Critical Review Form

Clinical Prediction or Decision Rule

The TIMI Risk Score for Unstable Angina/Non-ST Elevation MI: A Method for Prognostication and Therapeutic Decision Making; *JAMA* 2000; 284: 835-842

Objective: "To provide a tool that potentially could be applied in clinical settings in which patients with USA/NSTEMI present for evaluation" (p 836).

Methods: Utilizing patients from two trials comparing unfractionated heparin (UFH) with enoxaparin (TIMI IIB and ESSENCE), the authors sought to utilize information which could be ascertained shortly after patient presentation to permit efficient triage and medical management acutely. The total cohort was 7081 consisting of subjects presenting within 24-hours of an episode of USA/NSTEMI at rest with at least one of the following: ST-segment deviation or transient (<20 minutes) STE on ECG, documented history of CAD, or elevated serum cardiac markers. Exclusion criteria included planned re-vascularization within 24-hours, correctable cause of angina, or contraindications to anticoagulation. Subjects were randomized to UFH or LMWH. The TIMI score was derived on TIMI UFH cohort.

The endpoint was the composite of all-cause mortality, new or recurrent MI, or severe recurrent ischemia prompting urgent re-vascularization at 14-days. Twelve predictor variables (Table 1, p 837) underwent univariate analysis and were then included in multivariate backward stepwise logistic regression if $p < 0.20$. Variables associated with $p < 0.05$ in the logistic regression model were retained and a simple arithmetic summary score derived based on the presence or absence of these significant predictors. Because patients might not have readily available prior cardiac cath results, the authors tested the model's stability when 10, 25, or 50% of subjects lacked such information using a "Monte-Carlo simulation" (unreferenced).

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).	Yes, retrospective application to TIMI IIB and ESSENCE data base so Level IV CDR based on the currently reported study (although subsequent trials have validated the CDR prospectively (Ann EM 2006; 48: 252-259).

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?	Common predictors were included, but may not apply to important subsets (women, minorities, cocaine-induced chest pain) who present less typically with different pathophysiological processes.
1b	Were all important predictors present in significant proportion of the study population?	Unknown. No information on prevalence of variables was presented.
1c	Does the rule make clinical sense?	Yes, the rule is elegantly simple and easily applied, although one would probably still require a reminder system (pocket card, PDA available at **www.TIMI.org**) for appropriate application among infrequent users.
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)?	Not prospectively validated on the current cohort. Therefore, a Level IV CDR.
3	*How well did the validation study meet the following criteria?*	
3a	Did the patients represent a wide spectrum of severity of disease?	Uncertain because demographic information on populations (age, gender, proportion with DM, atypical presentations, CCU admissions, hospital length-of-stay, etc.) not provided.
3b	Was there a blinded assessment of the gold standard?	The authors do not clearly state what definition was used for AMI or USA, who made these determinations, how discrepancies were resolved, or whether outcome assessors (or data abstractors) were blinded to the TIMI score and/or study hypothesis.
3c	Was there an explicit and accurate interpretation of the predictor variables & the actual rule without knowledge of the outcome?	The rule was not applied prospectively -- rather, it was derived retrospectively. Whether data abstractors or interpreting physician-investigators used subjective elements reliably and accurately is unknown because no details are provided to answer these questions. However, there is less chance for bias in a retrospective Level IV *derivation* trial where the outcome has already occurred.

3d	Did the results of the assessment of the variables or of the rule influence the decision to perform the gold standard?	No true Gold standard for USA exists. Although the authors likely used the WHO definition of AMI, this is not clearly stated. Elements of the TIMI score probably did contribute to their decision to obtain cardiac markers. Indeed, cardiac markers, part of the definition of NSTEMI, are also part of the TIMI score so the rule may be a self-fulfilling prophesy. Such bias might enhance the perceived diagnostic accuracy of the CDR before prospective validation.
4	How powerful is the rule (in terms of sensitivity & specificity; likelihood ratios; proportions with alternative outcomes; or relative risks or absolute outcome rates)?	The composite endpoint occurred in 16.7% of the derivation cohort and the model derived had a C-statistic (analogous to the area under the curve of an ROC curve) of 0.65. There were small numbers of patients at both extremes of risk score (0 and 1 combined 4.3% of cohort, 6 and 7 combined 3.4% of cohort). In comparison, in a subsequent ED validation of TIMI (*Ann EM* 2006; 48: 252) among all ED chest pain patients the breakdown was as follows: TIMI 0 = 32.6% and TIMI 1 = 26.1%. These extreme differences suggest a *spectrum bias* thereby limiting external validity without subsequent ED validation. Use of different age cut-offs or 5-year gradients did not alter the model's predictive power, nor did missing cath data at rates up to 50%. In the entire cohort there was a progressive, significant ($p < 0.001$) increase in the composite endpoint as the TIMI score increased. Although not significant, the trend persisted for each component of the composite endpoint individually. The authors do not present sufficient details to permit calculation of Likelihood Ratios, nor do they present the event rates non-stratified between UFH and LMWH in the validation cohorts. Figure 1 (p 838) gives the primary outcome at 14-days in proportions for the derivation cohort and

		Figure 3 (p 840) for the entire cohort by individual component of the composite endpoint. The recent ED validation of TIMI, however, does present sufficient information to permit construction of a 2x2 Table (see below).

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)?	No impact analysis is performed, but subsequent trials should assess external validity to EM, as well as physician comfort in using TIMI tool given obvious spectrum bias and less than 100% sensitivity.
2	What was the impact on clinician behavior and patient-important outcomes?	As above.

Limitations

1) **Spectrum bias limits generalizability (external validity) to ED use. The subjects of TIMI IIB and ESSENCE were a select group already felt to have USA or NSTEMI, not general ED patients with chest pain of uncertain etiology.**
2) **Methods do not detail investigators means of limiting bias: blinded data abstractors and outcome assessors, methods of adjudication, etc.**
3) **Results do not provide sufficient detail to calculate sensitivity/specificity/LR's on the validation cohort. Additionally, optimal cut-off score would be useful as clinicians decide how to utilize these risk stratifications in patient therapeutics and disposition.**

Bottom Line

TIMI score offers a simple numeric means by which to risk stratify patients with suspected USA/NSTEMI in allocating limited CCU and high-risk telemetry beds and more expensive therapeutic agents. The external validity of the TIMI score among ED patients with chest pain is not defined by this study and further trials (now completed, see below) should assess such ED utilization. The TIMI score is not 100% sensitive in predicting the 14-day outcomes of all-cause mortality, MI, or emergent re-vascularization and therefore it should not be solely relied upon to risk stratify patients.

TIMI Risk Score

Predictor	Point Value	Definition
Age > 65	1	
≥ 3 risk factors	1	FHx of CAD, HTN, hyperlipidemia, DM, current smoker
ASA use last 7 days	1	
Recent, severe symptoms of angina	1	≥ 2 anginal events in last 24 hours
Elevated cardiac markers	1	CK-MB or Troponin
ST-deviation ≥ 0.5mm	1	ST-depression or STE < 20 minutes
Prior coronary stenosis > 50%	1	

TIMI Risk Score & Primary Outcome Rate

Score	Risk of ≥ Primary Endpoint (derivation set)*
0 or 1	4.3%
2	17.3%
3	32%
4	29.3%
5	13.6%
6 or 7	3.4%

*** Primary endpoints include death, MI, or urgent re-vascularization within 14 days.**

2x2 Table from ED Validation of TIMI (Ann EM 2006; 48: 252)

TIMI Score	Primary Outcome Occurred	Primary Outcome Did Not Occur	TOTALS
0	8	467	475
1-6	128	855	983
TOTAL	136	1322	1458

Prevalence = 9.3%
Sensitivity = 94%
Specificity = 35%
LR+ = 1.46 (95% CI 1.37 – 1.54)
LR - = 0.17 (95% CI 0.08 – 0.33)