Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 43, No. 4, 2004
ISSN 0735-1097/04/$30.00
doi:10.1016/j.jacc.2003.10.031

The Prognostic Importance of Comorbidity for Mortality in Patients With Stable Coronary Artery Disease

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OBJECTIVES To identify the prevalent and prognostically important coexisting illnesses among single coronary artery disease (CAD) patients.

BACKGROUND As the population ages, physicians are increasingly required to make decisions concerning patients with multiple co-existing illnesses (comorbidity). Many trials of CAD therapy have excluded patients with significant comorbidity, such that there are limited data to guide the management of those patients.

METHODS To consider the long-term prognostic importance of comorbid illness, we examined a cohort of 1,471 patients with CAD who underwent cardiac catheterization between 1985 and 1989 and were followed up through 2000 in the Duke Databank for Cardiovascular Diseases. Weights were assigned to individual diseases according to their prognostic significance in Cox proportional hazards models, thus creating a new CAD-specific index. The new index was compared with the widely used Charlson index, according to prevalence of conditions, individual and overall associations with survival, and agreement.

RESULTS The Charlson index and the CAD-specific index were highly associated with long-term survival and almost equivalent to left ventricular ejection fraction. When considering the components of the Charlson index, diabetes, renal insufficiency, chronic obstructive pulmonary disease, and peripheral vascular disease had greater prognostic significance among CAD patients, whereas peptic ulcer disease, connective tissue disease, and lymphoma were less significant. Hemiplegia, leukemia, lymphoma, severe liver disease, and acquired immunodeficiency syndrome were rarely identified among patients undergoing coronary angiography.

CONCLUSIONS Comorbid disease is strongly associated with long-term survival in patients with CAD. These data suggest co-existing illnesses should be measured and considered in clinical trials, disease registries, quality comparisons, and counseling of individual patients. (J Am Coll Cardiol 2004;43:576–82) © 2004 by the American College of Cardiology Foundation

As people age, they are more likely to develop chronic medical conditions, including hypertension, vascular disease, arthritis, and cancer. Over 60% of persons ≥60 years old have two or more such chronic illnesses (1). Although studies of medical therapeutics typically focus on a single disease, such co-existing illnesses can potentially alter both the efficacy of therapies and the course of the primary disease. With the provision of new therapies to older patients, it has become increasingly important to understand the impact of co-existing illness, or "comorbidity," on long-term prognosis.

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In the case of patients with coronary artery disease (CAD), comorbid illness has typically been considered according to two systems: "coronary disease risk factors," or diseases that increase the likelihood of developing coronary disease, and the Charlson comorbidity index (2,3). The former approach involving risk factors for coronary disease does not consider a number of prevalent and morbid illnesses, including cancer, lung disease, and renal insufficiency. The latter measure, the Charlson index, considers 12 chronic conditions and corresponding weights according to their association with one-year mortality in a cohort of 559 patients treated in the General Medicine Department of New York University.

In this study, we sought to identify the chronic medical conditions that are important for CAD patients according to their prevalence and association with long-term mortality among a cohort of 1,471 patients followed up for over 10 years. We also examined the degree to which a new CAD-specific comorbidity index provided additional prognostic information compared with the widely used Charlson index.

METHODS

Patient population. All patients undergoing initial coronary angiography for symptoms of chronic CAD and found to have significant disease (≥75% stenosis) in one or more coronary arteries between July 1985 and June 1989 at Duke University Medical Center were identified using the Duke Databank for Cardiovascular Diseases. Of the patients meeting this criterion, a random 50% sample was selected for detailed assessment of comorbid illnesses.

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Manuscript received October 21, 2002; revised manuscript received September 22, 2003, accepted October 7, 2003.

Abbreviations and Acronyms

AIDS = acquired immunodeficiency syndrome
CAD = coronary artery disease
CHF = congestive heart failure
LVEF = left ventricular ejection fraction
MI = myocardial infarction

Relevant coronary disease data from history and coronary angiography were prospectively collected as previously described (4,5). Comorbidity information required to calculate the Charlson index was collected by chart review, according to the approach and definitions established by Charlson (2). Patients were followed up at six months, one year, and then annually by a mailed questionnaire, with telephone backup, as well as a National Death Index search for nonresponders through December 2000. Coronary disease severity was specified according to: 1) the number of epicardial coronary arteries involved; 2) a previously established index of coronary disease severity ranging from 0 to 100, based on the severity and location of lesions and their relative prognostic importance (i.e., a 75% right coronary artery lesion would be rated at 20; a 95% left main lesion would be rated at 100); 3) and left ventricular ejection fraction (LVEF).

Analysis. We used Cox proportional hazards regression models, using time to all-cause mortality as the dependent variable, to develop a new CAD-specific comorbidity index and to compare the relative prognostic association of the new index with the Charlson index (6,7).

CAD-specific index. To consider the likely possibility that comorbid illnesses may have different associations with mortality for CAD patients, we entered all non-cardiac elements (excluding myocardial infarction [MI] and congestive heart failure [CHF]) of the Charlson index, prevalent among the study population, along with tobacco abuse, hypertension, hyperlipidemia, and family history, into a proportional hazards model containing age, gender, LVEF, and CAD severity to create a CAD-specific index. Continuous variables were transformed to conform to model assumptions. After the final model was determined, a weight for each comorbidity component was derived using the log hazard ratios from the model. A weight of 2 was assigned to diabetes, and weights for the other components were calculated relative to diabetes and then rounded to the nearest integer. Then, any component with a derived weight of 0 was dropped before creating the final CAD-specific index. To avoid spurious associations, the CAD-specific model was first developed on a training sample involving a random 50% of subjects and then tested on the remaining 50%. As both samples resulted in similar indexes, the final index was derived for the full sample. To verify the stability of the low prevalence conditions, bootstrap estimations were also done. Bootstrap samples (400 samples of the same size as the original population, but with patients drawn randomly, with replacement, from the full study population) were created. The model was fit on these bootstrap samples and then tested on the original sample to estimate the degree to which the predictive accuracy of the model would deteriorate when applied to an independent sample of patients (8).

Comparisons of CAD-specific index and Charlson index. After deriving a CAD-specific index, we compared its association with survival to that of the Charlson index. Proportional hazards models involving the same patients were specified, adjusting for age, gender, LVEF, CAD severity, and either the CAD-specific index or the Charlson index. First, we compared the original Charlson index scores with the new scores for specific conditions. Second, model likelihood ratio chi-square values were compared as a reflection of the association with survival. Third, the relative discriminatory ability of each index was also considered by a comparison of model likelihood ratio chi-square values. Fourth, calibration was considered by plotting predicted survival probability versus actual survival probability, stratified by 10 intervals of predicted survival probability. Finally, to consider relative prognostic associations when the Charlson index and CAD-specific index disagreed, we plotted Kaplan-Meier curves for three sets of patients: those whose CAD-specific index scores fell within the interquartile range at each Charlson score (similar prediction); those whose CAD-specific index scores were above the 75th percentile at each Charlson score (CAD-specific index worse); and those whose CAD-specific index scores fell below the 25th percentile (CAD-specific index better). Analyses were repeated using the full Charlson index (including MI and CHF) and a new CAD-specific index that included these terms.

RESULTS

A total of 1,471 patients undergoing initial coronary angiography were included in the study and followed up for a mean of 13.6 years. Through December 2000, there were 633 deaths, and the mean time to death was 11.4 years. The clinical characteristics of these patients are listed in Table 1. The mean age at study entry was 60.9 years; 28% of the patients were female, and 8% were African American. Compared with patients without comorbid illnesses, those with one or more additional condition(s) were older and more likely to be female and had worse coronary disease severity according to more diseased epicardial vessels and a slightly lower mean LVEF.

The number of patients having each Charlson condition is listed in Table 2. As expected with a cohort of CAD patients, six of the seven most common conditions were risk factors for or direct manifestations of vascular disease, including MI, diabetes mellitus, peripheral vascular disease, CHF, and cerebrovascular disease. No patients had acquired immunodeficiency syndrome (AIDS) or moderate to severe liver disease at the time of coronary angiography. The

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Table 1. Demographic and Characteristics of 1,471 Patients With Coronary Artery Disease

	Total (n = 1,471)	Modified Charlson Index = 0 (n = 574)	Modified Charlson Index >0 (n = 897)	p Value
Age (yrs)	60.9 ± 9.6	60.1 ± 9.8	62.0 ± 9.3	< 0.001
Female (%)	28.0	25.4	31.2	0.02
Race (%)				0.34
African American	8.0	8.3	7.8	
White	90.9	90.9	90.7	
Other	1.1	0.8	1.5	
Hypertension (%)	55.7	52.8	59.3	0.01
Current smoking (%)	33.6	32.7	34.6	0.44
History of MI (%)	36.2	34.2	38.6	0.09
No. of diseased vessels (%)				< 0.0001
1	31.0	35.4	25.6	
2	30.5	30.1	31.0	
3	38.5	34.5	43.4	
CHF severity (%)				0.001
None	87.5	90.4	84.0	
NYHA class I	2.86	2.35	3.48	
NYHA class II	5.03	4.44	5.75	
NYHA class III	3.26	2.22	4.54	
NYHA class IV	1.36	0.62	2.27	
Chest pain course (%)				0.28
Improving	5.57	6.28	4.74	
Stable	34.66	36.05	33.02	
Progressing	48.41	47.13	49.92	
Unstable	11.36	10.55	12.32	
Ejection fraction (%)	50.8 ± 10.6	51.8 ± 9.8	49.5 ± 11.4	< 0.0001

Data are presented as the mean value ± SD or percentage of patients.
CHF = congestive heart failure; MI = myocardial infarction; NYHA = New York Heart Association.

greatest proportion of patients scored exhibited minimal comorbid disease.

In a comparison of conditions in the newly derived CAD-specific index with those of the Charlson index, a number of conditions increased in relative importance, including moderate to severe renal disease, chronic pulmonary disease, and peripheral vascular disease (Table 3). Other conditions were not found to be significantly associated with long-term mortality in the coronary disease population, including peptic ulcer disease, lymphoma, and connective tissue disease. For certain low-prevalence conditions, such as dementia, mild liver disease, hemiplegia, leukemia, moderate or severe liver disease, and AIDS, conclusions could not be drawn. Of the four conditions tested that were not specified by Charlson, ongoing tobacco abuse and hypertension were significantly associated with survival, whereas family history and hyperlipidemia were not. The distribution of Charlson and CAD-specific scores for all patients is depicted in Table 4.

As shown by unadjusted Kaplan-Meier curves, both the Charlson index and CAD-specific index stratified patients according to distinct survival patterns (Fig. 1). For the Charlson index, scores of 0, 1, and ≥2 yielded survival probabilities of 88.3% (95% confidence interval [CI] 85.9% to 90.3%), 84.7% (80.6% to 87.9%), and 68.9% (63.2% to 73.9%), respectively. For scores of 0 to 1, 2 to 3, and ≥4, the respective five-year all-cause survival probabilities for the CAD index were 89.2% (95% CI 86.9% to 91.1%), 81.6% (77.5% to 85.1%), and 67.9% (61.6% to 73.4%), respectively.

In proportional hazards models that adjusted for age, gender, and LVEF, both the modified Charlson index and the CAD-specific index were the strongest predictors of mortality according to chi-square values for each term, with

Table 2. Number (%) of Patients With Each Condition

Current smoker	494 (33.6%)
Hypertension	820 (55.7%)
Myocardial infarction	413 (28.1%)
Diabetes mellitus (total)	268 (18.2%)
Peptic ulcer disease	186 (12.6%)
Peripheral vascular disease	118 (8.0%)
Diabetes with end-organ damage	113 (7.7%)
Congestive heart failure	110 (7.5%)
Cerebrovascular disease	105 (7.1%)
Chronic pulmonary disease	95 (6.5%)
Any tumor	29 (2.0%)
Connective tissue disease	23 (1.6%)
Metastatic solid tumor	16 (1.1%)
Moderate or severe renal disease*	13 (0.9%)
Dementia	6 (0.4%)
Hemiplegia	4 (0.3%)
Mild liver disease	4 (0.3%)
Lymphoma	3 (0.2%)
Leukemia	2 (0.1%)
Moderate or severe liver disease	0
Acquired immunodeficiency syndrome	0

*Moderate renal disease includes patients with creatinine >3 mg/dl, whereas severe renal disease includes patients on dialysis or those who have undergone kidney transplantation.

Table 3. The Charlson Comorbidity Index as Compared With the CAD-Specific Index

Charlson Weights	Conditions	CAD-Specific Index
0	Current smoker	1
	Hypertension	1
1	Myocardial infarction	*
	Dementia	Limited cases†
	Peptic ulcer disease	Not significant‡
	Congestive heart failure	*
	Connective tissue disease	Not significant
	Mild liver disease	Limited cases
	Cerebrovascular disease	1
	Diabetes mellitus	2
	Chronic pulmonary disease	2
	Peripheral vascular disease	2
2	Hemiplegia	Limited cases
	Leukemia	Limited cases
	Any tumor	2
	Diabetes with end-organ damage	3
	Moderate or severe renal disease‡	7
	Lymphoma	Not significant
3	Moderate or severe liver disease	Limited cases
6	Acquired immunodeficiency syndrome	Limited cases
	Metastatic solid tumor	5

*Myocardial infarction and congestive heart failure were excluded from the CAD index, as these represent direct manifestations of coronary disease, rather than comorbid illness. †Limited cases denotes that there were not enough cases in our data set to reach a valid conclusion. ‡Not significant indicates that our models revealed these diseases were "not significantly" associated with survival. ‡Moderate renal disease includes patients with creatinine of >3 mg/dl, whereas severe renal disease includes patients on dialysis or those who have undergone kidney transplantation.
CAD = coronary artery disease.

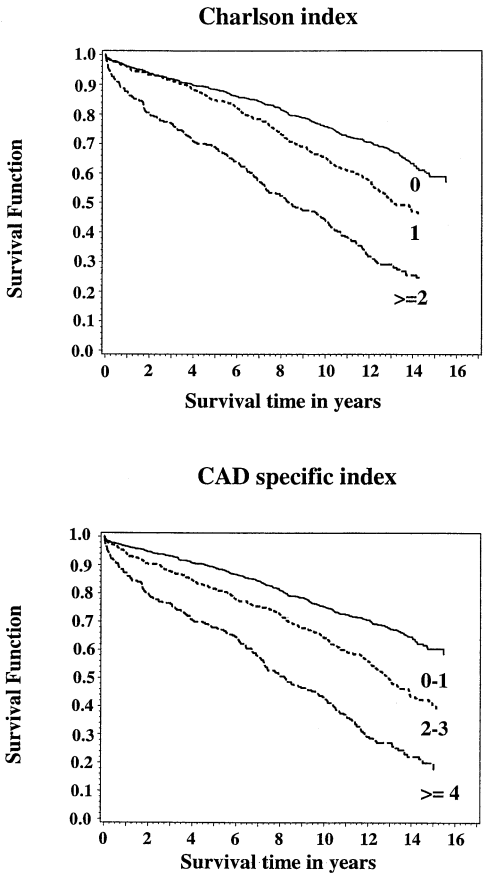

Figure 1. Kaplan-Meier survival curves for the Charlson and coronary artery disease (CAD) indexes. Patients were classified by their score, such that each graph depicts a similar number of patients in a particular risk category. There are approximately 55% of patients in the lowest risk group (Charlson score = 0; CAD score = 0 to 1), 25% at intermediate risk (Charlson score = 1; CAD score = 2 to 3), and 20% at highest risk (Charlson score = >2; CAD score = >4). Both indexes stratify risk well.

the CAD-specific index having the higher value (Table 5). When comparing the strength of association for the entire model, the model containing the CAD-specific index had a stronger association according to a significantly higher likelihood ratio chi-square value (modified Charlson index chi-square 243; CAD-specific index chi-square 277). When making a comparison between the two indexes, the CAD-specific index added significant prognostic information to a model containing the modified Charlson index (chi-square = 34, $p < 0.0001$), whereas the modified Charlson index did not add significantly to a model containing the CAD-specific index (chi-square = 0.8, $p = 0.36$). When comparing the overall indexes with their individual components, the addition of the component conditions of the Charlson index to a model containing the overall index had a significantly greater association with prognosis, further suggesting that the Charlson scores should be reweighted for our population to obtain a better estimate of survival (chi-square = 39, $p < 0.0001$). The addition of the components of the CAD-specific index to a model containing the overall index did not change the association with survival, indicating appropriate weights for our population (chi-square = 6.0, $p = 0.92$).

Table 4. Frequency of Scores by the Charlson and CAD-Specific Indexes

Charlson Index	Index Score	CAD-Specific Index
810 (55%)	0	286 (19%)
378 (26%)	1	539 (37%)
187 (13%)	2	220 (15%)
63 (4%)	3	183 (12%)
15 (1%)	4	133 (9%)
0	5	60 (4%)
12 (0.8%)	6	23 (1.6%)
5 (0.3%)	7	10 (0.7%)
1 (0.07%)	8	8 (0.5%)
0	9	4 (0.3%)
0	10	0
0	11	5 (0.3%)

CAD = coronary artery disease.

Figure 2 shows actual and predicted five-year survival for groups of patients stratified by index scores for both the Charlson and CAD-specific indexes. Both indexes showed good calibration with all points falling close to the line of perfect agreement. When considering discrimination according to *c* indexes for five-year survival predictions, both models yielded similar values (0.72 and 0.73, respectively). These values indicate that for all potential pairs of patients who either survived or died by five years, the proportional hazards models assigned greater risk approximately 73% of the time to those who died.

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Table 5. Cox Linear Regression Models

	Parameter Estimate	Standard Error	p Value	Hazard Ratio (95% CI)
Model 1: chi-square = 243.3, *df* = 5*				
Modified Charlson index†	0.34	0.04	< 0.0001	1.41 (1.30–1.53)
Age <62 yrs	0.04	0.01	0.0015	1.04 (1.01–1.06)
Age ≥62 yrs	0.07	0.01	< 0.0001	1.08 (1.06–1.10)
Female	−0.04	0.12	0.7151	0.957 (0.75–1.21)
Ejection fraction (%)	−0.05	0.01	< 0.0001	0.95 (0.94–0.96)
Model 2: chi-square = 276.7, *df* = 5*				
CAD-specific index‡	0.30	0.03	< 0.0001	1.34 (1.27–1.42)
Age <62 yrs	0.04	0.01	0.0026	1.04 (1.01–1.06)
Age ≥62 yrs	0.09	0.01	< 0.0001	1.10 (1.07–1.12)
Female	−0.06	0.12	0.6675	0.95 (0.75–1.20)
Ejection fraction (%)	−0.05	0.01	< 0.0001	0.95 (0.94–0.96)

*Two different slopes were used in both models 1 and 2 to represent the age effect. In model 1, for patients with age <62 years, the hazard increases 4% for every 1-year increase in age; for patients with age ≥62 years, the hazard increases 8% for every 1-year increase in age. †Modified Charlson index is the sum of original Charlson weights, with myocardial infarction and congestive heart failure removed. ‡CAD-specific index is the sum of new weights from the CAD population, with myocardial infarction and congestive heart failure removed.

CAD = coronary artery disease; CI = confidence interval; *df* = degrees of freedom.

Our final comparison examined survival for patients in whom the two indexes disagreed. For patients whose CAD-specific index score was above the 75th percentile at each given level of the Charlson index (higher risk), Kaplan-Meier curves demonstrated worse survival than for patients whose CAD-specific index and Charlson index agreed. Conversely, for patients whose CAD-specific index score fell below the 25th percentile, Kaplan-Meier curves also showed worse survival than for those in an intermediate range, though survival was not quite as poor for those in the higher CAD-specific index range. Thus, when the Charlson index and CAD-specific index disagreed, patients appeared to have higher mortality, correlating with the index that portended a worse prognosis. Among the discordant groups, a higher CAD-specific index was associated with the worst survival.

When analyses were repeated after including all Charlson conditions, including MI and CHF, the same trends were observed regarding the strength of association, calibration, discrimination, and outlier analyses.

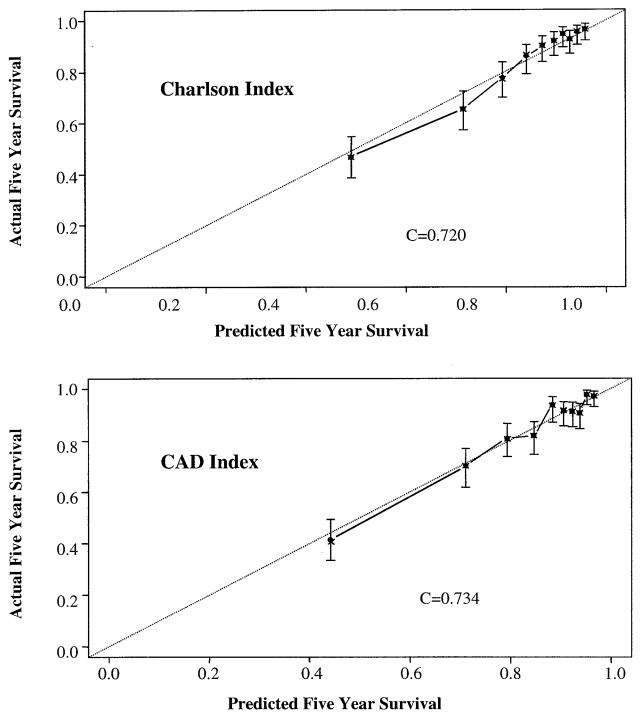

Figure 2. Actual versus predicted survival by each index. Both indexes show good calibration, with most points falling close to the line of perfect agreement. The coronary artery disease (CAD) index performed slightly better, as evidence by an improved *c* index.

DISCUSSION

This study demonstrates that comorbid illness, or illnesses that co-exist with coronary disease, is strongly associated with long-term survival. In proportional hazards models examining patients in the Duke Databank for Cardiovascular Diseases, the strength of this association between comorbid illness and survival was almost equivalent to that afforded by standard measures of coronary disease severity, including LVEF. These findings indicate that comorbid illness must be taken into account when considering the long-term benefit of coronary disease therapies in clinical trials, disease registries, quality comparisons, and counseling of individual patients. These findings are particularly important to the elderly, given their high prevalence of co-existing illness and the increasing numbers of elderly patients facing treatment decisions for CAD.

A second remarkable finding of this study was the relative stability of the prognostic significance of the Charlson comorbidity index among CAD patients. We were surprised to find that a measure of comorbid illness, based on one-year mortality, for 559 New York University general medicine patients would have an association with long-term survival similar to an index specifically developed and weighted to our CAD population. Our findings did suggest some modifications to the Charlson index that may make this measure more suitable to CAD patients. These modifications include assigning greater

weight to renal disease, diabetes with end-organ damage, chronic obstructive pulmonary disease, and peripheral vascular disease, as well as dropping some conditions from consideration due to their lack of prognostic significance (peptic ulcer disease, lymphoma, connective tissue disease) or low prevalence (dementia, liver disease, hemiplegia, leukemia, and AIDS) among CAD patients being considered for revascularization.

The highly significant correlation between comorbid illness and prognosis observed among our CAD patients has been previously investigated. Several previous studies have documented increased mortality among persons with specific index conditions. From the Framingham Study, we know that diabetics suffer worse outcomes than nondiabetics (9). Investigators have demonstrated through the use of the Coronary Artery Surgery Study (CASS) registry that patients with peripheral vascular disease and ongoing tobacco abuse have shortened long-term survival, whereas those with hyperlipidemia are unaffected (10–12). Shlipak et al. (13) examined over 100,000 patients and established renal disease as an independent risk factor for death after MI.

The philosophy of a score such as the Charlson index is to account for illnesses other than the condition of interest in comparisons of treatment and outcome. There is, however, some overlap in etiology and disease progression between the elements of our comorbidity index and the primary disease of interest. For example, peripheral vascular disease and cerebrovascular disease may be considered manifestations of underlying "vascular disease" that has progressed to affect multiple territories rather than distinct comorbid illnesses. Given this overlap, some components of our index may be considered to represent "disease staging" rather than wholly separate disease entities.

Clinical significance. These findings can be applied to a number of settings. Our study identifies, among CAD patients, prevalent and prognostically important co-existing illnesses that should be measured and considered in clinical trials and coronary disease registries regarding medical therapeutics. They also suggest that whenever possible, clinical trials should include subjects with significant comorbid illness, such as renal insufficiency, diabetes with end-organ damage, and chronic pulmonary disease, so that their results may be extrapolated to the entire spectrum of CAD patients.

Prognostic indexes regarding comorbid illness are also an essential component of quality assessment of health care providers. To derive fair inferences regarding mortality and process of care, comparisons must be balanced for prognostically important differences in patient characteristics. Both the CAD-specific index and the Charlson index can be employed in risk adjustment. In the case of studies involving a relatively small number of patient outcomes, these indexes should be entered as a single value to account for comorbidity. This approach of using a single comorbidity index reduces the number of candidate variables and the potential for identifying spurious associations. In the case of large studies involving substantially more outcome events, the component variables from either index should be added separately, independent of their index weights, such that the relative importance of each illness will be specifically adjusted to the data set of interest.

A final application of these data involves the consideration of medical evidence for individual patients at the bedside. Illnesses that are likely to significantly limit life-expectancy, such as renal disease and diabetes with end-organ damage, should be taken into consideration when discussing the long-term ramifications of CAD therapies. These indexes also identify high-risk patients in whom aggressive therapies may be targeted.

Study limitations. A limitation of both this study and the original comorbidity review by Charlson is the dependence on chart review to ascertain the presence of comorbidity (2). As with any retrospective study, the individuals initially recording the patient's history were not aware of our research question or comorbidity definitions. Therefore, some pertinent information on comorbid illness may not have been recorded or may have been recorded incorrectly. For this study, we operated with the conservative assumption that a condition was not present unless it had been documented. The effect of such an assumption would be to attribute a lack of illness in some patients, possibly incorrectly, thus diminishing the difference in comorbidity levels. If comorbidity information had been collected prospectively, we would expect the relationship between the CAD-specific index and mortality to be even greater.

Conclusions. We found that co-existing illness, or comorbidity, was strongly associated with long-term survival among CAD patients. The strength of this association was almost equivalent to that of standard CAD severity measures, including LVEF. This study also found that the long-established Charlson comorbidity index had a prognostic significance remarkably similar to that of a comorbidity measure specifically developed for our CAD population. Co-existing illnesses identified by this study that are prevalent and prognostically important should be taken into account when considering the long-term benefit of coronary disease therapies in clinical trials, disease registries, cohort studies, and advice to individual patients.

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