Review Article

# Risk Assessment Models in Acute Coronary Syndromes and Their Applicability in Singapore

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## Abstract

**Risk prediction models are critical in managing patients with acute coronary syndromes (ACS) as they identify high-risk patients who benefit the most from targeted care. We discuss the process of developing and validating a risk prediction model as well as highlight the more commonly used models in clinical practice currently. Finally we conclude by outlining the importance of creating a risk prediction model based on a Singapore population of ACS patients so as to further improve patient, hospital and research outcomes.**

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**Key words: Acute coronary syndrome, Outcomes, Risk prediction model**

## Introduction

Strategies for managing cardiovascular disease are evolving rapidly. This evolution and improvement in care is responsible for reducing mortality especially in patients presenting with acute coronary syndromes (ACS).[1] Nevertheless, there is room for further improvement in outcomes, particularly amongst high-risk patient subgroups in this population.[2-4]

Major international cardiology practice guidelines for the care of patients with ACS recommend that more aggressive management strategies are most applicable for the highest risk patients.[5-8] This includes the appropriate care setting, the use of early percutaneous coronary intervention (PCI), and pharmacotherapies such as antiplatelet and anticoagulation medications. Therefore the ability to identify these high-risk patients reliably is critical to improving overall outcomes.

Individual factors such as age or heart failure were recognised early on to be associated with worse outcomes in myocardial infarction (MI).[9] Since then, the number of factors known to correlate with prognosis has increased steadily. Although individual factors are important in the initial assessment of risk, the complexity of patients with ACS means that identifying single factors in isolation is rarely enough for clinicians to prognosticate accurately.

Risk prediction tools utilising multivariate models are hence integral to the process of risk assessment. Numerous models are now available to predict different outcomes from different ACS patient populations. In this review, we outline the modelling process and the better known risk models available for ACS patients as well as discuss how these risk models can be applied to our local population.

## Design of a Risk Prediction Model

In addition to being reliable and accurate, a risk prediction model must be representative of the population in which it is to be applied to. Although there is no standard method for constructing a prediction model, the general principle is similar.[10-15]

A patient population with the relevant disease condition is first identified. Patient data must be accurate and consistent and there must be sufficient outcome events before model construction should be attempted.

Expert clinical opinion and previously published models identify appropriate candidate variables. The variables with clinically and statistically significant univariate associations with the outcome are then incorporated into a multivariate model. It must be noted that although a multivariate risk model may have a statistically significant association with an event, it may not discriminate accurately enough to identify patients who will or will not have the outcome. The ability of the model to discriminate between patients who do and do not have an event is described by the model c-statistic.

The c-statistic is the proportion of all pairs of patients in the population, one with and one without the outcome,

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in which the patient with the outcome had the higher predicted probability of the event occurring. A model with completely random predictions, essentially no better than flipping a coin, would have a c-statistic of 0.5. Conversely, a model with a c-statistic of 1.0 would always discriminate between patients with and without events. As a general rule, a c-statistic of less than 0.6 has little clinical value, 0.6 to 0.8 has limited or modest value, and greater than 0.8 has sufficient discriminatory ability to be of clinical use.

After deriving the multivariate model, it must be validated before it can be considered to be a predictive model. In a population that contains enough outcomes, a randomly selected subset is usually used to derive the model whilst the rest of the population is used for validation.[15] Otherwise, a separate patient population or statistical techniques such as bootstrapping can be used to validate.[14]

Frequently, the risk model is then transformed into a nomogram for clinical use. There is usually a trade-off between the simplicity of use for a nomogram against its ability to stratify risk accurately. This was important previously when clinicians could not be expected to memorise complex formulas, but has become less so in view of the increasing use of mobile electronic devices that increase the ease of calculations. As such, clinical risk nomograms are becoming increasingly complex, incorporating more variables to improve ability to define risk.

**Risk Models for ACS in Common Clinical Use**

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for managing patients with unstable angina (UA) or ACS highlighted 3 commonly used models for stratifying risk in this population.[6] These are summarised in Table 1.

The TIMI (Thrombolysis in Myocardial Infarction) model for UA and NSTEMI (Non-ST segment elevation myocardial infarction) was derived from a clinical trial population to predict the likelihood of mortality, MI or severe recurrent ischaemia requiring urgent revascularisation within 14 days of risk assessment.[12] The model was derived from a comparatively small population of 1957 patients with an outcome rate of 16.7% at 14 days. It is a simple model to use with the risk score being derived from a summation based on the presence or absence of 7 clinical features. Because of its simplicity, the model c-statistic is 0.65 in the test cohort implying modest discriminatory ability for the combined outcome. It performs better when validated for the outcome of death alone (c-statistic 0.72 to 0.78) although this is still less than most other published mortality models that typically have c-statistic values greater than 0.8. Nevertheless, its simplicity enables it to be easily recalled and used for rapid bedside risk assessment.

Another clinical trial population based model is the PURSUIT (Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy) model.[13] It predicts the risk of either death alone or death and MI within 30 days of risk assessment in patients with UA and NSTEMI. As compared to the TIMI model, the PURSUIT model is a weighted score and requires more complicated calculations. It also illustrates how models incorporating a combined outcome in ACS populations usually have a much reduced c-statistic value than models that predict only mortality.

The GRACE (Global Registry of Acute Coronary Events) investigators have published models derived from the multinational GRACE registry predicting mortality in-hospital as well as at 6 months.[14,16] The in-hospital mortality model was derived from a population of 11,389 patients, encompassing the full spectrum of ACS, with a mortality rate of 4.6%. Like the PURSUIT model, it is a weighted score requiring more complex calculations than the TIMI UA/NSTEMI model. It differs from both the TIMI and PURSUIT models, as the patient population is a "real world" multinational ACS cohort thus potentially increasing its relevance to day-to-day clinical practice.

The "real world" nature of the GRACE model is reflected in predictors that were under-represented in previous models derived from clinical trial populations. Clinical trial populations have clearly defined enrollment criteria and hence certain patient subgroups may not be available for analysis. For instance, in GRACE, successfully resuscitated cardiac arrest on presentation and renal impairment were strongly predictive of mortality. Clinical trial models have not included these variables as patients with these conditions are frequently excluded from clinical trials. Similarly, heart failure (expressed as worse Killip class) was found to be more predictive in the GRACE model than in previous models. The GRACE in-hospital mortality model was recently revalidated and updated to account for the different ACS cohorts as well as the impact of continuous variables.[17]

In ST-segment elevation myocardial infarction (STEMI), the Global Utilization of Streptokinase and tPA for Occluded Coronary Arteries (GUSTO-1) and TIMI investigators have both described models predicting mortality in the short as well as long term.[9-11] Of note however, these models were derived from clinical trials evaluating the use of thrombolytics and thus predate the current era of primary PCI. The TIMI STEMI score was validated in a large general MI population (the United States National Registry of Myocardial Infarction 3), and found to have good discrimination among patients receiving thrombolysis. However, the model performance was reduced when applied to patients not receiving reperfusion therapy (c-statistic = 0.65).[18]

Table 1. Risk Assessment Models in Unstable Angina and NSTEMI

| | TIMI UA/NSTEMI[12] | PURSUIT[13] | GRACE In-hospital[14] | GRACE 6-months[16] |
|---|---|---|---|---|
| Year published | 2000 | 2000 | 2003 | 2004 |
| Derivation population | Clinical trial (TIMI-11B) | Clinical trial (PURSUIT) | International registry (GRACE) | International registry (GRACE) |
| Range of ACS | UA and NSTEMI | UA and NSTEMI | UA, NSTEMI and STEMI | UA, NSTEMI and STEMI |
| Number of patients | 1957 | 9461 | 11,389 | 15,007 |
| Adverse risk factors | Age >65 years | Advanced age | Advanced age | Advanced age |
| | >3 risk factors for CAD | Female sex | Higher Killip class | History of MI |
| | Prior coronary stenosis of ≥50% | Worst angina CCS class | Lower systolic blood pressure | History of heart failure |
| | ST-segment deviation on presentation | Higher heart rate | ST-segment deviation | Not having inpatient PCI |
| | At least 2 anginal events in prior 24 hours | Lower systolic blood pressure | Cardiac arrest during presentation | Lower systolic blood pressure |
| | Use of aspirin in prior 7 days | Signs of heart failure | Higher serum creatinine | Higher serum creatinine |
| | Elevated serum cardiac markers | ST-depression on presentation | Elevated serum cardiac markers | Elevated serum cardiac markers |
| | | | Higher heart rate | Higher heart rate |
| | | | | ST-segment depression |
| Predicted outcomes | Death, MI or revascularisation | Death and MI | Death | Death |
| Time to outcomes | 14 days | 30 days | In-hospital | 6 months |
| Published c-statistic | 0.65 | 0.81 (death only) | 0.83 | 0.81 |
| | | 0.67 (death or MI) | | |

ACS: acute coronary syndrome; CAD: coronary artery disease; CCS: Canadian Cardiovascular Society; MI: myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction; PCI: percutaneous coronary intervention; UA: unstable angina

More recently, risk models in STEMI based on primary PCI trial populations have been developed and validated. The PAMI (Primary Angioplasty in Myocardial Infarction) 6 month mortality model combined populations from the various PAMI trials and is a relatively simple bedside risk assessment tool.[19] Similarly, the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) investigators have published their model for mortality at 30 days and 1 year.[20] Although the TIMI, PAMI and CADILLAC models share similar variables, the CADILLAC model is the only one of the three that has left ventricular ejection fraction (LVEF) as a significant risk factor (Table 2).

In addition to mortality and ischaemic outcomes, other important events are now being examined by risk models. The CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines) Bleeding Score uses the large NSTEMI population in the CRUSADE registry to predict the risk of in-hospital bleeding.[15] The model was derived from a population of 71,277 patients with a 9.4% in-hospital bleeding rate. It incorporates baseline haematocrit, creatinine clearance, heart rate, sex, signs of heart failure, prior vascular disease, diabetes mellitus and systolic blood pressure with a model c-statistic of 0.72. Models such as this will help clinicians to further evaluate the risk in administering medications that may increase the risk of bleeding in a patient.

## Discussion

Although there are many risk models available currently for ACS, they share many common variables. Choosing which risk model to apply should therefore be dictated by the patient population in question, as well as the outcome of interest. The clinician should ideally understand the population from which the model was derived before using it to guide management. Clinical trial populations tend to enroll lower risk patients as compared to real world patient registries. In addition, trial populations generally have more vigorous patient follow-up and treatment plans which bias long-term outcomes favourably. Registry data has its limitations as well and these include less stringent event adjudication and variability across recruiting sites in terms of patient mix as well as management strategies.

At present there is no validated risk model derived from a Singaporean ACS patient population. In fact, most

Table 2. Risk assessment models in STEMI

| | TIMI STEMI[11] | PAMI[19] | CADILLAC[20] | |
|---|---|---|---|---|
| Year published | 2000 | 2004 | 2005 | |
| Derivation population | Clinical trial (InTIME II) | Clinical trial (PAMI trials) | Clinical trial (CADILLAC) | |
| Range of ACS | STEMI (thrombolysis) | STEMI (primary PCI) | STEMI (primary PCI) | |
| Number of patients | 14,114 | 3252 | 2082 | |
| Adverse risk factors | Advanced age | Advanced age | Advanced age | |
| | Lower systolic blood pressure | Higher Killip class | Higher Killip class | |
| | Higher heart rate | Higher heart rate | LVEF <40% | |
| | Higher Killip class | Diabetes | Anaemia | |
| | Anterior MI or LBBB | Anterior MI or LBBB | Renal insufficiency | |
| | Diabetes, hypertension or angina | | Triple vessel disease | |
| | Weight <67 kg | | Post PCI TIMI flow grade | |
| | Time to treatment >4 hours | | | |
| Predicted outcomes | Death | Death | Death | |
| Time to outcomes | 30 days | 30 days | 30 days | 1 year |
| Published c-statistic | 0.78 | 0.78 | 0.83 | 0.79 |

ACS: acute coronary syndrome; LBBB: left bundle branch block; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST segment elevation myocardial infarction; TIMI: Thrombolysis in Myocardial Infarction

published risk models are based on Western populations and their applicability to our local population should ideally be validated before routine clinical use.

Indeed, data from the Singapore Myocardial Infarct Registry showed that the incidence and outcomes of MI vary with ethnicity in Singapore.[21,22] Malays have twice and Indians 3 times the age-standardised rates of MI when compared to Chinese. The reasons for these differences remain conjectural, but there are higher rates of diabetes and lower HDL-cholesterol levels in Indians.[23,24] Despite having a higher incidence, there was no difference between Indians and Chinese in case fatality rates, whereas case fatality rates were higher for Malays than Chinese after adjusting for baseline characteristics. There is therefore a great need to fill this gap in our knowledge base.

A validated local risk prediction instrument for ACS will be valuable on at least 3 different fronts. Firstly, it can be used to stratify risk more accurately as it would have been derived and validated in a more representative patient population. This should translate into better decision making and hence better outcomes for the individual patient.

Secondly, it will facilitate quality improvement initiatives both on a hospital basis as well as on a national basis by giving a better assessment of clinical care. If the observed outcomes of a hospital are worse than those predicted by the risk model, this may serve as a trigger to identify deficiencies in care processes and delivery. Likewise, risk adjusted outcomes would assist in assessing the effectiveness of quality improvement programmes in ACS.

Finally, a local risk prediction tool would be crucial to further research in ACS in Singapore. The lack of valid risk adjusted outcomes currently hampers studies of comparative effectiveness and should serve as an impetus to the rapid development of such an instrument. Data collected by the Singapore Cardiac Data Bank as well as the individual hospitals should be used to develop and validate such a risk assessment model as soon as possible. This will hopefully result in better patient outcomes, hospital care processes and research opportunities in the future.

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