Emergency Medicine Reports

The Practical Journal for Emergency Physicians

Management Protocols for Acute Coronary Syndromes

Perhaps no aspect of emergency and cardiovascular medicine is evolving more rapidly than the pharmacological and procedural landscape devoted to the management of patients with acute coronary syndromes (ACS). As every emergency physician and cardiologist understands, making the right choice—whether it is drug therapy, a procedural coronary intervention (PCI), or some combination of both strategies—can make the difference between a favorable and unfavorable outcome.

The current issue of *Emergency Medicine Reports* provides a detailed, comprehensive analysis of the role of electrocardiography in the diagnosis of acute mycoardial infarction. The enclosed supplement provides evidence-based treatment pathways and pharmacotherapeutic strategies that will optimize outcomes of patients diagnosed with AMI or unstable angina. — The Editor

Low Molecular Weight Heparin Trials in Acute Coronary Syndromes

TRIALS	ESSENCE	TIMI IIB	FRIC	FRISC	FRISC II	FRAXIS
LMWH	Enoxaparin	Enoxaparin	Dalteparin	Dalteparin	Dalteparin	Nadroparin
Patients: #	3171	3910 (3-8 d) 2346 (8-43 d)	1482 (1-6 d) 1133 (6-45 d)	1506	(1) 2105 (2) 2457	3468
CP w/i	24 hr	24 hr	72 hr	72 hr	72 hr	48 hr
EKG Δ	57% (ST or T ↓ or other changes)	83% (ST or T ↓ or other changes)	100% (ST or T ↓)	100% (ST or T ↓)	(100%) (ST or T ↓)	(100%) (ST or T ↓)
NQMI	21%	34%	16%	38%	—	~ 16%
Primary end point	Death, MI, or RA at 14 d	Death, MI, urgent revasc at 8 and 43 d	Death, MI, or RA during days 6-45	Death or MI at 6 d	Death or MI at 30 d and at 6 months	CV death, MI, or RA at 14 d
Groups	LMWH UFH	LMWH UFH	LMWH UFH	LMWH Placebo	(1) LMWH Placebo (2) PCI No-PCI	LMWH × 6d LMWH × 14d IV UFH × 6d
Dose	1 mg/kg SC bid × 2-8 d	Up to 8 d: 30 mg bolus + 1 mg/kg bid; 8-43 d: 40 mg (< 65 kg) or 60 mg (≥ 65 kg) SC bid	Up to 6 d: 120 Anti-Xa U/kg SC bid; 6-45 d; 7500 anti-Xa SC qd	120 IU/kg SC bid× 6 d then 7500 IU qd X 42 d	120 IU/kg SC bid × 1-5 d + 7500 IU SC bid × 5-90 d	86 IU/kg IV bolus then 86 IU/kg SC bid
UFH dose	5000 U IV bolus + infusion	70 U/kg IV bolus + 15 U/kg IV infusion	5000 U IV bolus + 1000 U/hr infusion	UFH only used as a rescue drug[3]	UFH only used as a rescue drug[3]	5000 U IV bolus + 1250 U infusion
Death LMWH	—	—	—	6 d: 1.8* 40 d: 8.0	30 d: 3.1 90 d: 6.7*	—
MI (%) Placebo				6 d: 4.8 40 d: 10.7	30 d: 5.9 90d: 8.0	
Death LMWH MI	14 d: 16.6*[1] 30 d: 19.8*[1]	8 d: 12.4* 43 d: 17.3*[1]	6 d: 9.3 6-45 d: 12.3	—	—	14 d: (6 d R_x - 17.8) (14 d R_x - 20.0)
RA UFH (%)	14 d: 19.8 30 d: 23.3	8 d: 14.5 43 d: 19.7	6 d: 7.6 6-45 d: 12.3	—	—	14 d: 18.1
LMWH **Major Bleed[2] (%)**	30 d: 7.0	8 d: 1.5 43 d: 2.9*	6 d: 1.1 6-45 d: 0.5	6 d: 0.8 40 d: 0.3	90 d: 3.3	6 d & 14 d nadro at 6 d: 1.0 6 d nadro at 14 d: 1.5 14 d nadro at 14 d: 3.5*
UFH	30 d: 6.5	8 d: 1.0 43 d: 1.5	6 d: 1.0 6 d-45 d: 0.4	—	—	6 d UFH at 6 d: 1.0 6 d UFH at 14 d: 1.6
Placebo	—	—	—	6 d: 0.5 40 d: 0.3	90 d: 1.5	—

d, day(s); RA, recurrent angina; UFH, unfractionated heparin; NQMI, non-Q wave MI; Revasc, revascularization (PTCA, CABG); CV, cardiovascular; w/i, within; NA, not applicable; SC, subcutaneous; nadro, nadroparin; LMWH, low molecular weight heparin; CP, chest pain.

* $P < 0.05$

[1] = Difference primarily due to need for fewer revascularization procedures.

[2] = Major hemorrhage defined: FRISC: ↓ hemoglobin of 20 g/L, required transfusion, was intracranial, or caused death or cessation of study treatment. In ESSENCE & TIMI IIB: bleeding resulting in death, transfusion of ≥ 2 units of blood, a ↓ hemoglobin of 30 g/L, or a retroperitoneal, intracranial, or intraocular hemorrhage. In FRAXIS: symptomatic bleeding associated with a ↓ hemoglobin > 2g/dL, retroperitoneal or intracranial hemorrhage, or if transfusion required or death caused.

[3] = UFH also was used, but the trial was not designed to compare UFH with a LMWH.

Trials Using GP IIb/IIIa Inhibitors in Non-ST-Segment Elevation Acute Coronary Syndromes with Mandated PCI‡

TRIAL	EPIC	EPILOG	EPISTENT	CAPTURE	IMPACT II	RESTORE
Agent	Abciximab	Abciximab	Abciximab	Abciximab	Eptifibatide	Tirofiban
Entry Criteria	Elective to emergent: MI w/i 12 hrs requiring rescue, early post-MI angina, UA w/i 24 hrs, or vessels at high risk for closure	Elective or urgent PCI pts w/ a stenosis of ≥ 60% (Not pts with acute ischemia)	Elective or urgent PCI pts w/ a stenosis of ≥ 60% (Not pts with acute ischemia)	Refractory UA defined as: CP + EKG Δ on admission, then more CP *or* EKG Δ despite medical Rx	Elective, urgent, or emergent PCI pts	Pts undergoing PCI w/i 72 hrs of presentation w/ UA, NQMI, or MI with ST ↑
Patient Number	2099	2792	2399	1265	4010	2141
Primary End Point	Death, MI, CABG, repeat emergent PCI, *or* stenting at 30 d	Death, MI, *or* urgent revasc (CABG or PCI) at 30 d	Death, MI, *or* urgent revasc (CABG or PCI) at 30 d	Death, MI, *or* urgent revasc (CABG or PCI) at 30 d	Death, MI, *or* urgent revasc (CABG or PCI) at 30 d	Death, MI, *or* any revasc (CABG or PCI) at 30 d
Drug Dosing	Abcix bolus (0.25 mg/kg) and inf (10 mcg/min)	Abcix bolus (0.25 mg/kg) and inf (0.125 mcg/kg/min to max of 10 mcg/min)	Abcix bolus (0.25 mg/kg) and inf (0.125 mcg/kg/min to max of 10 mcg/min)	Abcix bolus (0.25 mg/kg) and inf (10 mcg/min)	Eptif 135 mcg/kg bolus, then inf at: LD: 0.5 mcg/kg/min HD: 0.75 mcg/kg/min	Tirofiban bolus (10 mcg/kg) and inf (0.15 mcg/kg/min)
Drug Duration	12 hrs (started w/i 1 hr of PCI)	12 hrs (started w/i 1 hr of PCI)	12 hrs (started w/i 1 hr of PCI)	18-24 hrs *before* PCI then 1 hr after PCI	20-24 hrs beginning after access established	36 hrs after angioplasty guidewire was across the lesion
Vase Sheaths	Removed 6 hrs after end of inf	Early removal and meticulous wound care	Early removal and meticulous wound care	Removed 4-6 hrs after end of inf. Meticulous site care.	Removed 4-6 hrs after end of PCI	Early removal
Randomized Groups	Three Arms: Abcix bolus + abcix inf Abcix bolus + placebo inf Placebo bolus + placebo inf	Three Arms: Placebo + stand UFH Abcix + stand UFH Abcix + LD UFH	Three Arms: ST + placebo ST + abcix Angio + abcix	All with early angiography and had culprit lesions. Then, two arms: Abcix bolus + abcix inf Placebo bolus + placebo inf Then, PCI performed	Three Arms: LD Ept infusion HD Ept infusion Placebo bolus + placebo inf	Two Arms: Tiro bolus + tiro inf Placebo bolus + placebo inf
1° End Point (30 d)						
IIb/IIIa	8.3*[3]	5.3* (Both abcix groups)		11.3*	LD: 9.2, HD: 9.9	10.3, 8.0[3]
Placebo	12.8	11.7		15.9	11.4	12.2, 10.5[5]
2° End Point (6 m)[2]						
IIb/IIIa	27.0*	22.8 (stand); 22.3* (LD)		31	LD: 10.5, HD: 10.1	
Placebo	35.1	25.8		30.8	11.6	
1° End Point (30 d)[1]						
ST + Placebo			10.8			
ST + IIb/IIIa			5.3*			
Angio + IIb/IIIa			6.9*			
Major/Intermediate Bleeding[4]						
IIb/IIIa	14*	3.5 (stand); 2.0 (LD)	1.5 (ST + angio groups)	3.8*	LD: 5.1, HD: 5.2	2.4
Placebo	7	3.1	2.2	1.9	4.8	2.1

Key: PCI (percutaneous coronary intervention) includes angioplasty, directional atherectomy, and/or stenting; CABG, coronary artery bypass grafting; MI, myocardial infarction; Abcix, abciximab; Ept, eptifibatide; Tiro, tirofiban; inf, infusion; LD, low-dose; HD, high-dose; pts, patients; Angio, angioplasty; ST, stent; Vasc, vascular; Rx, treatment; UFH, unfractionated heparin; d, day(s); m, months; w, with; w/i, within; hrs, hours.

‡ All patients in the trials received aspirin and heparin.

* $P < 0.05$

[1] Death, MI, or urgent revascularization.

[2] Death, MI, or any revascularization (except IMPACT II which was only death or MI).

[3] Data for abciximab bolus plus infusion group. The abciximab bolus only group was not different from placebo.

[4] Major bleeding defined by TIMI criteria for all reported trial results.

[5] These numbers reflect the combined end point when only emergent or urgent PTCA was considered ($P = 0.052$).

Supplement to *Emergency Medicine Reports*, April 23, 2001: "Electrocardiographic Diagnosis of Acute Coronary Syndromes in the Emergency Department." *Authors:* **William J. Brady, MD, FACEP,** Associate Professor of Emergency Medicine, Department of Emergency Medicine; Associate Professor of Internal Medicine, Department of Internal Medicine; Program Director, Emergency Medicine Residency, Department of Internal Medicine; Vice Chairman of Emergency Medicine, Department of Emergency Medicine, University of Virginia School of Medicine, Charlottesville, VA; **Andrew D. Perron, MD,** Assistant Professor of Emergency Medicine, Department of Emergency Medicine; Medical Director, First Med, Department of Emergency Medicine, University of Virginia Health System, Charlottesville, VA; **Edward Ullman, MD,** Department of Emergency Medicine, University of Virginia School of Medicine; Charlottesville, VA.

Trials Using GP IIb/IIIa Inhibitors in Non-ST-Segment Elevation Acute Coronary Syndromes (PCI Not Mandated)‡

TRIAL	PARAGON	PURSUIT	PRISM	PRISM-PLUS
Agent	Lamifiban	Eptifibatide	Tirofiban	Tirofiban
Entry criteria	CP w/i 12 hrs + EKG Δ (ST temp ↑ or ↓ or T ↓)	CP w/i 24 hrs + [EKG Δ (ST temp ↑ or ↓ or T ↓) *or* enzyme ↑]	CP w/i 24 hrs + [EKG Δ (ST temp ↑ or ↓ or T ↓) *or* enzyme ↑ *or* evidence prior CAD]	CP w/i 12 hrs + [EKG Δ (ST or T ↓) or enzyme ↑]
Patients				
Number	2282	10948	3232	1915
EKG Δ (%)	100	92	75	90
Enzyme ↑ (%)	36	45	25	45
Revascularized	25	38	38	54
Primary end point	Death *or* nonfatal MI at 30 d	Death *or* nonfatal MI at 30 d	Death, MI, *or* refractory ischemia at 48 hrs	Death, MI, *or* refractory ischemia at 7 d[4]
Drug therapy	3-5 d[2]	≤ 72 hrs[2]	48 hrs	48 hrs[2]
Randomized groups	Five arms: Placebo Lam (LD or HD) (w/ or w/o UFH)	Three arms: Placebo HD or LD Ept (UFH)[3]	Two arms: Tiro UFH	Three arms: Tiro[5] UFH Tiro + UFH
Invasive procedures[1]	Discourages × 48 hours	Physician discretion	Discouraged during 48 hour infusion	Discouraged during 48 hour infusion; Encouraged 48-96 hours
Outcome (primary end point) (%)	30 d: No difference 6 m: LD Lam ± UFH 13.7* Placebo 17.9	30 d: HD Ept 14.2* Placebo 15.7 (No difference between groups in those with only medical Rx)	2 d: Tiro 3.8 UFH 5.6 30 d: Tiro 15.9 UFH 17.1	7 d: Tiro + UFH 12.9 UFH 17.9 30 d: Tiro + UFH 18.5* UFH 22.3 6m: Tiro + UFH 27.7* UFH 32.1
Major/intermediate bleeding (%)	UFH 5.9* Lam 7.8 UFH + Lam 10.5	Ept 10.6 Placebo 9.1*	Tiro 0.4 Heparin 0.4	Tiro + UFH 4 UFH 3

Key: PCI (percutaneous coronary intervention) includes angioplasty, directional atherectomy, and/or stenting; CP, chest pain; MI, myocardial infarction; CAD, coronary artery disease; LD, low-dose; HD, high-dose; w/, with; w/o, without; w/i, within; UFH, unfractionated heparin; Ept, eptifibatide; Lam, Lamifiban; Tiro, Tirofiban; hrs, hours; d, day(s); m, months; temp, temporary; Rx, treatment.

‡ All trials included aspirin for all patients and all contained patients with non-Q-MI. Some trials permitted patients who had temporary ST-segment elevation. PCI (percutaneous coronary intervention) includes angioplasty, directional atherectomy, and/or stenting.

* $P < 0.05$

[1] Includes diagnostic catheterization, PCI, CABG.

[2] If intervention was performed at end of drug therapy, the study drug could be infused for an additional 24 hours (PURSUIT), 48 hours (PRISM PLUS), or 12-24 hours (PARAGON) after the procedure.

[3] Heparin was optional.

[4] The 30-day and 6-month end points also included rehospitalization.

[5] Tirofiban alone arm dropped early in study because of increased adverse effects.

Common Markers Used to Identify Acute Myocardial Infarction

MARKER	INITIAL ELEVATION AFTER AMI	MEAN TIME TO PEAK ELEVATIONS	TIME TO RETURN TO BASELINE
Myoglobin	1-4 h	6-7 h	18-24 h
CTnI	3-12 h	10-24 h	3-10 d
CTnT	3-12 h	12-48 h	5-14 d
CKMB	4-12 h	10-24 h	48-72 h
CKMBiso	2-6 h	12 h	38 h
LD	8-12 h	24-48 h	10-14 d

CTnI, CTnT = troponins of cardiac myofibrils; CPK-MB, MM = tissue isoforms of creatine kinase; LD = lactate dehydrogenase.

Adapted from: Adams JE III, Abendschein DR, Jaffee S. Biochemical markers of myocardial injury: Is MB creatine kinase the choice for the 1990s? *Circulation* 1993;88:750-763.

Please note: Tables printed in this supplement have appeared in one of the following *Emergency Medicine Reports'* issues: Bosker G, Robinson DJ, Jerrard DA, et al. Acute Myocardial Infarction: Current Clinical Guidelines for Patient Evaluation, Thrombolysis, and Mortality Reduction. 1999;14:143-152; Kleinschmidt K. Acute Coronary Syndromes (ACS): Pharmacotherapeutic Interventions—Treatment Guidelines for Patients with and without Procedural Coronary Intervention (PCI), Parts I and II. 2000;23:257-272, 273-284.

ACUTE CORONARY SYNDROMES — PRACTICAL, EVIDENCE-BASED GUIDELINES FOR OUTCOME-EFFECTIVE MANAGEMENT

Patients With Unstable Angina, Non ST-Segment Evaluation Myocardial Infarction (NSTEMI), and ST-Segment Elevation MI - With and Without PCI.
Adapted, updated, and based upon ACC/AHA Recommendations (September, 2000) for UA/NSTEMI and ACC/AHA 1999 MI Guidelines.

CHEST PAIN TRIAGE

Developed by Kurt Kleinschmidt, MD, FACEP, for *Emergency Medicine Reports* (November, 2000)

Acute Coronary Syndrome (ACS): Pharmacotherapeutic Interventions For UA/NSTEMI— An Evidence-Based Review And Outcome-Optimizing Guidelines For ACS Patients With And Without Procedural Coronary Intervention (PCI)

TRIAGE ASSESSMENT
- Pain description • Age • Sex • CAD Hx
- Cocaine • Risk factors for CAD

Non-Ischemic / Non-Cardiac → Evaluate and treat suspected etiology

Possible or definite ACS

12-LEAD ECG WITHIN 10 MINUTES
- Intravenous access
- Oxygen
- Continuous ECG monitor
- Aspirin
- Consider
  - — Cardiac markers
  - — Beta-blockers
  - — Nitroglycerin
  - — Morphine sulfate

ST-segment elevation or new or presumably new bundle branch block

Treat with:
- Beta-blockers
- Unfractionated heparin (preferred) or enoxaparin
- Nitroglycerin
- Morphine sulfate

≤12 hours / >12 hours chest pain

Institution capable of performing PCI → YES / NO

Persistent symptoms → NO / YES

- NO (PCI): Institutional policy is to routinely perform catheterization and then a procedural coronary intervention[2] or CABG → YES / NO
  - YES: Cardiac catheterization → Procedural coronary intervention or CABG
  - NO: Contraindication to thrombolysis or cardiogenic shock → YES / NO
    - YES: Cardiac catheterization → Procedural coronary intervention or CABG
    - NO: Thrombolysis
      - Alteplase or
      - Reteplase or
      - Streptokinase or
      - Tenecteplase

      (Door → needle time < 30 minutes) → Clinical evidence of reperfusion (Chest pain and EKG with resolution) → NO / YES
      - NO: Cardiac catheterization
      - YES: Continued medical mgmt.
- NO (Persistent symptoms): Medical management
- YES (Persistent symptoms):
  - Consider reperfusion
  - Aggressive medical therapy

ST-segment depression or T-wave inversion

Treat with:
- Beta-blockers
- Enoxaparin (preferred) or unfractionated heparin[1]
- Tirofiban[2]
- Nitroglycerin
- Morphine sulfate

Chest pain is refractory or recurrent or patient has prior CABG or MI → Early cardiac catheterization → Abnormal / Normal
- Abnormal: Procedural coronary intervention or CABG
- Normal: Discharge and follow-up as needed

Good clinical response → Early conservative medical management → Hospital Course Becomes Complicated
- Recurrent chest pain
- Hemo instability
- New EKG change
- CHF starts
- Dysrhythmias

→ YES / NO
- YES: Assess LV function → <40% / ≥40%
  - <40%: Abnormal
  - ≥40%: Stress test → Abnormal / Normal
    - Abnormal: Assess LV function
    - Normal: Medical therapy discharge
- NO: Abnormal

No EKG change or normal EKG

RISK STRATIFY
- Complete H & P
- Consider
  - — Serial EKGs or continuous segment monitoring
  - — Second set cardiac markers (at ≥ 6 hours after chest pain onset)
  - — If first troponin obtained at < 6 hours, obtain second set between 6-12 hours
  - — 2-D echocardiogram
- Observation 4-12 hours
  - — Emergency department
  - — Chest pain unit
  - — 24 hours observation
  - — Admission
- Pain relief (initiate or intensify)
  - — Beta-blocker
  - — Nitroglycerin
  - — Morphine sulfate

IF ANY ONE OF THE FOLLOWING:

HX —	• Prior coronary, peripheral, or cardiovascular disease • Rest angina > 20 minutes in patient with moderate likelihood • Accelerating tempo of angina within preceding 48 hours
PE —	• Age > 70 years old • Congestive heart failure • Hypotension, bradycardia, or tachycardia
ECG —	• ST-segment depression (> 0.05 mv) or transient elevation with pain • T-wave inversion of > 0.2 mv with pain • Pathological Q waves • Sustained ventricular tachycardia
MARKERS—	• TnT or TnI elevated

YES → **Enoxaparin (preferred)** or unfractionated heparin[3]

NO → LOW RISK
- Treat suspected etiology
- Consider stress testing to provoke ischemia (prior to discharge or as an outpatient)
- Follow-up as needed

EKG change or marker increase

YES → **Tirofiban[4] (preferred) if PCI not anticipated. Abciximab (preferred) if PCI anticipated.**

NO → Medical management (includes enoxaparin or unfractionated heparin)

IF ANY ONE OF THE FOLLOWING:
- Recurrent angina • CHF • Hemodynamic instability
- Sustained V-tach • PCI within 6 months • Prior CABG

YES → Early PCI

NO → Continued medical therapy

[1] Dalteparin or nadroparin are alternative options.
[2] Abciximab can be considered if patient is going to have a procedural coronary intervention. Eptifibatide is also an alternative.
[3] Dalteparin or nadroparin are alternative options.
[4] Eptifibatide is an alternative option.