The Effects of Digitalis on Survival in High-risk Patients with Coronary Artery Disease

The Coronary Artery Surgery Study (CASS)

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SUMMARY To examine whether digitalis use is associated with an increased mortality in certain high-risk subsets of patients with coronary artery disease, we analyzed the data of 14,547 patients in the Coronary Artery Surgery Study (CASS) registry who had significant coronary artery stenosis (≥ 70% narrowing) and received medical treatment for their disease. At the time of entry, 2600 patients (18%) were taking a digitalis preparation. At a mean follow-up of 4½ years, the cumulative mortality rate for these patients was 18%, compared with 5% for the 11,947 patients not taking digitalis (p < 0.001). Univariate analysis showed significant differences between the two groups in the following baseline variables: prior infarction, multiple infarction, age, degree of congestive heart failure (CHF), extent of disease, cardiomegaly and wall motion abnormalities.

Cox regression analysis of the entire population failed to show digitalis to be one of the 13 variables independently predictive of survival. High-risk subsets of patients with CHF, myocardial infarction within 2 months preceding entry and patients with prior cardiac arrest or arrhythmia were analyzed separately by Cox analysis. The number of vessels diseased and left ventricular wall motion were the two most important variables predictive of survival in each group. Digitalis therapy failed to enter the final model in any subset of patients studied. The expected mortality of our study population classified according to the degree of CHF was similar to the observed mortality whether the patients were on or off digitalis.

This study fails to confirm the findings of earlier reports showing a substantial mortality associated with digitalis use in certain high-risk subsets of patients with coronary artery disease. Although we could demonstrate no benefit in terms of survival for patients receiving digitalis in this population study, we conclude that digitalis therapy is not likely to be an independent risk factor contributing significantly to mortality in patients with coronary artery disease.

DIGITALIS and dispute have long been companions in the medical literature. At the turn of this century, Lewis1 held the view that digitalis therapy was best suited for the treatment of edema in cases of atrial fibrillation. Christian2 opposed this view and presented evidence that the drug was equally effective in cases of heart failure and sinus rhythm. More contemporary is the debate regarding the efficacy of chronic maintenance digitalis therapy for the treatment of heart failure.3-7 This has been heightened by reports of a high prevalence of toxic reactions, particularly in elderly patients.8 Controversy regarding the use of digitalis glycosides in acute myocardial infarction in the absence of supraventricular tachyarrhythmias exists because of the recognized hazards of toxic arrhythmias, the disputed hemodynamic benefits and the deleterious effects of enhanced myocardial oxygen consumption in the setting of obstructive coronary artery disease.9-14

While the efficacy of digitalis therapy has long been an issue, only recently has it been suggested that treatment with digitalis increases the mortality of certain coronary disease patients. Moss and co-workers15 reported a 30% increase in mortality at the end of 4 months in persons who survived an acute myocardial infarction and who had congestive heart failure (CHF) and complex ventricular premature complexes (VPCs) if they received digitalis therapy compared to similar patients not treated with digitalis. Bigger et al.16 found a fivefold increase in mortality at the end of 1 year in postinfarction patients receiving digitalis after adjusting for relative nondigitalis risk factors.

We examined the data available in the Coronary Artery Surgery Study (CASS) registry to determine if any deleterious effect of digitalis on patient survival could be uncovered in a very large population of patients whose coronary artery disease was precisely defined by angiography and who have been followed prospectively for an average of 4½ years.

Methods

Patients

The study population consisted of 14,547 patients who had significant coronary artery stenosis and known digitalis status at the time of enrollment in the CASS registry and received medical treatment for their diseases. All patients with a history of coronary artery bypass surgery were excluded from analysis. Annual clinical follow-up was mandatory for all patients. The mean follow-up period was 55 ± 19 months, and vital status was known in 99.8% of the population. The patients included 12,215 men, mean age 53.8 years,
and 2336 women, mean age 56.8 years. Twenty-six hundred patients (18%) were taking digitalis at the time of entry into the study.

The methods used in obtaining, storing and analyzing the clinical, hemodynamic, angiographic and follow-up data available on the CASS registry patients have been reported in detail.17

Coronary artery disease was documented by angiography that was performed by the brachial or femoral approach. Significant lesions were considered as either 70% or more reduction in luminal diameter in any view of the right, left anterior descending or left circumflex artery or ≥50% luminal narrowing of the left main coronary artery. Stenoses of large diagonal or marginal branches were considered as lesions of the left anterior descending and circumflex arteries, respectively. Abnormalities in left ventricular wall motion were assessed subjectively from the 30° right anterior oblique view of the cineventriculogram and characterized by using a left ventricular wall motion score as previously described.17 The ejection fraction was calculated by the area-length method.18

Since the principal aim of this analysis was to determine the rate of survival for patients treated with digitalis compared with those not treated with digitalis, three subsets of patients were identified as being at high risk for mortality and in whom the use of digitalis might be more prevalent.

**Congestive Heart Failure**

There were 1380 patients with clinical CHF whose functional impairment at baseline was New York Heart Association (NYHA) class II or worse. Clinical CHF was considered present in any patient who complained either of inappropriate shortness of breath with mild exercise or regular daily activity or described orthopnea or paroxysmal nocturnal dyspnea. The diagnosis was also made when either pedal edema, pulmonary rales or an S4 gallop were present on physical examination. The mortality was 25% at the end of the first year of follow-up for this group of patients.

**Recent Myocardial Infarction**

There were 1592 patients who had a myocardial infarction within 2 months before their entry into the study. At the end of 1 year, the mortality for this group was 10%.

**Cardiac Arrest/Arrhythmia**

Eight hundred seventeen patients had a history of cardiac arrest at baseline. In addition, 1236 patients taking antiarrhythmic medications at the time of entry were included in an attempt to define a group of patients who would be at higher risk for mortality due to serious ventricular arrhythmias. The 1-year mortality for this group of patients was 13%.

**Statistical Analysis**

The univariate differences between the 2600 patients receiving digitalis and the 11,947 patients not receiving digitalis were analyzed with the chi-square for categorical variables and with a t test for quantitative variables. Survival analyses were done using the actuarial method, and the statistical significance was determined by the log-rank test.19 Since approximately one-half of the CASS registry patients who had significant coronary artery disease underwent bypass operations within 90 days of their enrollment angiogram,17 two separate definitions of medically treated patients were used in this study. By the first definition, all patients were initially considered as being medically treated; those who subsequently underwent coronary bypass surgery were included in the analysis until the time of surgery, at which point they were censored (method I). By the second definition, all patients who underwent bypass surgery within 90 days of enrollment were excluded from analysis (method II). All analyses in this study were run separately on the two resulting medically treated populations. The outcome variables and survival rates were similar in every instance.

To determine which variables were predictive of survival and, in particular, to see whether digitalis would enter independently, we used a stepwise Cox regression procedure.20 This procedure identifies variables that contain independent prognostic information after adjusting for the other variables used in the analysis. The process is stepwise, and at each step the variable that contains the most additional predictive power is added to the model. The process stops when the remaining unselected variables no longer contribute statistically significant predictive power. The Cox model can handle both discrete and continuous patient variables, and uses the partial information from patients who have survived for varying intervals. Like the actuarial method, it also takes into account the entire survival curve, not just survival at a particular time.

In addition to analyzing baseline clinical, hemodynamic and angiographic variables to study the relationship between digitalis and mortality, we examined all baseline variables to determine the extent to which digitalis therapy would be predicted. This was done by linear discriminant analysis using actual digitalis therapy as the dependent variable and the baseline characteristics as the independent variables. The regression coefficients of the variables most predictive of digitalis use were then used to construct a single linear discriminator that we denoted as "P-Dig." This mnemonic represents the likelihood (predictive value) that any given patient would receive digitalis therapy. To adjust the estimated relationship between digitalis and mortality in this analysis, a regression was performed with mortality as the dependent variable and the covariates, digitalis therapy and our discriminant function, P-Dig as the independent variables. The average value of the variable P-Dig was also used to calculate an expected mortality for each subgroup tested as a means of isolating the mortality effects due to baseline variables other than digitalis.
Results

Digitalis and Comorbidity

As anticipated, the cumulative mortality was higher for the 2600 patients receiving digitalis at entry compared with the 11,947 patients not receiving digitalis (18% vs 5%, p < 0.001). Analysis of the entire study population showed significant differences in important baseline variables between the two groups and are presented in table 1. Significantly more digitalis patients had suffered prior infarctions that were more often multiple, and three times as many were taking diuretics. There was somewhat more three-vessel disease in the digitalis population. Patients taking digitalis were significantly older, had more advanced clinical CHF, threefold the incidence of cardiomegaly and fourfold the incidence of significant wall motion abnormalities. There was a higher prevalence of diabetes among the patients taking digitalis, but no difference in the prevalence of hypertension. Three times as many patients taking digitalis were receiving antiarrhythmic medication, but the occurrence of sudden death was similar for the two groups.

Prediction of Mortality

Entire Study Population

When Cox regression analysis was applied to the entire study population, 13 variables were identified as being independently predictive of survival and are listed in table 2. The model failed to show digitalis to be independently predictive of survival over the entire follow-up period. Since this represents an analysis of a large and heterogenous population, we focused our attention on smaller, more homogenous subsets of patients at higher risk of dying. For the purposes of this report, we define medically treated patients according to method II.

Congestive Heart Failure

A stepwise Cox analysis of the 974 patients with CHF (identified by method II) showed the following variables to be independent predictors of survival: the number of vessels diseased, left ventricular wall motion score, NYHA functional class, the use of diuretics, and age. In the first step of this analysis, the initial, or unadjusted, chi-square statistic for digitalis was 44.8, indicating that a significant relationship between digitalis and mortality exists when no adjustment is made for the effects of any of the other variables. This relationship disappears when such an adjustment is made, as indicated by the final chi-square for digitalis of 1.94, a value below the 0.05 level of significance.

Figure 1A shows the cumulative survival over 5 years for the 265 patients in this group not receiving digitalis therapy. The survival by year was 89%, 79%, 75%, 69% and 63%, respectively. The rate of survival over 5 years for the 609 patients with CHF who were receiving digitalis therapy was significantly (p < 0.0001) lower (70%, 58%, 49%, 43% and 39%). Figure 1B shows the survival curves for these same two groups of patients after adjusting by stratification on four of the variables that entered the Cox model, i.e., NYHA functional class, left ventricular wall motion score, the use of diuretics and age. The adjusted survival rates are approximately the same for those taking and not taking digitalis and fall to 50% at the end of 5 years in both groups.

Recent Infarction

A stepwise Cox analysis of the 892 patients with recent infarction showed that the significant determinants of mortality were the presence of edema, left ventricular wall motion score, the number of vessels diseased, age and the presence of rales. Digitalis did not enter the final model as a variable with independent significance and had an adjusted chi-square of 3.1, again a reasonably small value.

The unstratified cumulative survival curves for patients with recent infarction (fig. 1C) show that those receiving digitalis therapy had a seemingly greater mortality throughout the follow-up. These same curves, however, become superimposed (fig. 1D) when they are replotted after stratifying the two groups of patients according to the number of vessels diseased, age, left ventricular wall motion score, and the presence of clinical CHF, rales or edema.

Prior Cardiac Arrest/Arrhythmia

For the 1183 patients who had a history of cardiac

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Coronary Patients Receiving and Those Not Receiving Digitalis</th>
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<tr>
<td>Variable</td>
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<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Prior MI</td>
</tr>
<tr>
<td>Multiple MI</td>
</tr>
<tr>
<td>Diuretics</td>
</tr>
<tr>
<td>Three-vessel disease</td>
</tr>
<tr>
<td>Older than 60 years</td>
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<tr>
<td>NYHA II-IV</td>
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<tr>
<td>Cardiomegaly</td>
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<tr>
<td>Asynergy</td>
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<tr>
<td>Mortality</td>
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</table>

Abbreviations: MI = myocardial infarction; NYHA = New York Heart Association functional class.
Selected High-risk Subset

Because an earlier report\textsuperscript{15} indicated a three-factor interaction between digitalis usage, CHF and complex VPCs in patients with recent infarction, we analyzed the number of 4-month mortality events in 1592 patients with recent infarctions classified according to the presence of CHF, complex VPCs (defined as patients with prior cardiac arrest or on antiarrhythmic medication) and the use of digitalis. The method I definition of medically treated patients was used in this analysis. The associated mortality rates for the various combinations of these variables are presented in table 3. Included for comparison are the mortality rates reported by Moss et al.\textsuperscript{15} for a similar subdivision of 812 patients with recent myocardial infarctions. Our data show no significant differences in the mortality rates for the various subdivisions of patients when analyzed according to the use or nonuse of digitalis. In contrast, the Moss data show a significantly higher mortality in the 26 patients with CHF and complex VPCs who received digitalis therapy (38\%) compared with a 2\% mortality among the 56 patients with CHF and complex VPCs who did not receive digitalis.

Fifty-one patients in our series had suffered an acute myocardial infarction within 2 months of enrollment and, in addition, were in CHF and had either a prior cardiac arrest or were taking antiarrhythmic medication on entry into the study, multivariate analysis using the Cox model showed the most important predictors of survival were the number of vessels diseased, left ventricular wall motion score, age, left ventricular end-diastolic pressure, NYHA functional class and prior myocardial infarction. The adjusted chi-square for digitalis was 0.43.

The cumulative survival curves for these patients separated according to the use of digitalis are presented in figures 1E, unstratified, and 1F, stratified according to selected variables. Again, the adjusted curves are nearly superimposed.

**Predictors of Digitalis Therapy**

(Subject vs Expected Mortality)

The clinical and angiographic variables that predicted the use of digitalis therapy as determined by multi-
ple regression analysis are listed in table 4. A single linear discriminant function was constructed to express the estimated probability (P-Dig) that any given patient would receive digitalis therapy, and this was then used as a covariate to adjust the estimated relationship between digitalis and mortality. The effect of this adjustment on the overall mortality of our study population classified according to the degree of CHF present and the presence or absence of digitalis therapy is shown in table 5. The average value of the variable P-Dig is given for each subgroup. This value was used to calculate an expected mortality for the subgroup; that is, a mortality predicted from baseline variables other than digitalis. The expected mortality in each subgroup is remarkably similar to the observed mortality whether the patients were or were not receiving digitalis. (See Appendix for details of calculation.)

Discussion

Our retrospective analysis of data gathered prospectively in a very large number of patients with angiographically defined coronary artery disease fails to show any deleterious effect of the use of digitalis in any subset of patients with symptomatic ischemic heart disease. Although the question of the efficacy of digitalis therapy in the various syndromes of ischemic heart disease, particularly in the setting of acute myocardial infarction, has been controversial, only recently has it been suggested that digitalis therapy increases the mortality of some coronary patients by as much as 30%. Using a stepwise multiple logistic regression analysis that controlled for confounding variables, Moss et al. reported that digitalis use contributed to the increased mortality observed after 4 months of follow-up in a high-risk subset of 812 survivors of acute myocardial infarction. A deleterious effect of digitalis was observed in patients with CHF in the coronary care unit and complex VPCs on predischarge Holter recording, but in no other patient groups analyzed. Bigger et al. published, in abstract form, their findings from a similar retrospective analysis of 508 patients who survived an acute myocardial infarction. They found the risk of dying within 1 year was increased fivefold in patients taking digitalis, but this mortality was not restricted to patients with left ventricular dysfunction and ventricular arrhythmias. The implications of these comparatively large-scale studies are profound because they suggest that postinfarction survival may be increased by withholding or discontinuing the use of digitalis.

Before embarking on a prospective randomized trial of digitalis therapy in this special subset of patients, we felt that the very large coronary disease population available in the CASS registry could be analyzed in sufficient detail to uncover any such association if it truly existed. Unique in comparison to any other such population, the CASS registry patients are precisely characterized by angiographic descriptors of the extent of coronary disease and left ventricular function. Since these variables are the major determinants of survival in patients with coronary artery disease, any study

<table>
<thead>
<tr>
<th>TABLE 3. Digitalis-associated Mortality After Infarction — CASS Data Compared with Those of Moss et al.</th>
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<tbody>
<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Absent Arrest-arrhythmia/Complex VPC</td>
</tr>
<tr>
<td>CASS/Moss Present CASS/Moss</td>
</tr>
<tr>
<td>No digitalis</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Digitalis</td>
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<td>n</td>
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<tr>
<td>Mortality</td>
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Figure 2. One-year cumulative survival rates for postinfarction patients with congestive heart failure and history of cardiac arrest or arrhythmia. No Dig = patients not receiving digitalis therapy; Dig = patients receiving digitalis therapy.

Table 4. Clinical and Angiographic Variables Predictive of Digitalis Therapy

- Prior myocardial infarction
- Use of diuretics
- Use of antihypertensive agents
- Use of β blockers
- S3 gallop
- Enlarged heart
- Left main coronary disease
- Left ventricular score
- Age

A single linear discriminant (P-Dig) expressed the above
of the relationship of digitalis therapy to mortality would be lacking if it did not contain angiographic variables. Additionally, all CASS registry patients have now been followed an average of 4½ years, and vital status information is available in 99.8%.

Initial analysis of our study population showed significant differences in prognostically important baseline variables (table 1) between the 2600 patients receiving digitalis therapy and the 11,947 patients not receiving digitalis therapy. As in the populations analyzed by Moss and Bigger, digitalis served as a therapeutic marker for the sicker patients in our study. However, multivariate analysis that included not only clinical, but also angiographic variables, failed to show significant relationship between digitalis and mortality in either our overall population or in any of the four high-risk subsets.

Although we have not examined patients identical to those studied by Moss and Bigger, our selected high-risk subset of patients who had suffered an acute myocardial infarction within the preceding 2 months and who had CHF and also had a history of cardiac arrest or were taking antiarrhythmic medication represent a close approximation in terms of risk of dying. At 4 months, this subset of patients had a mortality rate of 20%, compared with 13% in the similar, if not identical, patients in the Moss study. At 1 year, this subset of patients had a mortality rate of 30%, compared with 44% in the Bigger study. More important, when analyzed by the Cox model, digitalis did not enter as a variable independently predictive of survival in this special subset of patients. We entered angiographic variables into the model, whereas the Moss and Bigger studies did not.

In examining a population with ischemic heart disease for the possible deleterious influence of digitalis therapy, it appears critical that angiographic variables be considered in addition to clinical variables. Applying the Cox model to our entire study population, we found three angiographic variables — the number of vessels diseased, left ventricular wall motion score and proximal left anterior descending coronary disease — to be variables with independent predictive power, whereas digitalis therapy did not enter the model. In our three high-risk subsets, we also found that angiographic variables entered the Cox model as significant predictors of outcome. For the subset with CHF, both the number of vessels diseased and left ventricular wall motion score entered the model, whereas digitalis did not. Similarly, in the subset with recent infarction, the same two angiographic variables entered the model as being independently predictive of outcome, while digitalis failed to enter the model. In the group of patients with prior cardiac arrest or taking antiarrhythmic agents, the left ventricular wall motion score, the number of vessels diseased and left ventricular end-diastolic pressure all entered the final model. Again, digitalis was not independently predictive of outcome. Thus, the lack of angiographic variables in the two studies that have indicated a deleterious effect of digitalis could account for their observation of a digitalis effect on survival.

Supporting this contention are the results of our analysis in which variables that predicted the use of digitalis therapy were used to form a single linear discriminant function that we identified as P-Dig. Using this function to estimate an expected mortality, that is, a mortality predicted from baseline variables other than digitalis, we found that the expected mortality was almost identical to the observed mortality whether patients were or were not receiving digitalis (table 5). From such an analysis, we conclude that the excess mortality observed in patients taking digitalis is attributable to the characteristics contained in the variable we called P-Dig.

The major 4-month mortality of 38.5% in the digitalis-treated patients with CHF and complex VPCs reported by Moss could be spurious. Of the 972 patients initially constituting that study population, 160 were excluded from the final analysis because of missing values. The residual 812 patients included 39 of the 41 patients who died of cardiovascular causes. A disproportionate cluster of patients who died among the 812 patients with requisite values for analysis could account for the unusual distribution of mortality observed in the study. It is difficult to explain, otherwise, why, among the 678 patients not taking digitalis, there was no gradient in mortality between those with and those without CHF. Indeed, certain patients (those not receiving digitalis) with pitting edema, pulmonary rales and complex VPCs had the lowest mortality in the series.

### Table 5. Mortality in CASS Registry by Functional Class and Digitalis Therapy (Observed vs Expected)

<table>
<thead>
<tr>
<th></th>
<th>No CHF (12,927)</th>
<th>I (240)</th>
<th>II (541)</th>
<th>III (576)</th>
<th>IV (263)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No digitalis (n = 11,947)</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Mortality (%)</td>
<td>P-Dig</td>
<td>0.337</td>
<td>0.432</td>
<td>0.467</td>
<td>0.501</td>
</tr>
<tr>
<td>Expected</td>
<td>5</td>
<td>10</td>
<td>12</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Observed</td>
<td>5</td>
<td>7</td>
<td>12</td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td><strong>Digitalis (n = 2600)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>P-Dig</td>
<td>0.455</td>
<td>0.664</td>
<td>0.680</td>
<td>0.763</td>
</tr>
<tr>
<td>Expected</td>
<td>8</td>
<td>16</td>
<td>20</td>
<td>30</td>
<td>54</td>
</tr>
<tr>
<td>Observed</td>
<td>9</td>
<td>17</td>
<td>21</td>
<td>29</td>
<td>54</td>
</tr>
</tbody>
</table>

Abbreviation: P-Dig = estimated probability that any given patient would receive digitalis therapy.

Of the relationship of digitalis therapy to mortality would be lacking if it did not contain angiographic variables. Additionally, all CASS registry patients have now been followed an average of 4½ years, and vital status information is available in 99.8%.

Initial analysis of our study population showed significant differences in prognostically important baseline variables (table 1) between the 2600 patients receiving digitalis therapy and the 11,947 patients not receiving digitalis therapy. As in the populations analyzed by Moss and Bigger, digitalis served as a therapeutic marker for the sicker patients in our study. However, multivariate analysis that included not only clinical, but also angiographic variables, failed to show significant relationship between digitalis and mortality in either our overall population or in any of the four high-risk subsets.

Although we have not examined patients identical to those studied by Moss and Bigger, our selected high-risk subset of patients who had suffered an acute myocardial infarction within the preceding 2 months and who had CHF and also had a history of cardiac arrest or were taking antiarrhythmic medication represent a close approximation in terms of risk of dying. At 4 months, this subset of patients had a mortality rate of 20%, compared with 13% in the similar, if not identical, patients in the Moss study. At 1 year, this subset of patients had a mortality rate of 30%, compared with 44% in the Bigger study. More important, when analyzed by the Cox model, digitalis did not enter as a variable independently predictive of survival in this special subset of patients. We entered angiographic variables into the model, whereas the Moss and Bigger studies did not.

In examining a population with ischemic heart disease for the possible deleterious influence of digitalis therapy, it appears critical that angiographic variables be considered in addition to clinical variables. Applying the Cox model to our entire study population, we found three angiographic variables — the number of vessels diseased, left ventricular wall motion score and proximal left anterior descending coronary disease — to be variables with independent predictive power, whereas digitalis therapy did not enter the model. In our three high-risk subsets, we also found that angiographic variables entered the Cox model as significant predictors of outcome. For the subset with CHF, both the number of vessels diseased and left ventricular wall motion score entered the model, whereas digitalis did not. Similarly, in the subset with recent infarction, the same two angiographic variables entered the model as being independently predictive of outcome, while digitalis failed to enter the model. In the group of patients with prior cardiac arrest or taking antiarrhythmic agents, the left ventricular wall motion score, the number of vessels diseased and left ventricular end-diastolic pressure all entered the final model. Again, digitalis was not independently predictive of outcome. Thus, the lack of angiographic variables in the two studies that have indicated a deleterious effect of digitalis could account for their observation of a digitalis effect on survival.

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The major 4-month mortality of 38.5% in the digitalis-treated patients with CHF and complex VPCs reported by Moss could be spurious. Of the 972 patients initially constituting that study population, 160 were excluded from the final analysis because of missing values. The residual 812 patients included 39 of the 41 patients who died of cardiovascular causes. A disproportionate cluster of patients who died among the 812 patients with requisite values for analysis could account for the unusual distribution of mortality observed in the study. It is difficult to explain, otherwise, why, among the 678 patients not taking digitalis, there was no gradient in mortality between those with and those without CHF. Indeed, certain patients (those not receiving digitalis) with pitting edema, pulmonary rales and complex VPCs had the lowest mortality in the series.
However, in terms of mortality, no beneficial effect of digitalis therapy could be demonstrated in our study. The efficacy of digitalis therapy may reside only in the alleviation of symptoms of CHF (morbidity) and not materially influence overall mortality in a population study such as this. Only recently has it been demonstrated in a well-controlled, randomized, double-blind, crossover trial that digoxin confers clinical benefit to patients with CHF unaccompanied by atrial fibrillation. Moreover, the authors of that study showed that the presence of a third heart sound was the strongest correlate of the response to digoxin. Analyzing the subset of our patients who had a third heart sound, we could find no influence of digitalis therapy on mortality outcome. Clearly, the findings of our study shed no light on the controversy relating to the efficacy of chronic maintenance digitalis therapy for the treatment of CHF.

Our CASS population is a somewhat select group of coronary artery disease patients presenting to medical clinics distributed throughout the United States and Canada in that all of the CASS patients qualified for coronary arteriography. Moreover, of those who had important stenoses of the coronary vessels, nearly half underwent coronary bypass operations within 2–3 months of study. To eliminate whatever selection bias these considerations may have contributed to our study population, we analyzed our data using two separate definitions of medically treated patients. Whether we include (method I) or exclude (method II) patients who underwent coronary bypass surgery within 90 days of angiography, digitalis therapy had no impact on their short- or long-term mortality.

Based on this analysis, we could not confirm the findings of two earlier studies that showed a significantly higher mortality in certain patients with coronary disease treated with digitalis. Our data suggest that any apparent association between digitalis use and mortality, particularly in coronary patients at high risk, may be dissipated by controlling for appropriate angiographic and hemodynamic variables in addition to clinical variables. In view of these considerations, we feel it would be a premature judgement to withhold digitalis therapy, when clinically indicated, on the grounds that a substantial mortality risk has been validly established with its use in patients with coronary artery disease.

Acknowledgment
We gratefully acknowledge the secretarial assistance of Mary-Grace Lett in the preparation of this manuscript.

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Appendix 1
Construction of P Dig

We intended to find a single linear combination of baseline variables that could be used to predict digiogxin therapy. The 14,547 CAD patients
were grouped according to NYHA functional class, leading to five
groups: 0 = no CHF, 1 = CHF/no impairment, 2 = mild impairment,
3 = moderate impairment, and 4 = severe impairment. Within each
impairment category, a multiple linear regression was computed on 20
baseline variables, with digitalis (yes/no) the dependent variable.

As anticipated from the baseline differences of the digitalis users and
those nonusers, many variables were independently predictive of digi-
talis therapy. Based on a combination of significance of the regression
coefficients and on consistency of sign of the coefficients across impair-
ment groups, two groups of variables were selected: one for the nonCHF
patients and one for the four other impairment groups. We thought that a
different model for digitalis might hold, depending on CHF status.

The two resulting linear predictor equations are:

**No CHF**

\[
\text{P Dig} = \alpha + 0.00625 (\text{entry year}) + 0.0144 \cdot (1 \text{ if female}) - 0.0415 \cdot (1 \text{ if hypertensive}) + 0.0489 \cdot (1 \text{ if diabetic}) + 0.0490 \cdot (1 \text{ if previous MI}) + 0.166 \cdot (1 \text{ if diuretic}) - 0.00932 \cdot (1 \text{ if } \beta \text{ blockers}) + 0.0744 \cdot (1 \text{ if } S_2 \text{ gallop}) + 0.0760 \cdot (1 \text{ if years}) + 0.0559 \cdot (1 \text{ if enlarged heart}) + 0.0116 \cdot (\text{LVSCOR}) + 0.00496 \cdot \text{(Age in years)}
\]

**CHF**

\[
\text{P Dig} = \alpha + 0.0571 \cdot (1 \text{ if male}) + 0.0490 \cdot (1 \text{ if previous MI}) + 0.375 \cdot (1 \text{ if diuretic}) - 0.0474 \cdot (1 \text{ if antihypertensives}) - 0.0505 \cdot (1 \text{ if beta blockers}) + 0.0744 \cdot (1 \text{ if } S_2 \text{ gallop}) + 0.0923 \cdot (1 \text{ if enlarged heart}) + 0.000041 \cdot (1 \% \text{ RCA stenosis}) + 0.000082 \cdot (1 \% \text{ LMCA stenosis}) + 0.00755 \cdot (\text{LVSCOR}) + 0.0064 (\text{age in years})
\]

where MI = myocardial infarction, LVSCOR = left ventricular wall
motion score, RCA = right coronary artery, and LMCA = left main
coronary artery.

The constant \(\alpha\) was chosen in each impairment category so that the
distribution of P Dig would approximately reflect the actual propor-
tion on digitalis. In both CHF and non-CHF patients, the single most im-
portant variable was whether or not the patient was on diuretics, this being
another marker of CHF and its severity.

**Use of P Dig to Adjust Mortality**

P Dig was used to adjust mortality as a covariate in a multiple linear
regression of mortality on actual digitalis and exposure (in years) and to
compute expected mortality, within NYHA class, for those receiving
digitalis and those not receiving it.

In the first method, it could be seen whether actual digitalis therapy
would be independently predictive of survival after adjusting for P Dig
—the predicted therapy, so to speak.

The second method went as follows. The relationship of P Dig to
mortality was estimated separately within each impairment category
and digitalis status, which gave five separate regression coefficients, when
averaged over digitalis status. These coefficients were applied to the
difference in mean value of P Dig between those receiving and not
receiving digitalis in the five categories, to arrive at an expected differ-
ence in mortality between the two groups. Then, based on the overall
mortality in each impairment category, the expected difference was
converted to expected mortality rates for the two groups. Thus, the total
expected mortality in each impairment category is set equal to its ob-
erved value, and two expected mortalities within each category are
functionally dependent.

**Appendix 2**

**Physicians and Operating Clinical Sites**

University of Alabama in Birmingham — William J. Rogers, M.D.,* Richard O. Russell, M.D., Albert Oberman, M.D., Nicholas T. Kou-
choukos, M.D.; Albany Medical College — Julio A. Sosa, M.D.,* Martin F. McKneally, M.D.,* Thomas M. Older, M.D., Eric D. For-
ter, M.D., Joseph McIlhudd, M.D.; Loma Linda University — Melvin P. Judkins, M.D.,* Patrick M. Moloney, M.D.; Boston University —
Thomas J. Ryan, M.D.,* Robert L. Berger, M.D., David P. Faxon, M.D., Donald A. Weiner, M.D., Laura F. Wexler, M.D.; Marshfield
Medical Foundation, Inc. — William O. Myers, M.D.,* Richard D. Sautter, M.D.,* John N. Bowell, M.D., Dieter M. Voss, M.D., Robert
D. Carlson, M.D.; Massachusetts General Hospital — J. Warren Harthorne, M.D.,* W. Gerald Austen, M.D., Robert Dinsmore, M.D.,
Frederick Levine, M.D., John McDermott, M.D., Frederick Poulin, M.D.; Mayo Clinic and Mayo Foundation — Robert L. Frye, M.D.,*
Hugh C. Smith, M.D., Michael B. Mock, M.D., Ronald E. Vliesstra, M.D., Richard E. Fulton, M.D.

Miami Heart Institute — Arthur J. Gosselin, M.D.,* Parry B. Larsen, M.D., Paul S. Swaye, M.D.; Michael Heart Institute — Martial
G. Bourassa, M.D.,* Jacques Lesperance, M.D., Bernard R. Chef-
man, M.D., Claude Goulet, M.D., Claude M. Grondin, M.D.; New
York University — Ephraim Glassman, M.D.,* Michael Schloss,
M.D., O. Wayne Isom, M.D.; St. Louis University — George C.
Kaiser, M.D.,* J. Gerard Mudd, M.D.,* Henrick B. Barner, M.D.,
John E. Codd, M.D., Hillel M. Laks, M.D., Denis H. Tyras, M.D.,
Robert D. Weiss, M.D., Vallee L. Willman, M.D.; St. Luke’s Hospital
Center, New York, New York — Harvey G. Kemp, Jr., M.D.,* Airlie
Cameron, M.D.; Stanford University — Edwin L. Alderman, M.D.,*
James F. Silverman, M.D.,* Edward B. Stinson, M.D.; Medical Col-
lege of Wisconsin — Felix Tristani, M.D.,* Robert J. Flemmma, M.D.,
Harold R. Brooks, M.D.; Yale University — Lawrence S. Cohen,
M.D.,* Alexander S. Geha, M.D., Graeme L. Hammond, M.D., Rene
Langou, M.D., Richard K. Shaw, M.D.

**Coordinating Center**

University of Washington — Lloyd D. Fisher, Ph.D.,* Mary Jo
Gillespie, M.S., Kathryn B. Davis, Ph.D., J. Ward Kennedy, M.D.,
Richard A. Kronmal, Ph.D.

**Central Electrocardiographic Laboratory**

University of Alabama at Birmingham — L. Thomas Sheffield,
M.D.*

**Chairman of Steering Committee**

Thomas Killip, M.D., Henry Ford Hospital, Detroit, Michigan
National Heart, Lung, and Blood Institute
Eugene Passamani, M.D., Peter L. Frommer, M.D., Kent R. Bailey,
Ph.D., Suzanne Mullin, R.N.

*Denotes principal investigator.
The effects of digitalis on survival in high-risk patients with coronary artery disease. The Coronary Artery Surgery Study (CASS).
T J Ryan, K R Bailey, C H McCabe, S Luk, L D Fisher, M B Mock and T Killip

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