Quantitative Measures of Electrocardiographic Left Ventricular Mass, Conduction, and Repolarization, and Long-Term Survival After Coronary Artery Bypass Grafting

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Quantitative Measures of Electrocardiographic Left Ventricular Mass, Conduction, and Repolarization, and Long-Term Survival After Coronary Artery Bypass Grafting

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Background—Quantitative ECG measures of left ventricular mass and repolarization predict outcome in population-based cohorts and patients with hypertension. We assessed the prognostic value of preoperative quantitative electrocardiography in patients who underwent isolated coronary artery bypass grafting.

Methods and Results—For 6 years we followed 8166 patients who underwent primary isolated coronary artery bypass grafting between 1990 and 2003, all of whom had routine preoperative ECGs. With use of specialized digital software, quantitative measures were recorded on ventricular rate, P duration, PR interval, QRS duration, QT interval, QRS axis, Sokolow-Lyon and Cornell voltages, and ST-segment depression and slope. There were 1516 deaths. After adjustment for age, gender, clinical characteristics, left ventricular ejection fraction, and other confounders, death was independently predicted by ventricular rate (adjusted hazard ratio [AHR] for 90 versus 60 beats per minute, 1.34; 95% confidence interval [CI], 1.21 to 1.50; $P<.0001$), PR interval (AHR for 200 versus 150 ms, 1.05; 95% CI, 1.00 to 1.10; $P<.0001$), QRS duration (AHR for 120 versus 80 ms, 1.24; 95% CI, 1.07 to 1.44; $P<.0001$), Sokolow-Lyon voltage (AHR for 3.5 versus 1.5 mV, 1.18; 95% CI, 1.05 to 1.31; $P<.0001$), and ST-segment slope (AHR for −0.1 versus 0 mV, 1.16; 95% CI, 1.02 to 1.31; $P<.0001$). We derived a quantitative ECG score and demonstrated that, with the exception of age, it was the most powerful predictor of long-term death.

Conclusions—Quantitative ECG measures of left ventricular rate, mass, and repolarization are predictive of mortality among patients who underwent isolated coronary artery bypass grafting. These findings suggest that quantitative electrocardiography may be valuable for risk stratification in patients with severe coronary artery disease. **(*Circulation*. 2007;116:888-893.)**

Key Words: coronary disease ■ electrocardiography ■ prognosis ■ surgery

Quantitative ECG measures have been shown to be important predictors of survival and cardiovascular risk in population-based cohorts,[1,2] patients with hypertension,[3] and patients with heart failure.[4] For example, ECG left ventricular hypertrophy has long been known to be a predictor of cardiovascular risk in healthy subjects.[5] Similarly, data from population-based studies have shown that even minor abnormalities of the ST segment and T wave are correlated with greater risk of major cardiovascular events.[6] Recent interest has also focused on QRS duration, a measure of left ventricular conduction, which is a predictor of outcome in patients with heart failure and other patients considered to be at increased risk for sudden cardiac death.[4,7,8]

Clinical Perspective p 893

The value of quantitative electrocardiography in other routine clinical settings is less clear. As in most institutions, our hospital routinely obtains a preoperative ECG in patients who must undergo coronary artery bypass grafting (CABG). Given the prognostic associations of quantitative ECG measures of outcome in population-based and heart failure cohorts, we asked whether quantitative ECG measures obtained as part of routine clinical care may be predictive of long-term outcome in patients who undergo CABG, one of the most common cardiovascular procedures.

Methods

Patients

As previously described, the Cardiovascular Information Registry of the Cleveland Clinic Foundation, which was begun in 1972, is a repository of systematically collected and maintained data on every adult surgical procedure ever performed within the institution.[9] In addition to information on surgical procedures, data are collected on demographics, standard cardiovascular risk factors, coronary angio-

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graphic findings, left ventricular function, and key comorbidities such as renal and pulmonary disease.

The cohort for the present study included 8166 patients who underwent primary isolated CABG between 1990 and 2003. All patients had an ECG obtained at the Cleveland Clinic as part of their routine preoperative evaluation within 2 weeks of surgery. Patients with atrial fibrillation, prior pacemaker implantation, Wolff-Parkinson-White syndrome, or pathological Q waves on their initial ECG were excluded.

Permission was obtained from the Institutional Review Board to analyze registry data for outcomes research. The requirement for written informed consent was waived.

Digital Electrocardiography

During the study period, all ECGs obtained at the Cleveland Clinic were recorded with a Marquette MUSE System. Digital ECG files were retrieved and analyzed with use of General Electric's Magellan Software System (GE Healthcare, Menomonee Falls, Wisc). The software provides detailed data on the duration and amplitudes of all segments of the P wave, QRS complex, ST segment, and T wave in all 12 leads, with amplitudes recorded to the nearest 100th of a millivolt and times recorded to the nearest millisecond.

We focused on global QRS duration as well as measures of left ventricular mass and ST segment changes. Sokolow-Lyon left voltage was calculated by addition of the amplitude of the S wave in lead V1 to the amplitude of the maximum R wave in lead V5 or V6.[10] Cornell voltage was calculated by addition of the amplitude of the R wave in lead AVL to the amplitude of the S wave in lead V3.[10,11] ST segment deviation at the J point, at the midpoint of the ST segment, and at the end of ST segment were extracted. ST slope was calculated as the difference between ST segment deviation at the end of the ST segment and at the J point. Presence or absence of left or right bundle-branch block was determined according to standard criteria.

End Points

The primary end point was time-related all-cause mortality relative to surgery, an end point which we have previously argued is a wholly objective, clinically relevant, and unbiased measure.[12,13] Mortality was assessed by use of the Social Security Death Index. We have previously shown that among patients systematically followed in the Cardiovascular Information Registry, the Social Security Death Index has a sensitivity of 97%.[14] High specificity of the Social Security Death Index has also been documented.[15] A secondary end point was 30-day mortality.

Statistical Analyses

Continuous variables are described as median (interquartile range [IQR]) whereas categorical variables are described as number (percent). Cumulative mortality plots were constructed by use of the Kaplan-Meier method,[16] with differences according to quartiles of different ECG measures tested by the log-rank χ^2 statistic.

Assessment of the association between quantitative ECG measures and time to death was performed with Cox proportional hazards regression.[17] The proportional hazard assumption was tested by scaled Schoenfeld residuals as well as inspection of hazard ratio plots over time.[18] Linear assumptions for continuous variables were relaxed by restricted cubic splines.[18] Patients were grouped according to quintiles of predicted 10-year survival probabilities to assess model calibration and to compare predicted Kaplan-Meier survival to actual Kaplan-Meier survival; this process was repeated over 100 bootstrap resamplings. An additional set of survival analyses was performed with wholly parametric, time-decomposed, multiphase hazard regression as described previously[19]; these analyses yielded results that were not materially different from the Cox analyses. Analyses of the secondary end point, 30-day mortality, were performed with logistic regression with backward variable selection.

An ECG score was generated on the basis of the estimated restricted cubic spline function for the Cox model. Ideally the validity of this score would be determined by its application to an external data set. However, as we are not aware of any external data that contain the kind of detailed clinical and quantitative ECG information we have, we opted for an alternative approach, namely out-of-bagging, a process similar in concept to the leave-one-out bootstrap.[20] We obtained bootstrap samples and used each sample to compute a prediction model that incorporated the ECG score and potential confounders; all demographic, clinical, and angiographic variables listed in Table 1 were included. Each bootstrap sample left out, on average, ≈37% of the data, which we refer to as the out-of-bag data. The prediction model was applied to the out-of-bag data to calculate an error rate, namely 1 − the c index.[21] The c index is the generalized form of the c statistic for censored data[21]; despite the presence of heavy censoring in this index, which specifically incorporates censoring information, is arguably reasonable and reliable.[22] Use of the c index as a measure of prediction error has been previously reported.[23]

TABLE 1. Baseline Characteristics According to QRS Duration in 8166 Participants

Characteristic	Value
Demographic and clinical	
Age, y	64 (57 to 72)
Female, n (%)	2159 (26)
Body mass index, kg/m^2	28 (25 to 31)
Treated diabetes mellitus, n (%)	2231 (27)
Hypertension, n (%)	5810 (71)
Current or recent smoker, n (%)	5180 (63)
Carotid stenosis, n (%)	2020 (25)
Peripheral vascular disease, n (%)	2433 (25)
Prior myocardial infarction, n (%)	3219 (39)
NYHA class ≥III, n (%)	2955 (26)
Canadian Angina Class >3, n (%)	1334 (16)
Emergency operation, n (%)	207 (3)
IABP use, n (%)	123 (2)
Creatinine, mg/dL	1.1 (0.9 to 1.3)
LVEF, %	50 (45 to 50)
Time since January 1, 1990, at time of surgery, y	5.4 (3.1 to 7.9)
Angiography, %	
Maximum LAD stenosis	80 (70 to 95)
Maximum LCx stenosis	80 (50 to 90)
Maximum RCA stenosis	80 (50 to 99)
Maximum left main stenosis	0 (0 to 40)
ECG findings	
Ventricular rate, bpm	67 (59 to 77)
P wave duration, ms	112 (100 to 120)
PR interval, ms	164 (148 to 184)
QRS duration, ms	92 (84 to 104)
Sokolow-Lyon voltage, mV	2.1 (1.6 to 2.6)
Cornell voltage, mV	1.5 (1.1 to 1.9)
End ST depression, mV	0.14 (−0.35 to 0.63)
ST slope, mV	0.29 (0.0 to 0.59)
QT interval, ms	404 (380 to 428)
QRS axis, degrees	16 (−9 to 42)

Values are medians (25th to 75th percentiles) unless otherwise indicated. NYHA indicates New York Heart Association; IABP, intraaortic balloon pump; LVEF, left ventricular ejection fraction; LAD, left anterior descending coronary artery; LCx, left circumflex artery; and RCA, right coronary artery.

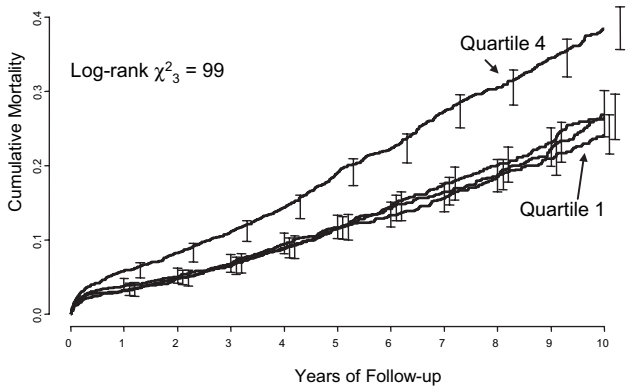

Figure 1. Mortality risk according to quartiles of QRS duration.

To determine the relative importance of each variable, we recalculated the prediction error after randomly permutation of that variable in the out-of-bag data; a variable with a high degree of importance would be expected to yield a greater change in prediction error. The process was repeated 100 times to estimate relative importance values for the ECG score and other key covariates.

All analyses were performed with SAS version 9.1.3 (SAS Institute Inc., Cary, NC) or S-Plus 2000 Professional Software (Insightful, Inc, Seattle, Wash) with Harrell's Design and Hmisc Libraries.[18] All probability values were 2-sided and only considered significant if $P<0.05$.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Preoperative Characteristics

Preoperative characteristics are shown in Table 1. Median QRS duration for the entire population was 92 ms (IQR, 82 to 104). Median values for Sokolow-Lyon voltage and Cornell voltage were 2.2 mV (IQR, 1.6 to 2.6) and 1.5 mV (IQR, 1.1 to 1.9), respectively. Median amount of ST segment depression at the end of the ST segment was 0.14 mV (IQR, −0.35 to 0.63). Median ST slope was 0.29 mV (IQR, 0 to 0.059). Complete left bundle-branch block was noted in 323 (4%) patients, and right bundle-branch block was present in 313 (4%) patients.

ECG Findings and Mortality

During a median follow-up of 6 years, 1516 patients (19%) died. Unadjusted associations of ECG measures and mortality

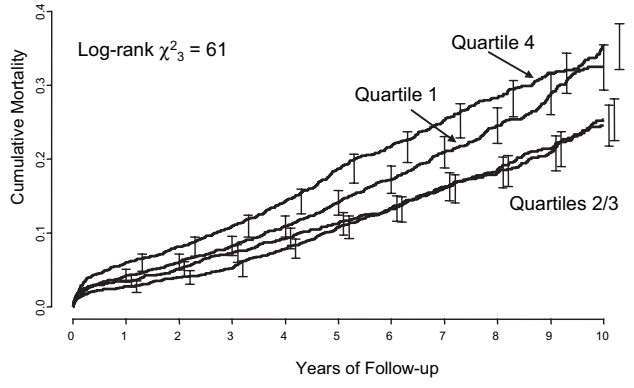

Figure 2. Mortality risk according to quartiles of Sokolow-Lyon voltage.

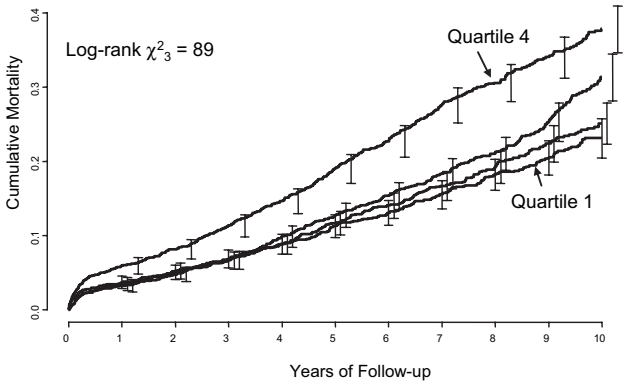

Figure 3. Mortality risk according to quartiles of Cornell voltage.

are shown in Figures 1 through 5. Correlates of increased mortality risk included longer QRS duration (Figure 1), higher Sokolow-Lyon voltage (Figure 2), higher Cornell voltage (Figure 3), greater ST segment depression (Figure 4), and greater negativity of ST segment slope (Figure 5).

Multivariable Analyses

After accounting for all the potential covariates listed in Table 1, higher heart rate, longer PR interval, longer QRS duration, greater Sokolow-Lyon voltage, and greater negativity of ST segment slope were independent ECG predictors of death ($P<0.0001$ for all) (Table 2). We found no statistically significant interactions between ECG measures or between ECG measures and a number of preselected clinical covariables.

ECG Score and Prognostic Validation

An adjusted ECG score was generated with the confounder-adjusted parameter coefficients for each of the independently predictive ECG variables (see Appendix for equation). A strong gradient was apparent whereby increased ECG score was strongly predictive of death (Figure 6), even after accounting for all the covariates listed in Table 1 (Figure 7). By out-of-bagging validation, ECG score was the second strongest predictor of death, exceeded only by age (Figure 8).

Thirty-Day Mortality

During the first 30 days after surgery, 111 deaths (1.4%) occurred. By both univariable and multivariable analyses, the

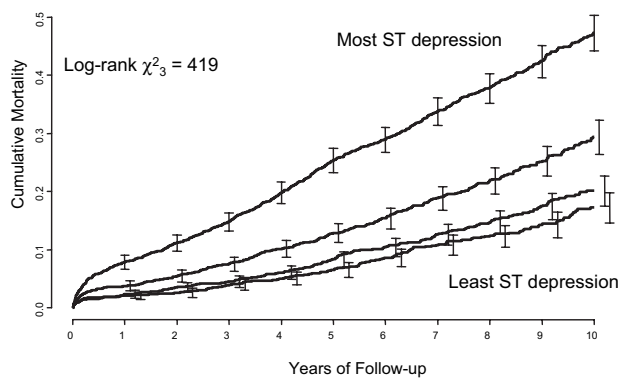

Figure 4. Mortality risk according to quartiles of amount of ST-segment depression in lead V5.

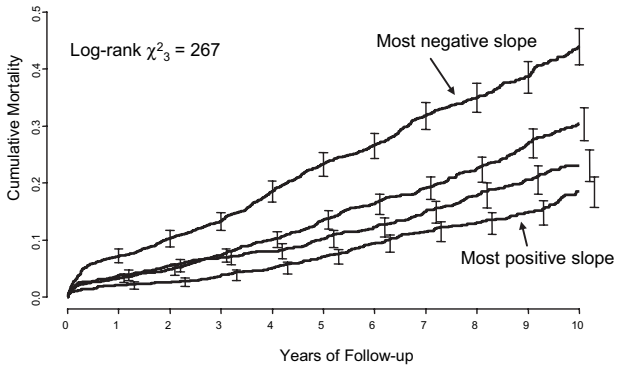

Figure 5. Mortality risk according to quartiles of ST slope in lead V5.

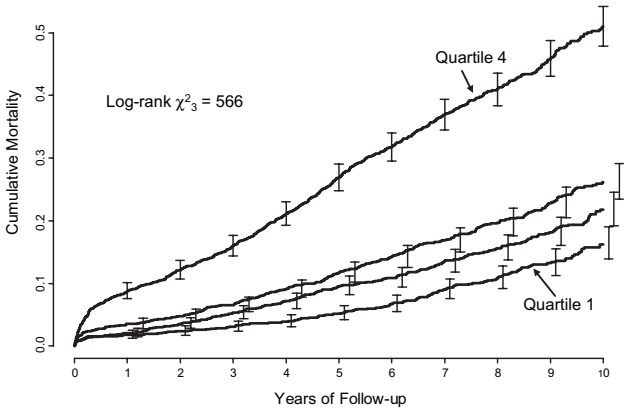

Figure 6. Mortality risk according to quartiles of ECG score (see Appendix for equation).

only ECG predictor of 30-day mortality was the amount of ST-segment depression in lead V5 (by quartiles of most ST depression to least ST depression, mortality of 2.0%, 1.4%, 1.2%, and 0.9%; *P* for trend, 0.002). In a multivariable logistic regression model that included the variables listed in Table 1, the only independent predictors of death were intraaortic balloon pump use (adjusted odds ratio, 13.88; 95% confidence interval, 8.11 to 23.76; $P<0.0001$), no thoracic artery graft (adjusted odds ratio, 2.75; 95% confidence interval, 1.26 to 6.00; $P=0.011$), and amount of ST segment depression in lead V5 (adjusted odds ratio for 0.2 mV compared with none, 1.07; 95% confidence interval, 1.04 to 1.10; $P<0.0001$). The association of ST segment depression with 30-day mortality was markedly nonlinear, with a threshold effect noted at 0 mV; ST segment elevation was not predictive.

Discussion

In a large cohort of patients who underwent primary isolated CABG, 5 easily obtained quantitative ECG measures independently predicted long-term mortality. Consistent with observations made in nonsurgical populations,[1,3,4,7,8,10,24] death risk was higher with higher heart rate, longer PR interval, longer QRS duration, greater Sokolow-Lyon voltage, and more negative ST segment slope. With the exception of ST segment depression, ECG measures were not predictive of 30-day mortality. To our knowledge, the present study represents the first attempt to link quantitative findings from routine preoperative ECGs to long-term outcome in patients who must undergo CABG.

The present results parallel recently reported findings among patients with chronic hypertension.[3,7] As discussed elsewhere, ECG left ventricular hypertrophy is reflected by both QRS voltage and QRS duration.[7] By taking advantage of digital quantitative data, we were able to show that ECG left ventricular hypertrophy is not a dichotomous phenomenon. Both by univariable and multivariable analyses, Sokolow-Lyon voltage predicted death according to a J-shape with higher risks at highest and lowest values (Figure 2), whereas Cornell voltage followed a more typical continuous pattern (Figure 3); the reasons for this are unclear and will require further investigation. Our findings that link negative ST segment depression, a marker of abnormal ventricular repolarization, with mortality also parallel previous reports based on population-based cohorts.[1,6] We generated a composite confounder-adjusted ECG risk score and demonstrated its strong prognostic validity by use of the out-of-bagging technique; of note, except for age the ECG risk score was the strongest predictor of death (Figure 8). Taken together, the present study provides further evidence to support routine use of quantitative ECG measures for clinical risk stratification.

Some important limitations need to be acknowledged. Our population was a relatively healthy one for patients who underwent cardiac surgery and excluded patients with important valvar disease, atrial fibrillation, and prior Q wave myocardial infarction. Because of software limitations, we could not measure time-voltage areas, which have been shown to be strong correlates of left ventricular hypertrophy.[25] We considered only baseline preoperative ECGs and

TABLE 2. Results of Multivariable Proportional Hazards Analyses for Electrocardiographic Predictors of Time Free of Death

Variable	Comparison	Hazard Ratio (95% CI)	*P*
Ventricular rate, bpm	90 vs 60	1.34 (1.21 to 1.50)	<0.0001
PR duration, ms	200 vs 150	1.05 (1.00 to 1.10)	<0.0001
QRS duration, ms	120 vs 80	1.24 (1.07 to 1.44)	<0.0001
Sokolow-Lyon voltage, mV	3.5 vs 1.5	1.18 (1.05 to 1.31)	<0.0001
ST segment slope, mV	−1.0 vs 0.0	1.16 (1.02 to 1.31)	<0.0001

All variables were considered continuous, with relaxation of assumptions of linearity by restricted cubic splines. Hazard ratios are adjusted for all variables in Table 1 as well as for number of internal thoracic artery bypass grafts placed. CI indicates confidence interval.

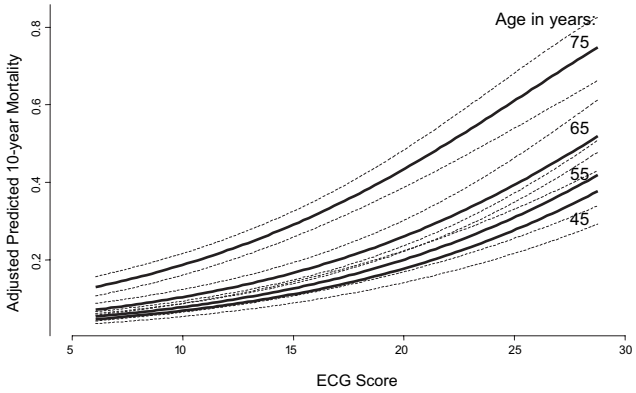

Figure 7. Predicted 10-year mortality according to ECG score according to age after accounting for all potential confounders listed in Table 1. All continuous covariates were set to median values; categorical variables were set to modes. Note absence of any threshold value.

did not systematically obtain routine follow-up measurements, as was done, for example, in the Losartan Intervention for Endpoint Reduction (LIFE) trial.[3] Another arguable clinical limitation is that, unlike QRS duration, quantitative measures of Sokolow-Lyon voltage and ST segment depression and slope are not routinely reported on standard ECGs. However, current ECG software has the capability to report them. Although QRS duration and voltage and ST segment depression are predictive of long-term mortality, it is not known whether specific pharmacological intervention, such as the use of angiotensin receptor blockers, can modify outcome specifically among CABG patients.[26] Recently, some patients with prolonged QRS intervals may have been treated with cardioverter-defibrillator and/or cardiac resynchronization therapy[27]; the beneficial effects of these treatments, if any, would have led to an underestimation of the importance of prolonged QRS duration as a predictor of long-term outcome in patients who undergo isolated CABG.

Despite these limitations, we found that routine preoperative quantitative ECG measures of heart rate, conduction, left ventricular mass, and repolarization are independently predictive of long-term mortality among patients who undergo isolated CABG. Future research will be needed to confirm these findings and to determine how best to use ECG measures for risk stratification and to modify long-term postoperative management.

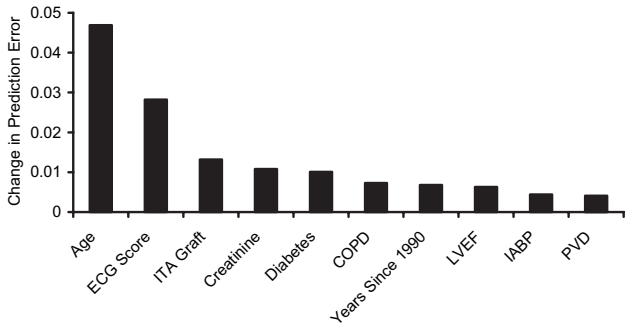

Figure 8. Change in out-of-bagging determined prediction error (see Methods for details). Only the 10 most important variables are shown. Results are based on 100 bootstrap samples with prediction errors calculated by application of models to out-of-bag samples after random permutation of each covariate. ITA indicates internal thoracic artery; COPD, coronary obstructive pulmonary disease; LVEF, left ventricular ejection fraction; IABP, intraaortic balloon pump; and PVD, peripheral vascular disease.

Appendix

The equation for the ECG score:

ECG score = $10 \times (0.0020805218 \times$ ST segment slope $+ 0.021994013 \times$ ventricular rate $- 1.1811993e{-}05 \times$ MAX (ventricular rate $- 53,0)^3 + 1.9686654e{-}05 \times$ MAX (ventricular rate $- 67,0)^3 - 7.8746617e{-}06 \times$ MAX (ventricular rate $- 88,0)^3 - 0.0020579794 \times$ PR interval $+ 8.2754258e{-}07 \times$ MAX (PR interval $- 136,0)^3 - 1.4068224e{-}06 \times$ MAX (PR interval $- 164,0)^3 + 5.7927981e{-}07 \times$ MAX (PR interval $- 204,0)^3 + 0.0063538696 \times$ QRSD duration $- 0.00012443304 \times$ Sokolow-Lyon voltage $+ 5.1974407e{-}11 \times$ MAX (Sokolow-Lyon voltage $- 1129,0)^3 - 9.4513461e{-}11 \times$ MAX (Sokolow-Lyon voltage $- 2060,0)^3 + 4.2539054e{-}11 \times$ MAX (Sokolow-Lyon voltage $- 3197.5,0)^3$)

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Disclosures

None.

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CLINICAL PERSPECTIVE

Most physicians think of ECG interpretation as primarily based on pattern recognition. However, the ECG contains highly refined quantitative data that can reflect a number of abnormalities of cardiac electrophysiology and structure. We analyzed outcomes of 8166 patients who underwent isolated first-time coronary artery bypass grafting and were followed for a mean of 6 years. All patients had a routine preoperative ECG that was stored in a computerized database, which allowed recovery of raw digital signals. We found that long-term death risk was predicted by 5 quantitative measures: higher ventricular rate, longer PR interval, longer QRS duration, lower or higher Sokolow-Lyon voltage, and more negative ST-segment slope. We generated and validated a prognostic ECG score that can be easily programmed into a computer; this score was the most important predictor of long-term mortality with the exception of age. The present findings suggest that the ECG may be a powerful quantitative prognostic instrument, particularly when focused on measures of cardiac conduction, left ventricular mass, and ventricular repolarization. As most ECGs are now obtained within sophisticated computer systems and networks, future research should focus on how to extend the ECG beyond qualitative pattern recognition for diagnosis to quantitative score generation for prognosis.