that of the moderately obstructive group showed a statistically significant difference, but the difference was not significant between the mildly and moderately obstructive subsets. This prognostic disparity was reported by Bruschke et al.\textsuperscript{12} Although the group studied had arteriography in 1968 or before, severe lesions seemed to have been missed infrequently. New techniques improve definition and additional viewing angles may demonstrate more clearly certain lesions.

Ninety-four women had normal or almost normal coronary arteriograms and normal ventriculograms in association with what was diagnosed as angina pectoris by standards considered reliable on the basis of previous investigations.\textsuperscript{4, 6} None of these patients died, had bypass surgery, or had myocardial infarction during the follow-up period. Day and Sowton\textsuperscript{13} reported that none of 22 women thought to have angina and normal arteriograms died within 2 years. More than half of the 761 women without severe obstructive disease still had pain at most recent follow-up. Reassurance and symptomatic therapy were not as effective in this group as might be expected.

Before initiation of the follow-up study, we realized that many of the 236 patients who had severely obstructive lesions had operations of some type after arteriography, and that these dropouts would distort the survival curves of the remaining patients. Only 69 patients who would have been candidates for bypass surgery did not have an operation of some type, but 31 of these patients had single-artery disease, leaving a group of only 38 with multivessel disease who could be expected to be at reasonably high risk. Five-year survival was 80.6% for the multivessel subset of surgical candidates. This rate is about the same (81.6%) as for 40 female surgical candidates unselected for age in another study.\textsuperscript{14} The small number of surgical candidates who did not have operation and the selection bias prevent confident conclusions. Disregarding surgical candidacy, 5-year survival of women who had severe obstructions was 74.1%. This compares with 72.8% for men younger than 50 years old (calculated from Proudfoot et al.\textsuperscript{14}). The survival rate for young women who have severe obstructive coronary disease is probably about the same as that for young men.

Acknowledgment

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