AMERICAN COLLEGE OF EMERGENCY PHYSICIANS
SCIENTIFIC ASSEMBLY
1999

Serum Markers of Ischemia

New serum markers of ischemia have become available that may change the evaluation of chest pain and the diagnosis of myocardial ischemia. Should they be adopted in your practice? This question will be addressed through a critical analysis of the literature and the use of case presentations.

- Discuss the literature on serum markers of ischemia.
- List the serum markers of ischemia and their advantages and disadvantages.
- Define the impact of new serum markers of ischemia on the management of acute chest pain.

TU-80
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12:30 PM - 1:25 PM
Room # N227
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FACULTY

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Formatting Note: The slides of the presentation are imbedded in the syllabi to aid those people wishing to follow the syllabi and slide presentation simultaneously.

Serum Markers of Ischemia

Lecture Outline

Section I: Defining the Issues
Section II: Overview of Cardiac Marker Characteristics
Section III: Risk Stratification
Section IV: How to Use Cardiac Markers in 1999
Section V: How Not to Use Markers

SECTION I: DEFINING THE REAL ISSUES

1. Chest pain is common

Many patients present to the ED with chest pain - approximately 5 million presentations per year

- 1 -2 million have an acute coronary syndrome (ACS ie. MI or unstable angina USA)
- Therefore the majority do not
- For every 1 patient admitted with R/O MI 1-2 have no significant cardiac disease
- Cost for "unnecessary admissions" is many billions of dollars per year

- "Missed MI" - most costly form of litigation against Emergency Physicians (EP's)
- Studies suggest a missed MI rate of 1.9 to 8%

Probably closer to 1% as older studies had non-emergency physicians etc

2. Missed ACS potentially puts the patient at very high short term and long term risk

- The mortality for missed MI in outpatients has been reported as approximately 25% (McCarthy, Lee)
- "Misses" occur because of - young patient age, physician inexperience, atypical presentations, failure to perform an ECG, failure to correctly read the ECG
- The one year mortality of USA is approximately 15%

3. "R/O MI" is a Dangerous Preoccupation

- Traditionally cardiac markers have been used to R/O MI
- Until recently they have not been used, or where not useful for "R/O unstable angina"
- Unstable angina now represents > 50% of the final diagnosis's for patients admitted with ACS
- Unstable angina has a poor short term prognosis and cannot be missed
- **On the other hand** a significant number of patients with MI never need specific interventions and as many of 30% of MI's are silent!

4. The real role of the EP in chest pain

- **Do not send patients home to die**, do not admit patients that do not need inpatient services

Within this broad scheme what we really care about is: death, CHF, malignant arrhythmia's, admission for patients for specific interventions (e.g. urgent PTCA, thrombolytics)

- Prevent USA from progressing to MI
- Prevent MI from progressing to death
- Treat arrhythmia's

- For admitted patients **send them to the correct level of care**, CCU, COU, Floor etc

Therefore it is at least theoretically possible to envision the out patient treatment of specific patients with MI or USA. If a group of patients could be selected that do not need arrhythmia treatment and do not need PTCA or thrombolytics then all other therapies could be given as an outpatient (eg aspirin). In fact such a schema has been presented by the American AHCPR and the British - for low risk patients.

5. Risk stratification is the key concept in the management of patents with USA and MI. Both for defining whom and where to admit patients, and the level of therapy that is required.

- Cardiac markers are only useful within the above scheme if they add information to:
  - Define who needs admission and who can be sent home
  - To direct the level of therapy required
  - They can only be viewed as adjuncts to usual risk stratification tools like H and P and ECG

5. How much risk is acceptable (specially for sending patients home from the ED)

- Almost never is there a discussion as to how much risk is acceptable
- A level of risk that can be proven cost effective for sending patients home may not be acceptable to the individual EP who directly bears the

5a. Patient expectations

SECTION I
Defining the Issues
How Much Risk is Ok
Davis et al. Ann Emerg Med 1996
- Scenario presented: risk for MI 5%, death 0.2% inpatient, 1% outpatient
- ?? Admit or DC
- Patients desire: 31% said go home
- Physicians desire: 6% said go home
- Physicians themselves would go home
- Physicians better understood the risk

- Davis et al note that the risk patients may be willing to accept is significantly more than physicians are willing to risk.
- However knowing that a patient may have a higher risk threshold does not protect a physician from litigation
- Patients rarely understand the true risk they are taking

5b. Cost effectiveness of admitting low risk patients

- for patients sent home how many adverse events is it acceptable to miss (since we can never pick up every event)
- almost no one has addressed this question
- British studies suggest a missing less than of 5% of MI's is acceptable (?? missed USA)
- almost certainly not cost effective to admit patients with less than 1% risk for adverse events see figure 1.

Figure 1.

Best Case Scenario
Assume 0.5% mortality/serious morbidity in a low risk group
Assume if sent home all low risk patients they would die if a bad event occurred
Assume if admitted all would live
Assume the extra cost of admission for low risk is $3000 dollars

Then: If we can select out a group of 100 patients with 0.5% bad event rate then:
Cost would be 600,000 dollars

If sent all these 100 patients home, one would die

Therefore admission of all low risk patients would cost $600,000 per life saved

Worst case Scenario
Admission of low risk patients *may cost millions of dollars per life* saved

Before we can really go further with risk stratification, society, the medical profession, someone has to decide the acceptable level of risk for sending patients home. Until this is done a clear algorithm cannot be developed for risk stratification since we don't know how sensitive the algorithm needs to be.

6. Cardiac markers for R/O MI - how sensitive must they be

Even if R/O MI was the right question (and it is not) - how good would the cardiac maker need to be to be used a sole criteria for sending patients home

- *Since* right now we miss less than 1% of MI's *then* if we where to rely on a cardiac marker alone to R/O MI in the ED it would need to be > 99% sensitive (and at least 50% specific) within the time frame of the ED visit.

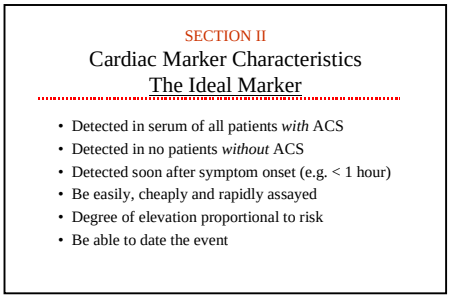
(This if course says nothing about ruling out USA)

SECTION II: OVERVIEW OF CARDIAC MARKERS

1. History
- 1954 Karmen found SGOT (AST) found to rise in the blood of post MI patients, began the era of cardiac markers
- Vying for your cardiac maker dollar and even the label "gold standard cardiac marker are a number of new comers:
  - · CK-mb mass and isoforms
  - · Myoglobin
  - · Troponin I and T

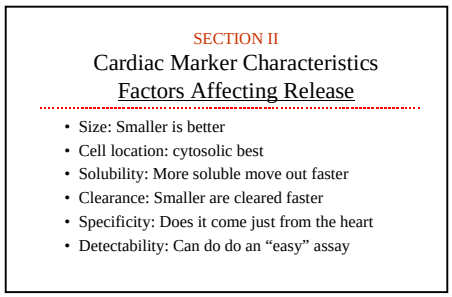
·Myosin light chains, Myosin heavy chains, Heart fatty acid binding proteins, GPBB, and many others

2. The Ideal Cardiac Marker



- Detected in the serum of ALL patients with ACS
- Detected in serum of NO patients without ACS
- Be detected within a very short time of pain onset eg. 1 hour
- Be easily and rapidly performed
- Degree of elevation would be proportional to patient risk

3. Factors Determining Marker Release Characteristics
(Adapted from Adams et. al. Circ. 1993)



1. **Size:** Contrary to popularly accepted dogma "smaller is better". The smaller the molecule the more rapidly it is released into the serum.
2. **Cell localization:** Cytosolic proteins are released more rapidly than structural proteins.
3. **Solubility:** Low solubility proteins move slowly out of the myocardium.
4. **Clearance:** Generally the smaller the molecule the faster it is cleared from the serum. Makers that are rapidly cleared ar
5. **Specificity:** Most macromolecules found in cardiac muscle are also found in skeletal muscle. In addition is a cell is damaged it tends to alter the macromolecules it produces and reproduces proteins produced in utero or early life (return to ontogeny). This means damaged cells may all start to "look" the same.
6. **Specificity for irreversible injury:** It is very controversial if release of cytoplasmic protein represents irreversible injury. Prolonged release of structural proteins is generally considered good evidence that irreversible injury has occurred.
7. **Detectability:** This requires that accurate and easy to use assays are available. It also assumes that the assays are reproducible. Generally proteins that are normally in low levels or undetectable in the serum unless injury is present make the best markers.

4. Limitations of the Current Literature on Cardiac Markers

- In order to prove that a cardiac marker was 99% sensitive we would need over 250 patients with MI (i.e. not total chest pain patients). Since the rule in rate in most studies is 5-10%, we would need a study of at least 5000 (and perhaps as many as 20,000 depending on your assumptions) patients to determine if the test was "sensitive enough".

Most studies of cardiac markers enroll a few hundred patients, which is completely inadequate to answer the question if the marker if sensitive enough for routine use.

- Many studies use different cutoffs for each cardiac marker. This makes comparison between studies very difficult. The cutoffs are frequently retrospectively defined and my not be accurate in the general population.

- The timing of the assays differs between studies. Some use the time "zero" i.e. T 0 as the time the patient reaches the ED. Some use time "zero" as the time form pain onset. Obviously these can be very different and affect how one reads the results of the tests.

Some Definitions

Sensitivity - ability of a test to detect those individuals with the disease
Specificity - how often a positive test really represents a patient with the disease

- These characteristics are independent of the prevalence of disease in the population

Predictive values: the ability of a test to rule in (positive predictive value) or rule out the disease (negative predictive value).

- These rates depend on the prevalence of disease in the population being studied.

3. Summary of marker characteristics
Notes: "Sensitivity at ED presentation" assumes 4 hours from onset of pain.

CK - Creatine Kinase

SECTION II
Cardiac Marker Characteristics
CK

• Definition of positive:	Varies
• Peak Level:	?? 18 hours
• Assay speed:	Fast
• Sensitivity at 4 hours:	< 40%
• Peak sensitivity for MI:	95%
• Sensitivity of USA:	< 5%
• Duration of detection:	36-48 hours
• False Positives:	Many

- Has been employed for many years. Present in all muscle and not specific for cardiac muscle.

CK-MB (Mass)

CK-mb is a subform of CK more specific for cardiac muscle. It can be measured as enzymatic activity or as mass. The mass assays are more sensitive and specific for MI than activity, these assays use a monoclonal assay. The following corresponds to CK-mass assays which are far superior to the CK- activity assays
False Positives: Renal disease, cardiomyopathy, significant muscle injury,

SECTION II
Cardiac Marker Characteristics
CK-mb (mass)

• Definition of positive:	7-15ng/ml
• Peak Level:	?? 12 hours
• Assay speed:	Rapid
• Sensitivity at 4 hours:	60%
• Peak sensitivity for MI:	95-98%
• Sensitivity of USA:	?? 5%
• Duration of detection:	36-48 hours
• False Positives:	Much less than CK

hypothyroidism

Comments:
- It reminds controversial if CK-Mb mass can be detected in the blood of patients with ischemia without infarction. Small elevations in CK-MB (mass) may represent "micro-infarctions"
- Some authors believe that a ratio of Ck-mb (mass) to total CK is a more sensitive maker than CK-MB(mass) alone though this is very controversial

CK-MB (subforms)

When CK is released into the blood it undergoes enzymatic change. The two subforms are CK-Mb1 and Ck-mb2 and this change in proportion is said to occur faster than the rate of rise of total CK-mb. A study from Baylor in over 1000 chest pain patients of whom 121 had MI confirmed, suggests the following:

- Assay time very fast (6 minutes)
  - Sensitivity 96% (at 6 hours from onset of pain)
  - Specificity 93% (at 6 hours at onset of pain)

SECTION II
Cardiac Marker Characteristics
CK-mb (isoforms)

• Definition of positive:	??
• Peak Level:	?? 12 hours
• Assay speed:	Rapid
• Sensitivity at 4 hours:	80%*
• Peak sensitivity for MI:	95-98%
• Sensitivity of USA:	?? 5%
• Duration of detection:	??
• False Positives:	Much less than CK

The results are compelling but as yet have not be reproduced in another population with a large series. Remember even at 6 hours the sensitivity was 96% that is 4% of MI's would be missed if one relied solely on this assay.

Myoglobin

Myoglobin is found in all muscle and is not specific for cardiac muscle. It tends to be released rapidly from damaged cells and the peak levels maybe missed as it is also rapidly cleared.

SECTION II
Cardiac Marker Characteristics
Myoglobin

• Definition of positive:	100ng/ml (40% or 2x)
• Peak Level:	3-5 hours
• Assay speed:	Rapid
• Sensitivity at 4 hours:	90%*
• Peak sensitivity for MI:	90%
• Sensitivity of USA:	?? 5%
• Duration of detection:	5-12 hours
• False Positives:	Many

False positives: renal disease, any muscle injury.

Comments: The studies of myoglobin are all relatively very small, usually with less than 100 patients and rarely with more than 200 patients.

Troponin's

SECTION II

Cardiac Marker Characteristics

Troponin I

• Definition of positive:	0.1-0.4 ng/ml
• Peak Level:	?? 12 hours
• Assay speed:	Rapid
• Sensitivity at 4 hours:	60%*
• Peak sensitivity for MI:	98%
• Sensitivity of USA:	35% (sickest group)
• Duration of detection:	7-14 days
• False Positives:	Few if any

Troponin I and T are found in cardiac muscle and are very specific for cardiac muscle. Troponin I is more specific for cardiac muscle than troponin T. They have a long T1/2 in the serum making them good markers for ruling out ischemia many hours or days after symptom onset. They are also positive in a subset of patients traditionally accepted as having USA.

Comments: Troponin T characteristics are similar to troponin I. It is difficult to comments on which is the best test as new assays are being developed all the time, each one apparently more sensitive than the last.

5. Troponins Vs. CK-MB

Troponins are more powerful at "adverse event prediction". CK-mb is more specific for MI - because it is used in the definition. That is to say numerous patients will have positive troponins, but negative CK-mbs, and these patients will be classified as not having an MI. This is because troponins also pick up a subset of patients traditionally though of as having USA.

The most important question though is this: **if the CK is negative and the troponin is positive is the patient low or high risk:** the patient is high risk. Troponins are much more powerful for event prediction.

Other Markers

Heart Fatty acid binding protein
Myosin light and heavy chains FABPs (fatty acid binding proteins)

Fibrinopeptide A levels
Glutathione peroxidase activity
Thrombin-antithrombin III
P-selectin
C-reactive protein

SECTION III: Risk Stratification

1. The Real Question

- How do cardiac makers allow us to *further risk stratify* patients over and above H and P and ECG within the concepts outlined above.

How Well Can We Do Without Cardiac Makers

Stratification by History

Section III
Risk Stratification
History

Within Chest Pain as a Group the Following is True

High Risk Features	Lower Risk Features
Male Sex	Very short duration
Age > 60	Very long duration
Prior MI	Needle or sharp pain
Tight, heavy pain	Age < 35
Left arm pain	
Sweating	

- A number of studies suggest that patients can be categorized in board terms into risk groups on the basis of historical features

It is essential to note the presence of low risk features or the absence of high risk features - does not exclude ischemia

Traditional cardiac risk factors are almost completely useless in risk stratification in the ED. These risk factors like - hypertension, diabetes, family history, smoking etc pale in comparison to a history of chest pain as predictors of acute ischemia. See table following

RISK FACTORS AND PREDICTING ACUTE CORONARY EVENTS

Risk factor	**Relative Risk of ACS**	
	Male	**Female**
Hypercholesterolemia	1.3	1.1
Smoking	2.4	2.0
Hypertension	1.0	1.6
Family History (age < 50)	1.5	1.2
Clinical Variables		
Chest pain or pressure	**12.1**	**25**
St Segment Elevation or flattening	8.7	3.9
T wave peaking or inversion	5.3	4.0

From: Javes Rl et al. J Clin Epidemiology 1992 45(6):621-626
A study of 5773 patients in 6 hospitals

The sensitivity or specificity of specific chest pain features/ radiation etc is less well appreciated.

Stratification by Physical Examination

30 year ago Killip noted that patients with ischemia and heart failure had a worse prognosis than patients with no heart failure. The degree of heart failure correlates with out come. The Goldman criteria incorporate this concept and also the addition of SBP, which when less than 110 portends a worse prognosis.

Section III
Risk Stratification
Physical Examination

Class	Findings	Mortality
I	No heart failure	6%
II	Mild:rales at base, S3, JVD	17%
III	Pulmonary Edema	38%
IV	Shock	81%

Killip Am J Cardiol 1967

Stratification by ECG

Numerous studies have noted the single best prediction toll in patients with ACS - above history - is the ECG. Even in patients that rule in by enzymes - risk stratification can be performed very well simply by ED and serial ECG readings.

Section III
Risk Stratification
ECG

High Risk	Low Risk
ST Elevation	Normal
ST depression	Non-specific ST-T
T Inversion	
LBBB	
Paced Rhythm	
Dynamic Changes V. high risk	

A Normal or near normal ECG selects out a low risk group for adverse events.

Summary of the Pertinent ECG Literature

- **Brush criteria:**

469 patients with suspected MI where studied to determine the effectiveness of the initial ECG for determining complications needing intervention. 469 patients entered the study, *169 had normal or near normal ECG's*, 2 patients had MI (1 %), 1 patient had a serious arrhythmia.

No deaths due to cardiac complications if the ECG was normal.

Section III
Risk Stratification
The Normal ECG

Brush Criteria NEJM 1984

- 467 patients with chest pain as in-patients
  - 169 normal or near normal ECG
    - 2 had MI, 1 serious arrythmia, no deaths
  - 302 patients had positive ECG
    - 14% had life threatening arrhythmia's
    - 17 X risk of death

• Hamm et al 1997
Hamm et. al. of 770 patients, 331 *normal ECGS*, only 5 cardiac events (1.5%) in the next 30 days.

Section III
Risk Stratification
The Normal ECG

Hamm et al NEJM 1997

- 770 patients followed for 30 days
- 331 had normal ECG's
  - 5 had cardiac events* (1.5%)
- 158 had ST depression
  - 14 had cardiac events (8.9%)

*** Death or MI**

Section III
Risk Stratification
The Normal ECG

Kalson et al Eur Heart J 1994

- 7157 patients, outcomes at 3 days

Normal ECG: 1% MI, 3% serious events
If ischemia on ECG: 27% serious events
If abnormal no ischemia: 20% serious events

Other Studies

• **Hollander et. al.** of 460 patients admitted to a telemetry unit 261 had normal ECG's and in this group there where no serious arrhythmia's needing therapy.

• **Bell et. al**. noted similar trends but had a higher rate of complications than other studies have noted. In their study of 4lO patients with chest pain noted *141 had normal ECGs and of these of these:* 39 had Ml, one died in CCU and the overall death rate was 2.1 % . No life threatening arrhythmia's in CCU.

• **Fesmire et. al.** in a study from 1989 examined the outcomes in 459 consecutive admitted patients with suspected acute coronary syndromes. They classified ECG's as normal, abnormal or positive for ischemia. They noted that patients with normal ECG's (65 patients) had no life threatening (O% Cl 0-6%) complications even though 2 ultimately ruled in for MI (3%).

2. Risk Stratification: Putting it all together - Without Cardiac Enzymes

History, physical examination and ECG should be used in conjunction for best risk stratification.

• **Roan et al.** of 7115 consecutive patients, 811 had MI's. The probability of MI in patients with normal ECG's was dependent on the chest pain history. A good history of ischemia was associated with more MI and worse prognosis than a poor history.

• **Siros et. al.** studied 486 admitted patients with chest pain, divided then into two groups. Group 1 where considered low risk if they fit Brush's ECG criteria and in addition needed no intervention in the ED and had no comorbid disease. All other patients where considered high risk. Of the low risk patients (n=262) three had serious complications or death (1. 1 %).

Combined these studies suggest that in a patient with chest pain and a normal or near normal ECG and no comorbid disease the overall complication rate is around 1 %.

The GOLDMAN Criteria

Section III
Risk Stratification
THE GOLMAN STUDY

- > 10,000 patients
- Derivation phase 6000 patients
- > 4600 prospectively studied
- Aim: Clinical and ECG criteria that predict events
- Looked at adverse events at 72 hours

NEJM 1996 June 6th

The most famous risk stratification paper is by Goldman Et el NEJM June 6th 1996.
In patients with chest pain the ECG is first evaluated for evidence of ischemia then by historical features.

Section III
Risk Stratification
THE GOLMAN STUDY

- "Clinical Risk Factors"
  - SBP < 110
  - Rales above bases bilaterally
  - Known unstable coronary diease
    - new onset angina, post infacrtion angina, angina after procedure
  - Pain like prior MI

Historical or examination risk factors for adverse events included:

• Known unstable ischemic heart disease

- worsening prior angina
- post infarction angina
- post PTCA or bypass angina

- pain similar to previous MI
- Systolic BP < 110
- Rales heard above the bases

Section III
Risk Stratification
THE GOLMAN STUDY

The ECG Criteria (if not known to be old)

- Suspected MI
  - ST elevation > 1mm
  - Q waves in 2 leads
- Suspected ischemia
  - ST depression > 1mm
  - T inversion in 2 leads

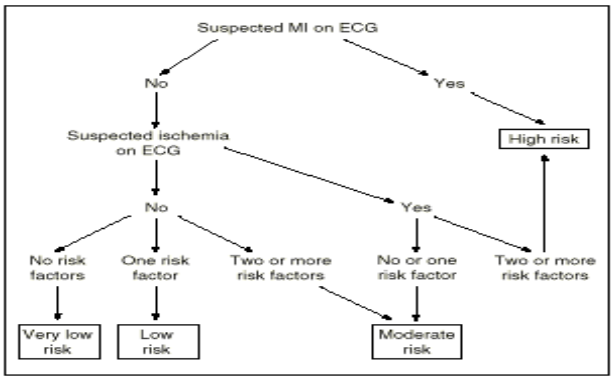


Figure 1. Derivation of the Four Initial Risk Groups on the Basis of Data Available at the Time of Presentation in the Emergency Department.
Myocardial infarction (MI) was suspected if the electrocardiogram (ECG) showed ST-segment elevation of 1 mm or more or pathologic Q waves in two or more leads, and these findings were not known to be old. Ischemia was suspected if the ECG showed ST-segment depression of 1 mm or more or T-wave inversion in two or more leads, and these findings were not known to be old. Risk factors included systolic blood pressure below 110 mm Hg, rales heard above the bases bilaterally on physical examination, and known unstable ischemic heart disease, defined as a worsening of previously stable angina, the new onset of postinfarction angina or angina after a coronary-revascularization procedure, or pain that was the same as that associated with a prior myocardial infarction. The difference between each adjacent pair of risk groups was significant (P<0.001).

Outcomes

Risk Group	**No. of Events in 24 hours**	**0-72 hours**
Very Low Risk	0.4%	0.6%
Low	1.7%	3.9%
Moderate	3.3%	7.8%
High	11.1%	16.1

Section IV: How to Use Cardiac Markers in 1999

Stated another way, how do cardiac makers add to the risk stratification of patients.

1. CK-Mb as a Risk Stratification Tool

Some authors have suggested that ED CK-mb can be used to risk stratify patients and help with disposition.

- **Hoekstra et al Acad Emerg Med 1994**

Looked at 5120 patients from 53 hospitals to determine the usefulness of CK-mb within 3 hours of presentation from predicting MI or cardiac events
5120 patients - excluded those with ST segment elevation 369 (7.1%) with no ST elevation developed an MI -
24% of MI patients had cardiac complications
- complication rate in non-MI patients was 0.4%

Section IV
Maker Use in Risk Stratification
CK-mb alone

Hoekstra et al Acad Emerg Med 1994

- > 5000 ED patients, 53 centers
- Single CK-mb in ED
  - missed 22% of MI's
  - missed 56/160 complications
- If CK positive then high risk
- Not stratified by ECG

However:

- CK-mb testing in the ED missed 22% of MI's and 56 of 160 total complications occurred in patients without elevated CK-mb in the ED
- Patients where not stratified by ECG, that is we do not know what additional information CK-mb gave to the H and P and ECG and this of course is the most important question

2. Troponins additional Value to H and P and ECG

A number of studies have suggested that troponins can be used in addition to H and P and ECG to further risk stratify patients in to a lower risk group.

- **Ohman et al NEJM 1996**

Section IV
Maker Use in Risk Stratification
Troponin T

- **Ohman et al NEJM 1996**
- 855 patients within 12 hours of pain onset, ECG changes
- Outcome: Death, MI, bypass
- If troponin T negative = 3.9% event rate, 11.8% if positive
- Gave additional prognostic info. in all ECG groups
- **ECG near normal & Troponin neg. = 0/114 events**
- **ECG near normal & Troponin pos. = 2/49 events**

855 patients within 12 hours of symptom onset and ECG changes
All got troponin T levels draw
Looked at prognostic significance of ECG, CK-Mb and Troponin
30 days endpoint, death, MI, bypass surgery, angioplasty
Troponin T positive = 0.1 ng/ml

Results: 801 patients - 289 had a positive troponin T
Troponin T positive = more mortality in all ECG subgroups
0/114 deaths if near normal ECG and negative troponin T
2/49 deaths if near normal ECG and positive troponin T

- **Antman et al NEJM 1996**

Section IV
Maker Use in Risk Stratification
Troponin I

- **Antman et al. NEJM 1996**
- 1404 patients, pain in last 24hors, ECG changes
- Mortality if Positive = 3.9%
- Mortality if Negative = 1.0%
- Added prognostic information to ECG

1404 patients with chest pain and ECG changes
Pain > 15mins but less than 6 hours in the last 24 hours
All had troponin I determinations made - o.4ng.ml considered positive
Looked at outcomes at 42 days

Results:
104 patients, 573 had a positive troponin
Mortality was 3.7 if troponin I positive
Mortality was 1.0% if troponin I negative
Each 1 ng/ml increase was associated with increased risk
- when troponin I > 9 mortality was 7.5% at 42 days
Independent predictor of death

Comments: Troponin I in this high risk group added useful prognostic information to the ECG

- **Hamm et al NEJM 1997**

Section IV
Maker Use in Risk Stratification
Troponin I

Hamm et a. Dec 1997

- 771 patients, German ED. Trop > 6 hours after pain
- Outcome: Death or MI at 30 days
- If negative troponin I events rate 0.3% (1.1% if T neg.)
- If normal ECG 5/331 had adverse events
- Added prognostic information to ECG
- **If normal ECG and neg. troponin I = 0 events**

773 patients chest pain for less than 12 hours and no ST elevation
Troponin I positive = O.1ng/ml
Looked at endpoint of death or MI at 30 days

Results: In all ECG subgroups Troponin I was predictive of events
If normal ECG and negative troponin I 0/331 events
All patients with an event that had a normal ECG had a positive troponin I

Comments: The most powerful study in favor of troponins to date. But was in a German ED not a US ED so ?? patient population. Used a very sensitive troponin I assay

- **Polanczyk et al J Am Coll Cardiol 1998**

Section IV
Maker Use in Risk Stratification
Troponin I

Polanczyk et al JACC 1998

- 1047 patients in US ED, 3 hour level, 0.4ng/ml cutoff
- Major complications in first 72 hours (PTCA etc)
- Troponin additive to ECG and history
- If low risk and Trop neg. 1/217 (0.5%) had events
- If low risk and Trop pos. 1/27 (3.7%)had events
- ↓ Sensitive than prior studies - ? Assay ?Low risk group

1047 patients in a US ED setting
Admitted patients with chest pain
Looked at major cardiac complications in the first 72 hours - included heart block, arrhythmia's etc but also PTCA and bypass surgery
Looked at samples < 3 hours after presentation
Definition of a positive test was 0.4ng/ml

Results: Found that initial troponin I was only 18% sensitive for major cardiac events in the first 72 hours
Ck-mb found to be more sensitive for cardiac events than troponin I
Within a model of independent predictors the initial troponin was additive to other history and ECG evidence of ischemia
If low risk by other criteria 1/27 (3.7%) had adverse events if troponin I positive)
If low risk by other criteria and troponin I negative 1/217 (0.5%) had adverse events

Comments: This study is very divergent from prior studies. The power of troponin I appears less than the previous studies but this may be explained by a number of key factors. The cutoff for a troponin I in this study was a high 0.4ng.ml and not 0.1ng/ml as in other studies. The endpoints in this study included PTCA etc whereas other studies have used death or MI as the major endpoints.

Summary:

The question then remains " what additional value do cardiac markers have in patients with chest pain, over and above history and physical examination and ECG". Currently troponins appear to add additional information to usual criteria and a patient that is otherwise low risk and has a positive troponin probably should be cared for in the COU and possibly the CCU.

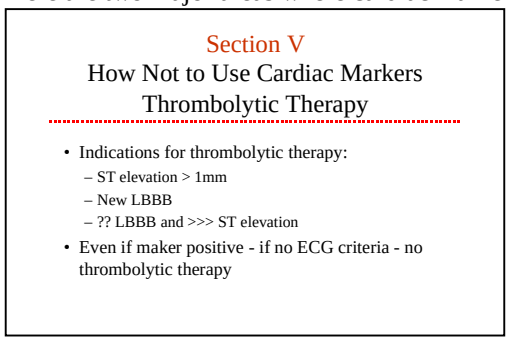
Low risk patients with negative troponins probably are very low risk and can be managed as out patients

Disposition endpoints:

The Goldman criteria are the single best validated criteria for risk stratification. Using these criteria to stratify into very low, low and high risk groups allows best use of hospital and outpatient services. The addition of troponins may have some role for deciding who to discharge (if negative after 6 hours from pain onset and an ultrasentive assay is used). it is not clear how a positive troponin moves a patient to a higher risk group within the Goldman model. The best evidence suggests a positive test should move the patient up a category as they have independent predictive value.

SECTION V: HOW NOT TO USE CARDIAC MARKERS

There are two major areas where cardiac markers are missed used: to determine if thrombolytic therapy should be used, and to send other wise high risk patients home.



• Indications for **thrombolytic therapy** are chest pain greater than 20minutes and ST elevation or new LBBB or LBBB with certain

specific attributes. Cardiac makers are not useful in this decision..

• In patients with an ACS with **ECG changes** (either ST depression or T inversion) are high risk patients ***NO MATTER WHAT THE TROPONIN STATUS!***

Section V
How Not to Use Cardiac Markers
As independent data

If high risk by history or ECG
and maker negative
Then they are still **moderate to high risk**!!!!!

EG. Hamm et al if ST depression and neg. troponin I - risk was 1.4% (CI as high as 5-8%)

In the paper by Hamm there were 355 patients with ST depression or T inversion on ECG. Of these 18 had cardiac events, 16 where troponin I positive and 2 troponin I negative. The absolute event rate for Troponin I negative patients with positive ECG was only 0.6% (95% CI 0-2%).

However 11% of patients that had events where troponin I negative! For patients troponin T negative the event rates are all significantly higher. This is to say that Troponins either positive or negative are not helpful in triage decisions in-patients with high risk EKG'S. A 2% event rate is probably too high for us to accept. Studies of intensive in-patient therapy for high-risk patients with unstable angina definitively show a reduction in MI and death. These patients should not be sent home!

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