

Part 5: Acute Coronary Syndromes

The American Heart Association and the American College of Cardiology,^{1,2} the European Society of Cardiology^{3,4} and others⁵ have developed comprehensive guidelines for the in-hospital management of patients with ST-elevation myocardial infarction (STEMI)² and for unstable angina (UA) and non-ST-elevation MI (NSTEMI).¹ The International Liaison Committee on Resuscitation (ILCOR) Acute Coronary Syndromes (ACS)/Acute Myocardial Infarction (AMI) Task Force reviewed the evidence specifically related to diagnosis and treatment of ACS/AMI in the out-of-hospital setting and the first hours of care in the in-hospital setting, typically in the emergency department (ED).

Much of the research concerning the care of the patient with ACS has been conducted on in-hospital populations rather than in the ED or out-of-hospital settings. By definition, extending the conclusions from such research to the early ED management strategy or the out-of-hospital setting requires extrapolation classified as level of evidence 7.

Diagnostic Tests in ACS and AMI

The sensitivity, specificity, and clinical impact of various diagnostic strategies in ACS/AMI have been evaluated. These include signs and symptoms, cardiac markers, and 12-lead electrocardiogram (ECG). The standard ILCOR/AHA levels of evidence (described in Part 1: "Introduction") pertain largely to therapeutic interventions. For this reason, in the evaluation of evidence for diagnostic accuracy the reviewers used the Centre for Evidence-Based Medicine (CEBM) levels of evidence for diagnostic tests (http://www.cebm.net/levels_of_evidence.asp). The CEBM levels are cited as "levels" and the ILCOR/AHA levels of evidence are designated with "LOE," for "level of evidence."

Neither signs and symptoms nor cardiac markers alone are sufficiently sensitive to diagnose AMI or ischemia in the prehospital setting or the first 4 to 6 hours in the ED. The 12-lead ECG in the ED and out-of-hospital settings is central to the initial triage of patients with possible ACS.

Diagnostic and Prognostic Test Characteristics of Signs and Symptoms of ACS/AMI^{W221A,W221B}

Consensus on Science

Diagnosis. Four CEBM level 1B validating cohort studies⁶⁻⁹ and 9 CEBM level 2A-4 studies¹⁰⁻¹⁸ do not support the use of any clinical signs and symptoms independent of ECG, cardiac biomarkers, or other diagnostic tests to rule in or rule out ACS/AMI in prehospital or ED settings. Although some signs are more sensitive and specific than others, no sign or

symptom evaluated exceeded 92% sensitivity in the higher LOE studies (most reported sensitivity of 35% to 38%) or 91% specificity (range 28% to 91% in highest CEBM levels).⁷

Prognosis and clinical impact. In 3 CEBM level 1a systematic reviews,^{10,19,20} 10 CEBM level 1b validating cohort studies^{6-9,21-26} and 21 CEBM level 2a-4 studies,^{11-13,15-18,27-40} a variety of signs and symptoms assisted in the diagnosis of ACS/AMI and had clinical impact (defined as triage and some treatment and investigational decisions) on the out-of-hospital emergency management and risk assessment for coronary atherosclerosis and unstable syndromes.

Treatment Recommendation

Signs and symptoms of ACS/AMI may be useful in combination with other important information (biomarkers, risk factors, ECG, and other diagnostic tests) in making triage and some treatment and investigational decisions in the out-of-hospital setting and the ED. Signs and symptoms are not independently diagnostic of ACS/AMI.

Diagnostic and Prognostic Test Characteristics of Cardiac Biomarkers for ACS/AMI^{W222A,W222B}

Consensus on Science

Diagnosis. All literature reviewed showed that biomarkers (creatinine kinase [CK], creatine kinase myocardial band [CK-MB], myoglobin, troponin I [TnI], troponin T [TnT]) were helpful in the diagnosis of ACS/AMI. But only 6 studies⁴¹⁻⁴⁴ (CEBM level 4^{45,46}; ILCOR LOE 7) showed a sensitivity of >95% within the first 4 to 6 hours of the patient's arrival in the ED. Multimarker strategies^{20,41-43,45-61} (CEBM level 1b; ILCOR/AHA LOE 7 [extrapolated from in-hospital setting]), and serial marker testing over time^{41-43,45-49,51,56,58,60-69} (CEBM level 1b; ILCOR/AHA LOE 7 [extrapolated from in-hospital setting]) improved test performance. Six out-of-hospital studies⁷⁰⁻⁷⁵ (CEBM level 1b) showed consistent lack of support for the use of cardiac biomarkers in diagnosing AMI in the out-of-hospital phase (sensitivity 10% to 25%; specificity 92% to 100%).

Prognosis. Two systematic reviews (CEBM level 1a)^{76,77} and 21 additional studies⁷⁸⁻⁹⁸ (18 CEBM level 1b and 3 ILCOR/AHA LOE 7) documented consistent ability of cardiac biomarker testing to identify patients at increased risk of adverse outcome. One systematic review (CEBM level 1a)⁷⁶ suggested that risk assessment cannot be based exclusively on cardiac biomarker results (30-day mortality range for patients with suspected ACS and negative troponin results: 0.7% to 4.4%).

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Treatment Recommendation

Emergency physicians should obtain cardiac biomarkers for all patients with suspected ACS/AMI. Serial time points (increasing interval from onset of symptoms to testing), and multimarker strategies greatly improve sensitivity for detection of myocardial ischemia or infarction but are insensitive for ruling out these diagnoses in the out-of-hospital setting or within the first 4 to 6 hours of evaluation in the ED.

ED Interpretation of 12-Lead ECG for STEMI*Consensus on Science*

Diagnostic characteristics—out-of-hospital. One meta-analysis plus 5 prospective nonrandomized consecutive case series of patients with chest pain (CEBM level 1b–1c)^{99–104} and 5 review articles ILCOR/AHA LOE 7^{11,20,105–107} showed that trained out-of-hospital care providers (paramedics and nurses) could identify ST-segment elevation accurately in the resting out-of-hospital 12-lead ECG of patients with chest pain suspected of having STEMI. The out-of-hospital care providers achieved a specificity of 91% to 100% and sensitivity of 71% to 97% compared with emergency physicians or cardiologists. Of note, left bundle branch block paced rhythm and idioventricular rhythm may affect the diagnostic test accuracy because they were excluded in some studies and not mentioned in others.

Prognostic characteristics—ED. ST elevation (>1 mV elevation in 2 or more adjacent limb leads or in 2 or more adjacent precordial leads with reciprocal depression) was the most discriminating single ECG feature for diagnosis of STEMI (likelihood ratio [LR] of 13.1; 95% confidence interval [CI], 8.28–20.6).¹¹ Emergency physicians blinded to biomarker results established the diagnosis of STEMI using admission ECGs with a very high specificity of 99.7% (95% CI, 98%–99.9%; LR+ 145; 95% CI, 20.2–1044), although sensitivity was low at 42% (95% CI, 32%–52%)^{103,108,109} (CEBM 1b–1c; ILCOR/AHA LOE 7).¹¹

Treatment Recommendation

Out-of-hospital. Trained out-of-hospital personnel can accurately identify acute STEMI in prehospital 12-lead ECGs obtained in patients with ACS. The ECG is used in combination with chest pain symptoms, assessment of risk factors, and other diagnostic tests to rule out alternative diagnoses. Out-of-hospital interpretation of a single 12-lead ECG with stringent inclusion criteria (ie, ST elevation >0.1 mV in 2 or more adjacent precordial leads or 2 or more adjacent limb leads and with reciprocal depression) has a high specificity for the diagnosis of STEMI.

ED. In the ED the interpretation of a single 12-lead ECG with rigid inclusion criteria (see above) is discriminating for the diagnosis of STEMI with a relatively low sensitivity but a high specificity for this diagnosis.

Acute Therapeutic Interventions

Few studies have been published to guide out-of-hospital interventions for ACS and AMI. Extrapolating from the evidence for many of the adjunctive therapies used in-hospital within 24 to 48 hours may provide some guidance for out-of-hospital and early ED management.

Adjunctive Therapies**Oxygen Therapy**^{W224}*Consensus on Science*

One animal study (LOE 6)¹¹⁰ showed a reduction in infarct size when supplementary oxygen was provided during left anterior descending coronary artery occlusion. One human study (LOE 5)¹¹¹ showed improvement in ECG findings, but one double-blind, randomized human trial (LOE 2)¹¹² of supplementary oxygen versus room air failed to show a long-term benefit of oxygen therapy for patients with MI.

Treatment Recommendation

Supplementary oxygen should be given to patients with arterial oxygen desaturation (arterial oxygen saturation [Sao₂] <90%). Given the safety profile of oxygen in this population and the potential benefit in the patient with unrecognized hypoxia, it is reasonable to give supplementary oxygen to all patients with uncomplicated STEMI during the first 6 hours of emergency management.

Aspirin (Acetylsalicylic Acid)^{W225A,W225B}*Consensus on Science*

Eight randomized controlled trials (RCTs) (LOE 1)^{113–120} showed decreased mortality rates when acetylsalicylic acid (ASA) (75 to 325 mg) was given to hospitalized patients with ACS. The International Study of Infarct Survival (ISIS)-2 trial used 160 mg/day orally (odds reduction=0.23; 95% CI, 0.15–0.30).¹¹⁵

Four RCTs (LOE 1)^{115,116,120,121} and 3 additional studies (LOE 7)^{122–124} indicated decreased mortality rates when ASA was given as early as possible.

Two studies (LOE 1)^{125,126} addressed specific ASA dose, but the standard of 160 mg enteric-coated ASA has still been maintained from ISIS-2. Two studies showed that chewed (LOE 3)¹²⁷ or soluble (LOE 6)¹²⁸ ASA provides more rapid bioavailability than swallowed tablets. Two nonblinded studies (LOE 7)^{124,129} showed that 50 mg of intravenous (IV) ASA was >90% effective in inhibiting thromboxane A₂ and inhibits platelets effectively.

One post hoc study suggested decreased mortality rates with out-of-hospital administration of ASA (LOE 7).¹²³

Seven hospital-based RCTs indicated that giving ASA to patients with suspected ACS is safe (LOE 1).^{113–115,117,118,120,121}

Treatment Recommendation

It is reasonable for dispatchers to advise the patient with suspected ACS and without a true aspirin allergy to chew a single dose (160 to 325 mg) of ASA. It is also reasonable for EMS providers to administer ASA because there is good evidence that it is safe and that the earlier ASA is given, the greater the reduction in risk of mortality.

Limited evidence from several very small studies suggests that the bioavailability and pharmacologic action of other formulations of ASA (soluble, IV) may be as effective as chewed tablets.

Heparins^{W226A}*Consensus on Science*

UA/NSTEMI. Six in-hospital RCTs (LOE 1)^{130,131} and LOE 2^{121,132,133} <24 hours; LOE 1¹³⁴ <36 hours) and additional

studies (including 7 meta-analyses,^{135–141}) documented similar or improved composite outcomes (death, MI or recurrent angina, or recurrent ischemia or revascularization) after giving low-molecular-weight heparin (LMWH) instead of unfractionated heparin (UFH) to patients with UA/NSTEMI within the first 24 to 36 hours after onset of symptoms. No study evaluated the early use of LMWH versus UFH in the first 6 hours of management. Extrapolation (LOE 7) from 1 RCT¹³³ and 1 meta-analysis (LOE 1)¹³⁵ suggests that changing from one form of heparin to another (crossover of antithrombin therapy) during initial treatment of an acute event may not be safe or effective in patients with UA/NSTEMI. There is no evidence that LMWH is superior to UFH in the group of patients who will receive early percutaneous coronary intervention (PCI).

STEMI. In 2 RCTs (LOE 1¹⁴²; LOE 2¹⁴³) and additional studies, including one meta-analysis (LOE 1),¹⁴⁴ LMWH (specifically enoxaparin) improved overall TIMI flow¹⁴⁵ (coronary reperfusion) and ischemic outcomes better than UFH when given to patients with STEMI within 6 hours of onset of symptoms. TIMI flow grade was defined by investigators from the TIMI study¹⁴⁵ as the degree of reperfusion, ranging from 0 for no flow through 3 for complete, brisk flow.

Two studies (LOE 1¹⁴⁶; LOE 2¹⁴⁷) in the out-of-hospital setting documented improved composite outcomes with LMWH (specifically enoxaparin) in comparison with UFH, when given to patients with STEMI as adjunctive therapy to fibrinolysis. This must be balanced against the increase in intracranial hemorrhage in patients >75 years of age receiving LMWH (enoxaparin) that was observed in one of these RCTs (LOE 2).¹⁴⁷

In patients with STEMI proceeding to PCI, there is no evidence in favor of LMWH.

In one RCT (LOE 1)¹⁴⁸ there was no difference in the incidence of death, reinfarction, or recurrent angina with LMWH (enoxaparin) in comparison with UFH when given to patients who were ineligible for reperfusion therapy.

Treatment Recommendation

UA/NSTEMI. In the ED giving LMWH instead of UFH in addition to aspirin to patients with UA/NSTEMI may be helpful. There is insufficient evidence to identify the optimal time for administration after onset of symptoms. In-hospital administration of UFH is recommended if reperfusion is planned within the first 24 to 36 hours after onset of symptoms. There is insufficient evidence to recommend for or against treatment with LMWH in UA/NSTEMI in the out-of-hospital setting. Changing from one form of heparin to another (crossover of antithrombin therapy) during an acute event is not recommended.

STEMI. LMWH is an acceptable alternative to UFH as ancillary therapy for patients with STEMI who are <75 years of age and receiving fibrinolytic therapy. LMWH should not be given if significant renal dysfunction (serum creatinine >2.5 mg/dL in men or 2 mg/dL in women) is present. UFH is recommended for patients ≥75 years of age as ancillary therapy to fibrinolysis. Heparin may be given to STEMI patients who do not receive reperfusion therapy. These include patients at high risk for cardioembolic events and those on prolonged bedrest. UFH or LMWH may be used. Patients receiving LMWH should have no significant renal dysfunction.

Clopidogrel^{W228A}

Consensus on Science

In 2 in-hospital, randomized, double-blind, controlled trials (LOE 1)^{149,150} and 4 post hoc analyses (LOE 7),^{151–154} clopidogrel was effective in reducing the combined event rate (stroke, nonfatal infarction, deaths from cardiovascular causes, refractory ischemia, heart failure, and need for revascularization) in patients with suspected ACS with evidence of ischemia but no infarction. In these studies clopidogrel was given within the first 4 hours of presentation to the hospital in addition to standard care (ASA, heparin) to patients with ACS who had a rise in serum level of cardiac biomarkers or new ECG changes consistent with ischemia but no ST-segment elevation.

One large randomized, double-blind, controlled trial (LOE 7)¹⁵⁵ documented no significant increase in risk of bleeding with clopidogrel in comparison with ASA. One large multicenter RCT (LOE 1)¹⁵⁶ documented a significant reduction in adverse ischemic events at 28 days after elective PCI when clopidogrel was given at least 6 hours before elective PCI.

One multicenter, randomized, double-blind, controlled trial (LOE 1)¹⁵⁷ documented a significant reduction in the composite end point of an occluded infarct-related artery (defined by a TIMI flow grade of 0 or 1) on angiography or death or recurrent MI before angiography when clopidogrel (300 mg oral loading dose) was given at the time of initial management (followed by a 75-mg daily dose for up to 8 days in hospital) to patients up to 75 years of age with STEMI who were treated with fibrinolysis, ASA, and heparin (LMWH or UFH).

In one large prospective STEMI trial (the CURE [Clopidogrel in Unstable angina to prevent Recurrent Events] trial),¹⁵² preoperative clopidogrel administration was associated with a trend toward increased postoperative reoperation for bleeding in the 2072 patients who underwent coronary artery bypass graft (CABG) surgery. A second prospective trial (LOE 1)¹⁵⁷ failed to show any increase in bleeding in the 136 patients who underwent CABG within 5 to 7 days of receiving clopidogrel. A subsequent risk-to-benefit ratio analysis concluded that the bleeding risk with clopidogrel in patients undergoing CABG was overestimated.¹⁵⁴

Treatment Recommendation

Give a 300-mg oral loading dose of clopidogrel in addition to standard care (ASA, heparin) to patients with ACS within 4 to 6 hours of contact if they have

- A rise in serum cardiac biomarkers or new ECG changes consistent with ischemia when a medical approach or PCI is planned in the absence of ST-segment elevation
- STEMI in patients up to 75 years of age receiving fibrinolysis, ASA, and heparin

Although in one large trial¹⁵² preoperative clopidogrel administration was associated with increased postoperative reoperation for bleeding, the recent CLARITY TIMI 28 trial¹⁵⁷ did not document increased bleeding in patients undergoing CABG within 5 to 7 days of receiving clopidogrel.

Current ACC/AHA recommendations² advise withholding clopidogrel for 5 to 7 days before planned CABG.

It is reasonable to give clopidogrel 300 mg orally to patients with suspected ACS (without ECG or cardiac marker changes) who have hypersensitivity to or gastrointestinal intolerance of ASA.

Glycoprotein IIb/IIIa Inhibitors

Consensus on Science

UA/NSTEMI. Two studies (LOE 1¹⁵⁸; LOE 2¹⁵⁹) and 2 meta-analyses (LOE 1)^{158,160} showed a reduction in the combined end point of death or recurrent ischemia when glycoprotein (GP) IIb/IIIa inhibitors were added to standard therapy (including ASA and heparin) for patients with high-risk UA/NSTEMI treated with PCI. High-risk features include persistent ongoing pain due to ischemia, hemodynamic or rhythm instability due to ongoing ischemia, acute or dynamic ECG changes, and any elevation in cardiac troponins attributed to ACS.

Two studies (LOE 1)^{158,161} and 3 meta-analyses (LOE 1)^{160,162,163} failed to show a reduction in the combined end point of death or recurrent ischemia in patients with UA/NSTEMI treated with tirofiban or eptifibatid without PCI. Two studies (LOE 1)^{164,165} showed that abciximab given in addition to standard therapy but without PCI in patients with UA/NSTEMI did not reduce the combined end point of death or recurrent ischemia. No published studies evaluated the out-of-hospital use of GP IIb/IIIa inhibitors. Three studies (LOE 1)^{158,160,163} showed the safety (as defined by low incidence of major hemorrhagic complications) of GP IIb/IIIa inhibitors when given to ACS patients within 24 to 48 hours of onset of symptoms.

STEMI. In multiple studies (LOE 1^{166,167,168}; LOE 2^{130,169–174}; LOE 4¹⁷⁵; LOE 7¹⁷⁶) there was no reduction in the combined end point of death or recurrent ischemia when tirofiban or eptifibatid were given in combination with reduced-dose fibrinolytics to patients with STEMI in the absence of PCI.

Two RCTs (LOE 1)^{165,177} in patients with STEMI treated with abciximab and fibrinolytics showed no reduction in the combined end point of death or recurrent ischemia. One meta-analysis (LOE 1)¹⁷⁸ showed reduction in short-term reinfarction rate when abciximab was given with fibrinolytics or PCI, whereas the benefits in mortality-rate reduction were seen only in patients treated with PCI. One RCT failed to show a benefit with tirofiban in addition to standard therapy when given out-of-hospital (LOE 2).¹⁷¹ Another study demonstrated the feasibility of using abciximab in the out-of-hospital setting (LOE 7).¹⁷⁵ A third study showed a trend toward improved patency of infarct-related artery with PCI (LOE 3).¹⁷⁹

Treatment Recommendation

High-risk UA/NSTEMI. If revascularization therapy (PCI or surgery) is planned, it is safe to give GP IIb/IIIa inhibitors in addition to standard therapy (including ASA and heparin) to patients with high-risk UA/NSTEMI in the ED. This therapy may reduce the risk of death or recurrent ischemia. High-risk features of UA/NSTEMI are defined in the consensus on science statement above. If revascularization therapy is not planned, the recommendation for use of GP IIb/IIIa varies by drug. Tirofiban and eptifibatid may be used in patients with high-risk UA/NSTEMI in conjunction with ASA and LMWH

if PCI is not planned. But abciximab can be harmful in patients with high-risk UA/NSTEMI if early (eg, 24 hours) PCI is not planned.

STEMI. Abciximab is not currently recommended in patients receiving fibrinolytics for STEMI. In patients treated with PCI without fibrinolysis, abciximab may be helpful in reducing mortality rates and short-term reinfarction. There is no evidence documenting a better outcome by giving GP IIb/IIIa inhibitors out of hospital or early in the ED.

Reperfusion Strategies

Out-of-Hospital Fibrinolytics for STEMI^{W227A}

Consensus on Science

One meta-analysis (LOE 1)¹⁸⁰ and multiple studies (LOE 1^{181,182}; LOE 2^{183–185}; LOE 3^{147,186–188}; LOE 4^{189–192}; LOE 5¹⁹³; LOE 7^{102,194–196}) documented reduced time to injection of fibrinolytics when given by out-of-hospital providers (physicians, nurses, or paramedics) to patients with STEMI and no contraindications to fibrinolysis. In most studies the duration of symptoms was from 30 minutes to 6 hours. Using the same criteria, 1 meta-analysis (LOE 1)¹⁸⁰ and 8 additional studies (LOE 1^{181,197}; LOE 2^{184,198}; LOE 3¹⁸⁷; LOE 4^{191,192}; LOE 5¹⁹⁹) documented reduced risk of mortality with out-of-hospital fibrinolysis.

Treatment Recommendation

Out-of-hospital administration of fibrinolytics by paramedics, nurses, or physicians using an established protocol is safe and feasible for patients with STEMI and no contraindications. This requires adequate provisions for the diagnosis and treatment of STEMI and its complications, including strict treatment directives, fibrinolytic checklist, ECG acquisition and interpretation, defibrillators, experience in ACLS protocols, and the ability to communicate with medical control. Physicians may give out-of-hospital fibrinolytics to patients with symptoms compatible with ACS and signs of true posterior infarctions (no ST elevation).

Fibrinolytics in the ED Management of STEMI^{W227B}

Consensus on Science

A prospective cohort study (LOE 3)²⁰⁰ and 11 additional studies (LOE 3^{201–208}; LOE 4²⁰⁹; LOE 5^{210,211}) documented reduced delay to injection of fibrinolytics and some decrease in mortality (LOE 3)^{200,212} and improved left ventricular function (LOE 3)²⁰⁶ when fibrinolytics were given in the ED to selected patients with STEMI (defined in studies with variable ST-elevation criteria with or without new onset left bundle branch block [LBBB] \pm posterior infarct) and no contraindications.

Treatment Recommendation

In the ED patients with symptoms of ACS and ECG evidence of either STEMI, (presumably) new LBBB, or true posterior infarction should be given fibrinolytics if fibrinolysis is the treatment of choice and there are no contraindications. The emergency physician should give fibrinolytics as early as possible according to a predetermined protocol.

Primary PCI Compared With ED or Out-of-Hospital Fibrinolysis^{W234A,W234B}

Consensus on Science

Six randomized studies (LOE 1),^{213–218} 3 meta-analyses (LOE 1),^{219–221} and 24 additional studies (LOE 2–4)^{222–245} compared primary PCI with fibrinolysis in patients with STEMI. These studies documented consistent improvement in the combined end point of death, stroke, and reinfarction when PCI was undertaken by skilled personnel in a high-volume center (ie, >75 procedures per operator annually) with minimal delay. Minimal delay was defined as balloon inflation ≤90 minutes after first medical contact (ie, contact with a healthcare provider who can make a decision to treat or transfer). In these studies the typical additional delay from decision to treat to either PCI or ED fibrinolysis was ≤60 minutes.

One study (LOE 1)²¹⁷ and a post hoc subgroup analysis (LOE 7)²⁴⁶ of fibrinolysis compared with PCI showed no difference in survival rates when fibrinolysis was initiated within 2 hours²⁴⁶ or 3 hours²¹⁷ after onset of symptoms.

One RCT and a 1-year follow-up of the same study (LOE 1)^{216,247} comparing early revascularization (eg, surgery, facilitated PCI, and primary PCI) with medical therapy in patients with cardiogenic shock showed decreased 6-month and 1-year mortality rates, especially for patients <75 years of age. Direct comparison of the outcome of primary PCI patients to patients who received only fibrinolytic therapy was not reported.

Treatment Recommendation

All patients presenting with STEMI within 12 hours of the onset of symptoms should be evaluated for reperfusion therapy (ie, fibrinolysis or PCI).

Primary PCI is the preferred reperfusion strategy in STEMI with symptom duration >3 hours if a skilled team can perform primary PCI in ≤90 minutes after first medical contact with the patient or if there are contraindications to fibrinolysis.

If the duration of symptoms is ≤3 hours, treatment is more time-sensitive, and the superiority of out-of-hospital fibrinolysis, immediate in-hospital fibrinolysis, or transfer for primary PCI is not established (see below for further discussion of transfer).

Early revascularization (ie, surgery, primary or early PCI, defined as PCI ≤24 hours after fibrinolysis) is reasonable in patients with cardiogenic shock, especially for patients <75 years of age.

Primary and Secondary Prevention Interventions

Traditional preventive interventions usually start with the first admission with a confirmed diagnosis of ACS. Therapeutic options include antiarrhythmics, β -blockers, angiotensin-converting enzyme (ACE) inhibitors, and HMG-CoA reductase inhibitors (statins). The current evidence indicates that with the exception of β -blockers, none plays a significant role in the out-of-hospital and ED management of ACS.

Antiarrhythmics^{W230}

Lidocaine

Consensus on Science

When lidocaine was given by physicians or paramedics for primary prophylaxis within the first 4 hours of a suspected STEMI in the out-of-hospital setting, 4 meta-analyses (LOE 1)^{248–251} and 2 RCTs (LOE 2)^{250,252} showed a trend toward increased mortality rates. In addition, 2 meta-analyses^{253,254} and 15 RCTs (LOE 1²⁵⁵; LOE 2^{256–269}), 1 case series (LOE 5),²⁷⁰ and 1 retrospective trial (LOE 5)²⁷¹ showed no effect of lidocaine on mortality in this setting. Only one small study (LOE 2)²⁷² showed a decrease in mortality with prophylactic lidocaine. Several trials (LOE 2^{258,259,262,264,265}; LOE 5²⁷⁰) reported more side effects (including paresthesias, tinnitus, confusion, bradycardia requiring treatment, seizures, coma, and respiratory arrest) in patients receiving prophylactic lidocaine.

Magnesium

Consensus on Science

Giving magnesium prophylactically to patients with STEMI has produced mixed results. One study (LOE 2)²⁷³ showed a decrease in mortality and symptomatic arrhythmias. One meta-analysis (LOE 1)²⁷⁴ and 2 RCTs (LOE 1²⁷⁵; LOE 2²⁷⁶) showed a decrease in mortality but no reduction in ventricular arrhythmias. One small RCT (LOE 2)²⁷⁷ showed that magnesium reduced the incidence of ventricular tachycardia, but it was underpowered to assess mortality. The definitive study on the subject is the ISIS-4 study (LOE 1).²⁷⁸ ISIS-4 enrolled >58 000 patients and showed a trend toward increased mortality when magnesium was given in-hospital for primary arrhythmia prophylaxis to patients within the first 4 hours of known or suspected AMI.

Disopyramide, Mexiletine, and Verapamil

Consensus on Science

One multi-antiarrhythmic meta-analysis (LOE 1)²⁷⁹ and 4 RCTs (LOE 2^{280–282}; LOE 7²⁸³) showed no effect on mortality when a variety of antiarrhythmic drugs (disopyramide, mexiletine, and verapamil) were given for primary prophylaxis by paramedics or physicians to patients within the first 4 hours of known or suspected AMI.

Treatment Recommendation for Antiarrhythmics

There is insufficient evidence to support the routine use of any antiarrhythmic drug as primary prophylaxis within the first 4 hours of proven or suspected AMI.

This conclusion does not take into account the potential effect of β -blockers discussed below.

β -Blockers

^{W232}

Consensus on Science

Two in-hospital RCTs (LOE 1)^{284,285} and 2 supporting studies (LOE 2)^{286,287} completed before the advent of fibrinolytics documented decreased mortality, reinfarction, ventricular fibrillation, supraventricular arrhythmias, and cardiac rupture in patients treated with β -blockers. In patients with AMI who received fibrinolytics, treatment with IV β -blockade within

24 hours of onset of symptoms reduced rates of reinfarction and cardiac rupture. IV β -blockade may reduce mortality in patients undergoing primary PCI who are not on oral β -blockers (LOE 7).²⁸⁸ β -Blocker therapy was initiated in the ED for most of these trials; only one included out-of-hospital administration.²⁸⁹

One small trial (LOE 2)²⁹⁰ showed a trend toward decreased mortality when IV β -blockers were given for unstable angina.

Treatment Recommendation

In the ED treat ACS patients promptly with IV β -blockers followed by oral β -blockers. β -Blockers are given irrespective of the need for revascularization therapies. Contraindications to β -blockers include hypotension, bradycardia, heart block, moderate to severe congestive heart failure, and reactive airway disease.

ACE Inhibitors^{W231}

Consensus on Science

Seven large clinical trials (LOE 1),^{278,291–296} 2 meta-analyses (LOE 1),^{297,298} and 11 minor trials (LOE 1)^{296,299–308} documented consistent improvement in mortality when oral ACE inhibitors were given to patients with AMI with or without early reperfusion therapy. ACE inhibitors should not be given if hypotension (systolic blood pressure <100 mm Hg or more than 30 mm Hg below baseline) is present or a contraindication to these drugs exists.

One large, randomized, double-blind, placebo-controlled trial (LOE 1)³⁰⁹ and 2 small randomized trials (LOE 2)^{310,311} in adults documented a trend toward a higher mortality rate if an IV ACE inhibitor was started within the first 24 hours after onset of symptoms in the hospital setting. There is no literature evaluating the therapeutic role of ACE inhibitors in the out-of-hospital setting.

Treatment Recommendation

Start an oral ACE inhibitor within 24 hours after onset of symptoms in patients with MI whether or not early reperfusion therapy is planned. Do not give an ACE inhibitor if the patient has hypotension (systolic blood pressure <100 mm Hg or more than 30 mm Hg below baseline) or if the patient has a known contraindication to these drugs. ACE inhibitors are most effective in patients with anterior infarction, pulmonary congestion, or left ventricular ejection fraction <40%.

There is no evidence to recommend for or against starting ACE inhibitors in the out-of-hospital setting. Avoid giving IV ACE inhibitors within the first 24 hours after onset of symptoms because they can cause significant hypotension during this phase.

HMG CoA Reductase Inhibitors (Statins)^{W233}

Consensus on Science

Nine RCTs (LOE 7)^{312–320} and additional small studies (LOE 3–7)^{321–323} documented a consistent decrease in the incidence of major adverse cardiovascular events (reinfarction, stroke, necessary intervention for recurrent angina, and rehospitalization) when statins were given within a few days after onset

of ACS. There are few data on patients treated within 24 hours of the onset of symptoms.

One retrospective analysis (LOE 4)³²⁴ and data from one registry (LOE 4)³²⁵ showed that patients presenting with ACS who are already taking statins should continue to take them.

There is no data on the initiation of statin therapy out-of-hospital or in the ED for patients with ACS.

Treatment Recommendation

It is safe and feasible to start statin therapy early (within 24 hours) in patients with ACS or AMI; once started, continue statin therapy uninterrupted.

Healthcare System Interventions for ACS/AMI

Novel strategies have been developed and evaluated to improve the speed and quality of care delivered to patients with ACS. Many strategies have been shown to be safe, effective, and feasible in the prehospital setting and ED. Such strategies include out-of-hospital 12-lead ECG and advance ED notification, interfacility transfer of the patient for PCI, and a combined strategy of interfacility transfer after fibrinolysis.

12-Lead Out-of-Hospital ECG and Advance ED Notification^{W235A,W235B}

Consensus on Science

Two RCTs (LOE 2),^{326,327} 6 nonrandomized controlled trials (LOE 3),^{101,328–332} 1 retrospective cross-sectional study (LOE),¹⁰⁶ and extrapolations from 2 feasibility studies (LOE 4³³³; LOE 3¹⁰³) showed a reduction of 10 to 60 minutes in the door-to-reperfusion interval for patients with STEMI when a 12-lead out-of-hospital ECG was obtained and interpreted by a physician, nurse, or paramedic and sent to the receiving hospital in advance (cellular ECG transmission or verbal communication).

One RCT (LOE 2)³²⁶ and 5 other studies (LOE 5^{103,334}; LOE 4³³³; LOE 3¹⁰¹; LOE 5³³⁵) showed that 12-lead out-of-hospital ECGs with advance notification undertaken by out-of-hospital personnel does not increase on-scene time interval significantly (0.2 to 5.6 minutes) in patients with suspected AMI.

Four studies (LOE 3^{103,334,336}; LOE 5³³⁵) showed that out-of-hospital personnel can acquire and transmit diagnostic-quality 12-lead out-of-hospital ECGs.

Treatment Recommendation

Routine use of the 12-lead out-of-hospital ECG with advance ED notification may benefit STEMI patients by reducing the time interval to fibrinolysis.

Advance ED notification may be achieved with direct transmission of the ECG itself or verbal report (via telephone) of the ECG interpretation by out-of-hospital personnel.

Interfacility Transfer for Primary PCI^{W237A,W237B}

Consensus on Science

Three RCTs (LOE 2)^{213,217,240} and one meta-analysis (LOE 1)²¹⁹ documented safety and improved combined event rate (30-day combined rate of death, reinfarction, or stroke) when patients with STEMI from hospitals without the capability for

primary PCI were transferred promptly for primary PCI at a skilled facility. A skilled facility provides access to PCI undertaken by a skilled operator in a high-volume center (ie, >75 procedures per operator annually) with minimal delay.^{214,225,226}

When combined in a meta-analysis (LOE 1),²¹⁹ 5 RCTs (LOE 2)^{213,217,233,240,241} showed reduced mortality rates when patients with STEMI from hospitals without the capability for primary PCI were transferred promptly to a facility with such capability.

In one RCT (LOE 2)²¹⁷ and one post hoc subgroup analysis of an RCT (LOE 7),²⁴⁶ it is unclear whether immediate out-of-hospital fibrinolysis, in-hospital fibrinolysis, or transfer for primary PCI is most efficacious for patients presenting with STEMI within 2 to 3 hours of the onset of symptoms.

Treatment Recommendation

For patients with STEMI presenting >3 hours but <12 hours from the onset of symptoms, interfacility transfer from hospitals that lack primary PCI capability to centers capable of providing primary PCI is indicated if such a transfer can be accomplished as soon as possible. Optimally PCI should occur ≤90 minutes from first medical contact (ie, contact with a healthcare provider who can make the decision to treat or transfer).

In patients with STEMI presenting ≤3 hours from onset of symptoms, treatment is more time-sensitive, and there is inadequate data to indicate the superiority of out-of-hospital fibrinolysis, immediate hospital fibrinolysis, or transfer for primary PCI.

The time recommendations do not apply to patients in cardiogenic shock. In such patients the evidence supports early revascularization therapy (primary PCI, early PCI, or surgery) compared with medical therapy.²¹⁶

Out-of-Hospital Triage for PCI^{W236A,W236B}

Consensus on Science

A single study (LOE 2)³³⁷ with insufficient power and some methodological concerns and a second post hoc subgroup analysis (LOE 7)²⁴⁶ failed to show that out-of-hospital triage for primary PCI was any better than out-of-hospital fibrinolysis in patients with STEMI in systems involving the presence of physicians in mobile intensive care units (MICUs).

No randomized studies directly compared out-of-hospital triage for primary PCI with fibrinolytics given at a community hospital.

Extrapolations from 3 RCTs on interfacility transfer (LOE 7)^{213,217,240} suggest that out-of-hospital STEMI patients may do better with direct triage to a primary PCI facility because of the potential for earlier treatment. A cost-effectiveness substudy of the Comparison of Angioplasty and Prehospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial³³⁷ using critical-care physicians during transport and for administration of fibrinolytics suggests that direct transport to a primary PCI facility may be more cost-effective than out-of-hospital fibrinolysis when transport can be completed in ≤60 minutes. But this study excluded patients considered to be at

high risk for complications during transfer (eg, cardiogenic shock).

Treatment Recommendation

There is some limited evidence to recommend out-of-hospital triage for primary PCI for patients with uncomplicated STEMI who are ≤60 minutes away from a PCI site in systems that use MICUs with physicians on board with the proviso that the delay from decision to treat to balloon inflation is ≤90 minutes. Further studies are required to define appropriate triage and transport criteria.

Interfacility Transfer for Early PCI^{W237A,W237B}

Consensus on Science

A strategy of fibrinolysis combined with transfer for early PCI (defined as PCI performed ≤24 hours after fibrinolysis) is supported by 6 randomized trials (LOE 1^{223,338,339} and LOE 2^{241,340,341}). The efficacy of this strategy is also supported by a post hoc nonrandomized comparison (LOE 3).³⁴² But this strategy is not supported by other RCTs (LOE 1^{343–345}; LOE 2^{223,240}) and other nonrandomized studies or secondary analyses of the above trials (LOE 7).³⁴⁶ Several meta-analyses showed no benefit of early PCI (LOE 1).^{347–349} All but one of these trials were carried out in the 1990s before the era of coronary stenting. These studies did not use modern drugs or contemporary PCI techniques.

The feasibility of fibrinolysis combined with transfer for early PCI is supported by 3 low-level studies. One study is a small trial in which PCI was performed routinely (LOE 7),³⁵⁰ one is a randomized trial of low-dose fibrinolytics compared with placebo before immediate cardiac catheterization and PCI as necessary (LOE 7),³⁵¹ and one is a retrospective analysis (LOE 7).³⁵²

The efficacy of early PCI for patients with cardiogenic shock was shown in an RCT that showed improved mortality at 6 months and 1 year with early revascularization (LOE 1),²¹⁶ especially in patients <75 years of age. This was supported by a retrospective analysis (LOE 7).³⁵³

One RCT (LOE 2) showed improvement in secondary nonfatal outcomes when early PCI was used for patients who did not achieve reperfusion after fibrinolysis.³⁵⁴

All of the above studies involved in-hospital fibrinolysis. The use of prehospital fibrinolysis followed by early PCI has not been studied.

Treatment Recommendation

There is inadequate evidence to recommend the routine transfer of patients for early PCI after successful fibrinolysis in community hospital EDs or out of hospital.

Transfer for early PCI is recommended as one strategy for early revascularization for patients with cardiogenic shock, especially patients <75 years of age; or with hemodynamic instability or persistent symptoms of ischemia after fibrinolysis.

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