Clinical, Electrocardiographic, and Biochemical Data for Immediate Risk Stratification in Acute Coronary Syndromes

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The recent evolution in therapeutic options for acute coronary syndromes (ACS) mandates early risk stratification in order to select the appropriate treatment strategy for individual patients. Simple clinical data derived from the patient's medical history and physical examination, a standard twelve-lead electrocardiogram (ECG), and determinations of biochemical markers of myocardial damage can be obtained in the emergency room and serve as a guide for deciding appropriate medical management and optimal use of available resources. Even the most important classification of the ACS is based upon a simple and dichotomous description of the ECG, where the presence of ST-segment elevation mandates an immediate attempt to restore coronary perfusion (either pharmacologically or mechanically), whereas its absence suggests pharmacological stabilization before further evaluation. Across the whole spectrum of ACS, clinical history data (such as older age, previous coronary events, and diabetes) and clinical variables (such as higher heart rate, lower blood pressure, and higher Killip class) are the most powerful prognostic determinants at multivariate analyses derived from large databases. The ECG adds significant and independent prognostic information using the analysis of qualitative (direction of ST-segment shift, associated T-wave inversion, and presence of conduction disturbances) and quantitative (number of leads involved, amount of ST- segment shifts, duration of QRS) characteristics. Biochemical markers of myocardial damage have also been identified as independent predictors of events. In addition, retrospective analyses of clinical trials have suggested that biochemical markers might serve as a guide to select pharmacological therapy. However, how to best combine electrocardiographic and biochemical data for immediate risk stratification remains to be further elucidated. **A.N.E. 2001;6(1):64–77**

acute coronary syndromes; prognosis; electrocardiogram; multivariate analysis

Immediate risk stratification in the emergency room is an important step for the appropriate management of patients with an acute coronary syndrome (ACS). Irrespective of the level of subsequent hospital care, simple clinical data derived from the patient's medical history and physical examination, a standard twelve-lead electrocardiogram (ECG), and determinations of biochemical markers of myocardial damage can be obtained in the emergency room and serve as a guide for deciding appropriate medical management and optimal use of available resources. Even the most important classification of the ACS is based upon a simple and dichotomous description of the ECG, where the presence of ST-segment elevation mandates an immediate attempt to restore coronary

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perfusion (either pharmacologically or mechanically), whereas its absence leads to pharmacological stabilization before further evaluation.

During the last 15 years, a number of megatrials of fibrinolytic agents have made possible the creation of huge databases on acute myocardial infarction (AMI) with ST-segment elevation, and to develop multivariate prognostic models based on baseline clinical, electrocardiographic, and enzymatic data.[1,2] On the other hand, only recently have similar databases become available for the non-ST-elevation patients, derived from trials with direct antithrombins, glycoprotein IIb/IIIa antagonists, and low molecular weight heparins: the most important sets of data available at this moment are those of the GUSTO IIb,[3] PURSUIT,[4] and OASIS II trials.[5] These data have allowed identification of subsets of patients with different risk of future events and those that may benefit from a more aggressive antithrombotic or mechanical therapy. In addition, recent advances in the biochemical determination of myocardial damage by means of troponin I and T levels offer a more sophisticated and easily available means of early risk stratification.

Despite the recent improvements in pharmacological and revascularization strategies, the patients considered at high risk on the basis of clinical (elderly, diabetics), electrocardiographic (ST-segment depression), and biochemical (even modest myocardial damage) characteristics continue to show a high incidence of unfavorable events: thus, particularly in the non-ST-elevation ACS, the ongoing trials with aggressive antithrombotic strategies are mainly focused on these subsets of patients. However, low risk patients need to be identified to avoid the risks derived from an aggressive approach and unnecessary resource use including hospitalizations.

In the present article, we will review only briefly the prognostic implications of the clinical, electrocardiographic, and enzymatic data available on admission in patients presenting with ST-segment elevation: this issue has been reviewed thoroughly by the Fibrinolytic Therapy Trialists,[6] the GUSTO-I Investigators,[2] and Califf & Mark.[7] We will focus instead on the differences in prognosis between the ST-elevation and non-ST-elevation patients and how to use early data for risk stratification in the non-ST-elevation ACS. Patients with non-ST elevation ACSs now represent the majority of those admitted to the Coronary Care Units in western countries.

Prognosis of ACSs in Patients with and without ST- Segment Elevation

Evolution in Terminology

The current distinction between ST-elevation and non-ST-elevation ACSs is important at the time of hospital presentation, and reflects the need for an immediate therapeutic decision about coronary reperfusion. The older terms "transmural" and "nontransmural" myocardial infarction (MI) were found not correlated with anatomical findings;[8] on the other hand, the differentiation between Q-wave and non-Q-wave infarction takes at least 24 hours to become evident, and is also influenced by the efficacy of reperfusion therapy.

Within the non-ST-elevation subset, a classical subdivision exists between MI and unstable angina, according to the WHO criteria for the definition of MI which require at least the doubling of the upper normal level of CK to define the presence of an MI.[9,10] This distinction has clear prognostic implications: in a recent analysis of the GUSTO IIb database, including 4488 patients with unstable angina and 3513 with non-ST segment elevation MI, mortality at one year was 11.1% in the MI group, and 7.0% in the unstable angina group ($P < 0.001$).[11] However, recent data suggest that this distinction should not be dichotomous: at least in patients with an abnormal ECG at presentation, a continuous relation exists between levels of CK or CKMB and prognosis, even within the normal or minimally increased levels;[12,13] moreover, the use of more sensitive markers of myocardial damage (such as CKMB mass and the troponins) has made it possible to identify a prognostic gradient even among the patients who would not meet the classical criteria for MI.[14] Based on these findings, which also have important therapeutic implications, a joint committee of the American College of Cardiology and European Society of Cardiology is currently working on redefining the diagnostic criteria for MI.

ST-Elevation vs Non-ST-Elevation and Non-Q-Wave MI vs Unstable Angina

GUSTO IIb is the only trial so far to encompass the whole spectrum of patients with ACSs: it included patients with symptoms of myocardial ischemia during the past 12 hours and ECG changes such as ST-segment elevation or depression or T-wave inversion. The main results of the trial,

Table 1. Incidence of Death and (Re)infarction at 30 Days, 6 Months, and 1 Year in the GUSTO IIb Trial According to ST-Segment Status and the Final Definition of MI versus Unstable Angina

	ST Elevation (n = 4125)	NonST Elevation MI (n = 3513)	Unstable Angina (n = 4488)
Death at 30 days	6.1	5.7	2.4*
Death at 6 months	8.0	8.8	5.0*
Death at 1 year	9.6	11.1#	7.0*
(Re)MI at 30 days	5.5	7.5#	4.8*
(Re)MI at 6 months	7.4	9.8#	6.2*

* $P < 0.001$ vs nonST-elevation MI (myocardial infarction).
# $P < 0.05$ vs ST-elevation MI. (From reference 11.)

which compared the efficacy of recombinant hirudin with that of heparin, have been published,[3] as were the details of the ECG classification used.[15] The 12,142 patients enrolled, 4125 of whom with ST-segment elevation and 8001 without ST-segment elevation were followed up for one year, collecting mortality and (re)infarction data for the first six months and only mortality for one year. Patients were treated at 337 hospitals in 13 countries according to state of the art strategies including drugs and revascularization procedures as indicated: these latter were carried out in 40% of the patients within the first six months, and their incidence was the same across strata.[3,15]

The incidence of death and reinfarction during follow-up is shown in Table 1.[11] It can be seen that the incidence of death was greater in the ST-elevation than in the non-ST-elevation group at 30 days, but this difference tended to diminish at 6 months, and disappeared after one year. In fact, at one year, the ECG group at highest risk of death was ST depression. Moreover, when the non- ST-elevation group is split into its two components of MI and unstable angina, the non- ST-elevation MI group has higher mortality than both unstable angina and ST-elevation MI at one year. Similar figures derive from series of patients reported from 1973 to 1995 and not coming from randomized clinical trials.[16] Thus, whereas patients presenting with ST elevation experience a higher incidence of in-hospital events, those without ST elevation experience a more prolonged unstable phase characterized by repeated hospitalizations, (re)MIs, and fatal events.

The different prognosis of ST-elevation and non-ST-elevation patients may be partly explained by differences in age, risk factors, and clinical history: the patients with non-ST-elevation ACS are significantly older, more frequently females, and have a higher prevalence of risk factors, previous MI, angina, revascularization procedures, and heart failure (Table 2). At angiography, the non—ST elevation patients (particularly those presenting with ST-segment depression) are more frequently found to have three vessel disease.[15]

Predictors of Mortality in ST-Elevation MI

The primary endpoint of most large trials of ST-elevation patients has been total mortality. Fewer data are available on the incidence and prediction of reinfarction in this population. As shown in Table 1, at six months, the incidence of reinfarction in the ST-elevation cohort of GUSTO IIb was the same as in the non-ST-elevation cohort.

As far as mortality is concerned, several multivariable predictive models have shown the value of the clinical and electrocardiographic data available upon hospital admission. Less clear evidence is available regarding the prognostic value of elevated biochemical markers on admission.

Clinical Variables

The prognosis of acute MI patients is largely influenced by the patients' characteristics at presentation either derived from clinical history or physical examination. The most powerful clinical predictors of 30-day mortality, in order of amount of predictive information, are older age, lower systolic blood pressure, worse Killip Class, higher heart rate, anterior MI location, and prior MI[2] (Table 3). In accordance with the value of Chi square displayed in Table 3, some of the baseline characteristics have a larger impact, whereas others have a lower (although statistically significant) importance. Among the most relevant examples are age

Table 2. Baseline Characteristics According to Admission ST-Segment Status

Characteristics	ST Elevation (n = 4125)	No ST Elevation (n = 8001)	P
Age, years	63 (53, 71)	66 (57, 73)	<0.001
Male	76	67	<0.001
Hypertension	40	48	<0.001
Diabetes	16	19	<0.001
Hypercholesterolemia	36	41	<0.001
Smoking: past/current	28/41	36/27	<0.001
Family history	37	41	<0.001
Previous MI	17	32	<0.001
Prior angina	48	76	<0.001
Prior CVD	2	3	<0.001
Prior PTCA	6	10	<0.001
Previous CHF	3	7	<0.001
PVD	7	9	0.001
Systolic BP (mmHg)	130 (115, 148)	139 (120, 151)	<0.001
Heart rate, beats/min	74 (64, 86)	74 (64, 85)	0.876
Killip Class II/III-IV	11/2	11/2	0.459
Time to hospital, hours	1.9 (1.0, 3.3)	2.0 (0.8, 4.1)	0.858
Time to treatment	3.8 (2.6, 5.6)	5.7 (3.6, 9.0)	<0.001

Numbers are percentages, when not otherwise specified. Numbers within parentheses are 25th and 75th percentiles. CVD = cerebrovascular disease; CHF = congestive heart failure; PVD = peripheral vascular disease; BP = blood pressure. (From reference 11.)

(2.4% mortality in the younger age groups vs 20.5% above 75 years), systolic blood pressure (30% if blood pressure < 100 mmHg, vs 7%-9% with blood pressure ≥100 mmHg), Killip class (5% for Killip I, 13.5% for Killip II, 32% for Killip III, and 58% for Killip IV), heart rate (7%-9% if heart rate < 100 vs 17% if heart rate ≥ 100 beats/min), previous MI (12% with prior MI vs 6% without prior MI) and diabetes (6% with diabetes vs 11% without diabetes).[2,6]

Table 3. Independent Clinical Predictors of 30-Day Mortality in Acute Myocardial Infarction Presenting with ST-Segment Elevation in the GUSTO-I Trial

Variable	Adjusted χ^2
Age, years	717
Systolic blood pressure, mmHg	550
Killip class	350 (3 df)
Heart rate, bpm	275 (2 df)
Location of infarction	143 (2 df)
Previous infarction	64
Age-by-Killip-class interaction	29
Height, cm	31 (4 df)
Time to treatment, hours	23
Diabetes	21
Weight, kg	16
Smoking	22 (2 df)
Choice of thrombolytic therapy	15 (3 df)
Previous bypass surgery	16
Hypertension	14
Prior cerebrovascular disease	10

Df = "degree of freedom." (From reference 2.)

Importantly, despite the fact that thrombolytic therapy appears to reduce mortality consistently in all of these subgroups of patients, the relative impact of the above mentioned clinical variables has not substantially changed across trials between 1986 and 1999[1,17,18]

The ECG

A number of studies have focused on the importance of the admission ECG in patients with suspected AMI. A first issue (relevant to immediate decision making) is the likelihood of developing an MI (i.e., abnormal CKMB levels) according to the ECG presentation. This probability is very low (3% overall) with normal or nonspecific ECGs[19] and becomes progressively higher in patients with negative T waves (32%), ST-segment depression (48%), ST-segment elevation (81%), and ST-segment elevation plus depression (89%).[15] Patients admitted with an actual MI but initially normal or not significant ECGs will develop significantly lower creatine kinase levels[19] and have lower mortality.[6,19]

Qualitative and quantitative characteristics may be combined for prognostic evaluation in patients

admitted with abnormal ECGs. From the qualitative point of view, the presence of bundle-branch block (BBB), the location of ST-segment elevation, concomitant ST depression, Q wave representing a previous MI, and distortion of the terminal portion of QRS complex have been found correlated with mortality. As far as quantitative indexes are concerned, the sum of ST segment deviations and the duration of the QRS complex have been found to independently predict mortality.

Bundle-branch block is a marker of poor prognosis, a consistent finding across trials of thrombolytic therapy [6] and registries.[20] The prevalence of BBB varies in relation to the population considered. Studies done in the prethrombolytic era estimated the prevalence of BBB in patients with MI to be 2.7%-13.4% for right and 0.3-8% for left BBB.[20] In the thrombolytic trial population, figures were much lower due to selection bias since the presence of bundle-branch block renders the early diagnosis of MI more difficult: a combined prevalence of 4% for BBB (type unspecified) in the FTT analysis,[6] and prevalences of 1% for right BBB and 0.5% for left BBB in the GUSTO-I population.[21] Higher prevalences were found in registries, which depict the real world situation: among 297,832 patients of the NRMI 2 registry, 6.2% had right and 6.7% left BBB.[20] A 10.9% prevalence of right BBB was found in a Spanish registry of 1238 consecutive patients admitted to three coronary care units.[22] In all of the reports, mortality rates were much higher in the presence of BBB.[6,20-22] A large part of the excess risk can be attributed to the greater extent of infarction and worse left ventricular function associated with BBB, since the incidence of heart failure and cardiogenic shock is higher in comparison with patients without BBB.[20,21] However, patients with BBB more frequently have characteristics associated with higher mortality, such as older age, history of infarction, congestive heart failure, angina, CABG, stroke, diabetes and hypertension;[20] in addition, despite these higher risk characteristics, BBB patients are much less likely than patients with no BBB to receive immediate reperfusion therapy or other proven medical treatments.[20] Recently, multivariable models derived from large databases have allowed to determine that, after adjustment for measured confounders, right BBB may be a stronger independent predictor of early death than left BBB. In fact, a case-control study from the GUSTO-I trial[21] and a report from the NRMI 2 registry[20] found that the adjusted odds ratio for early mortality were higher for right BBB, respectively 2.17 (CI 1.25-3.75) and 1.07 (CI 1.01-1.12), compared to left BBB. These recent observations reveal that despite the generally greater importance placed on left BBB as a poor prognostic factor in MI, right BBB should receive at least as much attention for risk stratification. Patients with transient BBB will have a significantly better prognosis than those with persistent BBB, respectively, 5.6% versus 19.4% 30-day mortality in a joint TAMI-9 and GUSTO-I database,[23] and 8% versus 76% hospital mortality in the Spanish right BBB registry.[22] Finally, as far as atrioventricular node conduction disturbances are concerned, first-degree or second-degree block and complete heart block have not been found to predict mortality, even at univariate analysis.[24]

Location of the ST-segment elevation has long been recognized as an important prognostic marker. In all of the databases, patients with ST elevation in the anterior leads have been found to have higher mortality in comparison with those with nonanterior MIs.[2,6] In multivariate analysis, the anterior location of the ST-segment elevation is an important independent predictor of mortality with an OR of 2.11 (CI 1.96-2.28) in comparison with inferior location and 1.48 (CI 1.20-1.82) in comparison with other locations.[2] In patients presenting with a new ST-segment elevation in the inferior leads, ECG evidence of prior MI (generally in the anterior or lateral leads) is associated with an increased mortality (OR, 2.47; CI, 2.02-3.00) at multivariate analysis.[24] On the other hand, ECG signs of a previous (inferior or lateral) MI in patients with new ST-segment elevation in the anterior leads are not associated with increased mortality.[24]

The presence of associated ST segment depression (usually precordial ST depression in patients with inferior ST elevation) carries a worse prognosis.[15,25,26] Patients with precordial ST segment depression have larger infarctions, more postinfarction complications, and more frequently show three-vessel disease at angiography.[15,25] At follow up, these patients will show higher mortality rates, particularly with ST depression in leads V_4 to V_6. For this reason, the sum of absolute ST-segment deviation (i.e., the sum of ST-segment elevations and depressions in all 12 leads, measured at 60 milliseconds after the J point) has been found to be the strongest ECG predictor of mortality, which

also added independent information to the clinical model.[24] The number of leads showing ST-segment elevation, a prognostic indicator known for years,[27] was found to be a strong univariable predictor, but provided no independent prognostic information in the complete clinical and electrocardiographic model.[24]

Finally, the duration of the QRS complex, or the distortion of its terminal part, on the admission ECG has been found independently correlated with mortality, particularly in patients with an anterior MI.[24,28] In the GUSTO-I database[24] a QRS duration of 100 vs 80 milliseconds was associated with an OR for 30-day mortality of 1.55 (CI 1.43-1.68) for anterior MI and 1.08 (CI 1.03-1.13) for other infarct locations. Limited to anterior MI, QRS duration was a strong independent predictor of mortality even in the combined clinical and ECG model. It has been suggested that when "late potentials" are of sufficient magnitude to affect the surface ECG, they may reflect extensive infarcts and involvement of the conduction system, and be associated with heart failure and re-entrant ventricular dysrhythmias.

Biochemical Markers of Myocardial Damage

Irrespective of the electrocardiographic presentation, creatine kinase elevation upon hospital admission is associated with an increased mortality. In the GUSTO IIb trial, patients were enrolled within 12 hours from symptom onset: 14% of the ST-elevation cohort had elevated CK levels at the time of hospital admission.[15] As shown in Figure 1, patients with CK elevations had a much higher mortality at 30 days. At six months, mortality rates in the ST elevation group were 6.0% (CI 5.2-7.0) with normal and 11.2% (CI 8.7-14.4) with elevated CK; in the ST elevation plus depression group, rates were 8.5% (CI 7.1-10.1) for normal and 15.4% (CI 10.8-21.4) for elevated CK levels. The mortality risk is nearly doubled in patients presenting with elevated CK levels. A similar study from the GUSTO IIa database using a central laboratory to determine CK levels observed a 30-day mortality rate of 10.5% in patients with CK-MB level > 7.0 ng/ml on admission, compared with 5.8% in those with CK-MB_7.0.[29] The higher risk of patients with abnormal CK/CK-MB levels on admission is in part related to later hospital arrival, which has been associated with increased mortality in most studies of MI.[6] Another possibility is that patients presenting with elevated cardiac enzymes have had recent prior epidoses of myocardial necrosis, either related to brief coronary occlusion or embolization, that place them at higher risk, analogous to higher risk of reinfarction.[30]

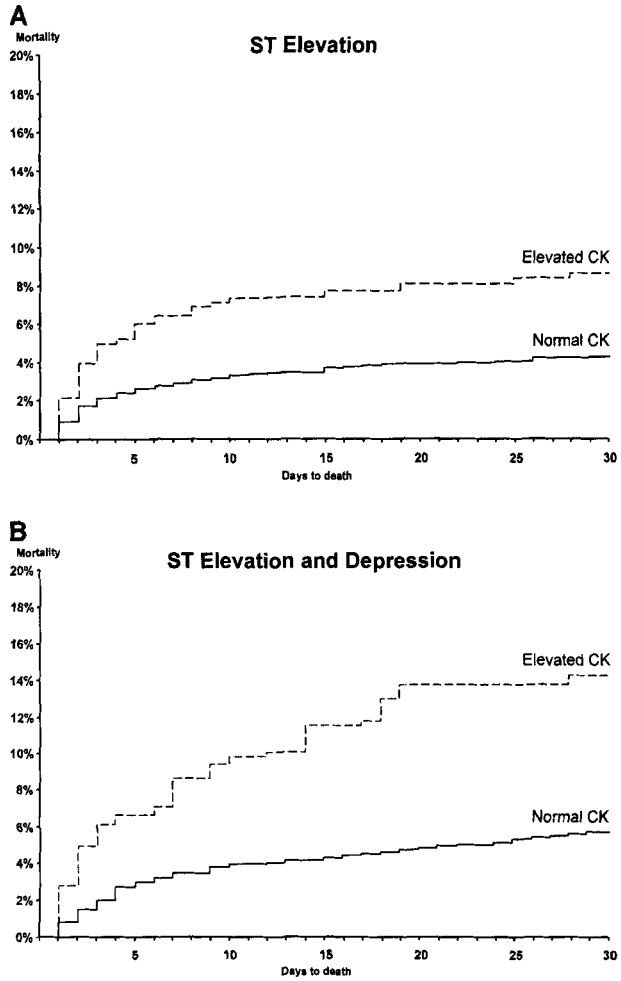

Figure 1. Kaplan-Meier estimates of probability of death up to 30 days in patients presenting with ST-segment elevation and normal or elevated CK levels. (A) panel, ST-segment elevation only. (B) ST-elevation plus depression. Data are from the GUSTO IIb database.

Similarly, elevated troponin T levels on admission have been shown to be an independent marker of increased mortality after correction for known clinical and ECG markers of prognosis.[31] In addition to the GUSTO IIa data, which first showed the predictive value of elevated troponin T levels in patients presenting within 12 hours of an ST-elevation MI,[29] a recent report from a GUSTO III substudy showed that 8.9% of 12,666 thrombolytic eligible patients had a positive bedside troponin T

test (using a first generation device with sensitivity threshold of 0.2 ng/mL): these patients had a longer duration of symptoms, and there was a strong correlation between the duration of symptoms before testing and the likelihood of testing positive.[31] Patients who were troponin T positive had significantly higher mortality (15.5%) than did negative patients (6.4%; P = 0.001), and they also had significantly higher rates of cardiogenic shock, congestive heart failure, asystole, and electromechanical dissociation, as well as bleeding. The association of elevated troponin T levels on admission and increased mortality was consistent among all of the prespecified subgroups (age, gender, infarct location, Killip class and place of enrollment), with a risk ratio of two to three in most cases.[31]

Early Risk Stratification in ACS Without ST-Segment Elevation

The non-ST-elevation ACSs encompass a wide spectrum of pathophysiological background, clinical presentations, and prognostic severity. According to the AHCPR 1994 Unstable Angina Guidelines,[32] patients can be classified as being at low, intermediate, or high risk on the basis of their clinical history, physical examination and ECG presentation. More recently, elevation of biochemical markers of myocardial damage have added to this armamentarium to provide early prognostic stratification.[32] The important concept is that patients presenting with ischemic chest pain and no ST-segment elevation can be risk stratified in the emergency room by using easily available clinical, electrocardiographic, and biochemical data, and that accurate risk stratification is essential to optimize management strategies.[33]

Prognostic Value of Clinical Data

An oriented evaluation of the patients' clinical characteristics and medical history is extremely powerful in identifying those at higher risk. As shown in Figure 2, the clinical predictors for one-year mortality in ACSs do not differ very much between the ST-elevation and non-ST-elevation presentations.[11] Older age and a history of diabetes, angina, MI, heart failure, bypass surgery, and pulmonary disease are significantly and independently associated with higher mortality in the non-ST-elevation cohort. Older age is by far the most important independent predictor of mortality, with an increase in death rate by 39% with each decade.

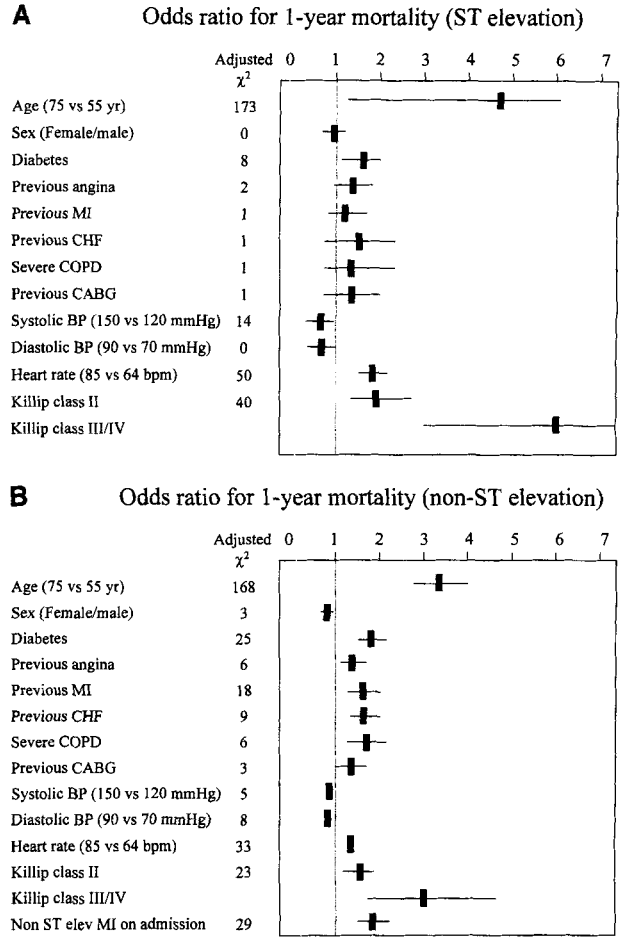

Figure 2. Adjusted odds ratios and 95% CIs for predictors of 1-year mortality in patients presenting with (A) or without (B) ST-segment elevation. CHF indicated congestive heart failure; COPD, chronic obstructive pulmonary disease; BP, blood pressure; HR, heart rate; MI, MI; CABG, coronary artery bypass grafting. (From reference 11.)

Female gender has been associated with worse outcome at univariate[34] but not at multivariate analysis, which shows the worst outcome for male patients.[34-37] Among the variables derived from the baseline clinical examination, lower blood pressure, higher heart rate, and worse Killip class also predict a higher mortality.[11] The classification of unstable angina proposed by Braunwald[38] is based on the clinical characteristics of chest pain and ongoing medical therapy, and was originally meant to group patients into physiopathologically homogeneous subsets. However, the various subgroups have also been shown to be associated with different outcomes,[39,40] particularly when combined

with the presence of ST depression on the baseline ECG, history of diabetes, and old age.[41] Patients presenting with chest pain at rest within the last 48 hours, and particularly those with a recent MI (Braunwald's class III B and C) have the worst prognosis and the most to gain from aggressive antithrombotic and interventional management.[39,40]

The Admission ECG

The ECG is the most accessible and widely used diagnostic tool for patients arriving at an emergency department with symptoms suggestive of acute myocardial ischemia and can provide immediate prognostic discrimination.

Normal ECG. Patients presenting without ST-T changes on the ECG are at very low risk both in the short and in the long term.[41-43] In a series of 596 patients admitted to an emergency room complaining of typical chest pain, only one of 114 with a normal ECG developed an MI, and five unstable angina, during subsequent hospitalization or three days of follow-up:[42] after multivariate analysis including the clinical and enzymatic variables, the authors concluded that "no single variable could identify low risk patients as well as a normal ECG." Among the 911 patients enrolled in the RISC study[43] those with normal ECGs during the initial three days of hospitalization had a 7.6% incidence of death or MI at one year, compared to 13.6% of those with T-wave inversion, 16.1% of those with ST elevation, 18.1% of those with ST depression, and 25.6% of those with ST elevation and depression (Fig. 3). In accordance with these data, a normal or unchanged ECG has been considered among the characteristics of low risk in the 1994 US Unstable Angina Guidelines.[32]

T-wave Changes. Patients presenting with dynamic T-wave changes (new negative T waves or positivization of previously negative T waves) without ST depression are considered at intermediate risk.[32] The one-year incidence of death and MI in the RISC study was significantly lower with inverted T waves in comparison with any other ischemic changes.[43] Among the 8011 patients in the non-ST-elevation cohort of the GUSTO IIb study,[15] those with isolated T-wave inversion had a 6-month mortality of 3.4% (95% CI 2.8-4.2), compared to 6.8% (95% CI 6.0-7.8) of those with ST-segment depression. However, these observations do not mean that patients with T-wave inversion have mild coronary disease, since the prevalence of risk factors and previous cardiac events in this group is similar to that of patients with ST-segment depression. Most of these patients have significant coronary artery disease, and during follow up they undergo revascularization procedures at a rate similar to that of the groups with a worse prognosis.[15] According to databases and clinical experience, patients with isolated negative T waves may represent a heterogeneous mix including the following subsets:

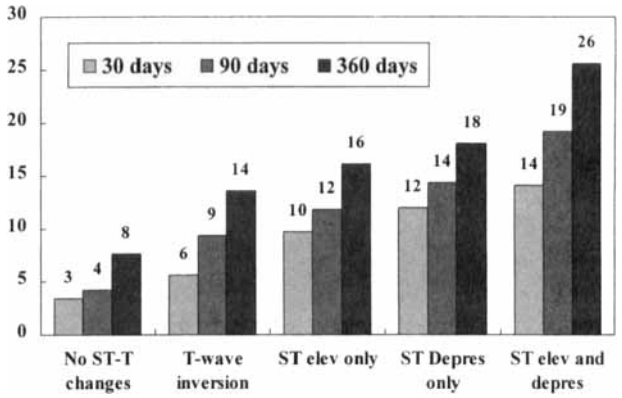

Figure 3. Incidence of death and MI during follow-up with regard to different ST-T segment changes in electrocardiogram at rest obtained during the initial 3 days of hospitalization (n = 911). (From reference 43.)

- subjects (particularly women) with normal epicardial coronary arteries (20% in the GUSTO IIb database),[15] where the symptom episode may be attributable to microvascular angina or nonischemic pain with benign long-term follow-up;[45]
- patients with left ventricular hypertrophy and hypertensive heart disease, also with nonsignificant coronary stenoses;
- patients with significant coronary artery disease, particularly of the left anterior descending artery, often presenting as "canyon" T waves in the anterior leads. Inverted T waves in ≥ 5 leads have been associated with worse outcome at multivariate analysis.[34]

The proportions of patients falling into these different categories may significantly affect the overall prognosis of the cohorts with isolated inverted T waves in different studies.

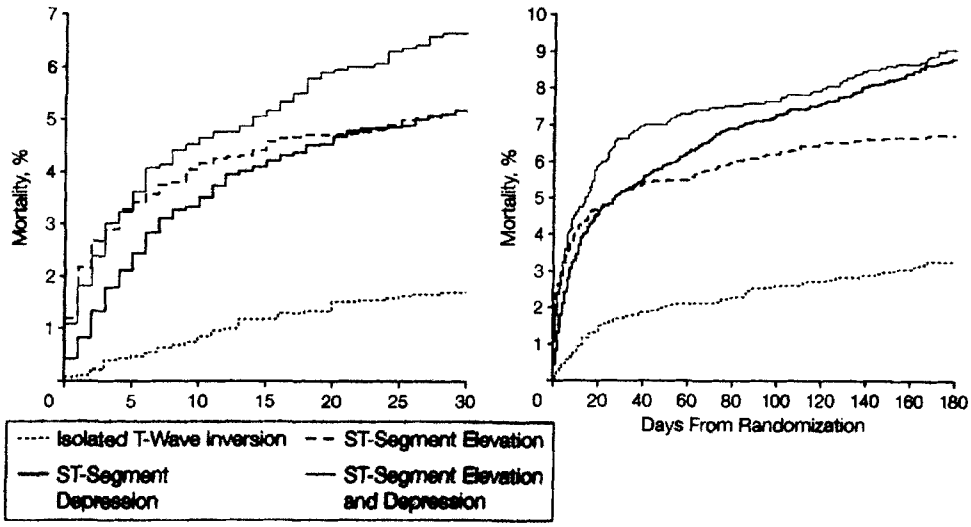

Figure 4. Kaplan-Meier estimates of probability of death up to 30 days (left panel) and 6 months (right panel) according to ECG presentation in acute coronary syndromes. (From reference 15, with permission.)

Patients with inverted T waves tend to have a benign in-hospital course even if they develop enzyme elevations,[15,46] but, if treated medically, may have a poor long-term prognosis.[47-49] Thus, an isolated T-wave inversion pattern with a high suspicion for ischemia should be considered as a warning to carry out a full diagnostic investigation, but the benign early prognosis suggests that acute intervention may be unnecessary.

ST-Segment Depression. Patients with ST-segment depression $\geq$ 0.05 mV during or shortly after a chest pain episode are at high risk of subsequent cardiac events, particularly in the case of symptoms at rest and not secondary to precipitating factors, such as an hypertensive episode, acute anemia, or tachycardia of any origin. The time-course of mortality in patients presenting with ST-segment depression within 12 hours of ischemic symptoms at rest has been followed in the GUSTO IIb cohort[15] and is shown in Figure 4. Overall, the prognosis of these patients is much poorer in comparison with that of patients presenting with inverted T waves; however, the most impressive observation is the relative behavior of this curve in comparison with that of patients with ST-segment elevation. During the first few days, mortality is higher in patients with ST elevation, but as early as 30 days after the index episode the two curves cross and tend to diverge progressively. At six months, mortality in the ST-depression cohort is 30% higher (8.9 vs 6.8%) and similar to that of patients with ST-segment elevation and depression (9.1%). Mortality during follow-up has been attributed to reinfarction and congestive heart failure, particularly in the elderly, and may reflect the higher incidence of severe coronary artery disease and left ventricular dysfunction observed in these patients.[51,52] However, after adjusting for the significant baseline predictors of mortality, the ECG category was highly significant in predicting both death and reinfarction ($P < 0.001$) and death ($P < 0.001$) at 30 days. In comparison with patients presenting with inverted T waves, ST-segment depression on admission was associated with an odds ratio of death and MI of 1.62 (95% CI 1.32-1.98), and of death of 2.07 (95% CI 1.82-3.69).

Data from the ECG core lab of the GUSTO IIb study showed that patients with isolated ST-segment depression have less severe outcomes in comparison with those presenting with ST depression and negative T waves: the incidences of death and death plus MI at 30 days were 4.1% and 11.0% for patients with ST depression only, and 7.4% and 14.5% for those with associated negative T-waves (data unpublished).

Smaller studies have shown poor outcomes for patients with chest pain at rest and ST-segment depression.[35,44,47,52-55] These observations have

been incorporated in accepted guidelines for risk stratification in unstable angina.[33]

Even ST-segment depressions of as little as 0.05 mV have been found prognostically important, as shown in the TIMI III registry.[46] In this study, the incidence of death or MI at one year was 16.3% in patients with 0.5 mm of ST-segment depression compared with 6.1% in those without any ST depression, with an adjusted relative risk of 2.45 (95% CI 1.74-3.45, $P < 0.001$). However, an analysis of 6060 patients with non-ST-elevation ACSs made by the ECG core lab of the GUSTO IIb study showed that ST depression > 0.05 mV was associated with a higher incidence of ischemic events at univariable but not at multivariable analysis.[55] As a result of these observations, the ECG criteria for inclusion of high risk patients in clinical trials, such as the GUSTO IV ACSs trial, is an ST-segment depression of 0.05 mV.

Quantitative Analysis of the ECG

A quantitative evaluation of the ECG variables of patients with non-ST-elevation ACSs has been recently presented by the GUSTO IIb ECG Core Laboratory Investigators.[55] At univariable analysis, a number of variables have been found associated with an increased incidence of adverse outcomes at 30 days (Fig. 5). These variables included the cumulative sum of ST depression, number of leads showing ST depression > 0.1 mV or > 0.05 mV, increased heart rate, QRS duration > 90 msec, number of leads showing inverted T waves, associated inferior or anterior ST elevation, and the depth of T wave inversion. However, after adding all these variables into the GUSTO IIb clinical model, only indexes of myocardium at risk such as cumulative sum of ST depression and number of leads with ST depression > 0.1 mV remained as independent predictors for 30-day death and death or MI, respectively. Other variables that added independent predictive information were small amounts of ST elevation in the anterior leads (≤ 0.1 mV) or the inferior leads (≤ 0.5 mV).

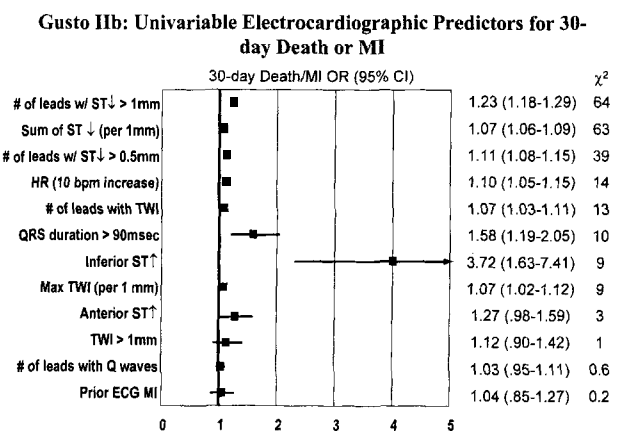

Figure 5. Odds ratios and 95% CIs for quantitative electrocardiographic predictors of death and MI at 30 days. (From reference 55.)

Biochemical Markers upon Hospital Admission

A number of studies have shown that biochemical evidence of even minimal myocardial damage during an ACS is a powerful and independent predictor of subsequent cardiac events.[13,15,29,56,57] However, since the release kinetics of CK and troponin markers from injured myocardial cells require at least a few hours for values to become abnormal, most patients admitted early after symptom onset will have normal values on admission and develop higher levels at later determinations. As an example, in the GUSTO IIa study, which enrolled patients with ischemic ECG changes within 12 hours of symptom onset, 35% of the patients were troponin T-positive on admission, but a further 44% became positive when sampled at 8 and 16 hours.[58] Therefore, at least 12 hours of observation with serial marker determinations are required in order to detect evidence of MI and select low risk patients.[59,60]

On the other hand, an earlier stratification by means of a single determination of biochemical markers (i.e., without waiting for serial determinations) would be desirable in order to identify candidates for early revascularization or aggressive antithrombotic therapy. This approach is becoming more attractive with the availability of sensitive and easily performed bedside assays, some of which are even whole blood assays. In the GUSTO IIb study, as previously mentioned, patients with elevated levels of total serum creatine kinase upon admission had a worse prognosis.[15] However, as shown in Figure 6, within the non-ST-elevation cohort, the negative impact of an elevated CK level on admission seems to be more evident in patients with ST-segment depression, whose mortality at 30 days is 5 to 6 times higher than that of patients with ST depression and normal CK, or of patients with inverted T waves and either normal or elevated CK levels. The combination of two markers, namely

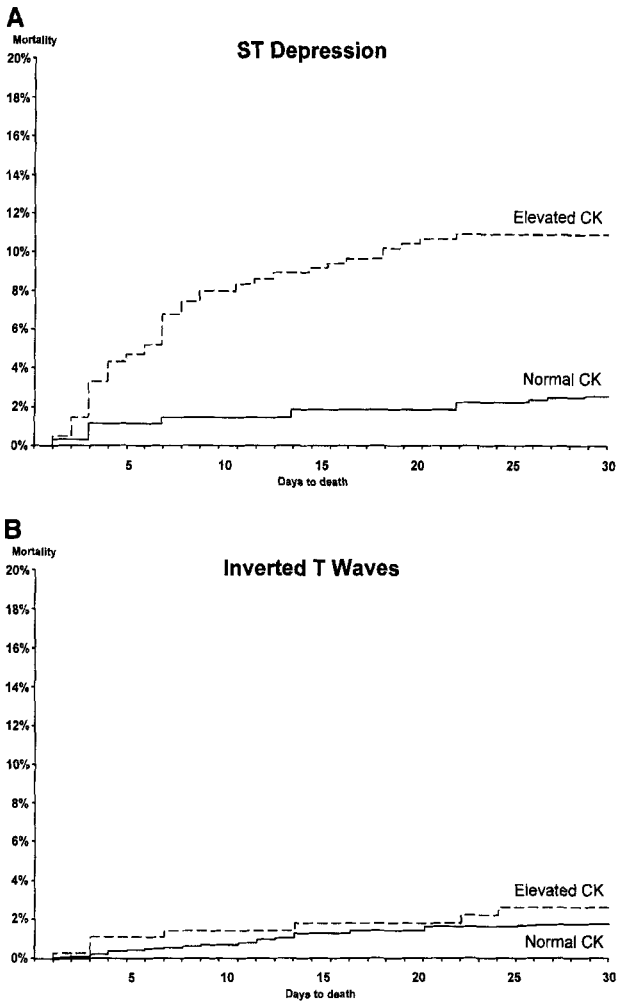

Figure 6. Kaplan-Meier estimates of probability of death up to 30 days in patients presenting with no-ST segment elevation and normal or elevated CK levels. (A) ST depression (± T-wave inversion). (B) inverted T waves only. Data are from the GUSTO IIb database.

myoglobin and $CKMB_{mass}$, has been shown to increase overall accuracy (0.77 - 0.85) for acute MI diagnosis in the emergency department using a single serum sample in patients presenting ≥ 2 hours after onset of symptoms;[61] in addition, patients with no ST-segment elevation and elevated values of both CKMB and myoglobin on admission have been identified as a high risk subgroup, with an incidence of death and MI at one year of 47% (A), compared to 26% of those with only one positive marker (B), and 4% of those with two negative markers (C) ($P < 0.0001$ A vs C and $P = 0.004$ B vs C). In the same study, which however included only a total of 155 patients, troponin T was less accurate than CKMB and myoglobin for early prediction of MI, but was the most important prognostic marker of cardiac death or MI at one year.[61]

A single determination of C-reactive protein or other inflammatory markers, such as fibrinogen and erythrocyte sedimentation rate, has been shown to predict outcome in patients with unstable angina, independently of other clinical and laboratory risk determinants.[62,63] However, the clinical value of measuring these markers, including how they might be used to optimize therapy, has yet to be established.[64]

The interaction of ECG presentation and serum markers in non-ST-elevation ACSs deserves further investigation in order to define how these measures may complement each other. As an example, whereas it is clear that ST segment depression and positive troponin levels are independent predictors of prognosis, the observation in the GUSTO IIb study that patients with ST depression and normal CK on admission have a relatively benign early prognosis, and that patients with inverted T waves may have a blunted risk excess with elevated CK levels on admission, raises the possibility of a more complex relationship of combining these factors in predicting risk.

Multivariable Modeling

Patients with non-ST-elevation ACSs are generally older and have a longer history of coronary artery disease in comparison with those with ST-segment elevation. However, when adjustments are made for baseline characteristics predictive of cardiac events at univariable analysis, multivariable predictors of death or death and MI are substantially the same across the whole spectrum of ACSs.[2,11,15,65] Age is by far the strongest predictor of mortality, followed by signs of left ventricular dysfunction, such as higher heart rate, lower blood pressure, and worse Killip class. ST-segment depression maintains a strong predictive value when added to clinical variables, as well as cardiac enzyme values when added to clinical and ECG data. The predictive value is generally greater for the composite endpoint of death and MI than for mortality alone.[11,12,15,65] The negative impact of positive cardiac enzymes at the time of presentation is particularly strong in the elderly.[65] After adjustment for baseline characteristics, several studies have shown that women tend to have better prognosis than men.[36,37,65]

Table 4. Therapeutic Options in Acute Coronary Syndromes 1990 vs 2000

Type of Syndrome	Year 1990	Year 2000
ST-elevation syndrome	Fibrinolytic therapy	Fibrinolytic therapy Primary PTCA Facilitated primary PTCA Rescue PTCA
Non-ST-elevation syndrome	Aspirin, unfractionated heparin (UFH)	Aspirin + UFH Aspirin + LMWH GPIIb/IIIa blockers + ASA + UFH Routine revascularization

LMWH = low molecular weight heparin; UFH = unfractionated heparin; PTCA = coronary angioplasty.

Therapeutic Implications of an Early Risk Stratification in ACSs

Over the last decade, a number of new therapeutic options have been developed both for the ST-elevation and the non—ST-elevation ACSs (Table 4). Selection of appropriate therapy for individual patients should be based on risk stratification, since the cost of therapy may range from very little (as in the case of low risk patients treated with aspirin) to several thousands of dollars (for a treatment with a low molecular weight heparin plus a GPIIb/IIIa antagonist plus PTCA and stenting). Not only the costs are of concern, but also the risks of aggressive pharmacological or interventional strategies should be balanced against the little, if any, benefit in low risk patients. On the other hand, simple clinical (e.g., age), electrocardiographic (e.g., ST depression), and biochemical (e.g., elevated troponin values) data available upon hospital admission may identify high risk patients candidates for treatment with more aggressive antithrombotics, such as low molecular weight heparins or GPIIb/IIIa antagonists, and percutaneous coronary interventions, all of which have clearly shown to reduce the relative risk of cardiac events by a magnitude of 15%-40% when administered to these patients. In the first few hours after hospital admission, continuous electrocardiographic monitoring and serial enzyme determinations may further define risk stratification, provide evaluation of effectiveness of initial treatment strategies and guide subsequent care.[65]

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