Advances in The Treatment of Acute Coronary Syndromes

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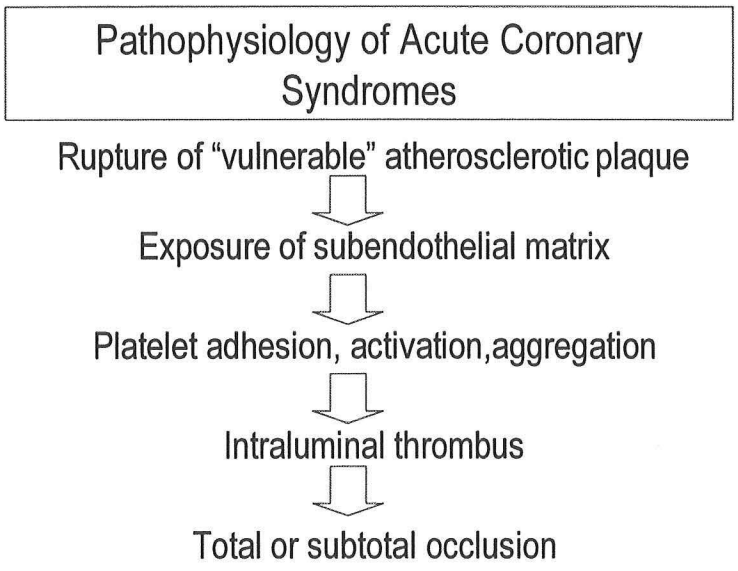
Over the past 2 decades, clinical and pathologic studies have examined the pathophysiology of the so-called acute coronary syndromes -- unstable angina, non-Q-wave (non ST elevation), and Q-wave (ST elevation) myocardial infarction (MI). In patients with these conditions, atherosclerotic plaque rupture leads to a variable amount of platelet adhesion and aggregation, vasoconstriction, and partially or totally occlusive thrombus formation.

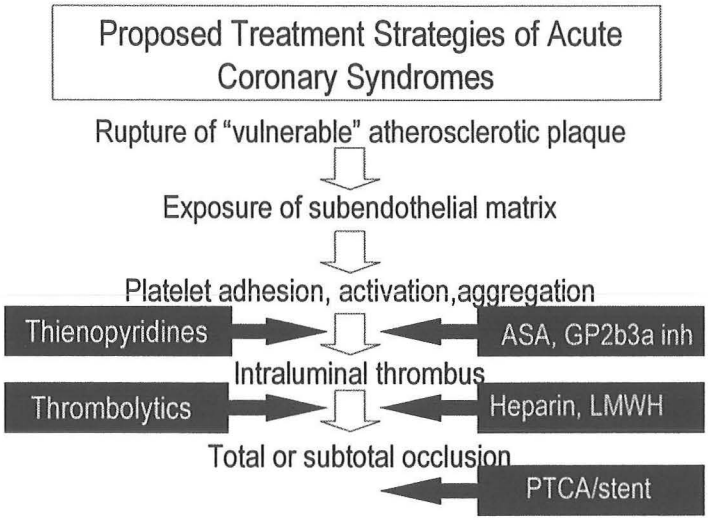


Patients with unstable angina pectoris or non Q-wave MI typically have a nonocclusive coronary thrombus, which is largely composed of aggregated platelets, whereas those with a Q-wave MI have a totally occlusive coronary thrombus, which is largely composed of thrombin and fibrin.

Angiographic and Angioscopic Findings in Acute Coronary Syndromes

	Stable Angina	Unstable angina, NQWMI	Q-wave MI
Angiographic thrombus	0-1%	40-75%	>90%
Stenosis morphology	Smooth	Ulcerated	Occluded
Total coronary occlusion	0-1%	10-25%	>90%
Angioscopy	No clot	White clot	Red thrombus

Based on the pathophysiology of acute coronary syndromes, a number of treatment options have been proposed, including (a) antiplatelet therapy, (b) thrombolytic therapy, (c) antithrombotic therapy, and (d) percutaneous coronary revascularization. The treatment of Q-wave MI -- with thrombolytic therapy or primary angioplasty -- has recently been discussed. Therefore, this discussion will focus on the medical treatment of patients with non Q-wave MI or unstable angina and the role of "invasive" (routine coronary angiography and revascularization) or "conservative" (maximal medical therapy, with catheterization and revascularization reserved for those with spontaneous or provocable ischemia) management.

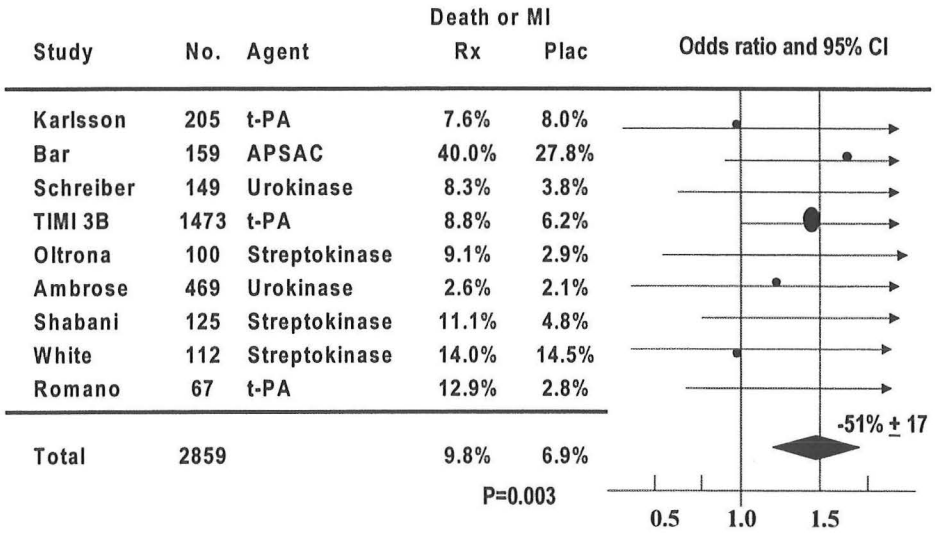


Thrombolytic Therapy

Studies have demonstrated conclusively that timely administration of thrombolytic therapy improves survival in patients presenting with ischemic chest pain and ST-segment elevation or a bundle branch block pattern on their electrocardiogram.[1] These patients usually have an occlusive coronary artery thrombus,[2] and administration of a thrombolytic agent restores antegrade coronary blood flow, thereby salvaging ischemic myocardium. Most patients with non ST-segment elevation MI or unstable angina also have an intracoronary thrombus, which is usually nonocclusive.[3, 4] Studies have shown that the administration of thrombolytic therapy to these subjects decreases the amount of angiographically visible intracoronary thrombus,[4] yet it increases the incidence of death and nonfatal myocardial infarction by approximately 50%.[5]

Additional evidence of the harm associated with thrombolytic therapy in patients with non ST elevation MI comes from the The Fibrinolytic Therapy Trialists' overview[1] of the Second and Third International Studies of Infarct Survival (ISIS-2[6] and ISIS-3[7]), the Gruppo Italiano per lo Studio della Streptochinasi (GISSI[8]), and the Late Assessment of Thrombolytic Efficacy (LATE[9] thrombolytic trials). These studies included 3653 patients with ST-segment depression, and the mortality was 15.2% for those treated with thrombolytic therapy and 13.8% for those not receiving thrombolytic therapy (the 99% confidence intervals ranged from a 12% reduction to a 44% increase in mortality with thrombolytic therapy).

Thrombolytic Therapy in Unstable Angina



Since most patients with non ST-segment elevation MI or unstable angina have an intracoronary thrombus, why is thrombolytic therapy not beneficial in them? The thrombus in these patients is platelet rich,[10] and thrombolytic therapy may be less effective in dissolving it. In addition, thrombolytic therapy generates plasmin and exposes clot bound thrombin, both of which activate platelets.[11, 12] Thus, thrombolytic therapy acts as a procoagulant and may convert a nonocclusive thrombus to an occlusive thrombus.

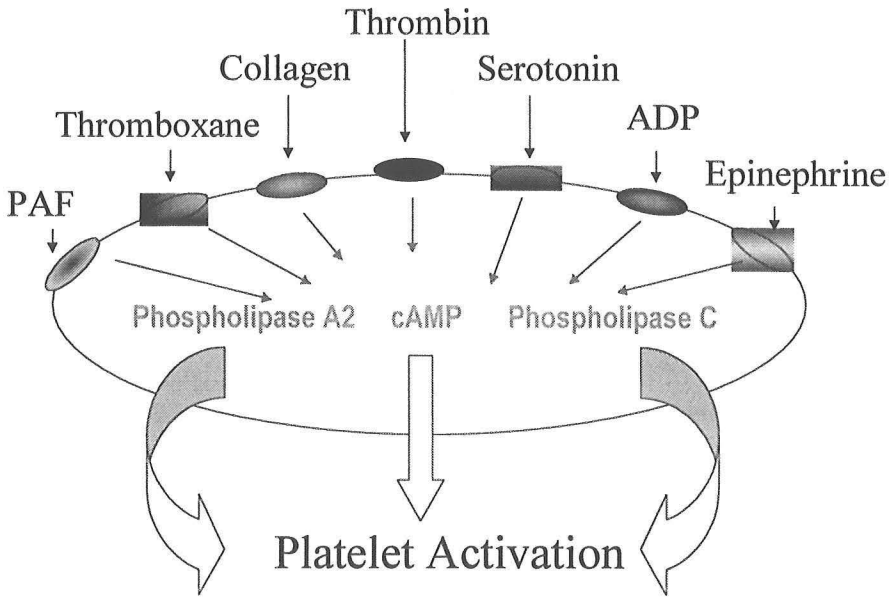
Antiplatelet therapy

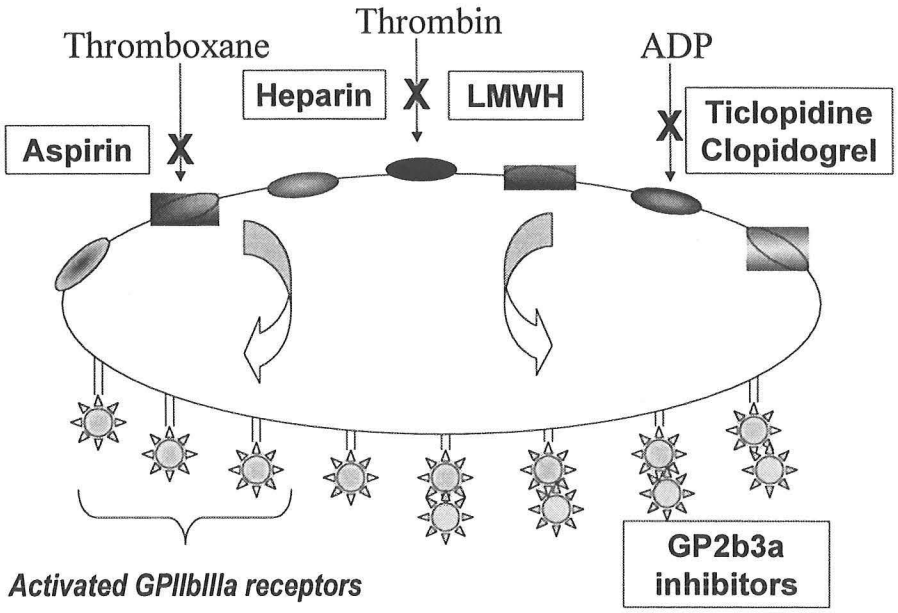
Coronary arterial injury initiates platelet adhesion, activation and aggregation, which promote arterial thrombosis. In response to vessel wall injury, exposed subendothelial von Willebrand factor (vWF) and collagen binds to platelet surface glycoprotein (GP)Ib-IX and 1a receptors. This initiates platelet activation, whereby platelets undergo morphologic changes into "spiny" spheres with long fine, filopodia and release the contents of their intracellular granules. The release of granular contents (i.e., ADP, serotonin, platelet activating factor, and vWF) induces activation of adjacent platelets and coronary arterial vasoconstriction. Activation of the platelet causes the surface GP IIb/IIIa receptors to undergo a conformational change, which expose their ligand binding site. Circulating fibrinogen binds to the activated GP IIb/IIIa receptor and crosslinks it to adjacent platelets, thus causing platelet aggregation.

Platelets in Acute Coronary Syndromes

- Adhesion
  - Glycoprotein 1b-IX or 1a to vWF and collagen
- Activation
  - Morphologic change ("spiny," filopodia)
  - Release of intracellular granules
  - Activation of surface GP2b3a receptors
- Aggregation
  - GP2b3a receptor binds circulating fibrinogen
  - platelet-fibrinogen crosslinking

Platelets can be activated by various agonists, including thromboxane, ADP, thrombin, collagen, vWF, thromboxane A2, serotonin, epinephrine, and platelet activating factor. These compounds bind to specific surface receptors on the platelet and initiate signal transduction pathways that ultimately cause activation of the GP IIb/IIIa receptor, the final common pathway for platelet aggregation. Thus, inhibition of platelet aggregation can be accomplished by interfering with the action of platelet agonists or by inhibiting the GP IIb/IIIa receptor, with the latter being more effective.



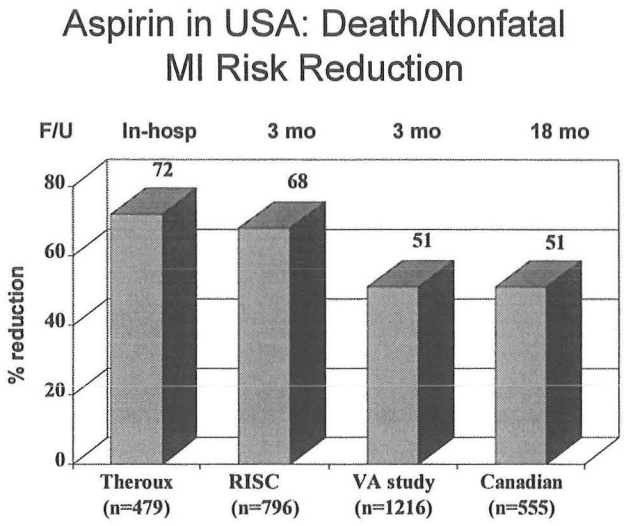


Cycoloxygenase Inihibitor (Aspirin)

Within platelets, aspirin blocks the synthesis of thromboxane A2, a vasoconstrictor and promoter of platelet aggregation, by irreversibly acetylating a serine residue (Ser 529) and thus inhibiting the cyclooxygenase and hydroperoxidase reactions necessary for the production of thromboxane A2. The benefits of aspirin in the treatment of unstable angina have been established in 4 well-controlled trials, 2 of which involved only men [13, 14] and 2 included men and women. [15, 16] In patients with unstable angina, aspirin reduced the risk of nonfatal myocardial infarction or cardiac death by 50 to 70%.

Aspirin in Unstable Angina

			Death & Nonfatal MI		
Trial	**Dose**	**Follow-up**	**Placebo**	**ASA**	**P value**
VA Coop (n=1338)	**325mg**	**3 mo**	**10.1%**	**5%**	**0.0005**
Canadian (n=555)	**1300mg**	**24mo**	**17%**	**8.6%**	**0.008**
Theroux (n=479)	**650mg**	**6d**	**12%**	**3.3%**	**0.01**
RISC (n=652)	**75mg**	**30d**	**13.4%**	**4.3%**	**0.0001**



The incidence of side effects with aspirin is relatively low, with the major toxicity being gastrointestinal bleeding. Its incidence is dose dependent and has ranged from 0.9% over 1 year in patients receiving 75 mg to 4.7% over 3 years in patients receiving 1200mg.[17]. Although aspirin is a potent inhibitor of platelet aggregation induced by arachidonic acid, it is a weak inhibitor of platelet aggregation induced by other agonists, such as ADP, thrombin, or epinephrine.

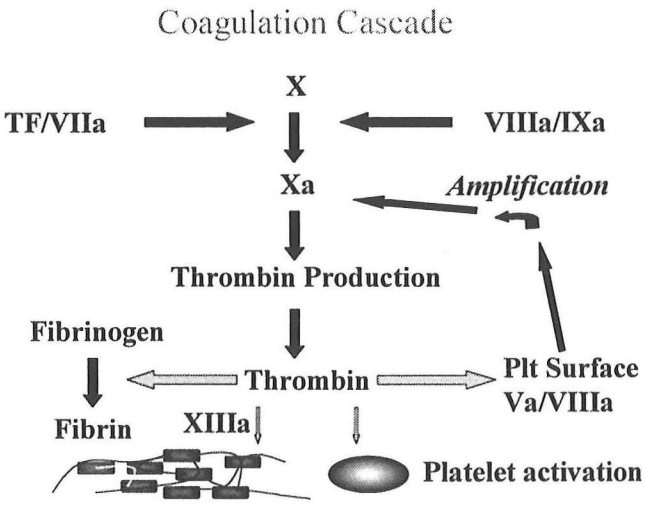
ADP Antagonists (Ticlopidine and Clopidogrel)

Ticlopidine (Ticlid) and Clopidogrel (Plavix) are thienopyridine derivatives that inhibit the binding of ADP to its receptor on platelets. The full antiplatelet effect of these agents requires 3 to 5 d of oral administration and persists for 4-8 days after drug discontinuation. Little is known about the efficacy of thienopyridines for the treatment of acute coronary syndromes. In an open trial,[18] 652 patients with unstable angina or non Q-wave MI were randomized within 48 hrs of hospital admission to receive either ticlopidine (250mg twice daily) or "standard therapy" which did not include aspirin or heparin. Ticlopidine had no beneficial effects at 15 days; at 6 months, cardiovascular mortality and nonfatal MI were reduced from 13.6% to 7.3% ($p<0.01$). Because of its delayed onset of action (3-5 days for maximal antiplatelet effect), ticlopidine is not recommended as initial platelet therapy for patients with unstable angina. It may be considered, however, for the patient with aspirin allergy. Severe hematologic abnormalities have been associated with the use of ticlopidine (e.g., thrombotic thrombocytopenia and agranulocytosis),[19, 20] so patients must receiving it must be monitored closely.

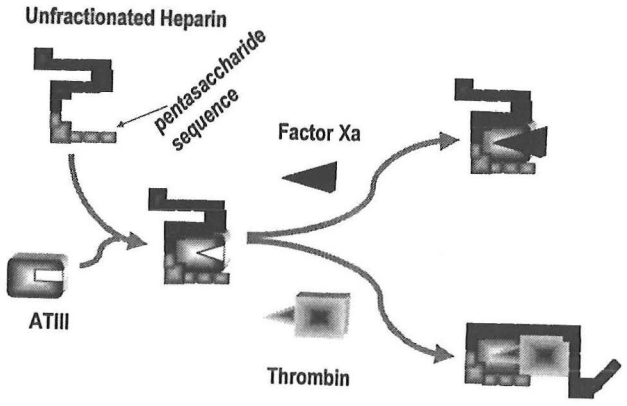
The combination of clopidogrel and aspirin is administered to patients having an intracoronary stent placed, as studies have shown this combination effective in decreasing acute stent occlusion over the subsequent month. However, no data are available regarding clopidogrel use in the treatment of patients with acute coronary syndromes. Such data will be available when the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study is completed. In this study, 9000 patients with non-ST segment elevation MI will be treated with aspirin and randomized to receive placebo or clopidogrel for 12 months in order to determine if clopidogrel use reduces the subsequent incidence of death or myocardial infarction.

Antithrombotic Agents (Unfractionated Heparin)

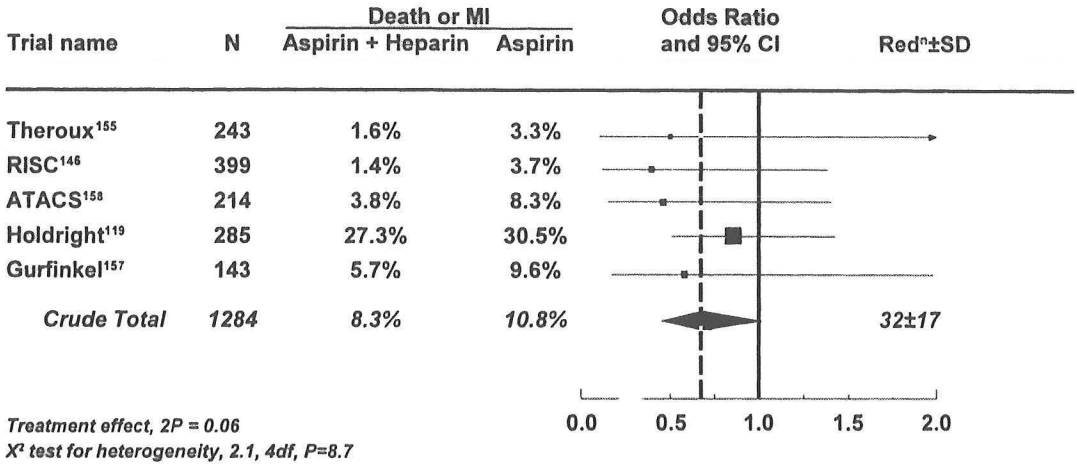
Antithrombotic agents are administered in the setting of acute coronary syndromes to prevent (a) continued activation of the coagulation cascade with additional thrombus formation and (b) platelet activation by thrombin, the most potent endogenous platelet activator identified. In addition to converting fibrinogen to fibrin, thrombin activates factor XIII which stabilizes the fibrin clot. Thrombin also activates factor V and VIII which promote further thrombin generation. As a potent platelet agonist, thrombin activates platelets and stimulates formation of a platelet-rich thrombus.



Heparin is the most commonly used antithrombotic agent. Commercial preparations of heparin are obtained from bovine or porcine sources (lung, liver, and intestinal tissue) and is a heterogeneous mixture of sulfated polysaccharides (e.g., glycosaminoglycans) ranging in weight from 3,000 to 30,000 Daltons. Its anticoagulant effects are dependent upon a specific pentasaccharide unit that binds to antithrombin III (AT-III). This binding induces a conformational change in AT-III, which greatly enhances its ability to inhibit thrombin (factor IIa) and factor Xa, thus activation of the coagulation cascade. AT-III bound heparin molecules must be of sufficient length (>18 saccharide units) and weight (> ~5400 Dalton) to form a ternary complex, which effectively binds to and inhibits factor IIa. Smaller AT-III bound heparin molecules (<18 saccharide units) can bind to and inhibit factor Xa, but not thrombin. Unfractionated heparin inhibits factors IIa and Xa to a similar extent, so that it possesses an antifactor Xa: antifactor IIa ratio of 1:1.



A number of trials have compared the use of standard heparin to placebo or aspirin in subjects with unstable angina.[14, 16, 21-24] Heparin has been shown to be superior to aspirin in relieving angina,[16, 25, 26] but there has been controversy as to whether the addition of unfractionated heparin to aspirin therapy reduces mortality and the incidence of myocardial infarction. Six randomized studies involving 1353 patients have compared heparin to control in aspirin treated patients with unstable angina or non Q-wave MI. Although individual studies did not show a significant reduction in the composite endpoint of death or MI, each demonstrated a trend toward benefit with unfractionated heparin therapy.



Results of trials comparing the combination of aspirin plus unfractionated heparin with aspirin in patients with unstable angina.

In a pooled analysis of these studies,[27] the incidence of nonfatal MI or death at weeks was 7.9% for those receiving combined heparin-aspirin therapy and 10.4% for those treated with aspirin alone during the first week of treatment (p=0.045); a relative risk reduction of 33%. The benefit was due almost entirely to a reduction in the risk of non-fatal MI. Compared to control, heparin therapy did not reduce the risk of recurrent ischemia 17.3% vs 22.6% (p=0.08), or revascularization procedures (1.25 [0.76-2.06]), but it was associated with a nonsignificant increase in major bleeding (1.5 % vs 0.4, respectively; p=0.28. Thus, while the data do not clearly show that aspirin plus heparin is superior to aspirin alone, there is a strong trend in support of this notion.

There is considerable disagreement as to the appropriate duration of heparin administration due, at least in part, to the fact that there are limited data available regarding the optimal duration of therapy. When administered for 6 or 7 days, heparin therapy was associated with a decreased incidence of death or MI.[16, 25, 28] In 2 studies in which heparin was administered for 2 days, it had no effect on myocardial ischemia or the incidence of MI or death.[23, 29]

Following cessation of heparin therapy, there may an increase in the frequency of myocardial ischemic events (so called "heparin rebound").[26, 30, 31] In the Montreal study,[30] there was a recurrence of angina a median of 9.5 hours after heparin was

discontinued. When heparin is discontinued, increased thrombin generation is observed within hours.[32]

Antithrombotic Agents (Low Molecular Weight Heparins)

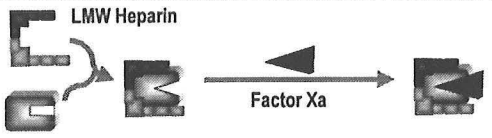
There are several limitations to the use of standard, unfractionated heparin. First, the heparin-ATIII complex does not inactivate factor Xa that is bound to platelets or thrombin that is bound to fibrin within the thrombus.[33] Thus, fibrin bound thrombin remains enzymatically active and may promote thrombus growth by activating local platelets and amplifying the coagulation cascade.[33, 34] Second, heparin binds to and is inactivated by a number of plasma proteins, including platelet factor 4 and thrombospondin (which are released in large quantities during platelet degranulation) and vitronectin.[35] Therefore, the use of heparin in platelet rich arterial thrombus may be limited. Third, the pharmacodynamic properties (e.g., inconsistent dose-response relation) of heparin make it difficult to achieve and maintain adequate therapeutic levels. Thus frequent laboratory monitoring of the activated partial thromboplastin time is necessary.

Limitations of Heparin

- Unable to inhibit fibrin-bound thrombin or platelet-bound Xa
- Unpredictable dose-response
  - Binds to endothelium and serum proteins
  - Inactivated by platelet products (e.g. PF4)
  - Requires frequent monitoring of aPTT
- Associated thrombocytopenia

Low Molecular Weight Heparin

- Prepared by digestion of heparin
- MW 4,000-6,500
- Binds and activates antithrombin III (1000x)
- Preferentially inhibits factor Xa > thrombin

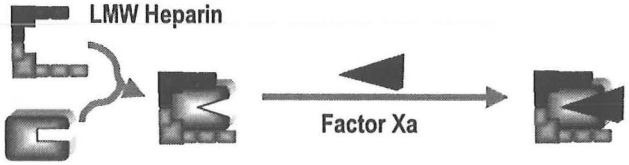


Low molecular weight heparins (LMWHs) are fragments of heparin (molecular weights of 4,000 to 6,500 Daltons) that are prepared by digesting heparin enzymatically, physically, or chemically. Most (50-75%) of LMWH molecules are <18 saccharide units long, so they are much more effective in inhibiting factor Xa than thrombin. The anti-Xa to antithrombin ratio is 2-4:1 for the various LMWHs. They can be administered subcutaneously - where they attain antithrombotic levels within 30 minutes of administration – or intravenously.

The LMWHs have several advantages over heparin. Because they do not bind plasma proteins (such as PF4, vWF, or thrombospondin) or endothelial cells, they are not neutralized, and their anticoagulant response is more predictable than heparin. Therefore, laboratory monitoring is not required. Second, LMWHs have a prolonged half life (4 hours), so they can be administered twice daily. Third, they can inhibit platelet bound factor Xa. Finally, heparin-induced thrombocytopenia occurs less frequently with LMWH.[34] Nevertheless, it should be avoided in the patient with known heparin-induced thrombocytopenia. LMWHs are cleared via the kidneys and generally should be avoided in patients with renal dysfunction.

Low Molecular Weight Heparin

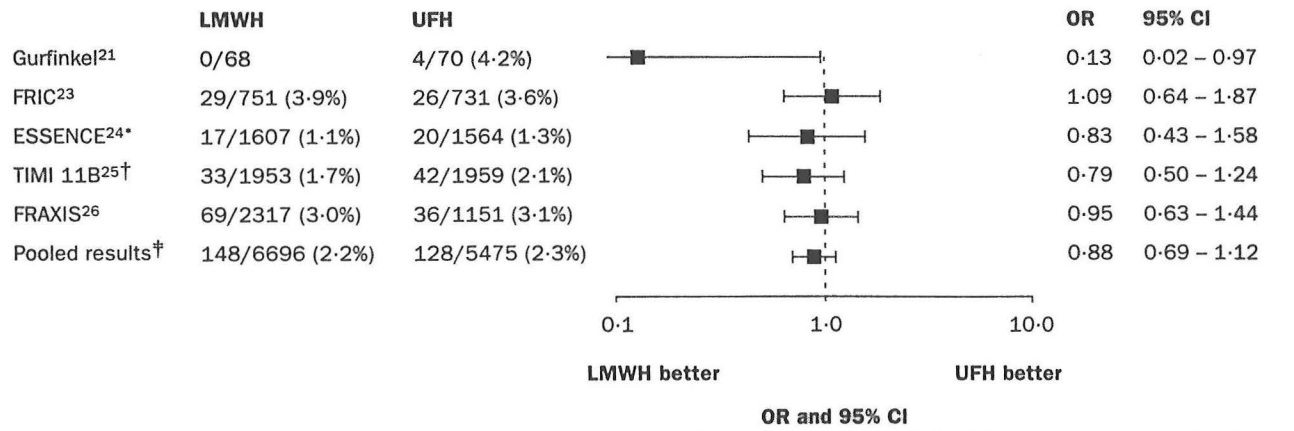
- More predictable anticoagulation (less binding to endothelium, PF4, vWF, thrombospondin, etc)
- Long half-life (3-6hrs)
- Reduced thrombocytopenia (<0.2 vs 2.6%)
- Inhibits fibrin-bound thrombin
- Does not prolong pTT (monitoring unnecessary)



In two placebo-controlled trials involving 1639 aspirin-treated patients,[24, 36] short-term (6 day) LMWH administration was associated with a 66% reduction in the incidence of death or myocardial infarction (from 5.2% to 1.6%; p=0.009).[37] The benefit was almost entirely due to a reduction in nonfatal myocardial infarction, with just one fewer death in the LMWH group than in the control group. Thus, the combination of LMWH and aspirin is superior to aspirin alone in preventing recurrent myocardial infarction.

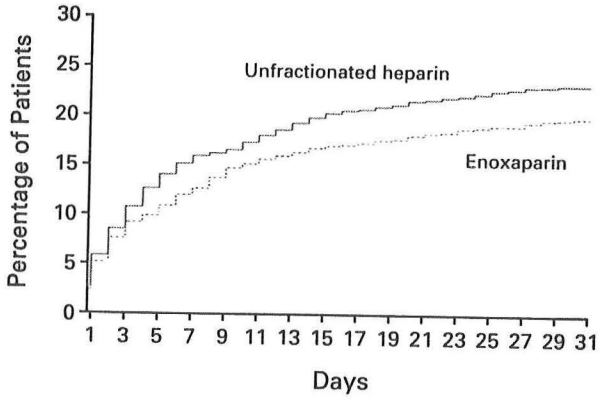
Since heparin is considered standard-of-care therapy for acute coronary syndromes, it is important to determine if there are advantages to using LMWH instead. Five trials[24, 38-41] involving 12,171 subjects compared short term (< 8 days) LMWH to unfractionated heparin in patients with unstable angina or non ST segment elevation myocardial infarction (Figure 2 of Eikelboom article). Three different LMWHs were studied, and overall, their use did reduce the incidence of death or myocardial infarction at 30 days.[37] However, the two trials conducted with enoxaparin --and a subsequent meta-analysis of these two trials -- did produce significant findings.[42]

Study	No.	Drug	Duration	Long-term	Endpts
Gurfinkel	138	Nadroparin	7d	No	Death, MI, Rec angina, Urgent revasc
FRIC	1482	Dalteperin	6d	40d	Death, MI, Rec angina
ESSENCE	3171	Enoxaparin	<8d	No	Death, MI, Rec angina
TIMI 11B	3910	Enoxaparin	<8d	35d	Death, MI, Urgent revasc
FRAXIS	3468	Nadroparin	6d	14d	Death, MI, Rec angina



Death or myocardial infarction at the completion of treatment in randomised trials of short-term low-molecular-weight heparin compared with unfractionated heparin in acute coronary syndrome without ST elevation

The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study (ESSENCE) trial[39] randomized 3171 patients with unstable angina or non ST-elevation MI to receive subcutaneous enoxaparin (1 mg/kg BID) or intravenous heparin onset for 8 days or until hospital discharge. Enoxaparin use was associated with a significant reduction in the composite endpoint of death, MI, or recurrent angina at 14 days and at 30 days. A reduction in recurrent angina accounted for most of the benefit. In addition, the group that received enoxaparin had a 16% lower incidence of urgent revascularization (PTCA or coronary artery bypass surgery) at 30 days. Major bleeding complications were similar for the enoxaparin and heparin treated patients. One year follow-up data demonstrated that the benefits of enoxaparin did not diminish with time.[43]



Kaplan–Meier Plots of the Time to a First Event over a Period of 30 Days for the Composite End Point of Death, Myocardial Infarction, or Recurrent Angina.

ESSENCE Study: 1 Year Outcome

	Heparin	Enoxaparin	p
Death/MI/AP	35.7%	32%	0.022
Death/MI	13.5%	11.5%	0.08
Dx Caths	59.4%	55.8%	<0.05
Revasc	41.2%	35.9%	<0.05

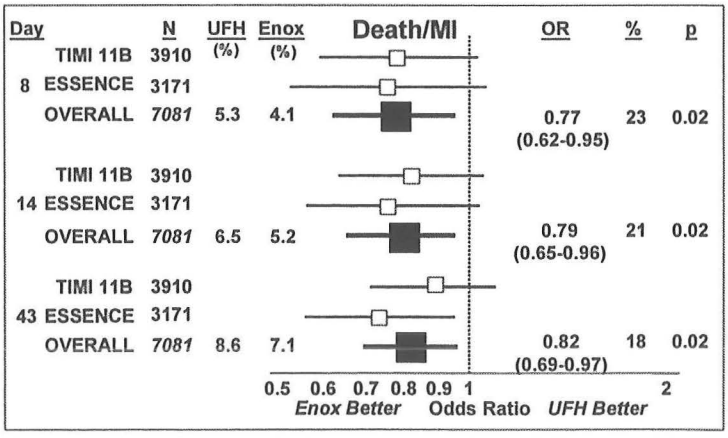
The Thrombolysis in Myocardial Infarction (TIMI)-11B trial was a randomized comparison of 3910 patients with unstable angina or non Q-wave MI. Patients received up to 8 days of weight-adjusted intravenous heparin or enoxaparin (30 mg IV bolus, then 1 mg/kg SQ BID, then up to 43 days of low-dose therapy at 40 or 60mg SQ BID). The enoxaparin was administered in such a manner to ascertain whether (a) enoxaparin was superior to heparin when administered during the hospitalization and (b) administration of enoxaparin beyond hospitalization resulted in incremental benefit. The primary endpoint was the composite of death, myocardial infarction, or the need for urgent revascularization. At, 8d, 14d, and 43 days, the relative risk reductions were 14%, 14%, and 12%, respectively (Figure). Prolonged administration of enoxaparin did not add additional benefit. As in the ESSENCE trial, there was no significant reduction in the incidence of death or MI; a reduction in the need for urgent revascularization accounted for most of the benefit observed with enoxaparin.

TIMI 11B Endpoints at 43 days

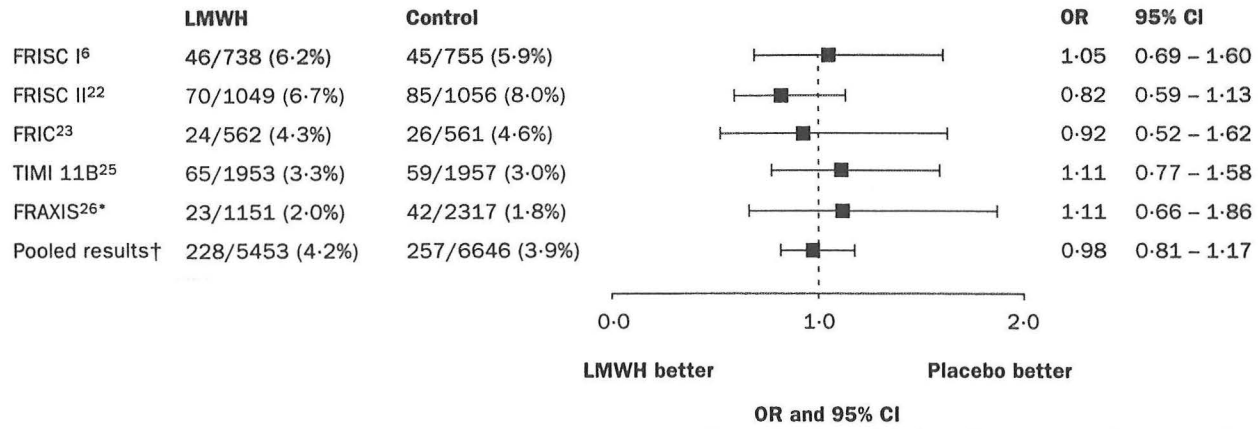
	LMWH (n=1957)	UFH (n=1953)	p value
Death/MI/Urgent Revascularization (%)	19.7	17.3	0.048
Death/MI (%)	8.9	7.9	0.28
Death (%)	4	3.8	0.81
MI (%)	6.6	5.5	0.14
Revascularization (%)	12.6	10.7	0.05

Neither the TIMI-11b or ESSENCE studies reported a significant reduction in death or myocardial infarction, but a pooled analysis[42] of both trials found that this endpoint was reduced by approximately 20% at 8, 14, and 43 days at the risk of increased minor bleeding (4.3% vs 10.0%; p<0.0001).

ESSENCE -TIMI 11B Meta-Analysis



Since resolution of intracoronary thrombus and healing of the underlying ruptured plaque may take weeks for completion, it has been proposed that long-term administration of LMWH may be necessary for the patient with an acute coronary syndrome. Five trials[36, 38, 40, 41, 44] have evaluated the benefit of long-term (35-40 days) administration of LMWH and found that continuing LMWH therapy beyond 7 days confers no benefit (no reduction in death or myocardial infarction, recurrent angina, or need for revascularization), but it is associated with an increased risk of major bleeding (excess of 12 major bleeds per 1000 patients treated).[37]



Death or myocardial infarction in randomised trials of long-term low-molecular-weight heparin compared with placebo in acute coronary syndrome without ST elevation (only includes events that occurred during long-term therapy)

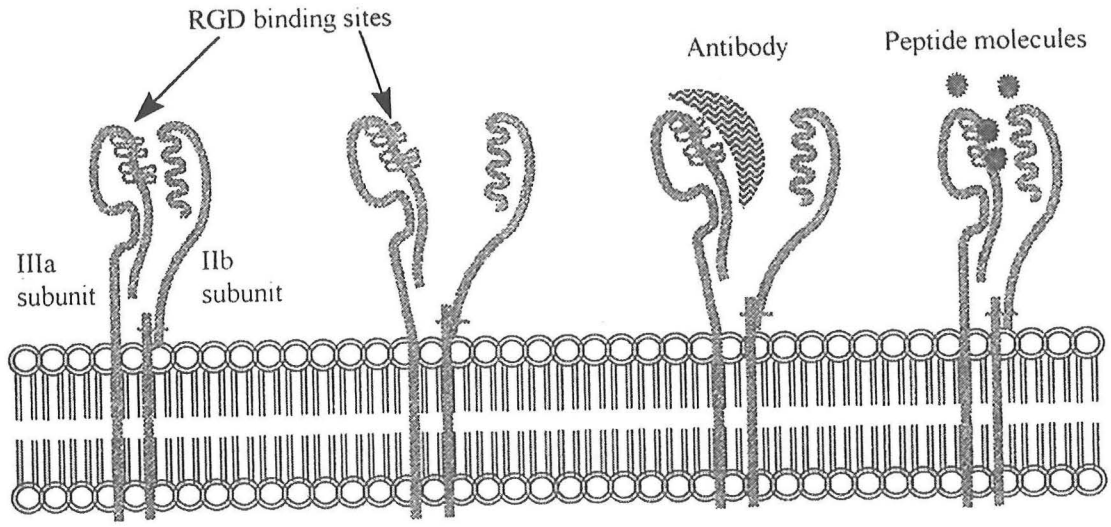
In summary, short-term subcutaneous enoxaparin administration may be superior to intravenous heparin in the treatment of acute coronary syndromes. Although some experts[37, 45] feel that there is a lack of compelling evidence (such as a meta-analysis with a p-value of <0.01) for a reduction in hard clinical endpoints (e.g., death or myocardial infarction) with enoxaparin use, a strong argument can be made for it use based upon its convenience and cost.[46] Although enoxaparin is more expensive than heparin (~ $155 vs $80), one study suggested that its use in unstable angina patients reduced total medical costs approximately $700. There are some disadvantages to using LMWH in the patient with an acute coronary syndrome. First, there is no convenient way to assess or monitor the status of anticoagulation in the patient who is referred for percutaneous intervention. Second, if bleeding complications occur, protamine is effective in reversing only some (30-60%) of the anticoagulant effects of LMWHs when used on a milligram for milligram basis.[47]

Glycoprotein IIb/IIIa antagonists

The GP IIb/IIIa receptor is a member of the integrin family, which are heterodimeric cell adhesion molecules. This receptor is found only on platelets and megakaryocytes and is responsible for platelet aggregation. It binds fibrinogen which crosslinks to other platelets via their GP IIb/IIIA receptors. The GP IIb/IIIa receptor contains two domains responsible for ligand binding. One domain is on the beta (IIIa)

subunit and its ligand is the peptide sequence arginine-glycine-aspartate (RGD) sequence, which is found on the alpha-chain of fibrinogen as well as fibronectin, vitreonectin, vWF, and thrombospondin. The other domain is on the alpha (IIb) subunit, and its ligand is the dodecapeptide HHLGGAKQAGDV, which is found only on the gamma chain of fibrinogen.

Resting platelets have 70,000-80,0000 GP IIb/IIIa molecules on their surface, which are in equilibrium with a pool of additional GP IIb/IIIa molecules stored in platelet alpha-granules. In their resting state, the GP IIb/IIIa molecules do not bind circulating fibrinogen. However, when the platelet is activated by an agonist, the GP IIb/IIIa receptor undergoes a conformational change, which exposes the ligand binding sites to circulating fibrinogen (see figure below).[48] Platelet cross-linking occurs when adjacent platelets with activated GP IIb/IIIa receptors bind to the same fibrinogen molecule. Some individuals have congenital absence of functional GP IIb/IIIa receptors, so called Glanzmann's thrombasthenia. Individuals with this autosomal recessive disorder have platelets that are normal in morphology and number and able to bind to subendothelial matrix (via GP1b-IX and 1a receptors). However, the platelets are unable to aggregate. Frequent and severe mucosal bleeding is the clinical manifestation of this condition.



GPIIb/IIIa receptor antagonists inhibit platelet aggregation by occupying the ligand binding site, thereby preventing fibrinogen binding and platelet cross-linking. By standard quantitative platelet aggregation studies, >90% platelet inhibition can be obtained with GP IIb/IIIa receptor antagonists. This compares to ~10% platelet inhibition with aspirin and ~30% platelet inhibition with the thienopyridines (clopidogrel or ticlopidine). Three GP IIb/IIIa receptor antagonists are currently FDA approved for use in the United States: Abciximab (ReoPro; Centocor, Malvern, PA), Tirofiban

(Aggrastat; Merck, West Point, PA), and Eptifibatide (Integrilin, Cor Therapeutics, South San Francisco, CA) (Table).

In 1985 a mouse monoclonal antibody against the human GP IIb/IIIa receptor was produced (so called 7E3).[49] In clinical trials, it caused profound thrombocytopenia. Subsequently, the Fab fragment of the murine monoclonal antibody was attached to the Fc region of a human antibody to form a chimeric antibody, known as abciximab (or c7E3). Abciximab binds to the beta (IIIa) subunit of the activated GP IIb/IIIa receptor and other integrins with the same beta subunit (e.g., vitronectin) avidly and irreversibly. Thus, it has an extremely long biologic half-life. One week following administration of abciximab, as many as 50% of GP IIb/IIIa receptors are blocked.[50] Since it is a chimeric antibody, abciximab is immunogenic. With the first administration of abciximab, ~6.5% of subjects develop a human antichimeric antibody (HACA).[51] With repeat administration, 25% of subjects have detectable HACA.[52] One-fifth of patients with HACA develop profound thrombocytopenia with abciximab administration.[53] Hence, repeat use of abciximab is not routinely recommended.

Synthetic GP IIb/IIIa receptor inhibitors have been engineered which mimic the RGD sequence found on the fibrinogen molecule. Tirofiban is a peptidomimetic agent with the geometric, stereotactic, and charge characteristics of the RGD sequence. Eptifibatide is a cyclic heptapeptide derived from the venom of the southeastern pigmy rattlesnake (*Sistruris M. barbouri*). The molecular structure of this venom was modified by substitution of lysine for arginine (thus a KGD sequence), enhancing its specificity for the GP IIb/IIIa receptor, whereas cyclization of the amino acid sequence enhanced the antiaggregatory potency of the compound.[48] Tirofiban and eptifibatide are often referred to as "small molecule" GP IIb/IIIa receptor inhibitors (molecular weights ~500 Daltons, as opposed to >47,000 Daltons for abciximab). They are highly specific, competitive GP IIb/IIIa receptor inhibitors with a short duration of action; platelet function returns to normal within 2-4 hours of drug cessation. Unlike abciximab, they are nonimmunogenic and, thus, less likely to cause thrombocytopenia.

In patients with acute coronary syndromes, substantial benefits are achieved with modest platelet inhibition with aspirin. Accordingly, there is substantial interest regarding whether more potent platelet inhibition further improves morbidity and mortality. Accordingly, 5 studies have studied the efficacy of GP2b3a inhibitors in patients with unstable angina or non-Q wave myocardial infarction.[54-56]

Outcome of Death/MI in Clinical Trials of GP IIb/IIIa Inhibitors in ACS Trials

Trial	No. pts	Drug	Placebo (%)	GP2b3a (%)
Prism	3232	Tirofiban	7.1	5.8
Prism-PLUS	1914	Tirofiban	11.9	8.7*
Pursuit	10,948	Eptifibatide	15.7	14.2*
Paragon	5200	Lamifiban	11.7	10.6
GUSTO 4	7800	Abciximab	8.0	8.7

* $p<0.05$

Administration of tirofiban to the patient presenting with an acute coronary syndrome has been shown to improve early and long-term outcome. In the PRISM PLUS study,[54] 1915 unstable angina or non Q-wave MI patients treated with aspirin and heparin were randomized to receive (a) placebo or (b) tirofiban (0.4 ug/kg bolus followed by 0.10 ug/kg/min infusion) for 48 hours. Thereafter angiography was encouraged (performed in 89% of the patients) and revascularization left to the discretion of the physician. If PTCA was performed, tirofiban infusion was continued for an additional 12-24 hours. The administration of tirofiban was associated with a 34% reduction in the rate of death, MI, or recurrent refractory ischemia at 7 days (primary endpoint) (12.9% vs 17.9%, p=0.004) The benefits of tirofiban were observed early (within 48 hours of administration and before revascularization was attempted) and were maintained at the 6 month follow-up period. Furthermore, in subgroup analysis, the benefits were present across all patient subgroups. Of the endpoints assessed, tirofiban decreased myocardial infarction and refractory ischemia, but it did not affect mortality. Importantly, the rate of major hemorrhage or intracranial hemorrhage was not increased in patients treated with tirofiban.

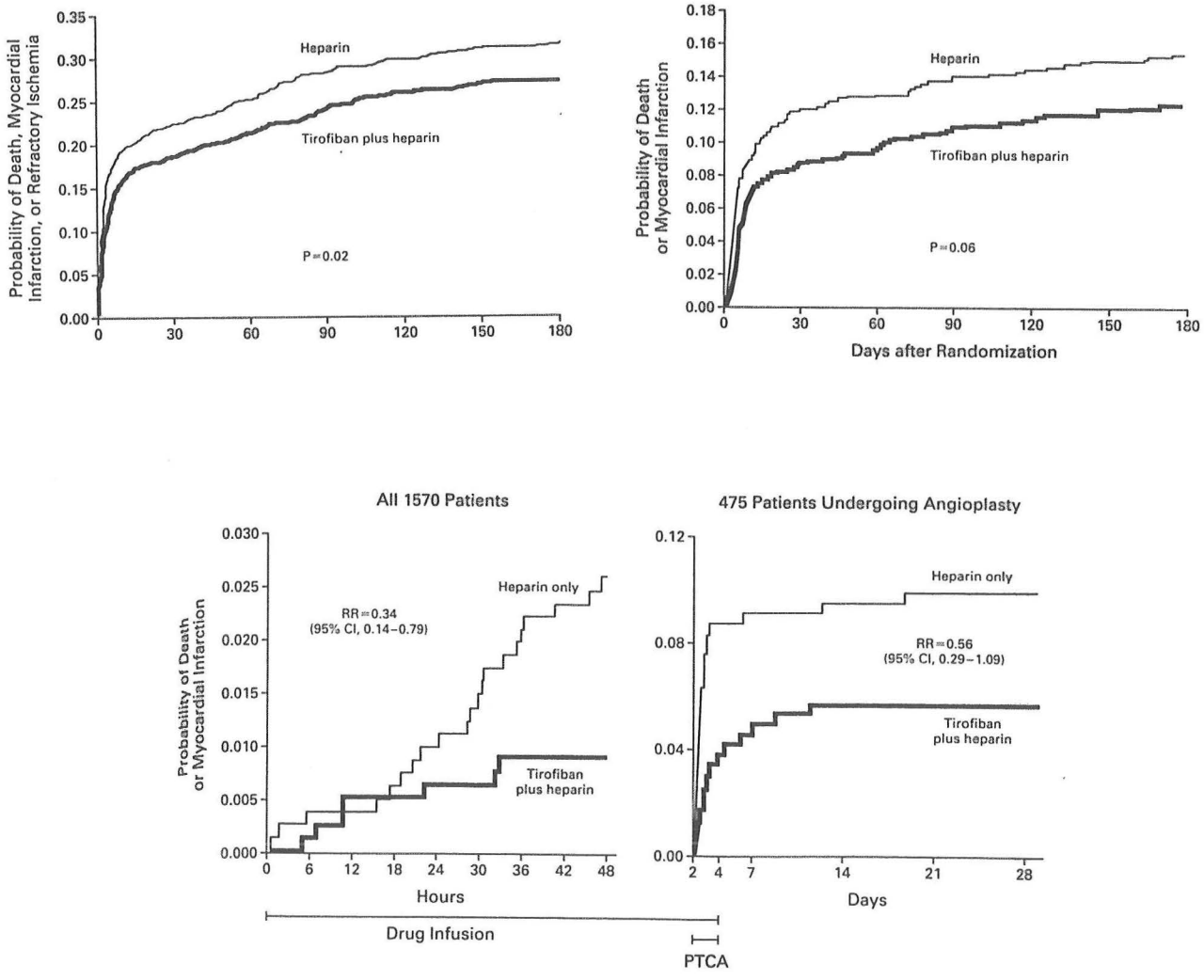
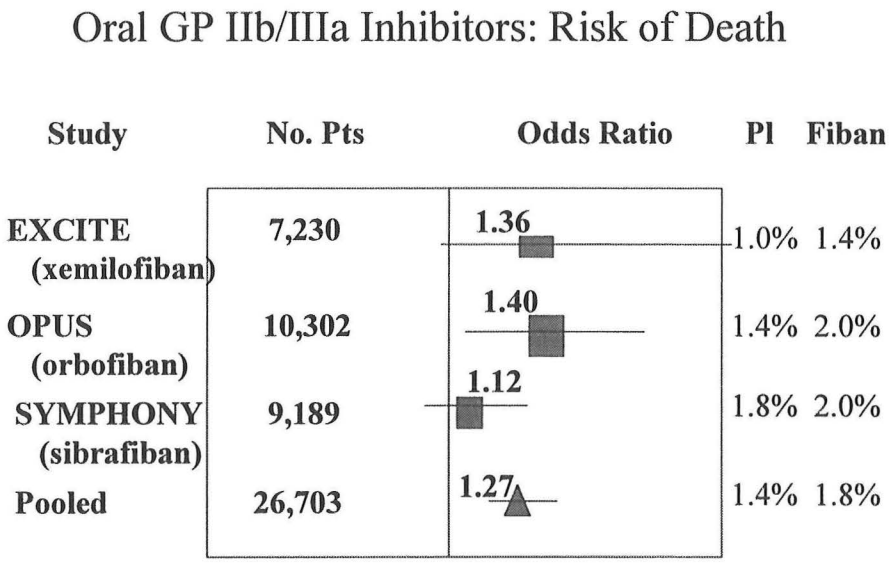


Figure 3. Kaplan–Meier Curves Showing the Cumulative Incidence of Death or Myocardial Infarction among Patients Randomly Assigned to Heparin or to Tirofiban plus Heparin.

Studies of other GP2b3a inhibitors in patients with unstable angina have shown mixed results. Prolonged infusion of abciximab, which has proven efficacy in patients undergoing percutaneous revascularization, did not reduce adverse cardiac events in the GUSTO-4 study of 7800 unstable angina patients. Nor has lamifiban – another peptidomimetic GP2b3a inhibitor – proven efficacious. In one of the largest trials – the PURSUIT trial[55] - 10,948 patients with unstable angina or non-Q wave MI were treated with aspirin and heparin and randomized to (a) placebo or (b) eptifibatide (bolus + 72 hour infusion). Eptifibatide was associated with a lower 30-day event rate of death or nonfatal MI (14.2% vs 15.7%, p=0.04) that trended towards significance (p=0.06) at the 6 month follow-up. The benefit was confined only to patients who subsequently underwent percutaneous revascularization; those who were treated medically or underwent coronary artery bypass surgery received no benefit from eptifibatide treatment. The disappointing results from these studies may represent differences in the GP2b3a inhibitors or insufficient dosing to achieve adequate platelet inhibition.

Since short-term (<72hrs) administration of GP2b3a inhibitors is effective in reducing early cardiac events in the unstable angina patient, it was hypothesized that long-term therapy (for 3-6 months) would provide additional benefit. Accordingly, several pharmaceutical companies synthesized GP2b3a receptor inhibitors that could be taken orally. Studies of long-term administration of oral GP2b3a inhibitors have demonstrated worse outcome with these drugs.



Patient Selection

Patients with unstable angina or non Q-wave MI present with a wide spectrum of risk for death and cardiac ischemic events. Recent studies have focused on identifying the "high

risk" patients that are most likely to benefit from newer, more intensive therapies (i.e., LMWH and GP IIb/IIIa inhibitors). For example, several studies[57-59] of patients with unstable angina have demonstrated that the serum level of cardiac troponin T or I provides useful prognostic information and permits the early identification of patients with an increased risk of death or nonfatal myocardial infarction. In an attempt to develop a simple risk score with broad applicability that is easily calculated at patient presentation, investigators analyzed the 7081 subjects enrolled in the TIMI 11b and ESSENCE enoxaparin trials.[60]

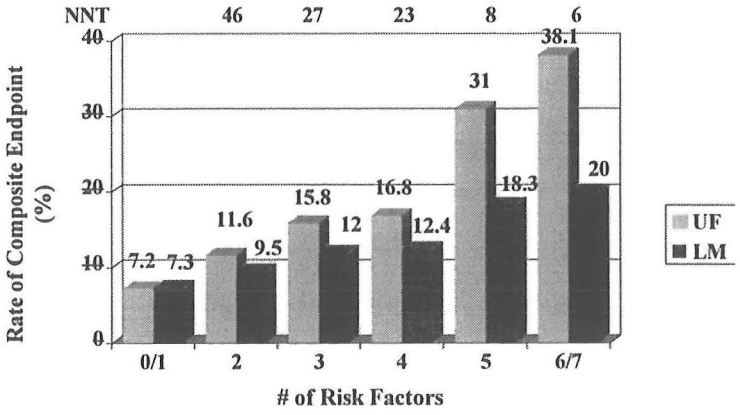
Seven clinical characteristics were identified as providing prognostic information. A TIMI "risk score" is obtained by summing the number of factors present. Cardiac event rates increased significantly as the TIMI risk score increased, and there was a significant interaction between the risk score and treatment.

The TIMI Risk Score for Unstable Angina/Non-ST Elevation MI
Antman et al, JAMA 2000:284;835

	P value	OR
• Age < 65 yrs	<0.001	1.75
• ≥ 3 risk factors for CAD	0.003	1.54
• Coronary stenosis ≥50%	<0.001	1.70
• ST deviation	0.005	1.51
• ≥ 2 anginal events/24hrs	0.001	1.53
• Aspirin use in past 7d	0.006	1.74
• Elevated cardiac markers	<0.001	1.56

Patients with low "risk scores" (TIMI score ≤2) had a low risk of adverse cardiac events and did not benefit from more intensive medical therapy with LMWH. Patients with "intermediate"(TIMI score 3-4) or "high" (TIMI score 5-7) scores did benefit from LMWH therapy. Thus the TIMI risk score categorizes a patient's risk of death and ischemic events and provides a basis for therapeutic decision making.

The TIMI Risk Score for Unstable Angina/Non-ST Elevation MI: The ESSENCE Study, n=3171
Antman et al, JAMA 2000:284;835



Invasive vs Conservative Strategy

Medical therapy to inhibit platelet and thrombus formation has proven effective in improving survival and preventing recurrent ischemia and infarction in patients with acute coronary ischemic syndromes. Nevertheless, residual coronary stenosis may lead to recurrent ischemia, infarction and death. Thus, there has been considerable interest in performing cardiac catheterization and prompt revascularization routinely in patients with unstable angina.

Four prospective studies have compared early "aggressive" therapy with early 'conservative," ischemia-guided therapy in patients with unstable angina or non-Q wave myocardial infarction to determine if it reduces subsequent cardiac events. The initial studies failed to demonstrate a decrease in mortality or nonfatal myocardial infarction with PTCA. However, the more recent studies have shown that an early invasive strategy is superior to a non-invasive approach, particularly in subjects considered not to be "low" risk. Stents and conjunctive GP2b3a receptor inhibitor therapy were utilized in the most recent studies, whereas they were not in the initial studies. These are known to decrease the incidence of urgent target revascularization, myocardial infarction, and restenosis and probably account for the reason the more recent trials have shown that invasive treatment is preferable.

In the ***TIMI IIIB study***, 1473 patients presenting within 24 hours of the onset of ischemic symptoms were prospectively randomized to an early invasive strategy (coronary arteriography within 18-48 hours followed by revascularization when the coronary anatomy was suitable) or an early conservative strategy (coronary arteriography and revascularization if initial medical therapy failed). All patients were treated with bed rest, aspirin, intravenous heparin, and anti-ischemic medications.

Overall, patients with unstable angina and non-Q wave myocardial infarction had low 6 week mortality (2.4%) and myocardial infarction or reinfarction (6.3%) rates. In the comparison of early invasive and early conservative therapy, the incidence of death and nonfatal myocardial infarction was similar for the two treatment strategies. The prespecified composite primary endpoint (death, myocardial infarction, or a positive exercise stress test at 6 weeks) occurred with similar frequency in both groups at 6 weeks (early invasive, 16.2%, early conservative, 18.1%; P=0.33). At one year [61], the incidence of death, nonfatal myocardial infarction, death or myocardial infarction, and duration of repeat hospitalization did not differ between the two treatment strategies.

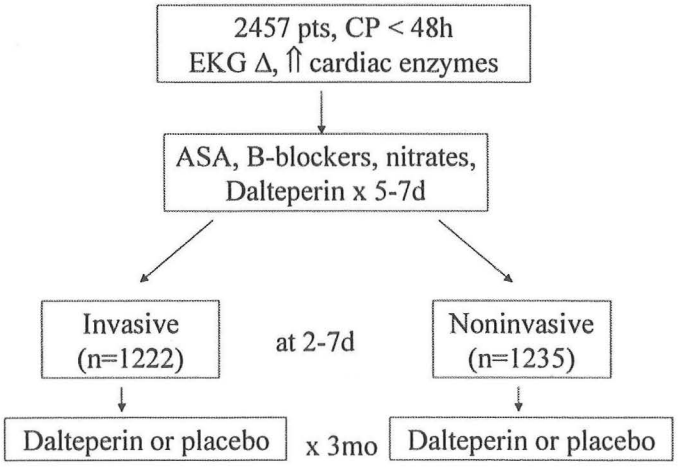
There are several criticisms of this study. First, percutaneous revascularization was performed solely with balloon angioplasty: stents and GP2b3a inhibitors were not available. Second, a high percentage of patients in the conservative group underwent revascularization (49% vs 61% of early invasive patients at 6 week follow-up), so they were not treated "conservatively." Finally, coronary arteriography revealed that > 50% of subjects had no or minimal coronary artery disease (1 or no vessels diseased), and such patients would do well regardless of treatment strategy.

The ***Veteran Affairs Non-Q wave Infarction Strategies in Hospital (VANQWISH) Trial*** randomly assigned 920 patients at 17 medical centers to either "invasive" management or "conservative" management within 72 hours of presentation and assessed the incidence of death or nonfatal myocardial infarction during an average follow-up of 23 months. Conservative management consisted of medical therapy and noninvasive testing, with cardiac catheterization and coronary revascularization performed in patients with spontaneous or inducible ischemia.

Patients assigned to the invasive strategy had a worse outcome had worse outcomes during the first year of follow-up. The frequency of death or nonfatal myocardial infarction was higher in the invasive strategy group than in the conservative strategy group before hospital discharge, at one month and at one year (Figure 5). The same was true for the rate of death. There was remarkable consistency among the study groups. The invasive strategy group fared worse at 73% of the medical centers and in no subgroup was the invasive strategy associated with a better outcome.

Compared with the TIMI IIIB study, fewer of the conservative strategy patients in the VANQWISH study underwent coronary angiography (24% before hospital discharge, 29% by 30 days, and 48% by one year). Nevertheless, the conservative therapy group had high rates of catheterization. Some have suggested that this may have decreased the power of the studies to show any difference in effect between the strategies. Scrutiny of the data reveals that the excessive early mortality in the early invasive strategy was in patients undergoing early coronary artery bypass surgery. There was no mortality in the patients randomized to invasive strategy who underwent angioplasty.

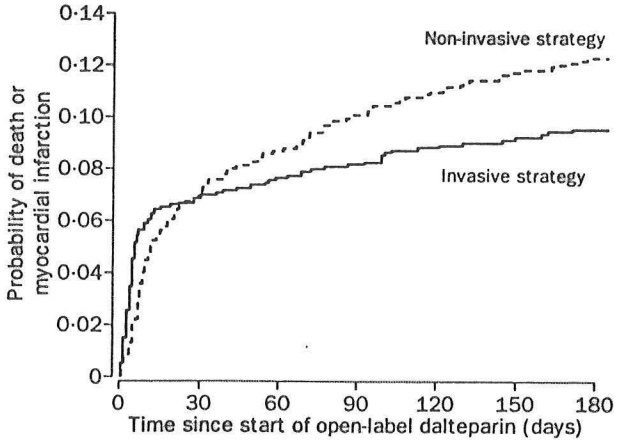
The ***Fragmin and Fast Revascularization during Instability in Coronary artery disease (FRISC II) study*** was a multicenter Scandanavian study in which 2457 subjects received intensive medical therapy (aspirin, beta blocker, low molecular weight heparin, HMGCoA reductase inhibitors, angiotensin converting enzyme inhibitors) for 48 hours before being randomized to continued (a) routine catheterization and revascularization -- stent and GP2b3a inhibitors permitted but infrequently used – or (b) medical therapy (with angiography and revascularization for recurrent spontaneous ischemia or an abnormal routine exercise stress test).



At 6 month follow-up, there was a decrease in the composite endpoint of death or myocardial infarction of 9.4% in the invasive group compared with 12.1% in the non-invasive group (22% risk reduction; p=0.031). This was due primarily to a 23% reduction in MI (7.8% vs 10.1%: p=0.45). The reduction in death was not statistically significant (1.9% vs 2.9%: p=0.10). Invasive strategy provided the greatest advantage at older age, in men, and with longer duration of angina, chest pain at rest, and ST segment depression (variabled which define "high risk" subjects). Conversely, women, young patients, and those without ST depression did not receive a benefit with an invasive strategy. The invasive strategy was associated with slightly more major bleeding episodes during hospitalization (1.6% vs 0.7%.) and ~50% fewer hospital readmissions over the 6 month follow-up. Thus, this trial showed that an early invasive strategy -- with procedures performed within 2-7 days of hospitalization -- lowers the risk of death and myocardial infarction in moderate-risk and high risk patients with unstable coronary-artery disease.

FRISC II: Death or MI at 6 months

	Aggressive	Conservative
Overall	9.1%	12.0%*
Men	8.9%	13.9%*
Women	10.5%	8.3%
Age > 65y	10.5%	15.8%*
Age < 65y	8.1%	8.1%

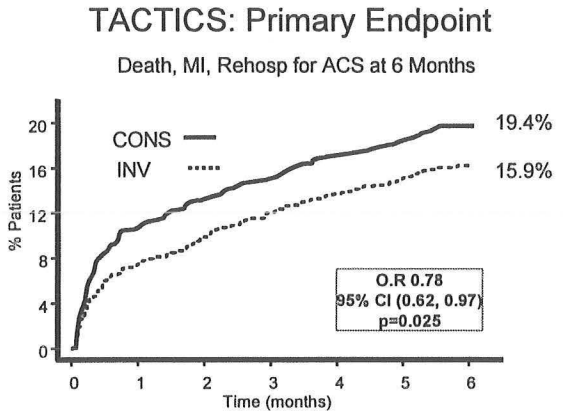


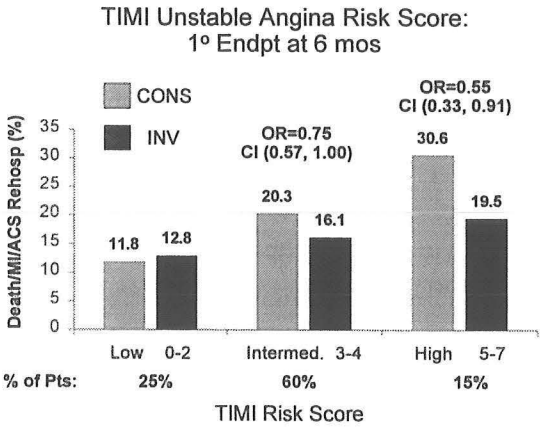
Probability of death or myocardial infarction in invasive and non-invasive groups

The most recent trial evaluating the utility of an invasive approach in unstable angina patients was the ***Treat Angina With Aggrastat and Determine The Cost of Therapy With an Invasive or Conservative Strategy (TACTICS) study***, also known as ***TIMI-18***. All 2220 patients with unstable angina or non Q-wave MI received "state-of-the art" medical therapy (aspirin, heparin, and GP2b3a) immediately and were then randomized to (a) routine catheterization and revascularization (stenting strongly encouraged for patients undergoing percutaneous revascularization) within 18 to 48 hours or (b) continued medical therapy, with revascularization for spontaneous or provocable myocardial ischemia.

At 6 month follow-up, the invasive strategy led to a 22% reduction in the composite endpoint (death, MI, or rehospitalization of acute coronary syndrome)(fomr 19.4% to 15.9%; p=0.025) and a 26% reduction in the incidence of death and MI (9.5% vs 7.3%: p<0.05). This latter was due entirely to a reduction in the incidence of MI; there was no difference in mortality. The benefit of an invasive strategy was confined to "moderate"or "high" risk patients (i.e., those with 3 or more of the TIMI risk factors previously discussed). Thus early use of "intensive" medical therapy with early (within 18-48 hrs) cardiac catheterization and revascularization reduces the risk of subsequent

myocardial infarction and readmission. A cost analysis of this approach is in process and will provide cost-benefit data.





Conclusions

In patients with unstable angina or non Q-wave MI, antiplatelet and antithrombotic therapy – but not thrombolysis -- reduces subsequent cardiac events. Newer therapies (ie., LMWH and GP IIb/IIIa inhibitors) provide more effective antithrombotic and antiplatelet inhibition and decrease recurrent angina and myocardial infarction in patients with unstable angina or non Q-wave MI; however, they do not appear to reduce mortality. Identification of unstable angina patients not at "low risk" for ischemic events provides a basis for therapeutic decision-making. Such patients benefit from intensive medical therapy and an early invasive strategy (i.e., cardiac catheterization with revascularization, if possible).

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