Critical Review Form
Clinical Prediction or Decision Rule

A 2-h diagnostic protocol to assess patients with chest pain symptoms in the Asia-Pacific region (ASPECT): a prospective observational validation study. Lancet. 2011 Mar 26;377(9771):1077-84.

Objective: **"to assess whether a predefined ADP would identify patients presenting to the emergency department with chest pain, who would be at low risk of harm if they were to be discharged early." (p. 1079)**

Methods: **This was a prospective, observational validation study of an accelerated diagnostic protocol (ADP) using the thrombolysis in myocardial infarction (TIMI) score and serial cardiac biomarkers. The study was conducted at 14 urban emergency departments (EDs) in 9 countries in the Asia-Pacific region (Australia, China, India, Indonesia, New Zealand, Singapore, South Korea, Taiwan, and Thailand). Consecutive patients 18 years and older with chest pain or discomfort of at least 5 minutes duration and in whom the attending physician planned to assess serial cardiac biomarkers were enrolled from November 2007 to July 2010. Exclusion criteria included:**

- **ST-segment elevation myocardial infarction**
- **A clear cause of symptoms other than acute coronary syndrome**
- **Inability to provide informed consent**
- **Patient considered inappropriate for enrollment by staff (e.g. terminal illness)**
- **Pregnancy**
- **Prior enrollment from a previous ED visit**
- **Inability to be contacted after discharge**

All data was collected prospectively by research nursing staff. Outcomes were assessed at 30 days from the initial visit by review of hospital records and telephone follow-up. Data coordination, monitoring, and analysis was performed at a university clinical research organization independent of the study sites, located in Australia.

The ADP consisted of a TIMI score (Table 1) of 0, absence of new ischemic changes on the initial ECG, and a normal point-of-care (POC) biomarker panel drawn on arrival and 2 hours after arrival. New ischemic changes on the ECG were defined as ST-segment depression ≥ 0.05 mV in 2 or more contiguous leads, T-wave inversion ≥ 0.1 mV, or q-waves ≥ 30 ms in width and ≥ 0.1 mV in depth in at least 2 contiguous leads. The POC biomarker panel consisted of troponin I, creatine kinase MB (CK-MB), and myoglobin and were available within 15 minutes of testing. The following

were considered to be positive biomarker results: troponin I ≥ 0.05 µg/L; CK-MB ≥ 4.3 µg/L or an increase of 1.6 µg/L or more over 2 hours; and myoglobin ≥ 108 µg/L of an increase of 25% or more over 2 hours.

The primary outcome was the incidence of any pre-defined major adverse cardiac event (MACE), defined as:

- **Death (unless clearly noncardiac)**
- **Cardiac arrest**
- **Need for emergency revascularization**
- **Cardiogenic shock**
- **Ventricular arrhythmia requiring intervention**
- **High-degree atrioventricular block requiring intervention**
- **Acute myocardial infarction (MI).**

The presence of a MACE was adjudicated by independent, local cardiologists using predefined, standardized reporting guidelines. The cardiologists were blinded to the index biomarker test and derived TIMI score, but had access to the clinical record, ECG, and serial troponin results from usual care.

Over the study period, 3651 eligible patients were enrolled, with 3582 completing 30-day follow-up. Of these 2234 (62.4%) were male, the majority were either white (n=1471, 42.1%) or Chinese (n=1174, 33.6%). A MACE occurred in 421 (11.8%) patients, with the most common being non ST-elevation MI in 363 (10.1%) of patients. There were 352 patients in the "low risk" group and 3230 in the "high risk" group.

Table 1. The TIMI Score

1. Age ≥ 65
2. Three or more risk factors: • **family history of coronary artery disease** • **hypertension** • **hypercholesterolemia** • **diabetes mellitus** • **current smoker**
3. Use of aspirin in the past 7 days
4. Significant known coronary stenosis (≥ 50%)
5. Two or more anginal events in the previous 24 hours or persisting discomfort
6. ST-segment deviation of ≥ 0.05 mV on the initial ECG
7. Increased troponin and/or CK-MB on initial bloodwork

Guide		Comments
I.	***Is this a newly derived instrument* (Level IV)?**	
A.	Was validation restricted to the retrospective use of statistical techniques on the original database? (If so, this is a Level IV rule & is not ready for clinical application).	No. This was a prospective validation of the rule on a new cohort of patients drawn from multiple study sites in multiple countries.
II.	**Has the instrument been validated? (Level II or III). If so, consider the following:**	
1a	Were all important predictors included in the derivation process?	N/A
1b	Were all important predictors present in significant proportion of the study population?	N/A
1c	Does the rule make clinical sense?	Yes. The TIMI score has been well-studied in the past (Jaffery 2007, Hess 2010, Graham 2013), and includes elements relevant to the risk and diagnosis of an acute coronary syndrome. The ADP requires a TIMI score of 0, the absence of new ischemic changes on the ECG, and normal cardiac biomarkers. These are all clinically relevant factors in the decision to perform further testing.
2	Did validation include prospective studies on several different populations from that used to derive it (II) or was it restricted to a single population (III)?	Yes. This prospective validation study was conducted in 9 countries in the Asia-Pacific region (Australia, China, India, Indonesia, New Zealand, Singapore, South Korea, Taiwan, and Thailand). While other prospective validation studies using the TIMI score have been performed in different populations (Pollack 2006, Chase 2006, Weisenthal 2010), we were unable to identify other studies assessing an ADP using a 2-hour TIMI score.
3	*How well did the validation study meet the following criteria?*	
3a	Did the patients represent a wide spectrum of severity of disease?	Yes. There was a wide variation in the presence and absence of risk factors among the enrolled patients, as well a wide variety of outcomes, including 363 (10.1%) with NSTEMI, 53 (1.5%) with STEMI, 32 (0.9%) requiring emergent revascularization, and 19 (0.5%) with cardiovascular death.
3b	Was there a blinded assessment of the gold standard?	Yes and no. There is no well-accepted gold standard in the diagnosis of acute coronary syndrome. The outcome of interest was a well-defined composite outcome

		including multiple major adverse cardiovascular events, the presence of which were adjudicated by independent, local cardiologists using predefined, standardized reporting guidelines. These cardiologists were blinded to the results of the index biomarker tests and the derived TIMI score. Most of the outcomes included were objective (including death, ventricular dysrhythmia, and AV block requiring intervention), although the need for emergency revascularization may be more subjective and influenced by local practice.
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	Yes. The TIMI score calculation, ECG interpretation, and biomarker assessment occurred at the initial hospital visit, at which time the outcomes could not be known. The ECG criteria were well-defined (ST-segment depression ≥ 0.05 mV in 2 or more contiguous leads, T-wave inversion ≥ 0.1 mV, or q-waves ≥ 30 ms in width and ≥ 0.1 mV in depth in at least 2 contiguous leads) as were the criteria for positive biomarkers (troponin I ≥ 0.05 µg/L; CK-MB ≥ 4.3 µg/L or an increase of 1.6 µg/L or more over 2 hours; and myoglobin ≥ 108 µg/L of an increase of 25% or more over 2 hours).
3d	Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	No. There was no true "gold standard" used in this study. The outcome of interest was a composite of major adverse cardiovascular events. Patients were assessed for these outcomes by review of the medical record and by telephone follow-up at 30 days. Follow-up was attempted in all patients, regardless of the TIMI score or the results of the ECG or initial cardiac biomarkers.
4	How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	There were 352 patients meeting all of the ADP criteria; of these, 3 (0.9%) had a MACE, resulting in the following characteristics (95% confidence interval): • Sensitivity 99.3% (97.9-99.8) • Specificity 11.0% (10.0-12.2) • NPV 99.1% (97.3-99.8) • PPV 12.9% (11.8-14.5) • Negative LR 0.1 (0.0-0.2) • Positive LR 1.1 (1.1-1.3) 569 patients had a TIMI score of 0; of these, 14 (2.5%) had a MACE, resulting in the following characteristics (95% confidence interval): • Sensitivity 96.7% (94.5-98.0) • Specificity 17.6% (16.3-18.9) • NPV 97.5% (95.8-98.6) • PPV 13.5% (12.3-14.8) • Negative LR 0.2 (0.1-0.3) • Positive LR 1.2 (1.1-1.2)

III.	**Has an impact analysis demonstrated change in clinical behavior or patient outcomes as a result of using the instrument? (Level I). If so, consider the following:**	
1	How well did the study guard against bias in terms of differences at the start (concealed randomization, adjustment in analysis) or as the study proceeded (blinding, co-intervention, loss to follow-up)?	All eligible patients meeting well-defined criteria were enrolled in a consecutive fashion. The individual criteria of the ADP were well defined and determined at the initial ED visit, prior to any knowledge of outcomes. Patients were excluded if it was determined that they would not be able to participate in 30-day follow-up, though the authors do not clarify how this determination was made. Assessment of outcomes (MACE) was performed by independent cardiologists who were blinded to the components of the ADP, including the calculated TIMI score and index test biomarkers. These outcome assessors were NOT blinded to the ECG findings, and there is no mention that they were blinded to the study purpose or the ADP itself. The authors do not mention if telephone follow-up was conducted by blinded personnel, or if standardized, validated questionnaires were used. Of those patients enrolled, 48 were lost to follow-up (30 in the high-risk group and 18 in the low-risk group) and hence were excluded from analysis. There was no sensitivity analysis performed to assess the potential impact of this loss to follow-up.
2	What was the impact on clinician behavior and patient-important outcomes?	N/A. The impact of the ADP was not assessed in this study.

Limitations:

1) Exclusion of patients who could not be contacted after follow-up limits external validity patients of lower socioeconomic status.

2) No sensitivity analysis was performed on patients lost to follow-up.

3) The methods involved in telephone follow-up were not well-described: no mention of blinding of personnel: blinded or use of validated or standardized questionnaires.

4) There is no true "gold standard" in the assessment of outcomes in chest pain patients. Instead, a composite outcome (MACE) is used whose components are not necessarily equivalent in terms of patient importance. This practice has been called into question (Kip 2008).

Bottom Line:

An ADP including a TIMI score of 0 and negative cardiac enzymes at 0 and 2 hours after arrival to the ED results in a population of patients at extremely low risk of major adverse cardiovascular event (3/352, 0.9%). Further prospective validation in a US cohort of patients may make clinicians here more comfortable using this protocol to safely discharge patients from the ED without stress testing or cardiac imaging. Impact testing should also be considered to assess how this ADP will affect the management of patients with low-risk chest pain.