Preinfarctional (Unstable) Angina—A Prospective Study—Ten Year Follow-Up

Prognostic Significance of Electrocardiographic Changes

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SUMMARY
One hundred and forty patients with preinfarctional (unstable) angina were followed for ten years for the purpose of determining the natural history and the prognostic significance of electrocardiographic findings. The cumulative survival rate for the 140 patients was as follows: 12 months: 82%; 24 months: 75%; 36 months: 69%; 60 months: 61%; and 120 months: 48%. Twenty-one percent (29 of 140) of the patients developed an acute myocardial infarction within eight months of the onset of the diagnosis of preinfarctional angina with an associated mortality of 41.4% (12 of 29). A combination of high-risk factors in a patient, e.g., frequent angina in the hospital, prior stable angina, and ischemic ST change during pain, identified his as a high-risk case. The high-risk subgroup (54) had a cumulative survival rate as follows: 12 months: 57%; 24 months: 47%; 36 months: 37%; 60 months: 27%; and 120 months: 19%. Thirty-five percent (19 of 54 patients) of this subgroup developed a myocardial infarction within three months of the onset of preinfarctional angina with an associated mortality rate of 63% (12 of 19 patients).

Additional Indexing Words:
Unstable angina Saphenous vein bypass Myocardial infarction Natural history of angina

The terms "impending coronary occlusion,"1 "acute coronary insufficiency,"2 "intermediate coronary syndrome,"3 "coronary failure,"4 "status anginosus,"5 "pre-infarction angina,"6 "unstable angina,"7 among others, have been used for patients who experience a sudden increase in frequency of angina, or more severe and prolonged cardiac pain than the usual angina. The pain often occurs at rest.

One hundred and forty patients with preinfarctional angina were followed for ten years. The objective of this study was to determine the survival rate of this group and to discover whether it was possible to predict the patient's prognosis on the basis of electrocardiographic findings. Now that saphenous vein graft bypass techniques for direct myocardial revascularization have been developed,8,9 recording the natural history of preinfarctional angina has become even more important. There are at present no specific criteria for selection of surgical candidates. The ubiquitous nature of angina makes it very difficult to pick out those patients with this symptom who would probably die without surgical intervention. It would be helpful if types of angina pectoris could be defined and distinguished by their natural history.

Materials and Methods
One hundred and forty consecutive patients who satisfied our criteria for preinfarctional angina, from a private practice (P.C.G.), were included in this study prior to 1961. The criteria were as follows:

Type 1. Initial onset of progressive, crescendo (increase in frequency, severity, and duration) angina and pain at rest in a patient previously free of symptoms.
Type 2. Same as in type 1, occurring suddenly in a patient with known stable angina.

Type 3. Episodes of prolonged pain at rest, of more than 15 min, not related to obvious precipitating factors such as anemia or arrhythmias.

The 140 patients were admitted to the hospital, usually within 48 hours but not later than two weeks after the onset of their preinfarctional symptoms. Patients were excluded from the study if in the first 48 hours electrocardiographic changes indicating an acute myocardial infarction developed or enzyme levels rose significantly. They were also excluded, when first seen, if significant cardiomegaly was present, or evidence of congestive heart failure, or if there was an associated disease that could shorten the patient's life. The 140 patients meeting the selection criteria were divided into groups according to the electrocardiographic findings noted at rest or occurring transiently during or just after an episode of pain. The transient findings included ischemic ST- and/or T-wave changes. Patients with known previous myocardial infarction or bundle branch block had old tracings documenting these findings.

Seven groups were noted with different electrocardiographic recordings as follows:

1. Ischemic ST-depression of the horizontal type of at least 1 mm (0.1 mV) or greater, with T wave inversion (17 patients)
2. Ischemic ST-depression without T-wave inversion (26 patients)
3. Old myocardial infarction pattern with or without transient ST or T wave changes (25 patients)
4. ST-elevation (5 patients)
5. Previous bundle branch block with or without transient ST or T wave changes (11 patients)
6. T wave inversion only (32 patients)

Each patient was included in only one group. Twelve patients in group 3 and one patient in group 5 had superimposed transient ST-depression during pain. In addition, seven patients in group 3 and two in group 5 had transient T wave inversion. These patients were not included in groups 1, 2, or 6.

The 140 patients were a uniform group in that they fulfilled our criteria for preinfarctional angina, and their illness was incapacitating. Fifty-four patients continued to have typical angina or prolonged ischemic pain after 48 hours of bed rest, despite maximum therapeutic measures. These patients began to respond poorly to nitroglycerin and required frequent doses of opiates for relief. A daily record of pain and the use of nitroglycerin was kept during the hospital period so that at the end of the ten years these 54 patients were separated and distinguished as an early high-risk subgroup.

Over the ten year period, data was compiled by personal follow-up examinations, telephone calls to family physicians, patients, or their families. In certain instances death certificates and autopsy reports were reviewed. The data included the following: age, sex, body build, family history, occupation, pre-existing conditions (hypertension, diabetes, myocardial infarction), pain characteristics, physical findings, laboratory findings, and patient's course. The patients were treated with periods of rest, nitrates (long-acting and sublingual nitroglycerin), sedatives, analgesia, and low calorie-low fat diets. The beta-blocker drugs were not available the latter part of this study. Ninety-one patients received warfarin and/or heparin.

Follow-up life table analysis was employed to determine survival by using the method described by Remington and Schork.40 One hundred and thirteen patients were followed to the time of death or 120 months. Twenty-seven patients were lost to follow-up prior to 120 months. A comparison of the yearly survival rates were made for the seven electrocardiographic groups using the standard normal z-test.

Results

Of the 140 patients in this study 113 were male and 27 female, a ratio of 4:1 (table 1). Tables 2 and 3 compare the clinical features of the total group and the high-risk subgroup with respect to age, electrocardiographic groups, and preinfarction criteria. The ages ranged from 35 years to 72 years. The average age was 56 years for the total group and 57 years for the high-risk subgroup. Patients with type 2 pain had prior stable angina for an average of 2.5 years. In addition, 25 of these type 2 patients had had a myocardial infarction that occurred on the average of 3.3 years earlier. Table 4 summarizes the main features of the high-risk subgroup.

Seventy-seven of the 140 patients expired. Fifty-five percent (63 of 114) of the males died, and 51% (14 of 27) of the females died. Seventy-three of these deaths were the result of coronary events such as sudden death, sudden death with angina, heart failure, or myocardial infarction. The other four patients died from noncoronary events: two had a cerebrovascular accident, one, carcinoma of the stomach, and one, an automobile accident.

Figure 1 depicts the probability of survival for the total group, the high-risk subgroup, and for each of the seven electrocardiographic groups. Patients in electrocardiographic groups 6 and 7 had a higher survival rate during the first two years when compared to patients of groups 1 and 2 (P < 0.05). Patients in group 5 had the worst

Table 1

Sex Distribution of the 140 Patients in the Seven Electrocardiographic Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>Total</th>
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<td>20</td>
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<td>27</td>
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Circulation, Volume XLVIII, August 1973
Table 2
Patient Population According to Age and Electrocardiographic Groups

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<tr>
<th>Age:</th>
<th>35-44</th>
<th>45-54</th>
<th>55-59</th>
<th>60-72</th>
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<td>T S T S T S T S T S T S</td>
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<td>4</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>T S T S T S T S T S</td>
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<td>2</td>
<td>2</td>
<td>3</td>
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<tr>
<td>T S T S T S T S</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>T S T S T S</td>
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<td>T S T S</td>
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<td>7</td>
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<td>3</td>
<td>9</td>
</tr>
</tbody>
</table>

T = Total group of 140 patients; S = High risk subgroup of 54 patients.

prognosis after the first two years. If the high-risk subgroup is subtracted from the total group, the remaining 86 patients have better prognosis. Figure 2 compares the cumulative survival rate of these three groups.

Figure 3 compares the number of deaths and myocardial infarctions that occurred within three months of the onset of preinfarctional angina for the total group and the high-risk subgroup. Two of these patients had severe chest pain for over 30 min and died suddenly on the way to the hospital. The other patients with infarctions were diagnosed in the hospital. Twenty-nine of the 140 (20.7%) patients developed an acute myocardial infarction and the mortality rate associated with this complication was 41.4% (12 of 29 patients) for this three month period. The total mortality during this period was 10% (14 of 140 patients). Fifteen of the 29 patients who developed an infarction were on anticoagulants. There were seven deaths in this group and five deaths in the 14 patients who were not on anticoagulants.

Nineteen of the 54 high-risk subgroup patients (35%) developed an acute myocardial infarction during the three month period with an associated mortality of 63% (12 of 19 patients). The total mortality during this period was 26% (14 of 54 patients). Table 5 compares the number of infarctions that developed prior to three months in both the total group and the high-risk subgroup with associated deaths broken down into each of the seven electrocardiographic groups. In table 6 the number of patients who developed infarctions are compared according to the three types of our preinfarctional criteria.

Table 7 compares the incidence of hypertension, diabetes, and hypercholesterolemia in the total and in the high-risk subgroup. Hypertension was considered present if the blood pressure was 140/90 or greater, and hypercholesterolemia if the cholesterol was over 240 mg %. Hypertension was present prior to the onset of angina. The incidence of diabetes is low for such patients. However, glucose tolerance tests were not performed on all patients, and all of those designated had been diagnosed as diabetic prior to this study.

During the first year after onset of preinfarctional angina 18% (25 of 140) of the patients died. Seventy-four percent (104 of 140) had less angina, and the anginal pattern of the remaining 8% (11 of 140) remained unchanged. It is difficult to evaluate change in the quality of these patients’ lives since many adjusted their exertion in order to reduce the anginal attacks. Approximately 50% of these patients resumed normal activity.

Discussion

The distinction between preinfarctional angina and more chronic varieties of angina may be difficult since they may overlap. In the present series, all patients demonstrated a clear change in their clinical status and satisfied the usual criteria for the preinfarction syndrome. As others have noted many of these patients will not develop myocardial infarctions. For this reason, the term “preinfarctional angina” is misleading, and this syndrome should be referred to as “unstable angina.” High-risk patients, with frequent and prolonged attacks of angina continuing after 48 hr of bed rest, not responding significantly to therapy,

Table 3
Clinical Presentation of Preinfarctional Angina According to Pain Criteria

<table>
<thead>
<tr>
<th>Type*</th>
<th>Total group</th>
<th>High risk subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of pts</td>
<td>No. of pts</td>
</tr>
<tr>
<td>1</td>
<td>27</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>109 (Prior MI-25)</td>
<td>51 (Prior MI-12)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>1 and 3</td>
<td>5</td>
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<tr>
<td>2 and 3</td>
<td>27</td>
<td>15</td>
</tr>
</tbody>
</table>

MI = Myocardial infarction; Pts = patients.
*See Methods section.

Table 4
Features of High-Risk Preinfarctional Subgroup

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent in-hospital pain</td>
<td>54 (100)*</td>
</tr>
<tr>
<td>ST change during pain</td>
<td>33 (62)</td>
</tr>
<tr>
<td>Normal ECG during pain</td>
<td>5 (.09)</td>
</tr>
<tr>
<td>Prior stable angina</td>
<td>51 (94)</td>
</tr>
</tbody>
</table>

*Percent in parentheses.
should be recognized since they have a very poor prognosis. In addition, 94% (51 patients) in our high-risk subgroup also had prior stable angina and all except five had electrocardiographic changes during an attack. Ischemic ST-depression occurred in 29 of these patients (seven with prior myocardial infarcts) and ST-elevation in four patients. These ST changes accounted for 62% (33 of 54) of the electrocardiographic changes in this high-risk subgroup. Twelve of the 54 high-risk patients died during the first month (average, eight days after admission). The earliest deaths in this high-risk subgroup occurred in two patients: one at 48 hours and the other at 72 hours after admission.

Patients with prior bundle branch block, especially after the second year in the study, had the worst prognosis. This may be accounted for by the fact that five of the patients in this group were between 55 and 60 years of age, and six were over 60 years of age. In addition, the six deaths in the group were sudden, with coronary occlusions suggesting, in view of the bundle branch block, that trifascicular block may have developed. The deaths were distributed equally between the two types of bundle branch block.

In the high-risk subgroup, those with electrocardiographic changes of ischemic ST depression (groups 1 and 2) or prior myocardial infarction (group 3), or those with prior stable angina had the highest incidence of acute infarction and associated death prior to three months (tables 5 and 6). Vakil reported an over-all incidence of 40.6% for acute myocardial infarctions within this same period in 360 cases with preinfaretional angina. Infarctions in that study occurred in 36% of the 190 patients treated with anticoagulant therapy, and this complication developed in 49% of 156 patients.
treated conservatively, with associated mortalities of 26 and 37% respectively. In a recent study, Fulton et al.\textsuperscript{12} reported an incidence of 14% of patients developing myocardial infarctions who had preinfarctional angina, with an 11% mortality due to this complication. The high mortality of the patients in our group with acute myocardial infarctions, superimposed on the preinfarctional syndrome was probably due to the fact that all except one of these patients had prior stable angina. In addition, six of the patients with stable angina also had a prior infarction. Furthermore, our patients were referred to a medical center, whereas Fulton’s cases were collected from the records of general practitioners and probably were seen much earlier in the evolution of their disease.

In another study, of 100 patients with acute coronary insufficiency who were medically treated, six developed an acute myocardial infarction and survived; the one-year survival rate was 85%.\textsuperscript{13} A follow-up study of 47 patients with unstable angina revealed 8% in-hospital deaths and 17% late deaths (within 14 months).\textsuperscript{14} The survival rates of these two studies are approximately the same as that found in our total group for the same follow-up periods. The Framingham study\textsuperscript{15} could predict that almost 30% of patients with angina (stable or complicated) over age 55 will die within eight years, or an average of 3.7% annually. The cases of preinfarctional angina were not separately analyzed in that study. The mortality rate for our 140 patients over the ten-year period averaged approximately 5% per year, and for the 54 high-risk subgroup patients, 8% annually. After subtracting the high-risk subgroup from the total, the remaining 86 patients had an annual mortality rate of 3.2%. The five-year mortality for these three groups are 8, 14.5, and 3.4%, respectively. These figures are much higher than for the ten-year period for the total and high-risk subgroups, since most of the deaths in these two groups occurred during the first five years. The average annual mortality for average age 56 years (similar to our total group) for the general population is 1.24% for the United States\textsuperscript{16} and 1.81% for South Carolina.\textsuperscript{17}

Our study is the first reported long-term follow-up study on preinfarctional angina. The immediate effectiveness of saphenous vein bypass grafts for coronary artery disease is recognized. In reviewing the literature to the present time, there have been approximately 229 patients reported that have had saphenous vein bypass graft surgery for preinfarctional angina, with an average operative mortality of 5%.\textsuperscript{18-25} These patients were not compared with similar groups treated medically. In addition, the lack of uniformity of criteria in these studies for

### Table 5

<table>
<thead>
<tr>
<th>Groups</th>
<th>T*</th>
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<th>T*</th>
<th>S</th>
<th>T*</th>
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<td>No. of pts</td>
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<td>25</td>
<td>12</td>
<td>5</td>
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<td>(23)</td>
<td>(50)</td>
<td>(24)</td>
<td>(41.7)</td>
<td>(20)</td>
<td>(25)</td>
<td>(9)</td>
<td>(16.6)</td>
<td>(15.6)</td>
<td>(20)</td>
<td>(20.8)</td>
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<td>from infarct</td>
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<td>(50)</td>
<td>(60)</td>
<td>(50)</td>
<td>(60)</td>
<td>(20)</td>
<td>(20)</td>
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</table>

Abbreviations: T = total group; S = high-risk subgroup; pts = patients.
*Percent in parentheses.

### Table 6

<table>
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<tr>
<th>Type</th>
<th>Total group</th>
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<th>High risk subgroup</th>
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<td>2 with prior infarct</td>
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<td>5†</td>
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*See Methods.
†Included in the total of type 2 without prior infarct.

### Table 7

<table>
<thead>
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<th>Type</th>
<th>Total 140 pts*</th>
<th>High risk group 54 pts*</th>
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<tbody>
<tr>
<td>Hypertension</td>
<td>46 (52)</td>
<td>29 (54)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (9)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>69 (49)</td>
<td>17 (31)</td>
</tr>
</tbody>
</table>

Pts = patients.
*Percent of patients in parentheses.
preinfarctional angina and paucity of information regarding long-term myocardial function and patient survival makes it very difficult to compare these surgical results with our medically-treated groups. Recently, several short-term follow-up studies were reported comparing surgically and medically treated groups. Scanlon et al. reported on 70 patients with accelerated angina. Forty-eight of these patients were treated surgically with a mortality of 12.5%; 22 patients treated without surgery had a mortality of 27%. The follow-up period for this study was not clearly stated. Another study, comparing 38 patients with preinfarctional angina treated with conventional medical therapy to 21 patients having aortic coronary bypass, with a mean follow-up of 6.4 months, revealed a mortality of 20% and 14%, respectively.

Coronary arteriography was not performed on our patients since this study began prior to 1961. However, all of the patients had an unequivocal history of angina, and 83% had electrocardiographic change at rest or during an episode of pain. Symptomatic coronary artery disease has been found to be accompanied by arteriographic evidence of moderate or severe obstruction of one or more major coronary vessels. Normal electrocardiograms can be found in patients in whom severe coronary artery disease could be demonstrated by coronary arteriograms. A recent study reported the natural history of severe proximal coronary disease as defined by cineangiography in 200 patients with a seven year follow-up. It was found that single vessel anterior descending disease has a 4% yearly attrition rate, or 30.5% seven year mortality; single right coronary or circumflex lesions 1.8% yearly death, or 12.5% in seven years; two-vessel disease, 44%; and three-vessel disease 70% mortality in seven years. Our total group mortality compares with that of the two-vessel disease group and our high-risk subgroup with that of three-vessel disease.

Acknowledgment
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