## RISK CHAPTER: ASSESSMENT OF RISK

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antman EM, Cohen M, Bernink PJ et al.</td>
<td>Observational study</td>
<td>Total N=7081</td>
<td>Inclusion: all patients in TIMI IIb and ESSENCE. Presented within 24 hrs of an episode of UA/NSTEMI at rest with at least one of the following: ST segment deviation on the qualifying ECG (either transient ST elevation or persistent ST depression of &gt;=0.5 mV in TIMI IIb and &gt;=0.01 mV in ESSENCE), documented history of coronary artery disease, and elevated serum cardiac markers. Exclusion: planned revascularization in 24 hrs or less, a correctable cause of angina, and contraindications to anticoagulation. Baseline characteristics: not stated</td>
<td>To apply the TIMI risk score to ESSENCE and TIMI IIb cohorts to predict risk Procedure: From the unfractionated heparin group of the TIMI IIb arm (N=1957), 12 baseline characteristics were screened as candidate predictor variables of risk of composite end point. A multivariate logistic regression model used to assess statistical significance of each variable. Variables that remained significant (p&lt;0.2) were tested in a multivariate stepwise backward elimination regression model. TIMI risk score then validated in 3 separate groups: the enoxaparin arm of TIMI IIb (N=1953),</td>
<td>N/A</td>
<td>14 days</td>
<td>Composite endpoint: All cause mortality, new or recurrent MI severe recurrent ischemia prompting urgent revascularization at 14 days. Death at 14 days MI at 14 days Death or MI at 14 days Urgent revascularisation at 14 days</td>
<td>Aventis Pharma</td>
</tr>
</tbody>
</table>
Primary endpoint occurred in 16.7% of test cohort.

**Multivariate analysis**

The following variables were significantly associated with increased risk of all-cause mortality, new or recurrent MI, severe recurrent ischemia prompting urgent revascularization at 14 days:

- Age ≥ 65 years
- At least 3 factors for CAD (family history of CAD, hypertension, hypercholesterolemia, diabetes, or current smoker)
- Significant coronary stenosis (e.g. prior coronary stenosis ≥ 50%)
- ST deviation
- Severe anginal symptoms (e.g. ≥ 2 anginal events in last 24 h)
- Use of aspirin in last 7 days
- Elevated serum cardiac markers (CK-MB and/or cardiac-specific troponin level)

**TIMI risk score: All cause mortality, new or recurrent MI, severe recurrent ischemia prompting urgent revascularization at 14 days:**

In the test cohort (UFH arm of TIMI IIb; N=1957), risk of the composite endpoint significantly increased with increasing number of risk factors (p<0.001 trend). The C-statistic = 0.65

TIMI Calibration: good calibration in the test group (Hosmer-Lemeshow statistic = 3.56, p=0.89)

Even when the TIMI model was assessed with missing values for significant coronary stenosis, prior coronary stenosis of 50% or more remained a significant predictor of composite endpoint.

For all three validation cohorts [enoxaparin arm of TIMI IIb (N=1953); enoxaparin group of ESSENCE (N=1607); and UFH group of ESSENCE (N=1564)], there was a significant increase in the rate of events as the TIMI risk score increased (p<0.001).

- C-statistic enoxaparin arm of TIMI IIb (N=1953) = 0.61
- C-statistic enoxaparin group of ESSENCE (N=1607) = 0.59
- C-statistic UFH group of ESSENCE (N=1564) = 0.65

**TIMI risk score: MI at 14 days**

In the total population of TIMI IIb trial (N=3910), death at 14 days increased significantly with increasing TIMI risk score (p<0.001 trend). C-statistic = 0.74

**TIMI risk score: MI at 14 days**

In the total population of TIMI IIb trial (N=3910), MI at 14 days increased significantly with increasing TIMI risk score (p<0.001 trend).
C-statistic = 0.66

**TIMI risk score: Urgent revascularisation at 14 days**
In the total population of TIMI IIb trial (N= 3910), urgent revascularisation at 14 days increased significantly with increasing TIMI risk score (p<0.001 trend). C-statistic = 0.68

**TIMI risk score: All cause mortality or MI at 14 days**
In the total population of TIMI IIb trial (N= 3910), death or MI at 14 days increased significantly with increasing TIMI risk score (p<0.001 trend). C-statistic = 0.63

Note: risk score developed and validated in RCTs, which may limit application to real-world clinical settings. Authors lacked quantitative data on serum cardiac markers (used as a dichotomous variable).

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<tbody>
<tr>
<td>Samaha FF, Kimmel SE, Kizer JR et al. Usefulness of the TIMI risk score in predicting both short- and long-term outcomes in the Veterans Affairs Non-Q-Wave Myocardial Infarction Strategies In-Hospital (VANQWISH) Trial. American Journal of Cardiology. 2002; 90(9):922-926. Ref ID: 3274</td>
<td>Observational study 3 Multicentre, Veteran’s Affairs cooperative study VANQWISH trial population</td>
<td>N total = 922</td>
<td>Inclusion: VANQWISH trial: people with non-Q wave MI randomised to conservative versus invasive strategy within 24-72 hours of onset of symptoms. Exclusion criteria: not stated Population baseline characteristics: not stated</td>
<td>Assess ability of TIMI risk score to predict outcome Procedure: TIMI risk score assigned to VANQWISH participants (4 risk groups) based on presence of TIMI risk predictors. Note that prior angiographic coronary stenosis data was not available, so history of MI, PCI, or CABG substituted for this variable. Severe angina defined as CCS class III-IV angina within prior 3 weeks. Predictive accuracy of multivariate model</td>
<td>N/A Procedure: As for intervention</td>
<td>Mean 23 months</td>
<td>Death, nonfatal MI, urgent revascularisation Death Nonfatal MI Urgent revascularisation C-index of multivariate model to predict these outcomes</td>
<td>COR Therapeutics and Schering Plough Research Institute</td>
</tr>
</tbody>
</table>
Effect size
At 30 days 10.3% of the VANQWISH participants had the combined endpoint: death, nonfatal MI, urgent revascularisation. At 1 year, 26.5% of the VANQWISH participants had the combined endpoint: death, nonfatal MI, urgent revascularisation.

Death, nonfatal MI, urgent revascularisation: TIMI risk score
The combined endpoint increased significantly as TIMI risk score increased (p=0.003 trend at 30 days; p<0.0001 at 1 year)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>C-statistic (95% CI) TIMI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/nonfatal MI/urgent revascularisation at 30 days</td>
<td>0.59</td>
<td>0.003</td>
</tr>
<tr>
<td>Death/nonfatal MI/urgent revascularisation at 1 year</td>
<td>0.60</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death at 1 year</td>
<td>0.65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nonfatal MI at 1 year</td>
<td>0.62</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Death/nonfatal MI at 30 days</td>
<td>0.61</td>
<td>0.01</td>
</tr>
<tr>
<td>Death/nonfatal MI at 1 year</td>
<td>0.64</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The TIMI risk score was not predictive of:
- 30 day death (p=0.07)
- 30 day nonfatal MI (p=0.12)
- 30 day urgent revascularisation (p=0.59)
- 1 year urgent revascularisation (p=0.57)

Model calibration (TIMI): Death, nonfatal MI, urgent revascularisation at 30 days:
Good overall fit between observed and expected event rate (p=0.72 Hosmer-Lemeshow statistic); although TIMI model over-predicted risk of adverse event.

Ref ID: 296
Reference
Study type/ Evidence level | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Source of funding
--- | --- | --- | --- | --- | --- | --- | ---
Bradshaw PJ, Ko DT, Newman AM et al. Validation of the Thrombolysis Observational study 3 | Total: 11,510 | Include: EFFECT RCT: two of the following three variables must be present: characteristic ECG changes; pain of assumed | Examine variables of age, systolic blood pressure and | N/A Procedure as for intervention | 30 days | death at 30 days | Canadian Institutes of Health Research

<table>
<thead>
<tr>
<th>Ref ID: 438</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference</strong></td>
</tr>
<tr>
<td>Bradshaw PJ, Ko DT, Newman AM et al. Validity of the GRACE (Global Observational study 3)</td>
</tr>
</tbody>
</table>
Registry of Acute Coronary Events (Multicentre, Canada; EFFECT study) acute coronary syndrome prediction model for six month post-discharge death in an independent data set. *Heart.* 2006; 92(7):905-909. Ref ID: 438

N= 10242 alive at hospital discharge
STEMI: 5697 (49.5%)
NSTEMI: 5812

Two of the following three variables must be present: characteristic ECG changes; pain of assumed ischemic origin; or elevated cardiac enzymes or markers.

Exclude: patients with AMI as an in-hospital complication. Heart rate outside the range of 50-150 beats/min or those who were in cardiogenic shock on admission.

Hospital discharge in the EFFECT trial.

Risk score and Stroke Foundation of Canada.

Effect size
Death at 6 months (NSTEMI population separately) was 8.8% and 7.0% in the whole cohort

Death at 6 months and 12 months increased with increasing GRACE risk score.

**Model discrimination: GRACE risk score in NSTEMI population only (N=5812)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>C-statistic (95% CI)</th>
<th>GRACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death at 6 months</td>
<td>0.78 (0.76 to 0.80)</td>
<td></td>
</tr>
<tr>
<td>Death at 1 year</td>
<td>0.78 (0.77 to 0.80)</td>
<td></td>
</tr>
</tbody>
</table>

Ref ID: 1155

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
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<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singh M, Reeder GS, Jacobsen SJ et al. Scores for post-myocardial infarction risk stratification in the community.[see comment].</td>
<td>Observational study</td>
<td>N NSTEMI = 717</td>
<td>Inclusion: people in Olmsted County with confirmed MI (STEMI and NSTEMI diagnosed on basis of cardiac pain, CK, and code)</td>
<td>Assess the utility of TIMI and PREDICT risk scores to predict 28 day death or 28 day death/MI. Procedure: Patient data collected by coordinator/physician on a standard form. Model</td>
<td>N/A Procedure: As for intervention</td>
<td>6.3 years</td>
<td>Death death/MI</td>
<td>NIH and Public Health Service</td>
</tr>
</tbody>
</table>
Exclusion criteria: not stated

Population baseline characteristics:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>68</td>
</tr>
<tr>
<td>% Male</td>
<td>66</td>
</tr>
</tbody>
</table>

discrimination refers to the ability to correctly distinguish higher from lower risks patients; evaluated by the C-statistic (similar to area under the curve). Model calibration indicated how closely predicted outcomes approximate actual event rate (assessed by graphing observed vs predicted event rates. A low probability by Hosmer-Lemeshow goodness-of fit test indicates poor calibration.

Effect size
After 6.3 years, 372 (52%) NSTEMI died
136 (19%) had nonfatal recurrent MI

Model discrimination: TIMI vs PREDICT

<table>
<thead>
<tr>
<th>Outcome (NSTEMI only)</th>
<th>C-statistic (95% CI) TIMI</th>
<th>C-statistic (95% CI) PREDICT</th>
<th>p value (TIMI vs PREDICT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death at 28 days</td>
<td>0.59 (0.53 to 0.66)</td>
<td>0.78 (0.73 to 0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death at 1 year</td>
<td>0.61 (0.56 to 0.66)</td>
<td>0.81 (0.77 to 0.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death/MI at 28 days</td>
<td>0.59 (0.53 to 0.65)</td>
<td>0.78 (0.67 to 0.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death/MI at 1 year</td>
<td>0.62 (0.57 to 0.67)</td>
<td>0.78 (0.74 to 0.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

TIMI risk model was significantly less accurate than PREDICT for predicting death or death/MI at either 28 days or at 1 year.

Model Calibration: TIMI vs PREDICT
TIMI had good calibration (Hosmer-Lemeshow goodness of fit p=0.61) for risk of death at 28 days, but calibration was lower at 1 year (Hosmer-Lemeshow goodness of fit p=0.11)
PREDICT had good calibration (Hosmer-Lemeshow goodness of fit p=0.36) for risk of death at 28 days and at 1 year (Hosmer-Lemeshow goodness of fit p=0.60).

Addition of ejection fraction to the PREDICT model significantly improved model discrimination (c-statistic PREDICT = 0.80 versus c-statistic PREDICT + EF = 0.83, p<0.001) for death at 28 days in the TOTAL MI population (STEMI + NSTEMI)

Addition of Charlson score to TIMI also significantly improved model discrimination (TIMI vs TIMI + Charlson score, p<0.0001 between c-statistics - STEMI + NSTEMI population)

Note: MI population was Caucasian and caution in extrapolating to more ethnically diverse MI populations.
<table>
<thead>
<tr>
<th>Evidence level</th>
<th>of patients</th>
<th>of follow-up</th>
<th>measures of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational study</td>
<td>N NSTE ACS = 1728</td>
<td>1 year</td>
<td>Not stated</td>
</tr>
</tbody>
</table>

Yan AT, Yan RT, Tan M et al. Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. [see comment]. *Eur Heart J.* 2007; 28(9):1072-1078. Ref ID: 138

### Inclusion: Canadian ACS-2 Registry: Between 2002-2003, patients > 18 years old presenting with suspected ACS (defined as symptoms consistent with acute cardiac ischemia within 24 h of onset) were recruited.

### Exclusion criteria: serious concurrent illness

### Population baseline characteristics:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67</td>
</tr>
<tr>
<td>% Male</td>
<td>67.4</td>
</tr>
<tr>
<td>% abnormal cardiac markers</td>
<td>55.8</td>
</tr>
<tr>
<td>% ST-deviation</td>
<td>26.1</td>
</tr>
</tbody>
</table>

Median TIMI risk score=3
Median PURSUIT risk score= 7
Median GRACE risk score= 117

Assess the utility of TIMI, GRACE and PURSUIT risk scores to predict in-hospital mortality in the Canadian ACS-2 Register.

Procedure: Treating physicians asked to classify patients as low, intermediate or high risk based on global assessment similar to ACC/AHA or ESC guidelines (encompasses medical history, physical exam, and laboratory investigations). Patient data collected by coordinator/physician on a standard form. Inhospital and 1 year death predicted using GRACE, PURSUIT and TIMI risk scores. Model discrimination refers to the ability to correctly distinguish higher from lower risks patients; evaluated by the C-statistic (similar to area under the curve). Model calibration indicated how closely predicted outcomes approximate actual event rate (assessed by graphing observed vs predicted event rates. A low probability by Hosmer-Lemeshow goodness-of fit test indicates poor calibration.

Procedure: As for intervention
Effect size
In-hospital death rate was 1.8% in those with NSTE ACS. Cumulative mortality at 1 year was 6.8%

The risk of in-hospital death or death at 1 year increased significantly as risk increased from low to intermediate to high risk in all 4 risk assessment tools (TIMI, GRACE, PURSUIT, Physician’s assessment).

In hospital management: CABG + PCI
As Physicians Assessment of risk increased from low-to high, the use of PCI and CABG increased significantly (p<0.0001 trend).
By contrast, PCI and CABG were performed significantly less as risk increased according to TIMI (p=0.06 trend), or GRACE (p<0.0001 trend) or PURSUIT (p<0.0001 trend) risk scores.

Model discrimination

<table>
<thead>
<tr>
<th>Outcome</th>
<th>C-statistic (95% CI) TIMI</th>
<th>p value</th>
<th>C-statistic (95% CI) GRACE</th>
<th>p value</th>
<th>C-statistic (95% CI) PURSUIT</th>
<th>p value</th>
<th>TIMI vs TIMI</th>
<th>TIMI vs GRACE</th>
<th>TIMI vs PURSUIT</th>
<th>PURSUIT vs GRACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death in hospital</td>
<td>0.68 (0.59 to 0.77)</td>
<td>&lt;0.001</td>
<td>0.81 (0.73 to 0.89)</td>
<td>&lt;0.0001</td>
<td>0.80 (0.71 to 0.88)</td>
<td>&lt;0.0001</td>
<td>0.02</td>
<td>0.036</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Death at 1 year</td>
<td>0.69 (0.64 to 0.74)</td>
<td>&lt;0.0001</td>
<td>0.79 (0.74 to 0.83)</td>
<td>&lt;0.0001</td>
<td>0.77 (0.72 to 0.81)</td>
<td>&lt;0.0001</td>
<td>0.001</td>
<td>0.006</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

NS difference between GRACE and PURSUIT models for in-hospital death or death at 1 year
PURSUIT had significantly better discrimination than TIMI for in-hospital death or death at 1 year
GRACE had significantly better discrimination than TIMI for in-hospital death or death at 1 year

Ref ID: 749

Reference
Yan AT, Jong P, Yan RT et al. Clinical trial–derived risk model may not generalize to real-world patients with acute coronary
Clinical trial--derived risk model may not generalize to real-world patients with acute coronary

Study type/ Evidence level | Number of patients | Patient characteristics | Intervention | Comparison | Length of follow-up | Outcome measures | Source of funding
--- | --- | --- | --- | --- | --- | --- | ---
Observational study | N NSTE ACS = 2925 | Inclusion: Canadian ACS-1 Registry. Between 1999-2001, patients > 18 years old presenting with suspected ACS (STE ACS or NSTE ACS) were recruited. | Assess the utility of GRACE and PURSUIT risk scores to predict in-hospital mortality in the Canadian ACS-1 Register. Procedure: Analysis restricted to people with NSTE ACS in the | N/A | Procedure: As for intervention | NR | Canadian Heart Research Centre and Key Pharmaceuticals
syndrome. 

Exclusion criteria: 
none

Population baseline characteristics:

<table>
<thead>
<tr>
<th>Age, years</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Male</td>
<td>65.8</td>
</tr>
<tr>
<td>% Abnormal cardiac markers</td>
<td>38.9</td>
</tr>
<tr>
<td>% ST-depression</td>
<td>19.4</td>
</tr>
<tr>
<td>% ST elevation</td>
<td>0</td>
</tr>
</tbody>
</table>

Canadian ACS-1 Register. Patient data collected by coordinator/physician on a standard form. In hospital PURSUIT risk score was modified from original (which was developed to predict 30 day mortality). GRACE and PURSUIT models used to predict in-hospital death. Model discrimination refers to the ability to correctly distinguish higher from lower risks patients; evaluated by the C-statistic (similar to area under the curve). Model calibration indicated how closely predicted outcomes approximate actual event rate (assessed by graphing observed vs predicted event rates. A low probability by Hosmer-Lemeshow goodness-of fit test indicates poor calibration.

Effect size
In-hospital death rate was 1.5% in those with NSTE ACS.

**Death in hospital: GRACE vs PURSUIT**
Calculated probability of in-hospital death was 1.0% (GRACE; median) and 1.4% (PURSUIT; median). Estimated probability of in hospital death was significantly higher in PURSUIT model compared with GRACE (p<0.001).

**Model discrimination: GRACE vs PURSUIT**
PURSUIT c-statistic = 0.84 (95% CI 0.79 to 0.89)  
GRACE c-statistic = 0.83 (95% CI 0.77 to 0.89)  
NS difference between models
In those > 65 years old, both PURSUIT (c-statistic 0.75) and GRACE (c-statistic 0.74) models had good discrimination.

**Model Calibration: GRACE vs PURSUIT**

GRACE had good calibration (Hosmer-Lemeshow goodness of fit p=0.40) and expected event rate and actual even rate were similar. PURSUIT had poor calibration (Hosmer-Lemeshow goodness of fit p<0.001) and consistently overestimated risk of in hospital death.

In those > 65 years old, GRACE (Hosmer-Lemeshow goodness of fit p=0.70) provided good calibration, whereas PURSUIT had poor calibration (Hosmer-Lemeshow goodness of fit p=0.006)

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<th>Outcome measures</th>
<th>Source of funding</th>
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</thead>
<tbody>
<tr>
<td>Boersma E, Pieper KS, Steyerberg EW et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. Circulation. 2000; 101(22):2557-2567. Ref ID: 1463</td>
<td>Observational study 1 Multicentre, 28 countries PURSUIT trial population</td>
<td>N total = 9461 N unstable angina=5129 N NSTEMI = 4308</td>
<td>Inclusion: PURSUIT trial: people presenting within 24 hours of ischemic chest pain (&gt; 10 min) with either transient ST-segment elevation (&gt;0.5 mm), transient or persistent ST-segment depression (&gt; 0.5 mm), T-wave inversion (&gt; 1.0 mm), or elevated CK-MB (above ULN). No age restrictions. Exclusion criteria: participants with persistent (&gt;30 min) ST-segment elevation; people with missing baseline data (8%) Population baseline characteristics: Age, years 64 % Male 65</td>
<td>Examine baseline variables associated with risk of mortality or mortality or MI at 30 days. Multivariable model then constructed to estimate risk score Procedure: Univariate and multivariate logistic regression analysis used to evaluate baseline predictors of 30 day death or 30 day death/MI. Predictive accuracy of</td>
<td>N/A Procedure: As for intervention</td>
<td>30 days</td>
<td>Death at 30 days</td>
<td>Death or MI at 30 days</td>
</tr>
</tbody>
</table>
Effect size
N=342 died at 30 days (3.6%)
N= 1075 had nonfatal re-MI at 30 days (11.4%)

Death at 30 days: Univariate Analysis
The following baseline variables were significantly associated with increased odds of death at 30 days:
Age
Rales
ST-segment depression
Congestive heart failure
Diabetes
Previous MI
MI (CK-MB elevation) at enrolment
Worst CCS class III or IV in the past 6 weeks
Prior cardiac medication use
Prior CABG
Enrolment in Latin America or Eastern Europe

Death at 30 days: Multivariate Analysis
After adjusting for other baseline variables, the following baseline variables were significantly associated with increased odds of death at 30 days:
Age
Baseline heart rate
Lower SBP
ST-segment depression
Rales
Male sex (females had lower risk compared with males)
Enrolment in Latin America

There were interactions between enrolment diagnosis (UA or MI) and age heart rate, PURSUIT medication, rales

Death or MI at 30 days: Univariate Analysis
The following baseline variables were significantly associated with increased odds of death or MI at 30 days:
- Age
- MI at enrolment
- Rales
- ST-depression
- Congestive heart failure
- Worst CCS class III or IV in the past 6 weeks
- Diabetes
- Previous MI
- Enrolment in Eastern Europe

Death or MI at 30 days: Multivariate Analysis
After adjusting for other baseline variables, the following baseline variables were significantly associated with increased odds of death or MI at 30 days:
- Age
- MI at presentation
- Worst CCS class III or IV in the past 6 weeks
- Baseline heart rate
- Lower SBP
- ST-segment depression
- Rales
- Male sex (females had lower risk compared with males)
- Enrolment in Latin America

Predictive accuracy
C-index for multivariate model for death at 30 days was 0.814
C-index for multivariate model for death or MI at 30 days was 0.670.

Simplified PURSUIT risk score for death at 30 days or death/MI at 30 days: awards points for each variable upon presentation and considered the most important prognostic factors:
- Age
- Gender
- Worst CCS-Class in previous 6 weeks
- Heart rate
SBP
Rales
ST-depression on presenting ECG.

Observed death at 30 days was 0.6% 2.2%, and 8.9% for first quartile of predicted risk, interquartile range (> 1% and ≤ 4%), and highest quartile (> 4%), respectively.

Observed death /MI at 30 days was 8.2%, 16.5%, and 24.1% first quartile of predicted risk, interquartile range (> 10% and ≤ 19%), and highest quartile (> 19%), respectively.

<table>
<thead>
<tr>
<th>Ref ID: 1910</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference</strong></td>
<td>observational study</td>
<td>N total = 100686</td>
<td>Inclusion: MINAP: community-based cohort of people hospitalised with ACS in England and Wales entered into MINAP database between Jan. 2003 and March 2005. All people&gt;18 years old admitted to hospital (index hospitalisation) with ACS and SBP 49-250 mm Hg and heart rate (HR) 20-200 bpm.</td>
<td>Compare discrimination of PURSUIT, GRACE, Simplified Risk Index (SRI), and EMMACE risk models to predict 30 day death.</td>
<td>N/A</td>
<td>Median = 261 days</td>
<td>Death during hospitalisation</td>
<td>Healthcare commission</td>
</tr>
<tr>
<td></td>
<td>Multicentre, 229 acute care hospitals in England and Wales MINAP Registry</td>
<td>N NSTEMI= 42582</td>
<td>Population baseline characteristics: whole cohort N=100686</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N troponin negative ACS= 7369</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N chest pain of uncertain origin = 3816</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N unconfirmed MI = 523</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>N other = 7051</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
% Elevated CK or troponin: 70
% normal ECG: 9
% T-wave changes only: 13
% ST-depression: 13
% ST elevation: 33
% LBBB: 5
% aspirin use before hospital admission: 22
% aspirin given on arrival to hospital: 29

without diabetes, renal disease (creatinine > 200 micromol/L), or angina.

Effect size
14.5% of the MINAP cohort (14611/100686) died by 1 year. 19.8% of deaths occurred within 24 h of admission. Median time to death was 18 days (7 days in STEMI and 32 days in NSTEMI)

The mortality rates in the MINAP cohort were always higher than the published mortality rate in each risk score derivation cohort: e.g.
Death at 30 days (PURSUIT cohort) = 3.6%
Death at 30 days (MINAP cohort) = 8.9%

In-hospital death (GRACE cohort)= 4.6%
In-hospital death (MINAP cohort)= 8.6%

6 month death (GRACE cohort)= 4.8%
6 month death (MINAP cohort)= 12.9%

Death at 30 days (SRI cohort ) = 6.0%
Death at 30 days (MINAP cohort) = 12.3%
As SRI score increased (arranged in quintiles), 24-h, in-hospital, and 30 day mortality all increased.

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Outcome</th>
<th>Independent Predictors</th>
<th>c-statistic in derivation cohort</th>
<th>N (MINAP cohort)</th>
<th>C-statistic in MINAP cohort (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PURSUIT</td>
<td>Death at 30 days</td>
<td>Age, SBP, HR, CHF, raised cardiac markers, ST-segment depression</td>
<td>0.81</td>
<td>49995</td>
<td>0.79 (0.78 to 0.80), p&lt;0.001</td>
</tr>
<tr>
<td>Risk Score</td>
<td>Outcome</td>
<td>C-index (95% CI)</td>
<td>C-index (95% CI)</td>
<td>C-index (95% CI)</td>
<td>C-index (95% CI)</td>
</tr>
<tr>
<td>------------</td>
<td>---------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diabetes</td>
<td>No diabetes</td>
<td>Chronic Renal Failure</td>
<td>No chronic renal failure</td>
</tr>
<tr>
<td>PURSUIT</td>
<td>Death at 30 days</td>
<td>0.74 (0.72 to 0.76)</td>
<td>0.79 (0.79 to 0.81)</td>
<td>0.81 (0.67 to 0.75)</td>
<td>0.79 (0.78 to 0.80)</td>
</tr>
<tr>
<td>GRACE</td>
<td>In-hospital death</td>
<td>0.77 (0.76 to 0.78)</td>
<td>0.81 (0.81 to 0.81)</td>
<td>0.71 (0.68 to 0.74)</td>
<td>0.80 (0.80 to 0.81)</td>
</tr>
<tr>
<td>GRACE 6 months</td>
<td>Death at 6 months</td>
<td>0.76 (0.75 to 0.77)</td>
<td>0.81 (0.80 to 0.81)</td>
<td>0.69 (0.66 to 0.72)</td>
<td>0.79 (0.79 to 0.80)</td>
</tr>
<tr>
<td>SRI</td>
<td>Death at 30 days</td>
<td>0.74 (0.73 to 0.76)</td>
<td>0.80 (0.79 to 0.81)</td>
<td>0.69 (0.64 to 0.74)</td>
<td>0.79 (0.79 to 0.80)</td>
</tr>
<tr>
<td>EMMACE</td>
<td>Death at 30 days</td>
<td>0.76 (0.74 to 0.78)</td>
<td>0.81 (0.80 to 0.81)</td>
<td>0.70 (0.64 to 0.75)</td>
<td>0.80 (0.79 to 0.81)</td>
</tr>
</tbody>
</table>

Overall, the various risk models had lower ability to discriminate between death and survival in higher risk groups (i.e. people with renal disease, or diabetes, or angina).
Note: SRI and EMMACE were certainly applied to the whole MINAP dataset, i.e. STEMI + NSTEMI. EMMACE also tested in the NSTEMI population of MINAP (N=42582; includes troponin + positive group)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granger CB, Goldberg RJ, Dabbous O et al. Predictors of Hospital Mortality in the Global Registry of Acute Coronary Events. Archives of Internal Medicine. 2003; 163(19):2345-2353. Ref ID: 1038</td>
<td>Observational study 3 Multicentre, 14 countries GRACE</td>
<td>N total = 11389</td>
<td>Inclusion: GRACE: all acute care hospitals in selected regions asked to recruit people presenting with acute ischemia and at least 1 of: ECG changes consistent with ACS, increased cardiac necrosis markers, and /or documentation of CAD. Exclusion criteria: participants who died within 24h of index hospitalisation. Population baseline characteristics:</td>
<td>Examine baseline variables associated with risk of in hospital death. Multivariable model then constructed to estimate risk score Procedure: Patient data collected by coordinator. Univariate and multivariate logistic</td>
<td>N/A Procedure: As for intervention</td>
<td>NR</td>
<td>Death during hospitalisation C-index of multivariate model to predict death during hospitalisation</td>
<td>Aventis Pharma</td>
</tr>
</tbody>
</table>
Age, years 66.3
% Male 66.5
% T-wave inversion or pseudonormalisation 28.4
% ST-depression 33.7
% ST elevation 35.3

Regression analysis used to evaluate baseline predictors of in hospital death. Predictive accuracy of multivariate model evaluated with C-statistic. Model then tested in GUSTO-2B participants and independent GRACE population.

Effect size
N=509 died in hospital. (median 3 days for ST-elevation; 6 days non ST-elevation ACS)

Death in hospital: Multivariate model
The following baseline variables were significantly associated with increased odds of death in hospital:
- Killip Class
- Age
- Low SBP
- Cardiac arrest
- Increased creatinine
- Initial cardiac enzyme findings
- ST-segment deviation
- Heart rate
- Diabetes
- Hypertension
- ST-segment elevation anterior
- ST-segment depression anterior
- Any significant Q wave
- Left bundle block branch
- Other ECG changes

C-statistic of model was 0.84 overall. In non-ST segment elevation GRACE group, c-statistic was 0.82.

C-statistic in separate validation cohort of GRACE (N=3972) was 0.85.
C-statistic in GUSTO-2B population (N=12142 full spectrum ACS) was 0.791. In non-ST segment elevation GUSTO-2B group, c-statistic was 0.81.
Simplified GRACE risk score for in hospital death: awards points for each variable upon presentation and considered the most important prognostic factors:

- Age
- Killip Class
- Heart rate
- SBP
- creatinine
- ST-deviation
- Cardiac arrest at admission
- Elevated cardiac enzymes

Note: GRACE risk score derived in population of ACS, in which 35% had ST-segment elevation. GRACE was used to capture a non selected patient population, but may have been biased by excluding those who died with 24h of hospitalisation. May also not help stratify very low risk groups. Unclear what cardiac markers were measured.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fox KA, Dabbous OH, Goldberg RJ et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE), [see comment]. BMJ. 2006; 333(7578):1091-1094. Ref ID 335</td>
<td>Observational study</td>
<td>N total = 43810</td>
<td>Inclusion: GRACE registry: people presenting with ACS (STEMI, NTSEMI, UA) between 1999-2005. All acute care hospitals in selected regions asked to recruit people presenting with acute ischemia and at least 1 of: ECG changes consistent with ACS, increased cardiac necrosis markers, and/or documentation of CAD. Exclusion criteria: participants who died within 24h of index hospitalisation.</td>
<td>Examine baseline variables associated with risk of death at 6 months. Multivariable model then constructed to estimate risk score. Procedure: Patient data collected by coordinator. GRACE score calculated for patients to determine risk of death or death/MI at 6 months. Multivariate logistic regression analysis used to evaluate baseline predictors of death at 6 months.</td>
<td>N/A</td>
<td>6 months</td>
<td>Death at 6 months</td>
<td>Death or nonfatal MI at 6 months</td>
</tr>
</tbody>
</table>
Baseline data: not reported  
Predictive accuracy of multivariate model evaluated with C-statistic. Model then tested in GUSTO-2B participants and independent GRACE population.

Effect size
Derivation population: N=1757 (9.1%) died at 6 months and there were N=1353 nonfatal MI by 6 months
Validation population: N = 1730 (9.0%) died at 6 months and there were N=990 nonfatal MI by 6 months

Death at 6 months: Multivariate model
The following baseline variables were significantly associated with increased odds of death at 6 months:
Age
Low SBP
Killip Class
Increased creatinine
Initial cardiac enzyme findings
Cardiac arrest
ST-segment deviation
Pulse
CHF
PVD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>population</th>
<th>C-statistic</th>
<th>GRACE risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death at 6 months</td>
<td>NSTEMI/UA-derivation cohort</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Death/nonfatal MI at 6 months</td>
<td>NSTEMI/UA - derivation cohort</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Death at 6 months</td>
<td>NSTEMI/UA- validation cohort</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Death/nonfatal MI at 6 months</td>
<td>NSTEMI/UA – validation cohort</td>
<td>0.73</td>
<td></td>
</tr>
<tr>
<td>Death at 6 months</td>
<td>NSTEMI-GUSTO IIB cohort (N=8011)</td>
<td>0.76</td>
<td></td>
</tr>
</tbody>
</table>

Simplified GRACE risk score for death or death/MI at 6 months: awards points for each variable upon presentation and considered the most important prognostic factors:
Age
Killip Class
Heart rate
SBP
creatinine
ST-deviation
Cardiac arrest at admission
Elevated cardiac enzymes

<table>
<thead>
<tr>
<th>Ref ID: 3883</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference</strong></td>
</tr>
</tbody>
</table>
N hospital survivors = 1057  
N (non-STEMI) = 450  
N unstable angina = 247  
Exclusion criteria: participants who had ACS due to noncardiac comorbidity, trauma, or surgery | GRACE risk score.  
Procedure: Patient data collected by coordinator.  
GRACE score calculated for patients to determine risk of death at 6 months, 1, 2, 3, and 4 years.  
Predictive accuracy of multivariate model evaluated with C-statistic. | N/A  
Procedure: As for intervention | 4 years | Death  
C-index of multivariate model to predict death | Not stated |

**Baseline data:**
- Age, y: 64.9
- % male: 63
- % PCI in-hospital: 21.3
- % CABG in-hospital: 11.7
- Median GRACE score: 116

**Effect size**
Of N=1143 people, 7.5% died in-hospital, 12.1% at 6 months, 14.8% at 1 year, 18.7% at 2 years, 25% at 3 years, and 39.2% at 4 years. At all time points, the risk of death increased with increasing GRACE score.

Study focussed on N=1057 hospital survivors
<table>
<thead>
<tr>
<th>Outcome</th>
<th>population</th>
<th>C-statistic GRACE risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death at 6 months</td>
<td>NSTEMI</td>
<td>0.82</td>
</tr>
<tr>
<td>Death at 1 year</td>
<td>NSTEMI</td>
<td>0.82</td>
</tr>
<tr>
<td>Death at 2 years</td>
<td>NSTEMI</td>
<td>0.83</td>
</tr>
<tr>
<td>Death at 3 years</td>
<td>NSTEMI</td>
<td>0.84</td>
</tr>
<tr>
<td>Death at 4 years</td>
<td>NSTEMI</td>
<td>0.83</td>
</tr>
<tr>
<td>Death at 6 months</td>
<td>UA</td>
<td>0.91</td>
</tr>
<tr>
<td>Death at 1 year</td>
<td>UA</td>
<td>0.90</td>
</tr>
<tr>
<td>Death at 2 years</td>
<td>UA</td>
<td>0.80</td>
</tr>
<tr>
<td>Death at 3 years</td>
<td>UA</td>
<td>0.80</td>
</tr>
<tr>
<td>Death at 4 years</td>
<td>UA</td>
<td>0.82</td>
</tr>
<tr>
<td>Death at 6 months</td>
<td>All ACS</td>
<td>0.81</td>
</tr>
<tr>
<td>Death at 1 year</td>
<td>All ACS</td>
<td>0.82</td>
</tr>
<tr>
<td>Death at 2 years</td>
<td>All ACS</td>
<td>0.81</td>
</tr>
<tr>
<td>Death at 3 years</td>
<td>All ACS</td>
<td>0.81</td>
</tr>
<tr>
<td>Death at 4 years</td>
<td>All ACS</td>
<td>0.80</td>
</tr>
</tbody>
</table>

Ref ID: 4162

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type/ Evidence level</th>
<th>Number of patients</th>
<th>Patient characteristics</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Length of follow-up</th>
<th>Outcome measures</th>
<th>Source of funding</th>
</tr>
</thead>
</table>
Population baseline characteristics: whole derivation cohort N=7520

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65.9</td>
</tr>
<tr>
<td>% Male</td>
<td>72</td>
</tr>
<tr>
<td>% STEMI</td>
<td>60.8</td>
</tr>
<tr>
<td>% NSTEACS</td>
<td>39.2</td>
</tr>
<tr>
<td>% T-wave changes</td>
<td>28.2</td>
</tr>
<tr>
<td>% ST-depression</td>
<td>30.1</td>
</tr>
<tr>
<td>% ST elevation</td>
<td>57.2</td>
</tr>
</tbody>
</table>

Effect size

AMIS score calculated with the averaged one dependence estimator algorithm.
7 risk factors incorporated in the AMIS score: age, Killip class, SBP, HR, pre-hospital cardio-pulmonary resuscitation, history of heart failure, history of cerebrovascular disease.

As AMIS score increased (5 risk levels very low – very high) in-hospital mortality increased.

Overall in-hospital mortality rate in the whole derivation cohort was 7.5%.
Overall in-hospital mortality rate in the whole validation cohort was 5.5%.
Overall in-hospital mortality rate in the whole external validation cohort was 7.6%.

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>Outcome</th>
<th>c-statistic in derivation cohort (NSTEACS only N= 2949)</th>
<th>c-statistic in validation cohort (NSTEACS only N= 1257)</th>
<th>c-statistic in external validation cohort (NSTEACS only N= 1817)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMIS</td>
<td>In-hospital death</td>
<td>0.868</td>
<td>0.851</td>
<td>0.859</td>
</tr>
<tr>
<td>TIMI</td>
<td>In-hospital death</td>
<td>0.794</td>
<td>0.839</td>
<td>0.773</td>
</tr>
<tr>
<td>SRI</td>
<td>In-hospital death</td>
<td>0.821</td>
<td>0.831</td>
<td>0.815</td>
</tr>
</tbody>
</table>

**Observational phase**: 3
d10 coronary care units Argentina

**Total**: 715

- Development phase: 473
- Validation phase: 242

Inclusion: patients admitted to coronary care units with a clinical diagnosis of UA if they fulfilled the following criteria: a) class III-IV angina beginning in the last 2 months (new onset angina) or previous stable angina increasing in frequency, duration of pain or occurring at lower threshold (progressive angina); b) last episode of pain at rest or at minimal exertion occurring in the previous 48 hours and lasting more than 10 minutes.

Exclusion: a) Braunwald class A (secondary angina) or class C (postinfarction angina); b) acute myocardial infarction defined as an elevation of creatine kinase at least twice the upper limit of normal values and a creatine kinase-MB fraction higher than 5% of the total creatine kinase value within the first 8 hours from the onset of the last episode of ischemic pain; c) left bundle branch block.

<table>
<thead>
<tr>
<th></th>
<th>Development phase (N=473)</th>
<th>Validation phase (N=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean +/-SD)</td>
<td>63.5 +/-11.8</td>
<td>63.7 +/- 11.2</td>
</tr>
<tr>
<td>Age &gt;=70 years</td>
<td>33.6%</td>
<td>33.1%</td>
</tr>
<tr>
<td>Male</td>
<td>66.8%</td>
<td>69%</td>
</tr>
<tr>
<td>Recent onset angina</td>
<td>63%</td>
<td>62%</td>
</tr>
<tr>
<td>Progressive angina</td>
<td>37%</td>
<td>38%</td>
</tr>
<tr>
<td>T wave deviation</td>
<td>30.4%</td>
<td>30.2%</td>
</tr>
<tr>
<td>T wave inversion</td>
<td>29%</td>
<td>24.8%</td>
</tr>
<tr>
<td>Positive troponin</td>
<td>20.9%</td>
<td>21.9%</td>
</tr>
</tbody>
</table>

Examine baseline variables associated with risk of death / AMI / refractory angina

Multivariable model then constructed an estimate risk score

Mean 8.5 days +/-9.3 days

Double end point: in-hospital death or AMI

Triple end point: in-hospital death, AMI or refractory angina

NR
Effect Size

14 patients (3%) died, 20 (4.2%) had an AMI and 33 (7%) developed refractory angina during hospitalisation. The incidence of the triple end point was 12.3% and 6.6% for the double end point.

Multivariate analysis showed that the following variables predict risk of in-hospital death / AMI/ refractory ischemia:
- ST-segment deviation on the electrocardiogram (scores 4 points)
- Age ≥70 years (score 2 points)
- Previous CABG (score 2 points)
- Troponin T ≥ 0.1 ng/mL (score 2 points)

Scores are added up and low risk is 0 -2 points, medium risk is 4-6 points and high risk is 8 – 10 points

C-statistic of the multivariate model was 0.76 overall

Incidence of triple end point (total population N=715): significantly increased with increasing risk score
- Low: 6%
- Medium: 19.2%
- High: 44.7%

Incidence of double end point: (total population N=715): significantly increased with increasing risk score
- Low: 2%
- Medium: 11.4%
- High: 27.6%

C-statistic risk score in whole population was 0.72 (95% CI 0.66 to 0.78) for triple endpoint