AMERICAN COLLEGE OF EMERGENCY PHYSICIANS
SCIENTIFIC ASSEMBLY
1999

New Concepts in the Management of Unstable Angina

New research has recently emerged that challenges our concepts of how unstable angina should be managed. The lecturer will review the current literature and compare available interventions. The pros and cons of various evaluation and treatment strategies will be discussed.

- Discuss the management of unstable angina.
- Distinguish which treatments are most effective.
- Examine the data regarding the treatment of unstable angina.

MO-14
Monday, October 11, 1999
9:00 AM - 9:55 AM
Room # N212
Las Vegas Convention Center

FACULTY

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The Topics
Please note that some
i) IIb/IIIa Platelet Inhibitors
Mel Herbert - the case against their use
see syllabus on this topic by Dr. Herbert course no.
ii) Cardiac Marker use in the ED
Mel Herbert - the case for their use
see syllabus on this topic by Dr. Herbert course no.
iii) Chest pain units in Emergency Medicine
Mel Herbert - the case for their deployment
See syllabus following
iv) Angioplasty vs. Thrombolytic Therapy for Acute MI
Mel Herbert - The case for angioplasty
see syllabus following
Please note that I (Dr. Herbert) feel that the use of PTCA for MI/USA has been overemphasized and does not necessarily represent a cost effective alternative to thrombolytic therapy. However for the sake of educational purposes I have been asked to will argue the positive on this point and will do so as far as it seems reasonable and supported by available data.

THE THEORETICAL ARGUMENT IN FAVOR OF PTCA

- PTCA results in better early patency than thrombolysis
- Early patency results in improved outcome (actually this is very questionable)
- PTCA does not put patients at risk of the dreaded complication of hemorrhagic stroke
- PTCA can be employed in patients without ST segment elevation, thrombolytics can only be used in patients with ST segment elevation
- New developments in PTCA - like stent placement - will further improve results with PTCA

Therefore PTCA, if done in a reasonable time frame by experienced people, it will result in better outcomes in patients with MI than thrombolysis

THE STUDIES OF PTCA VERSUS THROMBOLYTICS

There have been 8 trials (approximately 2300 patients) of PTCA versus thrombolytics for acute myocardial infarction. Combined, these data suggest an improved outcome in patients randomized to receive PTCA (mortality at 30 days being 4-5% in PTCA group and 7% in thrombolytic group).

The trials differ in the choice of thrombolytic, regime employed, patient selection, experience of the angioplasty team etc. Despite this the evidence is good that short term (30 day) mortality is improved by PTCA over thrombolytics.

In the largest trial to date, the ***GUSTO IIb study,*** *1138 patients* with less than 12 hours of chest pain and with ST segment elevation were randomized to receive accelerated TPA versus PTCA. The endpoint of the study was death, reinfarction or non-fatal stroke at *30 days.* 9.6% of PTCA patients and 13.7% of the thrombolytic group had one of the outcomes listed. This results was statistically significant and provides the best evidence to date that PTCA is superior to thrombolytic therapy.

The proponents of PTCA also note that all studies of PTCA versus thrombolytics were performed before the widespread use of IIb/IIIa inhibitors, which have been show to further improve the outcomes in PTCA patients. The addition of these agents will probably result in even greater mortality advantages to PTCA, though these same agents may also have a role in patients receiving thrombolytic therapy

The potentially most serious side effect of thrombolytic therapy is hemorrhagic stroke. In the GUSTO IIb trial, eight or 1.4% of TPA treated patients had a hemorrhagic stroke; none occurred in the PTCA group. The rate of all disabling stroke was 5 times higher (5 vs 1) in the TPA group (p=0.011).

The authors of a well performed meta-analysis that appeared in JAMA in Dec 1997 concluded:

" Based on outcomes at hospital discharge or 30 days (35% reduction in mortality favoring PTCA), primary angioplasty appears to be superior to thrombolytic therapy for treatment of patients with acute myocardial infarction, with the proviso that success rates for angioplasty are as good as those achieve in these trials. Data evaluating longer term outcomes, operator experience and time before treatment are needed before primary angioplasty can be universally recommended as the preferred treatment.

Table from: Sorin J. Brenner Angioplasty or Fibrinolysis for Acute MI? The GUSTO IIb study. Cleveland Clin J Med1998;65:75-110

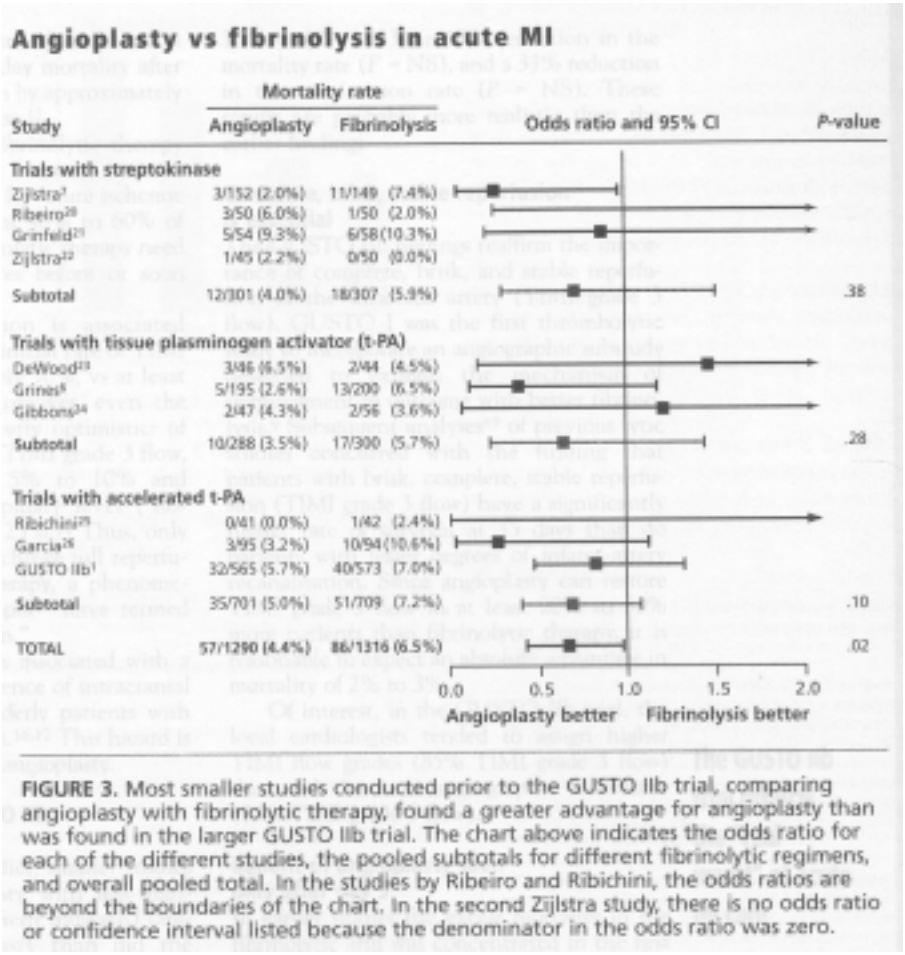


FIGURE 3. Most smaller studies conducted prior to the GUSTO IIb trial, comparing angioplasty with fibrinolytic therapy, found a greater advantage for angioplasty than was found in the larger GUSTO IIb trial. The chart above indicates the odds ratio for each of the different studies, the pooled subtotals for different fibrinolytic regimens, and overall pooled total. In the studies by Ribeiro and Ribichini, the odds ratios are beyond the boundaries of the chart. In the second Zijlstra study, there is no odds ratio or confidence interval listed because the denominator in the odds ratio was zero.

Summary:
The best current evidence suggests that PTCA is superior to thrombolytic therapy for patients with MI with some very important caveats: 1) the operator is experienced 2) PTCA can be performed rapidly (generally less than one 1 hour) and 3) the results of the PTCA are as good as those published in the current trials 4) #0 day outcomes are considered.

These results say nothing about costs. It is unlikely that PTCA will ever be proven cost effective for the average smaller community hospital. The investment required to set up and staff an angioplasty suite that can be activated in the requisite time is far to great for the average ED seeing just a few MI's per week. Far more important is rapidly providing aspirin, Beta-blockers, and rapid thrombolysis to all appropriate patients in as rapid a time frame as possible. In addition it remains to be proven if sustained reduction in mortality or MI can be achieved beyond 30 days.

Bibliography:

Weaver WD et al Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction. A quantitative review. JAMA 1997;278:2093-2098

Zijlstra F, et al A comparison of immediate coronary angioplasty with intravenous streptokinase in acute myocardial infarction. N Eng J Med 1993;328:680-684

Grines CL et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Eng J Med 1993;328:673-679

Gibbions RJ, et al. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Eng J Med 1993;328:685-691

DeWood MA. Direct PTCA vs intravenous t-PA in acute myocardial infarction: results of a randomized trial. In: Proceedings from the Thrombolysis and Interventional Therapy in Acute Myocardial Infarction Symposium VI. Washington DC: George Washington University: 1990:28-29

Riberiro EE et al. Randomized trial of direct coronary angioplasty versus intravenous streptokinase in acute myocardial infarction. 1993;22:376-380

Ribichini F, et al. Primary angioplasty versus thrombolysis in inferior acute myocardial infarction with anterior ST segment depression: a single center randomized study. J Am Coll Cardiol 1996;27:A-221. Absrct

Grinfeld L, et al. Fibrinolytics vs primary angioplasty in acute myocardial infarction (FAP). J Am Coll Cardiol 1996;27(suppl):A-222 Abstract

The Global use of stratagies to open accluded coronary arteries in acute coronary syndromes GUSTO IIb angioplasty substudy Investigators. A clinical trial comparing primary coronary angioplasty with tissue plasminogen activator for acute myocardial infarction. NEJM 1997;336:1621-1628

Zijlstra et al. Randomized comparision of primary angioplasty with thrombolytic therapy in low risk patients with acute myocardial infarction. J Am Coll Cardiol 1997;29:908-912

Garcia E, et. al. Primary angioplasty versus thrombolysis with t-PA in the anterior infarction. J Am Coll Cardiol 1997;29(suppl A): A-389 Abstract

CHEST PAIN UNITS IN EMERGENCY MEDICINE - THE CASE FOR

A real discussion of the utility of chest pain units is extremely difficult at this time. A number of fundamental questions need to be answered that are bigger than the question of weather chest pain units are good, or cost effective etc.

1. What is a chest pain unit?

- A place where LOW RISK CHEST PAIN patients can be monitored, ruled out and have a provocation test (like an exercise ECG) to rule out an acute coronary syndrome

- This "unit" can be in the ED or CCU or COU - the idea of it being in the ED is there is an intrinsic efficiency in having to not go through the entire admission process and handing of to new nurses and doctors etc.

- By definition any patient that is found to have an ACS or develops a complication is them admitted.

- Most patients in these units will be proven to not have any CAD

2. How did we get here?
   - Currently 5 million patients present with chest pain to ED's in the US per year
   - 3 million are admitted
     - Only 1million have an acute coronary syndromes
     - The "missed MI rate" is 1-5%
     - More dollars send on "missed MI" in emergency medicine than any other disease
   - The cost of admitting many patients without the disease is very very very large!
   - Chest pain units are an attempt to reduce the cost of the work-up of low risk patients

3. The stated aim of chest pain units
   - Reduce "Missed MI rate"
   - Reduce the total cost of work-ups for patients presenting to the ED with chest pain
   - Reduce the time of the work-ups

4. The rarely stated aim of chest pain units
    - Marketing your ED over the local competition!

5. The problem with the current literature

    - Rarely are the studies randomized
    - True cost data on admission versus CPU is extremely difficult to determine
    - The studies assume that having a chest pain unit will not actually increase the total number of patients put through a "rule out" protocol that may otherwise be sent home
    - **The most basic question has not been addressed: what is an acceptable miss rate - how much money are we allowed to send to find the very few patients with atypical presentations that have disease**
    - **What is the real endpoint - if low risk patients are sent home from the CPU - but at a later time are admitted for a more through work-up - then the CPU has not saved you money**

6. Do chest pain units do what they have been sent up for

    - Actually very little good literature on the subject
    - Most studies are simply descriptive reports of various hospitals experience, protocols and rule in/rule out rates
    - They have been criticized for very low rule in rates (well sparky that is the point of the unit - it is a different population)
    - Criticized because of all chest pain patients only a minority reach the criteria for admission to the unit (but this depends on the criteria the chest pain unit uses)
    - It is not celar who will pay for the units - in many setting money is made on admission - not on the CPU - so the "cost effectiveness" varies but practice setting

    The best evidence to date suggests:
    1. Patients like the time efficiency in the work-up's
    2. In the few randomized trials they appear to slightly reduce the cost of the CP work-up
    3. The "miss rate" for the low risk patients appears to be better than non-protocol driven ED work-up's

    References:
Hoekstra JW, Gibler WB Chest pain units: An idea whose time has come. JAMA Nov 26 1997;278:1701-1702

Zalenski RJ, et al. A national survey of emergency department chest pain centers in the united states. Am J Cardiol 1998;81:1305-1309

Roberts RR, Zalenski RJ, Mensah EK, et al Costs of an Emergency Department-based Accelerated Diagnostic Protocol vs Hospitalization in Patients With Chest Pain: A Randomized Controlled Trial. JAMA, 278:1670-1676, 1997

Note on Syllabus Formatting:

Please note that the slides used in this lecture are imbedded into the text of the syllabus as many people like to follow the slides and syllabus at the same time.

INTRODUCTION/SCOPE OF THE LECTURE

Coronary artery disease (CAD) remains one of the most common causes of death and morbidity in the US and one of the most frequent reasons for presentation to the ED. Each year 5 million patients present to ED's with a complaint of chest pain. Emergency Physicians must be *expert* at the diagnosis, early therapy and disposition of all patients with the suspected diagnosis. This lecture will concentrate on particularly those that are new and emerging. Detailed analysis and opinion on the pathophysiology of the disease as well as inpatient decision points, can be found in the reference section..

EPIDEMIOLOGY

- In 1996 there were approximately 750,000 admissions for MI and 1 million admissions for unstable angina
- Admission rates for chest pain syndromes are increasing
- Total number of hospital days in 1991 was 3.1 million (AHCPR)

DEFINITIONS

Definitions

" Unstable angina encompasses a spectrum of symptomatic manifestations of ischemic heart disease between stable angina and AMI"

Cairns et. al. Can J Cardiol 1996

PATHOPHYSIOLOGY

Angina is caused by a difference in oxygen supply relative to oxygen demand in cardiac muscle. Generally this is caused by an obstruction to flow in the coronary vessels (atherosclerotic plaque with or without thrombosis formation) or coronary vasospasm.

Unstable angina may be caused by:

- *Progression of atherosclerotic plaque*.
- *Plaque fissuring*. Results in exposure of endothelium to blood with thrombus formation.
- *Vasospasm*. Also can result from plaque fissuring and exposure of the underlying endothelium.
- *Increased oxygen demand*. Multiple potential causes. Anything that increases heart rate, blood pressure (and therefore afterload) or contractility can increase oxygen demand (usually called secondary unstable angina).

Plaque fissuring causes platelet aggregation and vasospasm. If the process produces complete lumen obstruction and is prolonged, then AMI will occur.

In recent years the plaque fissuring theory has taken a major role in our understanding of unstable angina. Approximately 80% of patients with unstable angina having angiography have evidence of plaque fissuring. Newer plaques, high in lipid and fleshy, are at high risk of fissuring. Fissuring tends to occur at the junction of the fibrous cap over the plaque and the normal endothelium.

Once a plaque has fissured a complex process of platelet aggregation and thrombosis is set up that involves numerous coagulation and cascade processes. ***A major part of current therapy as well as many emerging therapies are aimed at preventing platelet aggregation and blocking of thrombosis.***

AN INFECTIOUS ETIOLOGY FOR CORONARY ARTERY DISEASE ?

There is possibly an association between certain infectious diseases and CAD. There are a number of hypothesis for the causal mechanism of this association, including: accelerated atherogenesis due to immunological factors, direct infection of the vascular endothelium. The following abstract supplied by

Emergency Medicine Abstracts® outlines some of the flaws in the studies that have suggested an infective cause for CAD.

Chronic infection with H.pylori, CMV etc may just be an indicator of low socioeconomic class. More studies will be done but two important points need to be made: First, if proven true, anti-infective therapy and/or immunization against causative organisms maybe useful for the treatment of CAD. The second point is simply this: if you think this idea is completely insane, consider the role of H.pylori in peptic disease. A few years ago this seemed insane!!

CHRONIC INFECTIONS AND CORONARY HEART DISEASE: IS THERE A LINK? Danesh, J., et al, Lancet 350(9075):430, August 9, 1997

Some studies have reported associations between coronary heart disease (CHD) ai infection due to H. pylori and herpes viruses (specifically cytomegalovirus [CMV]), th are possibly related to local or systemic inflammation, endothelial injury, autoimmun processes and influence on classic risk factors. This British report reviewed the finc of these studies. The approximately 20 epidemiological studies (about 2,600 cases reporting associations between CHD and the presence of H. pylori most commonly involved relatively small study populations and often failed to adjust for potential confounders. The odds ratio (OR) for CHD in the setting of seropositivity was gener about 1.5, but ORs (which ranged between 0.5 and 8.0) and 95% confidence interva were widely variable in the individual studies. The findings of 18 epidemiologic stud (about 2,700 cases) of associations between Chlamydia pneumoniae antibody and generally reported ORs of 2.0 or higher with some noting a "dose-response" relatior (increasing ORs with increasing antibody titers), but differences in the design characteristics of these studies and variable 95% confidence intervals may complica interpretation of these findings. ORs reported in studies of associations between he virus and CHD have generally ranged between about 1.5 and 4.0, but the studies of involved small sample sizes, incomplete adjusting for confounders, atypical patient populations and "exploratory" analysis of the data. The authors believe that certaint regarding possible relationships between infection and CHD will require larger, prop designed studies. 62 references 12/97 - #1 Creamery, Pennsylvania 1-8 458-4779

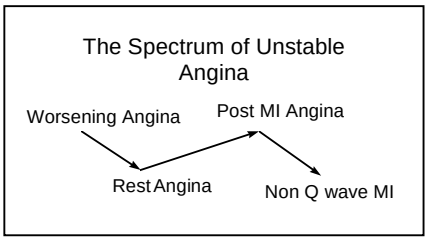
Currently a number of large trials are planned or underway to determine if anti-infective therapy has a role in acute and chronic coronary syndromes. ***Plaque rupture may be the result of a reactivation of the infection. Therefore, anti-infective therapy may suppress the ongoing unstable plaque.***

THE SPECTRUM OF UNSTABLE ANGINA

Perhaps the most important concept to understand in the treatment of unstable angina is that the disease is a spectrum and therefore the

aggressiveness of therapy is tailored to where on the spectrum the patient lies!!

We care about unstable angina for two major reasons: it can lead to sudden death through arrhythmias and secondly, if left untreated, can result in MI (which can result in sudden death or loss of cardiac function and CHF etc). The idea of unstable angina as a spectrum is that some patients with unstable angina are at very high risk of sudden death or acute MI while others have some risk, but not very great, at least in the next few days to weeks. For example:



A patients with chronic angina that gets pain after 10 minutes of walking, who now gets pain after walking for 9 minutes is classified as having unstable angina, but really is at low risk for acute complications. Alternatively a patient who had an MI last week, was sent home and now is having chest pain at rest or with minimal exertion is at very high risk of acute complications!! Clearly these two patients do no need the same level of therapy. This point becomes especially important when we talk about therapies that have significant side effects. If the therapy one is considering has no side effects, is well tolerated and is cheap, then the decision to use it would be simple. However, since all therapies have expense and side effects, one must weight the risk against the benefit of each therapy in each patient. In the next section I will cover each therapy and give some idea as to its costs, effectiveness and downsides.

The simplest way to risk stratify patients with chest pain is by history (typical histories are associated with worse prognosis than atypical histories) physical examination (patients with signs of CHF do worse than those without). The best risk stratification tool of the ECG. patients with abnormal ECG's have a high short term risk and should receive aggressive therapy. Patients with normal or near normal ECG are at lower risk and probably derive less therapy from aggressive therapies with significant side effects.

High Risk ECG features:

- ST segment elevation (if persist ant = MI and thrombolytics)

- ST segment depression
- Dynamic ST/T changes
- Deep symmetric T wave inversion
- Normal or non-specific ST-T changes portend a good prognosis

ED THERAPY

The aims of therapy are to:

- 1) prevent progression of the disease to MI,
- 2) treat specific complications like pulmonary edema and arrhythmias
- 3) control symptoms. To give expert care to patients with unstable angina one must again appreciate where the patient stands on the spectrum of the disease.

To help determine the benefit a patient may receive from any specific therapy, quotations of relative risk reduction, so often used in the literature, are of almost of almost no help! A better indicator of benefit is the concept of the "number needed to treat" ie. How many patients like the one in front of me do I need to give this therapy to save one life, or prevent one MI etc.

An example:

You have two drugs, both decrease mortality by 50%, which is the most effective drug?

A Little Math

- Drug A - decreases mortality 50% (from 10% to 5%)
- Drug B - decreases mortality 50% (from 1% to 0.5%)

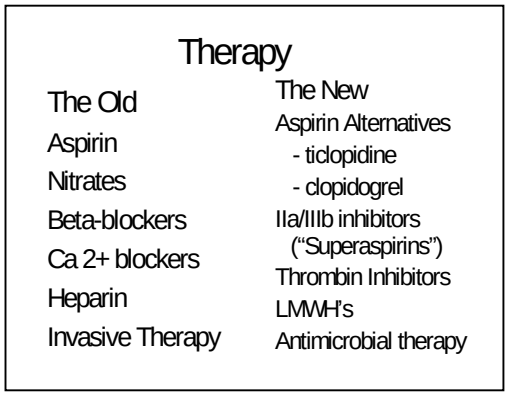
The answer is it depends on the absolute reduction is mortality not on the relative reduction!

A Little Math

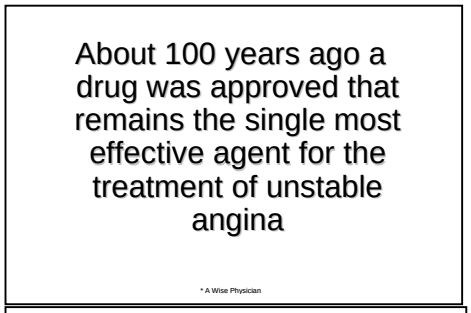
- Drug A - Absolute reduction = 5% (NNT = 20)
- Drug B - Absolute reduction = 0.5% (NNT = 200)

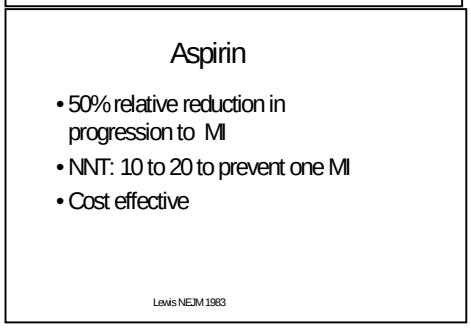
As far as possible in this section I will talk in terms of "number needed to treat".

THE TYPES OF THERAPY



ASPIRIN





The mainstay of therapy in unstable angina is aspirin.

- Aspirin reduces platelet aggregation and thrombus formation
- Aspirin reduces the progression to MI or cardiac death by 31 to 50% (Cairns 1985, Lewis 1983, RISC group 1990)
- ***NNT = approximately 10*** to prevent one MI or death
- Aspirin should be given to all patients except those with an aspirin allergy
- Recommended doses vary but 160 to 325 mg is usual.
- Chewing the aspirin possibly speeds onset of action

By far aspirin is the most effective and cost effective drug in the treatment of all acute coronary syndromes. Virtually all patients should get this drug. The only real contraindication is a true aspirin allergy.

ORAL ASPIRIN ALTERNATIVES

Oral Aspirin Alternatives

- Ticlopidine
- Clopidogrel

- Aspirin still king

- Work on the ADP dependant pathways of platelet aggregation
- In the acute setting, the onset of action of the oral aspirin alternatives is too slow to be clinically useful.
- Onset of action is approximately 10 days
- May have a role as additional therapy to aspirin in patients with Stents

Only one randomized trial has examined the use of Ticlopidine in USA - 652 patients received usual therapy (but no aspirin) and usual therapy plus ticlopidine. At 6 months follow-up there was a 46% relative reduction of death or MI (NNT approximately 16). This effect was not noted until l10 days after the therapy was commenced. (Balsano F et al. Antiplatelet treatment with ticlopidine in unstable angina. A controlled multicenter trial Circulation 1990;82:17-2).

Regular Heparin

In practice heparin is usually added to aspirin for further antithrombotic effect. A number of small trials suggest that heparin is superior and additive to aspirin therapy alone. Oler et.al. in a well designed meta-analysis concluded that regular heparin, added to aspirin reduced, mortality and MI while the patients received the heparin. The analysis suggested a 33% overall reduction in MI or death. It is very important to note that that the confidence intervals in these small studies are actually very large.

NNT = approximately 60.

Heparin

- Only 6 randomized trials (2 DB)
- All suggest a positive effect
- Meta-analysis: 33% relative reduction in MI/Death
- NNT = approximately 60
- Evidence still not 100% conclusive

Oler et. al. JAMA 1996

Please note that the patients in these studies were generally sicker than the average ED patient given the diagnosis of unstable angina. For lower risk patients one may need to treat many hundreds of patients before receiving benefit.

Regular Heparin

- Unstable angina ≠ Heparin
- Consider the risk/benefit for each patient!
- 400% increase in major bleeding
  - –1.5% major bleed in heparin
  - –0.4% major bleed in aspirin
  - –1 extra major bleed per 100 treated

In general a major bleed (intracranial, bleeding needing transfusion etc) will occur in about 1 in every 100 to 150 patients given heparin. *This is why not all patients given the label unstable angina should be given heparin.* Heparin should probably only be given to high or moderate risk patients

- The following table summaries the six randomized trial that Oler et.al. were able to identify as meeting strict methodological criteria.

Characteristics of 6 randomized trials of aspirin plus heparin vs aspirin alone to prevent myocardial infarction and death in patients admitted to the hospital with unstable angina.

Modified from: Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. JAMA 1996;276:811-81

Death, MI

Source	Blinding	Aspirin Dose, mg	PPT	Duration of Heparin Therapy (days)	Aspirin	Aspirin and Heparin	RR (95% CI)
Theroux et. al. 1988	Double	325 bid	1.5 to 2	6	4/121 (3)	2/122(2)	0.5(0.18-2.66)
RISC et al. 1990	None	75 daily	Not Stated	5	7/189(4)	3/210(1)	0.39(0.18-1.47)
Cohen et. al. 1990	None	80/325	2 X	3-4	1/32(3)	0/37(0)	0.29(0.06-6.87)
Cohen et. al. 1994	Participants	162.5	2X	3-4	9/109(8)	4/105(4)	0.46(0.24-1.45)
Holdright et. al. 1994	Participants	150	1.5 to 2	2	40/131(31)	42/154(27)	0.89(0.66-1.29)
Gurfinkel et al. 1995	Double	200	2 X	5-7	7/73(10)	4/70(6)	0.60(0.29-1.95)
Summary					68/655(10)	55/698(8)	**0.67(0.44-1.02)**

NITRATES

Nitrates

- Reduces pain, improves hemodynamics
- SL, IV, TD, PO
- IV underdosing!
- Lives saved ??

- It has not been conclusively shown that nitrates reduce mortality in unstable angina
- Nitrates have many positive effects on reducing ischemia and improving hemodynamics and are considered the standard of care.
- When dosing nitrates (especially in the IV form) remember to give adequate doses. One sublingual nitrate tablet provides about the equivalent of approaximately100-200 micrograms/minute of nitrate. So when running the IV nitro do not be afraid to turn it up to 200 micrograms a minute if needed!

BETA-BLOCKERS

Beta-Blockers

- Give to all patients without contraindications
- Aim for heart rate of around 60
- Beware worsening CHF
- NNT: 40 to prevent 1 MI

Yusuf JAMA 1988

There is good evidence that in patients with "impending MI", beta-blockers decrease the progression to MI. All patients with MI should receive beta-blockers unless there is a specific contraindication.

IV beta-blockers are especially indicated in patients with:

- severe chest pain
- recurrent or prolonged episodes
- marked ECG abnormalities
- hemodynamic instability
- hypersympathetic

ATENOLOL:

- 5 mg IV repeated q 5 min X 3 as required to achieve HR around 50-60
- Contraindicated in patients with decompensated heart failure or respiratory failure, second degree or higher AV block, SBP < 90

Stable patients can be given oral doses (50 to 100mg per day).

METOPROLOL:

- can be given as a similar dose with similar contraindications to atenolol

ESMOLOL

An ultrashort acting beta 1 selective beta-blocker that can be given as an IV infusion and is particularly useful in patients when it is unclear if beta-blockage will cause decompensation. A trial of esmolol can be followed by atenolol or metoprolol if the patient tolerates the esmolol infusion.

Generally an infusion is given at:

- 5 g in 100ml (50mg/ml) at 50-200micrograms/kg/min

(70kg person = 40ml/hr = 100micrograms/kg/min)

Esmolol is generally very expensive, up to $400 for a one day infusion.

Calcium Channel Blockers

Perhaps no area in MI and unstable angina therapy has created as much controversy as the use of calcium channel blockers. A well publicized study from caused headlines like "Your doctor may be killing you".

Calcium Channel Blockers
Nifedipine

- Nifedipine alone not indicated
- Nifedipine with Beta-blocker maybe beneficial

Muller et. al. Circulation 1984

- In 1995, a meta-analysis paper (in the journal Circulation) of routine use of ***nifedipine*** for secondary prevention of MI, strongly suggested that nifedipine increased mortality in patients with coronary heart disease! It was this paper that grabbed the headlines. It is probably true that nifedipine alone (in the absence of beta blockers) is harmful (HINT trial, Muller 1984). Combined nifedipine and beta-blocker may in fact be more helpful than beta-blocker alone (in patients requiring high doses of beta-blocker) (HINT trial).

Calcium Channel Blockers
Verapamil

- 2 BD, PC trials
  - – better than no beta-blocker
- 1 Trial of Metoprolol vs Verapamil long term
  - – 809 patients, equal outcome after Median 3.4 years

- In the APSIS trial, metoprolol was compared to verapamil in 809 patients with stable angina for the prevention of death and MI, and effect on quality of life. No difference was found between the two drugs after of minimum for 3 years follow-up (Rehnquist 1996).

Calcium Channel Blockers
Diltiazem

- Equal to beta-blockers in controlling pain*
- Better than nitroglycerin+
  - –less pain
  - –less MI/refractory angina

* Theroux JAAC 1984
\+ Gobel Lancet 1995

- Recently, intravenous ***diltiazem*** has been studied in patients with unstable angina, where it appears to significantly reduce ischemic events compared to nitroglycerin and equal to beta-blockers (Gobel 1995). Verapamil appears to be an effective alternative (Mehta 1982). Diltiazem may have its best role in patients with contraindications to beta-blockade.

• Where does this leave us? Calcium channel blockers like diltiazem that reduce heart rate should be used when indicated in patients with coronary artery disease. In the future, diltiazem may be routine therapy for unstable angina. Calcium channel blockers like nifedipine, that increase heart rate, may be detrimental in patients with underlying coronary artery disease when used alone. For now, if you need to use a calcium channel blocker in an MI patient or one with unstable angina, do not hesitate to use those that reduce heart rate. *The main indication for calcium channel blockers is for patients with contraindications to beta-blockers.*

Calcium Channel Blockers

- If they slow rate….they are great
- Second line to Beta-blockers
- Titrate to heart rate of around 60

DILTIAZEM

• 5mg over 2-5mins, repeated every 5-10 minutes up to a total dose of 50 mg if required. This can be followed by an infusion of 5mg/min up to 15mg/min

• Contraindications: Heart block, SPB < 90

Thrombolytic Therapy

Thrombolytic Therapy

- Nice idea but no cigar!
- TIMI IIIb no benefit
  - –TPA vs. placebo
  - –MI greater in TPA group
  - –4 cerebral bleeds in TPA vs. none

Circulation 1994

• A number of small studies have failed to show a benefit of thrombolytic therapy in unstable angina. Though the size of the intracoronary thrombi may be reduced, this has not translated into reduction in the prevalence of MI. Indeed most series show worse outcomes in patients treated with thrombolytics than in those left untreated (Knoury.et al.Ann Emerg Med 1996, Lewis et al. Am J Cardiol 1994)

Routine Invasive Interventions

The use of invasive therapy for unstable angina remains controversial. Patients can be divided into two groups for the purpose of discussion: those with refractory symptoms despite medical therapy, those patients whose symptoms are controlled by medical therapy.

INVASIVE THERAPY IN PATIENTS RESPONDING TO MEDICAL THERAPY

Invasive vs. Medical Therapy

- TIMI IIIb
- 1473 Patients, *Circulation 1994*
- Endpoint: Death, MI, Ischemia
  - –no difference
  - –less inpatient time in invasive group
  - –? cost effectiveness

- The TIMI IIIB trial was performed to ask the question if early aggressive non-medical intervention in patients with unstable angina reduced death, MI, or an unsatisfactory symptom limited exercise stress test at 6 weeks.

TIMI IIIB in 1473 patients compared: TPA versus placebo and early invasive strategies versus medical therapy.

- The primary endpoints for the TPA vs placebo group death, myocardial infarction or failure of initial therapy at 6 weeks. No difference was found. Overall, both MI and bleeding complications were more common in the TPA group.

- The comparison of early invasive therapy (including angiography within 24 hours with PTCA or Bypass in selected individuals) to medical therapy showed no difference at the 6 weeks end point. Length of hospital stay and rehospitalization where lower in the invasive group. The most cost effective strategy remains unclear.

Invasive vs. Medical therapy

- VANQUISH Trial
- 920 patients with non-Q-Wave MI
- Early agressive therapy vs. ischemia guided therapy
- Conservative therapy best at 1 year follow-up!

- In June 1998 in the NEJM the VANQUISH trial compared an early aggressive intervention strategy with a conservative "ischemia based intervention therapy in patients with non-Q-wave MI. Patients treated in the "conservative group had better outcomes out to 1 year follow-up.

INVASIVE THERAPY IN PATIENTS NOT RESPONDING TO MEDICAL THERAPY

Currently it is standard of care to proceed to invasive strategies in patients with unstable angina if medical therapy fails or if the patient shows severe ischemia on initial presentation (eg. chest pain with hemodynamic changes or large area of myocardium at risk on ECG analysis).

Following angiography it remains for the cardiologist to determine the best course for therapy be it medical, PTCA or bypass surgery.

Direct Thrombin Inhibitors

A number of agents are being developed that act as direct thrombin inhibitors. These potentially more potent drugs (than heparin or warfarin) are currently under investigation in a number of large trials. They act by binding to and inhibiting fibrin-bound thrombin , decreasing activation of platelets and the coagulation system.

Direct Thrombin Inhibitors
Hirudin
- Prototype Drug
  –GUSTO IIb > 12,000 patients
- MI/Death from 2.1 to 1.3%
- NNT > 100
- Effect lost by 30 days
- Cost per saved event?

Hirudin is the prototypical and most studied drug. In a large multi-center, multi-country, double blind, randomized study comparing Hirudin and Heparin in 12,142 patients with MI or unstable angina, Hirudin was associated with a lower incidence of death or MI in the first 24 hours of therapy (1.3% vs 2.1% P<0.001). This effect was lost by the 30 day endpoint of the study (though the trend favored Hirudin). There was a higher incidence of moderate bleeding in the Hirudin group (8.8% vs 7.7%). A study by Eric Topol comparing angiographic changes in unstable angina in patients given Hirudin versus Heparin suggested hirudin to be at least as good and possibility superior to heparin.

Direct Thrombin Inhibitors
Hirudin vs. Heparin
- **OASIS-II trial**
- **>10,000 patients**
- **Less MI or death at 7 days**
- **Effect no sig. at 30 days**
- **Bleeding rates higher in Hirudin group**

OASIS-II trial was published in the LANCET in Feb 1999
Showed an effect better than heparin for MI or death while the infusion was running but this effect was quicly attenuated after the infusion was ceased. Bleeding was more common and the drug is expensive. At this time these is little evidence to suggest the use of these agents as a routine in USA.

Direct Thrombin Inhibitors
Hirulog
- Similar action to Hirudin
- TIMI 7 study
- The HERO Study

- A similar agent ***Hirulog*** was studied in the HERO trial of 400 patients with MI given STK and randomized to

receive Hirulog or Heparin. Despite a little data dredging by the authors no clear differences in outcome were found.

Low Molecular Weight Heparin (LMWH)

LMWH

- Ease of use
- Safety
- No lab testing required
- Predictable

LMWH is a form of heparin that is smaller and less antigenic than regular heparin. It is given as a subcutaneous injection. Unlike regular heparin, it gives consistent and accurate anticoagulation when given in a weight based regime. PTT testing is not required (indeed the PTT assay is not affected by LMWH). There are at least five different LWMH's now available in the US.

There is increasing evidence that low molecular weight heparin is safer and at least a little more effective than regular heparin in the treatment of acute coronary syndromes. It is my opinion that regular heparin has served us well but it is time to change to LMWH. It also appears that not all LMWH's are created equal. Currently the best evidence suggests enoxaparin is the most effective LWMH for acute coronary syndromes.

LMWH
FRISC
- 1506 patients, *Lancet March 1997*
- Aspirin vs Dalteparin
- Death, MI, recurrent Ischemia
  - –1.8% vs 4.8%
  - –NNT about 30
  - –no increase in major bleeds

LMWH
FRIC TRIAL
- 1482 Patients, *Circulation July 1997*
- Standard Hep. vs Dalteparin
- Death, MI, recurrent Ischemia (6 days)
  - –7.6% reg hep. vs 9.3% LMWH
  - –trends favored reg heparin!
  - –qd LMWH no effect at 45 days

LMWH
ESSENCE TRIAL
- 3171 Patients, *NEJM Aug 1997*
- Standard Hep. vs Enoxaparin
- Death, MI, recurrent Ischemia
  - –19.8% reg. hep. vs 16.6% LMWH
  - –16% relative reduction
  - –NNT about 30
  - –no increase in major bleeds

Study	Comparison	Study Population	Primary Endpoints	Results	Conclusions
Direct Comparisons with Regular Heparin					
FRIC Circulation July 1997 *1482 patients*	Standard Heparin vs Dalteparin (bid 6 days then qd - 45days)	Unstable Angina (ST changes etc)	Death, MI, recurrent ischemia up to 45 days	First 6 days: 7.6% in reg Heparin 9.3% in dalteprin	Trends favored regular heparin!!!!! No effect of dalteparin vs aspirin at qd dose from 6 to 45 days
ESSENCE NEJM August 1997 *3171 patients*	Standard heparin vs enoxaparin Minimum of 48 hours	Unstable angina (Real disease, ST etc)	Death, MI, recurrent ischemia at 14 days	14 day endpoint: 19.8% in reg heparin 16.6% in enoxaparin	Significant. Mostly in recurrent ischemia, trends in death and MI. 16% relative reduction. **NNT = about 30** No increase in major bleeds!
Gurfinkel et. al. JACC August 1995 *219 patients*	Standard Heparin vs Nadroparin	Unstable angina and silent ischemia	Death, MI, recurrent ischemia while inpatient (usually 5-7 days)	Recurrent angina (too small to look at other endpoints 44% in regular heparin 21% in nadroparin	Significant. Smallest of the studies. All good trends favored th LMWH group! No major bleeds in the LWMH group.
Comparison with Placebo Controls					
FRISC Lancet March 1996 *1506 patients*	Dalteparin vs placebo (aspirin)	Unstable angina (ST changes)	Death or MI in first 6 days	6day endpoint: 1.8% in dalteparin 4.8% in aspirin only	Lost much effect by 40 days. **NNT: approx. 30** Compare with meta-analysis of

					reg. heparin vs aspirin NNT = approx: 60-80. No increase in major bleeds/

IIb/IIIa Platelet Receptor Blockers

It has become increasing obvious that there is a central role of the platelet glycoprotein IIb/IIIa receptor in the pathogenesis of acute coronary syndrome. Inhibition of this receptor blocks the final common pathway of the platelet aggregation. New monoclonal antibodies and peptide and non-peptide agents that block platelet aggregation via this mechanism. Inpatients undergoing PTCA these agents appear extremely effective. In the routine medical management of USA there is little evidence that they are effective or cost effective.

"SUPERASPIRINS"

Peptides/NonPeptide	Fab Fragment
Eptifibatide (Integrelin)	Abciximab (ReoPro)
Lamifiban	
Tirofiban	

A number of other large trials are now underway or have been recently competed in unstable angina and other coronary syndromes.

- PARAGON: Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organization Network - for the drug ***Lamifiban***

"SUPERASPIRINS"

EPILOG Trial

- 2792 patients, elective or urgent revascularization
- Outcome: Death, MI,Revascularization
- Results: 56% Relative Reduction
  - NNT 15
- Effect sustained to 6 months

NEJM June 1997:ABCiximab:ReoPro

In patients undergoing PTCA, abciximab is associated with real and sustained reduction in death or MI (see also the EPIC trial, CAPTURE trial and IMPACT-II)

The non-FAB Fragment forms in USA and PTCA

PRISM TRIAL

- Effect of Tirofiban on Mortality in USA
- 3232 Patients, 128 sites, 25 countries
- 39% had ECG changes
- Reduced ischemic events at 48 hours
- Effect lost by 30 days

PRISM PLUS TRIAL

- Tirofiban effect on ischemia in USA
- 1915 patients, 72 hospitals, 14 counties
- 90% with ECG changes
- Reduction in ischemic events out to 6 months
- Compare with results of PRISM

PRISM vs. PRISM Plus

- PRISM-Plus showed Tirofiban alone BAD
- PRISM showed Tirofiban alone GOOD
- ***What?***
- PRISM-PLUS had sicker patients
- Both studies show an effect early that diminishes rapidly over time

• The PRISM and PRISM plus trials randomized patients with USA to Tirofiban alone or in combination with Heparin. Though there is some discrepancy in the findings the flowing statements appears true:

- patients at very high risk, ECG's etc, a short term mortality and ischemia benefit is noted. This effect may be prolonged past 30 days in these same high risk patients.

- With holding PTCA in the acute phase of USA, and use of IIb/IIIa inhibitors before and during PTCA in these high risk patients does appear to be associated with the best outcomes

The PURSUIT TRIAL
NEJM Aug 1998

• 11,000 patients, Eptifibatide
• 1.5% MI or death reduction at 30 days
• Non-significant reduction in group not undergoing PTCA

• In patients not undergoing PTCA for USA there is little evidence that any agent results in sustained reduction in MI or death. please see lecture and syllabus by

Mel E. Herbert at this years ACEP conference on IIb/IIIa inhibitors for a more complete discussion on this topic

"SUPERASPIRINS"
Where Do We Stand

- Patients undergoing angiography
- ?? As routine in non-angio-patients
- ?? Sustained effect
- ?? Costs
- Oral compounds

Summary

- Unstable angina a more common reason for admission than MI
- Stratifying patients as to short term risk is essential in targeting therapy
- Aspirin remains (over 100 years after it was first approved in the US) the single most effective and cost effective drug for the treatment of all acute coronary syndromes

Summary

- Risk stratification key to therapy
- Aspirin reminds the gold standard
- LMWH better than regular heparin
- Medical therapy as good as Invasive
- "Superaspirins" work in PTCA patients – but probably not in non-PTCA patients

- Heparin may add benefit in high risk patients, low molecular weight heparin appears more effective, safer and easier to use
- Direct thrombin inhibitors add little if any advantage to therapy with heparin
- Beta blockers should be used where possible, use rate lowering calcium channel blockers in high risk patients when Beta-blockers are contraindicated
- IIb/IIIa inhibitors definitely appear effective in patients undergoing PTCA. In patients with unstable angina it is not clear if these agents give any long term benefit. • Oral IIb/IIIa agents are being developed but early studies show then to be potentially dangerous.

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