Ventricular Premature Complexes in Prognosis of Angina

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SUMMARY We studied the prognostic role of ventricular premature complexes occurring during 1 hour of electrocardiographic monitoring of 416 men with effort angina who had never had myocardial infarction, and compared mortality over 5 years with that of 1739 men with infarction before first observation. Multivariate analyses of survival identified the presence of ventricular premature complexes in 1 hour of monitoring, the presence of ST-segment depression on the standard ECG, and age as the variables making the most important independent contributions to risk of death (all causes and sudden coronary deaths) among the men with angina. The relatively lower age-adjusted 5-year mortality among men with angina compared with those who had a prior myocardial infarction reflects the lower prevalence in the former group of indicators of myocardial dysfunction, such as ventricular ectopic activity and ST-segment depression.

INTEREST in the relation of ventricular arrhythmia to fatal ventricular fibrillation has focused on the course of disease among patients with myocardial infarction (MI). Monitoring observations in coronary care units, epidemiologic studies using the routine 12-lead ECG and monitoring studies of patients who survived acute episodes have all marshalled observations supporting the view that frequent or complex ventricular premature complexes (VPCs) are associated with an excess risk of sudden death.1,2 In an earlier report from the Health Insurance Plan of Greater New York (HIP),6 we presented evidence on the independent contribution to increased risk of death associated with the presence of complex VPCs in 1 hour of ECG monitoring of 1739 men with prior MI. We know of no reports on the prognostic significance of ventricular ectopic activity in patients with angina but free of prior MI. Therefore, we studied 416 men with an unequivocal history of effort angina in the year preceding first observation, and identified characteristics of major importance in predicting mortality of men with angina who were free of prior infarction. We also examined the associations among these characteristics, and made comparisons, where appropriate, with outcome in male survivors of MI.

Methods

Details of the study’s methods have been published.6,7 In brief, over a period of almost 4 years (March 1972 through December 1975), 2155 study coronary heart disease (CHD) patients were identified from a population of 120,000 men ages 35–74 years insured by HIP — a prepaid group-practice plan providing comprehensive medical services. Standard baseline observations included interviews to establish personal characteristics and medical history, physical examination and laboratory determinations, a 12-lead ECG and 1 hour of single-lead ECG monitoring recorded on tape. Computer processing of these tapes produced write-outs on ECG paper of all possibly abnormal beats. Double reading of these sections by trained technicians and physicians then provided the basis for classifying patients by ventricular ectopic activity during the monitoring hour. Follow-up of these patients is now complete, with mortality status as of the last observation due before April 1, 1978 known for all patients. The final data, presented in part in this report, are based on an average observation period of 3.5 years (range 2–5.5 years). Four hundred eleven deaths occurred during this period, 349 among the 1739 men who had an MI before the baseline and 62 among the 416 men with angina but no antecedent MI. Patients were re-monitored at 6-month intervals up to a maximum of three times after the baseline. The medical management of the patients remained the responsibility of their physicians, to whom the study team routinely reported results of the baseline and follow-up findings.

Statistical analyses that take into account varying durations of follow-up after baseline were used to estimate cumulative probabilities for specified end points. Both bivariate and multivariate procedures were used to assess the influence of VPCs and other characteristics on mortality.8,9 Adjustment of the cumulative mortality shown in the figures for differences in age between groups was made by the direct method, applying specific rates for men 35–64 years and 65–74 years to the standard population, defined as the sum of all study patients — those with MI before baseline plus those with angina only.

Results

Patient Characteristics

Men with CHD became eligible for this study either by meeting criteria for acute MI within the 9 months before baseline examination or through a history of definite angina10 within the preceding 12 months. Comparisons are presented below, when appropriate,
between the 416 men with angina who had never had clinical or ECG evidence of definite or suspected MI and the 1739 men who sustained at least one MI (transmural or subendocardial) before entry into the study. The men with no prior MI are distinctly older than the others: 20% of the angina cohort are under age 55 years, compared with 32% of the MI men; men ages 65-74 years constitute 39% of the angina patients and 29% of the MI patients. Other large differences in prevalence of important clinical characteristics are seen in the age-adjusted rates presented in table 1. Far higher proportions of the men who had experienced MI, in comparison with those with angina only, had ECG abnormalities and congestive heart failure. The duration of known heart disease was, however, greater among the men with angina. The first diagnosis had been made 1 or more years before baseline in 80% of these patients, compared with 40% in the MI cohort. No important differences in prevalence are apparent with respect to the presence of hypertension or diabetes or to treatment with diuretics. A slightly higher proportion of the men with angina were on antiarrhythmic drugs (diphenhydantoin, procainamide, quinidine or propranolol) at the date of baseline (29% vs 19%), reflecting the greater likelihood of prescription of propranolol for anginal pain.

During the hour of ECG monitoring for ectopic activity, one-third of the men in the angina cohort, compared with over half the men with prior MI, had one or more VPCs (table 2). The prevalence difference between the two groups is especially marked with respect to complex VPCs: R on T, runs of two or more VPCs, and bigeminal or multiform premature complexes. The age-adjusted proportion with such forms was 15% for the angina cohort, compared with 27% for the men with prior MI. But among patients who had complex forms, no important differences appear between the cohorts in proportions of patients with the specified complex features, or in proportions with relatively high and low frequency of VPCs (table 3).

**Overall Mortality**

Figure 1 shows that over the 5 years after baseline examination, the men with angina who had never had an MI had a lower risk of death than age-comparable men who had survived infarction by the start of the observation period. After 5 years, the cumulative age-adjusted probability of death from all causes in the angina men was 18.0%, compared with 24.3% in the men with prior MI. During this observation period, men who had had an infarction showed 1.3 times the mortality risk (age-adjusted) found among the angina men (logrank $x^2(1) = 3.9, \, 0.01 < p < 0.05$). Sudden coronary deaths are defined in this study as those occurring within minutes of a patient’s usual state of health in the absence of symptoms or findings suggesting acute MI. In this respect, the men with prior MI

<table>
<thead>
<tr>
<th>Table 1. Prevalence of Specified Clinical Characteristics in Coronary Heart Disease Patients with and Without Prior Myocardial Infarction (MI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angina only</strong> (n = 416)</td>
</tr>
<tr>
<td>Age-adjusted* percentage with:</td>
</tr>
<tr>
<td>ST-segment depression</td>
</tr>
<tr>
<td>T-wave abnormality</td>
</tr>
<tr>
<td>One or more VPCs in monitoring hour</td>
</tr>
<tr>
<td>Heart rate ≥ 90 beats/min</td>
</tr>
<tr>
<td>Congestive heart failure by baseline date</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
</tr>
<tr>
<td>Taking diuretics</td>
</tr>
<tr>
<td>Duration of heart disease ≥ 1 year or more</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
</tbody>
</table>

*Adjusted to the age composition of the prior MI and no prior MI groups combined (n = 2155 men).
Table 3. Comparison of the Nature of Complex Ventricular Premature Complexes (VPCs) During 1 Hour of Baseline Monitoring in Coronary Heart Disease Patients with and Without Prior Myocardial Infarction (MI)

<table>
<thead>
<tr>
<th></th>
<th>Angina only (n) (%)</th>
<th>Prior MI (n) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men with any complex form in hour</td>
<td>65 (100.00)</td>
<td>462 (100.0)</td>
</tr>
<tr>
<td>Qualitative features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early VPC (R on T)</td>
<td>12 (18.5)</td>
<td>83 (18.0)</td>
</tr>
<tr>
<td>Runs of two or more VPCs</td>
<td>19 (29.2)</td>
<td>172 (37.2)</td>
</tr>
<tr>
<td>Early and/or runs</td>
<td>27 (41.5)</td>
<td>202 (43.7)</td>
</tr>
<tr>
<td>Bigeminy</td>
<td>26 (40.0)</td>
<td>208 (45.0)</td>
</tr>
<tr>
<td>Multiform VPCs</td>
<td>53 (81.5)</td>
<td>362 (78.4)</td>
</tr>
<tr>
<td>Multiformity is sole complex feature</td>
<td>28 (43.1)</td>
<td>158 (34.2)</td>
</tr>
<tr>
<td>Total number of VPCs in hour</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–9</td>
<td>12 (18.5)</td>
<td>109 (23.6)</td>
</tr>
<tr>
<td>10 or more</td>
<td>53 (81.5)</td>
<td>353 (76.4)</td>
</tr>
</tbody>
</table>

are at a still greater disadvantage: 5-year cumulative probability of sudden coronary death was 11.0%, compared with 4.7% for the men with angina only. Sudden coronary death was almost twice as likely in the MI men compared with those with angina alone (age-adjusted relative risk 1.9, $\chi^2(1) = 7.2, 0.005 < p < 0.01$). Sudden coronary deaths expressed as a percentage of all cardiac deaths were 41% for the angina cohort (18 of 44) and 53% for the MI cohort (149 of 279).

Age and Mortality

Increasing age is associated with increasing mortality in men with CHD, as in the general population. Because the men in the angina cohort are older than the MI survivors, rates are adjusted for age whenever comparisons are made. But the role of age in mortality differs between the two cohorts. An age-specific examination of survival (fig. 2) shows that differences in risk of death between men with and without prior MI are almost entirely due to the subgroup of men under age 65. The overall mortality differential between the younger men with and without prior MI reflects the relatively increased risk of sudden coronary death in the younger men in the MI cohort. This results in a disadvantage in the oldest men (ages 65–74 years) that is relatively more pronounced in the men with angina alone than in men who have had an MI. The age-related mortality differential among the men with angina closely resembles that found in the general US population.12

VPCs and Mortality

Among men with CHD — those with angina only and those with prior MI as well — the presence of VPCs during 1 hour of ECG monitoring identified a group at elevated risk of death over the ensuing 5 years. For the men with antecedent MI, mortality risk of those with only simple VPCs in the monitoring hour appears intermediate — somewhat above that for men free of VPCs and distinctly lower than that for the men with complex forms (fig. 3). Little difference in survival is found among the men with angina between those with complex VPCs and those with only simple VPCs in the hour, but mortality in both these groups far exceeds that in the men without ventricular ectopic activity in the hour (fig. 3). In an earlier report of this study that presented 3-year survival data for men with prior MI,6 analyzing these patients for the presence of complex beats in the monitoring hour offered an easily definable classification useful in survival analysis. The additional years of follow-up have resulted in a shift of the curve for the men with simple VPCs to show a risk over the 5-year period that appears somewhat higher.

![Figure 1. Mortality in men with coronary heart disease over 5 years after baseline, by experience of prior myocardial infarction (MI).](http://circ.ahajournals.org/)

![Figure 2. Five-year mortality in men with coronary heart disease, by age and experience of myocardial infarction (MI) before baseline.](http://circ.ahajournals.org/)
Sudden hour: (VPBs) in criminates well ining infarction without such with angina men Nevertheless, that of death, both risk 1.4, X2(l) logrank Xo. W (76)

FIGURE 4. Survival X2(l)

Mortality over 5 years after baseline monitoring in relation to ventricular premature beats (VPBs) in the monitoring hour: coronary heart disease patients with and without myocardial infarction (MI) before baseline.

than that of men without VPCs (age-adjusted relative risk 1.4, logrank χ²(1) = 5.5, 0.01 < p < 0.025). Nevertheless, among these men the dichotomy between those with and without complex VPCs in the monitoring hour still provides better separation with respect to risk of death (age-adjusted relative risk 2.1, logrank χ²(1) = 47.6, p < 0.0005). But among the angina men with no MI before baseline, the data fall more appropriately into a dichotomy between men with one or more VPCs in the monitoring hour and those without such complexes. This classification discriminates well between men at relatively high and low risks of death, both among the men with angina only and those with prior MI (fig. 4).

Multivariate Survival Analyses

To assess the role of VPCs in the prognosis of men with angina when other clinical features are taken into account, we used Cox's regression model for censored survival data.10 This procedure, using maximum-likelihood estimates, assesses the relative contributions of one or more covariates to the mortality risk. Table 4 summarizes findings for 11 two-variable Cox regression models. Each line of the table summarizes a model that includes the indicated clinical characteristic and age (dichotomized as ages 65–74 years vs ages 35–64 years).* We examined all clinical characteristics that in earlier analyses of men with prior MI had been associated with increased mortality risk. Table 4 shows the risk associated with the presence of the factor relative to that in its absence, with age controlled, and gives chi-squares testing the statistical significance of both age and the characteristic combined. No significant contribution to mortality risk is made by any of the variables below the fourth line of the table, when age is already present in the model. Important elevations in risk of death (all causes and sudden coronary deaths) are found in relation to VPCs, ST-segment depression, and T-wave abnormalities when these three features, controlled for age, are examined one at a time. The increased risk is found whether the arrhythmia is expressed as one or more VPCs vs none, or as complex VPCs vs no complex VPCs, but better contrast is apparent with the former classification. No increase in risk of death can be attributed to any of the other clinical features listed (variables 4–10, table 4). The statistically significant chi-squares associated with the models for these other characteristics in each case reflect the contribution of age to the risk.

Models that included all of these variables and specified subsets were also examined. Variables that made no statistically significant contribution to the likelihood function were successively eliminated. When age and the variables listed in table 4 as 1a and 2–10 were all included in the model, only three of the 11 variables made significant contributions to the likelihood function. These were the variables dichotomizing age, presence of VPCs and the presence of ST depression (χ²(11) = 56.6, p < 0.0005). Because the presence of T-wave abnormalities when examined individually with age made a significant contribution to risk (table 4, variable 3), a four-variable model including this variable was examined. Again, only age, ST depression and the presence of VPCs contributed significantly to risk (χ²(4) = 53.9, p < 0.0005). The apparent contribution by T-wave abnormalities when examined individually (controlling only for age) reflects the frequent finding of these abnormalities in the presence of ST depression.

The best fit is provided by the three-variable model (χ²(3) = 53.6, p < 0.0005). Table 5 gives the relative risks associated with the three variables when simultaneous adjustment is carried out. The relatively older men have 2.3 times the risk of death shown by

*Examination of mortality among the angina men under age 65 years shows no linear relationship with age, although an important increase in probability of death arises among the men aged 65–74 years. For this reason we defined age as a dichotomous variable in the Cox models. As the other variables included are dichotomous as well, this decision on age classification also permits simpler interpretation of the results.
TABLE 4. Estimated Relative Risks of Death Associated with the Presence of Individual Characteristics, Controlled for Age: 416 Men with Angina but No Myocardial Infarction (MI) Before Baseline. Two-variable Cox Regression Models

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Deaths from all causes</th>
<th>Sudden coronary deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted relative risk*</td>
<td>( x^2 ) (2)</td>
</tr>
<tr>
<td>1a. One or more VPCs vs no VPCs</td>
<td>2.5</td>
<td>31.2</td>
</tr>
<tr>
<td>1b. Complex VPCs vs no complex VPCs</td>
<td>1.8</td>
<td>22.2</td>
</tr>
<tr>
<td>2. ST depression vs no ST depression</td>
<td>3.5</td>
<td>46.8</td>
</tr>
<tr>
<td>3. T-wave abnormality vs no T-wave abnormality</td>
<td>2.9</td>
<td>36.8</td>
</tr>
<tr>
<td>4. Heart rate ( \geq 90 ) beats/min vs</td>
<td>1.3</td>
<td>17.4</td>
</tr>
<tr>
<td>heart rate ( &lt; 90 ) beats/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Congestive heart failure vs no congestive heart</td>
<td>1.5</td>
<td>18.2</td>
</tr>
<tr>
<td>failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Duration of heart disease ( \geq 1 ) year vs</td>
<td>1.2</td>
<td>17.5</td>
</tr>
<tr>
<td>( &lt; 1 ) year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Taking diuretics vs not taking diuretics</td>
<td>1.1</td>
<td>17.4</td>
</tr>
<tr>
<td>8. Taking digitalis vs not taking digitalis</td>
<td>1.4</td>
<td>18.2</td>
</tr>
<tr>
<td>9. Blood pressure elevated vs no elevated</td>
<td>0.9</td>
<td>17.3</td>
</tr>
<tr>
<td>10. Diabetes present vs absent</td>
<td>1.3</td>
<td>18.0</td>
</tr>
</tbody>
</table>

*Relative risk is computed from the estimated coefficients obtained from the Cox models. The 11 two-variable models in each case consist of age (ages 65–74 vs ages 35–64 years) and the characteristic specified.

†The chi-square test with two degrees of freedom is a measure of the statistical significance of the joint role of age and the specified characteristic in explaining the observed data in the Cox model.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All causes of death ( (n = 42) )</th>
<th>Sudden coronary deaths ( (n = 18) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative risk*</td>
<td>( t )</td>
<td>Relative risk*</td>
</tr>
<tr>
<td>Ages 65–74 yrs vs ages 35–64 yrs</td>
<td>2.3</td>
<td>3.2</td>
</tr>
<tr>
<td>One or more VPCs in hour vs no VPCs</td>
<td>2.0</td>
<td>2.5</td>
</tr>
<tr>
<td>ST depression vs no ST depression</td>
<td>2.9</td>
<td>4.0</td>
</tr>
</tbody>
</table>

\( x^2 (3) = 53.6 \quad p < 0.0005 \)
\( x^2 (3) = 28.7 \quad p < 0.0005 \)

Discussion

Studies of the natural history of angina in defined populations show that the risk of death among men with newly diagnosed angina closely resembles that among men after a first MI. An earlier study from
HIP of the incidence and prognosis of CHD among men under age 65 years at diagnosis reported identical mortality risk, over 4.5 years of observation, for 470 men after first MI and 275 men with angina but no antecedent infarction (17.5%, average 3.9% per year). Framingham data for 119 men first presenting with angina over a period of 14 years showed an average mortality of about 4% per year, "whether it arose de novo or in conjunction with a myocardial infarction." Most of the angina patients in this study had been symptomatic for more than 1 year by the date of baseline examination. Almost one-fourth of the MI patients had survived more than one acute episode by date of baseline. By definition, men with angina only had survived from onset of their angina without experiencing an infarction, and thus do not represent the universe of newly diagnosed angina. Our examination of their mortality centers on the role of specific factors — especially ventricular ectopic activity — in influencing risk of death, and on comparing them with MI survivors in this respect.

The 416 men free of prior infarction at baseline show an advantage in 5-year survival over the 1739 men with MI in this study when age alone is controlled. But when subgroups from the two cohorts are defined that are also comparable with respect to presence of VPCs and ST-segment depression, no important difference in survival is apparent in relation to experience of prior MI (fig. 5). We conclude that the difference in age-adjusted mortality between the patients with and without prior MI primarily reflects differences in the prevalence of important myocardial abnormalities such as ST depression, presence of VPCs and congestive heart failure. These clinical measurements are so strongly predictive that it seems reasonable to suggest that studies of the role of surgical or other treatment modalities in the prognosis of angina patients must control effectively for their influence.

Clinical observations have shown associations between decreased ejection fraction and MI, as well as between abnormal left ventricular contraction and the presence of VPCs, in all categories of angiographically defined coronary artery disease. A number of studies that have reported gradients in mortality in relation to angiographically determined levels of severity of coronary artery disease have also documented important roles for indicators of myocardial dysfunction. Ventriculographic abnormalities, abnormal hemodynamics and reduced left ventricular ejection fraction have been shown to have important influence on survival at different levels of coronary vessel involvement. Oberman has stressed the wide variation in natural history of patients with ischemic heart disease in relation to anatomic lesion and extent of left ventricular dysfunction.

An early report from this study documented the association of VPCs identified in 1 hour of monitoring with a number of characteristics thought to reflect

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**Figure 5.** Mortality over 5 years of men with and without myocardial infarction (MI) before baseline, by presence of ST-segment depression (STD) at baseline, and of one or more ventricular premature beats (VPCs) during the baseline monitoring hour.

**Table 6.** Estimated Relative Risks of Death in Relation to Age, Presence of Ventricular Premature Complexes (VPCs) in Monitoring Hour and ST-segment Depression (STD). Logrank Analysis: 416 Men with Angina but No Myocardial Infarction Before Baseline

<table>
<thead>
<tr>
<th></th>
<th>No VPCs in hour</th>
<th>One or more VPCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages 35–64 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>156</td>
<td>58</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Estimated relative risk</td>
<td>1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>Ages 65–74 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>82</td>
<td>38</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Estimated relative risk</td>
<td>3.4</td>
<td>6.5</td>
</tr>
</tbody>
</table>

Mortality comparison

<table>
<thead>
<tr>
<th></th>
<th>logrank $\chi^2$</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Among the eight defined groups</td>
<td>55.8</td>
<td>7</td>
<td>&lt; 0.0005</td>
</tr>
<tr>
<td>Men ages 65–74 years with both VPCs and ST depression compared with all other groups combined</td>
<td>28.1</td>
<td>1</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Men with any one or two of the three risk factors compared with men with none of these factors</td>
<td>16.4</td>
<td>1</td>
<td>&lt; 0.005</td>
</tr>
</tbody>
</table>

Abbreviation: df = degrees of freedom.
myocardial damage or impaired left ventricular function. These features included prior congestive heart failure and ECG abnormalities involving the ST segment and T waves. Patients with such abnormalities in the standard ECG have been shown on angiography to have impaired ventricular performance, which is not observed among coronary patients with normal ECGs. 26 VPCs recorded in 1 hour of monitoring of coronary patients (men with prior infarction and those with angina only) are associated with an increased risk of death over a 5-year period. This risk, which is particularly high with respect to sudden coronary death, has been shown to be independent of other indicators of myocardial dysfunction, such as ST-segment depression and congestive heart failure. 6 A recent study of the prognosis of 2566 men with coronary disease showed that ventricular arrhythmia on the standard ECG had an independent role in risk of death when adjustment was made for angiographically determined ejection fraction and severity of coronary vascular disease. 26

Some observations on the duration of ECG monitoring for ectopic activity were included in an earlier publication. 7 Of the CHD patients identified as being at high risk of sudden death based on the hour of ECG monitoring in this study, only one-fourth had VPCs on the standard (1-minute) ECG. Thus, the hour of monitoring significantly increased the size of the group shown to be at excess mortality risk. Over a 5-year follow-up, 167 sudden coronary deaths occurred in the study group. Of these, 73% had shown one or more VPCs and 45% had shown complex VPCs during 1 hour of baseline monitoring. Thus, despite the known hour-to-hour variability in ectopic activity among CHD patients, the single baseline hour provided strong prognostic information in this epidemiologic study.

We conclude that among men with ischemic heart disease, ventricular ectopic activity detected in 1 hour of monitoring identifies a group at elevated risk of death, whether or not MI has been previously diagnosed. VPCs and ST-segment depression, along with relatively older ages, are powerful predictors of mortality among the men with angina. For example, men ages 65–74 years who have both VPCs and ST depression are at four times the risk of death experienced by men of the same age, and at 14 times the risk of younger men without these abnormalities. Risk of sudden arrhythmic death, which is relatively high among patients with CHD, is further increased by the occurrence of ventricular ectopic activity, not only among men who have had an MI, but also among patients with angina only.

References

Ventricular premature complexes in prognosis of angina.
W Ruberman, E Weinblatt, J D Goldberg, C W Frank, S Shapiro and B S Chaudhary

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