Chapter 5

ACS; Acute Coronary Syndrome

1 Introduction

Guidelines on Acute Coronary Syndrome are edited based on 2010 CoSTR, with consideration for current status of medical services in Japan. The International Liaison Committee on Resuscitation (ILCOR) ACS–MI Task Force included expert reviewers from Africa, Asia, Australia, Europe, North America, and South America. These experts reviewed 25 topics related to the acute initial management of acute coronary syndrome (ACS), which was further categorized as unstable angina, non–ST-elevation MI (UA/NSTEMI) and ST-elevation MI (STEMI). Topics were identified based on previous recommendations, emerging science, and clinical importance, using an iterative writing process involving all Task Force members. The Task Force reviewed the evidence specifically related to diagnosis and treatment of ACS in the out-of-hospital setting and the first hours of care in the in-hospital setting, typically in the emergency department (ED). The evidence review took place over several years, with ongoing refinement of recommendations being made as new evidence was published. The purpose of the review was to generate current, evidence-based treatment recommendations for healthcare providers who serve as the initial point of contact for patients with signs and symptoms suggestive of ACS. The following is a summary of the most important changes in recommendations for diagnosis and treatment of ACS since the last ILCOR review in 2005.1–2

- The history and physical examination, initial ECG, and initial serum biomarkers, even
when used in combination, cannot be used to reliably exclude ACS in the prehospital and ED settings.

- In contrast, chest pain observation protocols are useful in identifying patients with suspected ACS and patients who require admission or may be referred for provocative testing for coronary artery disease (CAD) to identify reversible ischemia. Such strategies also reduce cost by reducing unnecessary hospital admissions and improve patient safety through more accurate identification of NSTEMI and STEMI.

- The acquisition of a prehospital 12-lead ECG is essential for identification of STEMI patients before hospital arrival and should be used in conjunction with pre-arrival hospital notification and concurrent activation of the catheter laboratory.

- Nonphysicians can be trained to independently interpret 12-lead ECGs for the purpose of identifying patients with STEMI, provided that appropriate and reliable STEMI criteria are used. This skill is of particular value in the prehospital setting where paramedics may independently identify STEMI, thus mitigating over-reliance on ECG transmission.

- Computer-assisted ECG interpretation can be used to increase diagnostic accuracy of STEMI diagnosis when used alone or in combination with ECG interpretation by a trained healthcare provider.

- STEMI systems of care can be implemented to improve the time to treatment. The following measures have been shown to reduce the time to primary percutaneous coronary intervention (PPCI): institutional commitment, use of a team-based approach, arranging single-call activation of the catheterization laboratory by the emergency physician or prehospital provider, requiring the catheterization laboratory to be ready in 20 minutes, having an experienced cardiologist always available, and providing real-time data feedback.

- Intravenous (IV) beta-blockers should not be given routinely in the ED or prehospital setting, but may be useful in a subset of patients with hypertension or tachycardia in the setting of ACS.

- The routine use of high-flow supplemental oxygen in ACS is not recommended. Instead, oxygen administration should be guided by arterial oxygen saturation.

- Reinforce the need for time targets for reperfusion beginning from the time of first medical contact (PMC). The clinical circumstances that favor fibrinolysis and PCI are discussed, including the role of prehospital fibrinolytics.

- The prophylactic use of antiarrhythmics is discouraged.

- Angiography and percutaneous coronary intervention (PCI) may be considered in patients with out-of-hospital cardiac arrest (OHCA) and return of spontaneous circulation (ROSC). It may also be acceptable to perform angiography in selected patients, despite the absence of ST-segment elevation on the ECG or prior clinical findings such as chest pain.

Despite progress in diagnostic and therapeutic strategies, numerous knowledge gaps have been identified during the discussions. These gaps include:
Much of the research concerning the care of the patient with ACS has been conducted
on in-hospital populations rather than specifically in the ED or out-of-hospital
settings. By definition, extending the conclusions from such research to the early ED management
or the out-of-hospital setting requires extrapolation.

- Strategies for improving layperson recognition of ACS and shortening time to diagnosis
  in vulnerable populations.
- The value of emergency dispatcher-initiated bystander administration of aspirin.
- Accurate decision rules for the early identification of patients with and without
  ACS in the prehospital and the ED settings.
- Feasibility of widespread paramedic interpretation of prehospital 12-lead ECGs versus
  reliance on transmission or computer interpretation.
- Impact on mortality of systems of care strategies designed to expedite reperfusion.
- The role of reperfusion including PCI in post-cardiac arrest care following either
  prehospital or in-hospital cardiac arrest, in the presence or absence of STEMI.
- The sensitivity and specificity of newer biomarkers for the detection of ACS.
- Is high-dose oxygen harmful in the setting of ACS?
- What is the role of analgesia and anxiolysis in patients with ACS?
- Optimal timing of platelet inhibition and anticoagulation in the prehospital and ED
  setting.
- While the time goals for reperfusion begin with first medical contact, time from
  symptom onset may be preferred, yet precise identification of this time point has been
  elusive.

The American Heart Association and the American College of Cardiology, the European
Society of Cardiology, Japanese Circulation Society, and others have developed
comprehensive guidelines for the in-hospital management of patients with STEMI and
UA/NSTEMI, and the reader is referred to these guidelines for more detailed
recommendations regarding the care of patients with ACS. The ILCOR CoSTR statements
are intended to supplement these other resources by having a specific focus on the
initial evaluation and treatment in the prehospital and ED phases of care. It is
envisioned that these CoSTR documents will be used to develop treatment guidelines to
assist providers during the initial acute phase of care.

2 Algorithm for Primary Care in Acute Coronary Syndrome (ACS)

The basic concept for management when patients with chest symptoms suggesting
ischemia request for an ambulance or present at a primary emergency medical facility
is the prompt diagnosis of ACS, followed by treatment with oxygen, aspirin, nitrates,
and morphine. In the emergency department, a disease history should be taken. The
diagnostic workup should include evaluations of disease acuteness and severity. A
12-lead electrocardiogram (ECG) has a central role in the primary triage of patients. If ST-segment elevation myocardial infarction (STEMI) is diagnosed, reperfusion therapy should be performed in close cooperation with a cardiologist. If ST-segment depression is present, high-risk unstable angina (UA) or non-ST-segment elevation myocardial infarction (NSTEMI) should be suspected. Patients should be admitted to a coronary care unit or comparable facilities in cooperation with a cardiologist. Such patients have high short-term risks of cardiac events (death, non-fatal myocardial infarction, and emergency revascularization) and usually receive drug therapy, as well as early invasive treatment strategies such as catheter intervention. In patients in whom ECG findings are normal or equivocal, risks can be further stratified according to chest pain assessment protocols used at each hospital, the time course of myocardial markers such as troponin, and 12-lead ECG findings. Echocardiography is useful for evaluating regional wall motion, left cardiac function, and mechanical complications (left ventricular free wall rupture, ventricular septal perforation, and papillary muscle rupture), as well as for differential diagnosis from other diseases (e.g., acute aortic dissection, acute pulmonary embolism, and acute pericarditis). Chest radiography is useful for assessing disease severity and for differential diagnosis from other diseases, but is not essential. Reperfusion therapy should not be delayed by waiting for the results of blood tests to confirm the diagnosis.
Figure 1. Acute Coronary Syndrome Algorithm

3 Diagnosis tests in ACS

The prognostic and diagnostic use of the signs and symptoms of ACS, cardiac markers, and 12-lead ECG can have enormous impact on the initial impression and management of patients with suspected ACS. As such, it is important to evaluate the sensitivity,
specificity, and clinical impact of various diagnostic strategies in ACS through a comprehensive evidence-based process.

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

1. Risk Stratification

1) Demographic Factors

(1) Prehospital Treatment Delay

Several studies performed outside Japan (LOE P1\textsuperscript{7, 8}; LOE P3\textsuperscript{9-49}) showed that demographic factors, such as older age,\textsuperscript{8, 11, 16, 19-25, 28-31, 35-39, 41} female gender,\textsuperscript{7, 10-13, 16, 19, 21, 22, 25, 26, 28-35, 37, 38, 42} nonwhite race,\textsuperscript{7, 8, 14, 15, 19-21, 27, 30, 38-40} low socioeconomic status,\textsuperscript{7, 9, 17, 18, 37, 38, 41} and living alone\textsuperscript{7, 19, 25} are independent predictive factors for prehospital treatment delay (symptom-to-door time).

An observational study (J-LOE P3\textsuperscript{43}) on 1410 Japanese AMI patients showed that female gender is associated with prehospital delay (symptom-to-admission time). Whereas other studies indicated that old age, female gender, nonwhite race and/or living alone did not show any association with prehospital delay times (LOE P2\textsuperscript{14}; LOE P3\textsuperscript{13, 17, 20, 24, 25, 36, 40, 41, 45-55}).

As many studies analyzed more than one demographic factor for prediction of treatment delay, and one factor may predict delay while another factor was not found to be independent for prediction of delay, 8 studies were mixed in identifying factors associated with treatment delays (LOE P2\textsuperscript{13, 17, 20, 24, 25, 36, 40, 41}).

(2) In-Hospital Treatment Delay

Several studies (LOE P2\textsuperscript{8}; LOE P3\textsuperscript{9, 10, 14, 19, 29, 39, 42, 56-63}; LOE 5\textsuperscript{64-66}) showed that demographic factors, such as older age,\textsuperscript{8, 19, 29, 39, 56-59, 61, 62, 64} female gender,\textsuperscript{8, 10, 19, 29, 39, 42, 56-59, 61-65} nonwhite race,\textsuperscript{8, 14, 19, 39, 56, 59-64, 64-66} low socioeconomic status,\textsuperscript{8, 9} and living alone\textsuperscript{19} are independent factors for in-hospital treatment delay (door-to-balloon, door-to-needle, or door-to-reperfusion time).

Five studies indicated that older age, female gender, nonwhite race and/or living alone did not show any association with in hospital delay times (LOE P3).\textsuperscript{49, 50, 55, 63, 67} Because most data on the impact of demographic factors on delay to treatment for patients with ACS have been derived from studies in North America, health care providers should be aware that different social security system or culture may also affect behavior of the ACS patients.

Various patient-related factors (e.g. age, gender, socioeconomic status, and living alone) impede seeking medical help rapidly, but also add to further in-hospital treatment delay. Health care providers should be trained to expeditiously identify patients with ACS irrespective of age, gender, socioeconomic status, or living arrangements (Class I).
2) Accuracy of History and Physical Examination for diagnosing ACS

(1) Diagnosis

Fourteen studies (LoE 268-71; LoE 372-81) did 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 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%).

Four LoE 1 studies52, 82-84 and 32 studies (LoE 3 to 524, 31, 53, 68-71, 73-76, 79, 85-103) suggest that individual clinical signs and symptoms lack sufficient sensitivity and specificity to be used alone and independent of ECG, cardiac biomarkers, or other diagnostic tests to rule in or rule out ACS in prehospital or ED settings.

(2) Prognosis and Clinical Impact

In 34 studies (LoE 172, 84, 92; LoE 224, 68-71, 87, 94, 95, 100, 104; LoE 331, 53, 73-75, 77-80, 83, 85, 86, 89, 90, 93, 96-99, 101, 105), a variety of signs and symptoms assisted in the diagnosis of ACS and had clinical impact (defined as triage and some treatment and investigational decisions) on the prehospital emergency management and risk assessment for coronary atherosclerosis and unstable syndromes.

Three LoE 1 meta-analyses/systematic reviews, 28, 72, 83, 84 studies LoE 3 to 524, 31, 53, 68-71, 73-76, 85-87, 89-95, 97-101, 103, 104 suggest that some clinical signs (eg, chest pain that radiates to the left arm, radiates to the right shoulder, or radiates to both arms, patients presenting with chest pain and sweating, S3 or hypotension, sweating, and/or vomiting, a history of risk factors [in addition to known coronary heart disease], and some demographic characteristics such as age) assisted in the diagnosis of ACS and had clinical impact (defined as influencing triage and some treatment and investigational decisions) on the out-of-hospital emergency management and risk assessment for ACS.

One LoE 5 study103 and extrapolations from 27 other studies LoE 3 to 524, 31, 53, 68-71, 73-76, 85-87, 89-95, 97-101, 103, 104 suggested that there are symptom clusters related to demographic factors such as age, race, and sex. These symptom clusters may have an impact on clinical decision making (defined as influencing triage and some treatment and investigational decisions). One systematic review/meta-analysis (LoE 182) found the sign of tenderness to chest wall palpation useful in ruling out a diagnosis of AMI.

Signs and symptoms alone are neither sensitive nor specific and should not be used without other data for making the diagnosis of ACS (Class III).

Signs and symptoms 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 for ACS in the out-of-hospital and ED setting (Class IIb).

3) ACS and Nitroglycerin
Five studies (LOE D2, 79, 106; LOE D4, 107, 108) using reduction in pain after nitroglycerin administration as an end point, found that reduction of pain does not reliably identify presence of ACS.

2. Interpretation of 12-Lead ECG for STEMI

1) 12-lead ECG

One study showed that prehospital or emergency ECGs had a sensitivity of 76% and a specificity of 88% for diagnosing acute cardiac ischemia in patients with chest pain (LOE D1). For diagnosing AMI, prehospital ECG had a sensitivity of 68% and a specificity of 97%. Two studies indicated that diagnostic accuracy of prehospital ECG can be improved by repeating the ECG on arrival in the ED and by serial measurement of cardiac markers (LOE D2, 110, 111). Two studies showed that computer-interpreted electrocardiography or field-transmitted electrocardiography can be applied if no adequate interpretation of the prehospital ECG is available on site (LOE D1, 112, 113).

In patients with suspected ACS, a 12-lead-ECG should be acquired and interpreted by prehospital or emergency providers as soon as possible after first patient contact (Class I). The interpretation should be used to for diagnosis and triage, including destination decisions and cardiac catheterization laboratory activation (Class IIb). If interpretation of the prehospital ECG is not available on-site, field-transmission of the ECG for expert interpretation may be reasonable (Class I). It is recommended that utilization of prehospital 12-lead-ECG, which leads to prompt initiation of specialized treatment for STEMI, should be considered in Japan.

2) Diagnosis of STEMI by nonphysicians

Eight observational studies reported paramedics can diagnose STEMI in the prehospital setting without transmission of a 12-lead ECG for physician consultation (LOE D3, 114-116; LOE D4, 117-120; LOE D5, 121). The limited evidence available about paramedic false-negative diagnostic decisions, including decisions not to obtain a 12-lead ECG, may affect paramedics’ true overall diagnostic accuracy. Eight observational studies reported that nurses can diagnose STEMI in the context of nurse-initiated fibrinolysis programs (LOE D3, 122; LOE D4, 117, 123-125; LOE D5, 126-128). The literature largely describes the ability of nurses to avoid false positive diagnosis in fibrinolysis programs without substantial evidence about false-negative decisions, which may affect true overall diagnostic accuracy.

It is reasonable for paramedics and nurses to identify STEMI on a 12-lead ECG independently as long as there is a program of mandatory initial training followed by ongoing concurrent medical oversight of all interpretations (Class IIa).

3) Computer-assisted ECG interpretation

Two studies found evidence of improved diagnostic accuracy with the use of computerized
ECG interpretation (LOE D5\textsuperscript{129, 130}). Eight studies either found no effect or equivocal effect of the use of computerized ECG interpretation on diagnostic accuracy (LOE 1\textsuperscript{112, 131-133}, LOE D5\textsuperscript{134-137}). Two studies found evidence that the use of computerized ECG interpretation decreased diagnostic accuracy (LOE D1\textsuperscript{138, 139}). Three studies showed computer ECG interpretation relating to ACS to be reliable (LOE D1\textsuperscript{138}; LOE 1\textsuperscript{112, 131}). The 'gold standard' used most commonly was expert 'electrocardiographer' review, although four studies used validated clinical diagnosis as the gold standard (LOE 1\textsuperscript{133}, LOE D1\textsuperscript{112}; LOE D1\textsuperscript{132}; LOE D5\textsuperscript{134}). Two studies report a higher specificity for the computer-interpretation (identifying true negatives), whilst the physicians had a higher sensitivity (identifying true positives) (LOE 1\textsuperscript{112}; LOE D1\textsuperscript{132}). Three studies found that computer interpretation had a greater influence on non-expert subject performance in interpreting ECGs than it did on more expert interpretation (LOE D1\textsuperscript{138}; LOE D5\textsuperscript{136}; LOE D5\textsuperscript{134}).

Pre-hospital ECG interpretation should be augmented with computer interpretation (Class I). Computer interpretation of the ECG may increase the specificity of diagnosis of STEMI, especially for clinicians less experienced in reading ECGs. The benefit of computer interpretation is dependent on accuracy, and therefore computer-assisted ECG interpretation should not replace, but may be used as an adjunct to, interpretation by an experienced clinician. The computer interpretation should be considered in the clinical context.

3. Diagnostic and Prognostic Test Characteristics of Cardiac Biomarkers for ACS

1) Protein markers of coronary ischemia

One of the typical diagnostic criteria for AMI, “the presence of CK elevated more than twice than the upper limit of normal” has been commonly used, while the 2007 Global Task Force of ESC, ACC, AHA and WHF updated the universal definition for AMI to recommend cardiac troponin as the preferred biomarker. Cardiac troponin assays are optimal for diagnosis of AMI if measurement is available. For evaluation of patients with suspected myocardial ischemia, the 2010 CoSTR recommended that diagnostic criteria should require a high-sensitivity troponin with a coefficient of variation at the 99th percentile less than or equal to 10% (Class IIa). The 2007 ACC/AHA guidelines classified serial measurements of cardiac markers as indicators of infarction size and myocardial necrosis into Class II a, while the 2010 CoSTR mentions nothing regarding infarction size using serial cardiac marker measurements. In recent research on new cardiac markers, more markers with higher sensitivity and specificity have been studied, the diagnostic efficacy of IMA (Ischemia-Modified Albumin), H-FABP (Heart-type Fatty Acid-Binding Protein), BNP (Brain Natriuretic Peptide), and copeptin has attracted attention. No new markers, however, have appeared with sufficient sensitivity and specificity.

Eight studies supported cardiac troponin testing alone in the diagnosis of acute myocardial infarction, when serum testing was drawn at least 6 hours from time of symptom
onset, ED presentation, or drawn serially (LOE D2\textsuperscript{149-142}; LOE D3\textsuperscript{143}; LOE D4\textsuperscript{144-147}).

No studies showed adequate sensitivity of cardiac troponin testing outside of the emergency department or short stay cardiac unit (LOE 2\textsuperscript{148}; LOE 4\textsuperscript{149-151}) including the ICU (LOE 4\textsuperscript{152}). Four studies showed increased sensitivity of new sensitive troponin assays compared with conventional troponin assays and supported their use to diagnose AMI (LOE D2\textsuperscript{153, 154}; LOE D3\textsuperscript{155}; LOE D4\textsuperscript{156}). Nine studies supported multimarker testing (CKMB, ischemia-modified albumin or myoglobin) in combination with cardiac troponin in the diagnosis of AMI (LOE D2\textsuperscript{140, 142, 154, 157-159}; LOE D4\textsuperscript{146, 157, 160}).

There were heterogeneous data on the use of troponin point-of-care testing in the diagnosis of ACS: Five studies supported the use of troponin POCT (LOE D2\textsuperscript{146}; LOE D4\textsuperscript{161-164}), and five studies opposed the use of troponin POCT in the ED/cardiac short stay units (LOE D3\textsuperscript{165}; LOE D4\textsuperscript{166-169}), two studies opposed the use of troponin POCT in the prehospital setting (LOE D4\textsuperscript{150, 151}), and one opposed the use of troponin POCT in the outpatient clinic setting (LOE D2\textsuperscript{150, 151}).

Clinicians should take into account the timing of symptom onset, the sensitivity, precision and institutional norms of the assay, and the release kinetics and clearance of the measured biomarker (Class I).

All patients presenting to the ED with symptoms suspicious of cardiac ischemia should have cardiac biomarker testing as part of an initial evaluation (Class I). A cardiac-specific troponin is the preferred biomarker (Class I). For patients who present within 6 hours of symptom onset suggestive of cardiac ischemia with negative cardiac troponin initially, it is recommended that a troponin level be remeasured between 6 and 12 hours after symptom onset (Class IIa). It is reasonable to use highly sensitive cardiac troponin assays, defined as having a 10% coefficient of variation at the 99th percentile, to evaluate patients with symptoms suspicious of cardiac ischemia. Multimarker evaluation with CKMB or myoglobin in conjunction with troponin in patients with symptoms suspicious of cardiac ischemia may be considered to improve the sensitivity of diagnosing AMI (Class IIb).

There is no evidence to support the use of troponin point-of-care testing (POCT) in isolation as a primary test in the prehospital setting to evaluate patients with symptoms suspicious of cardiac ischemia.

There is insufficient evidence to support the use of myoglobin, brain naturetic peptide (BNP), NTproBNP, D-dimer, C-reactive protein, ischemia-modified albumin pregnancy-associated plasma protein A (PAPP-A) and/or interleukin-6 in isolation as primary tests to evaluate patients with symptoms suspicious for cardiac ischemia.

2) Prognosis for discharge versus admission

In evaluating patients presenting to the ED with symptoms suggestive of cardiac ischemia, it is relatively easy to identify patients with ACS who require hospital admission and patients without the possibility of ACS. Among those in-between, who are at low to intermediate risk, identifying patients with or without ACS is difficult. The case history and physical examination, 12-lead-ECG, and cardiac biomarkers are used
in evaluation for ACS in the ED. For further testing, not every healthcare provider in every medical facility is able to perform exercise stress tests, nuclear myocardial perfusion imaging, echocardiography and CT angiography. These additional exams will be described in another section on diagnostic imaging.

There are no randomized controlled studies addressing clinical decision rules for ACS in the prehospital or ED settings. Existing studies do not adequately address the question because they are heterogeneous (LOE P1\textsuperscript{170}). There is not a single published clinical decision rule which is adequate and appropriate for identifying ED chest pain patients who can be safely discharged home from the ED (LOE P1\textsuperscript{170}).

Younger patients with no history of previous ischemic heart disease, atypical presentations, negative serial biomarkers and a non-diagnostic 12-lead ECGs have a very low short-term rate of adverse events. Five studies demonstrated that younger patients with no history of previous ischemic heart disease, atypical presentations, negative serial biomarkers and non-diagnostic 12-lead ECGs have a very low short-term rate of adverse events (LOE P2\textsuperscript{88, 171-176}). One study demonstrated that older patients are evaluated less effectively, and that the subset of older patients who can be safely discharged from the ED are less easily identified than younger patients (LOE P2\textsuperscript{88}).

Five studies demonstrated that the combined use of serial biomarkers and ECGs in selected patients (i.e., low risk, sensation-free, and clinically stable) can assist in the identification of a subset of patients who can be safely discharged from the ED (LOE P2\textsuperscript{88, 171, 172, 175, 176}). This statement is not directly age dependent although older patients demonstrate higher rates of ACS diagnosis and adverse outcome.

Nine studies demonstrated that scoring systems derived from inpatient populations (e.g. TIMI Risk Score or Goldman Criteria) are not appropriate for ED use and do not assist in the identification of patients who can be safely discharged from the ED (LOE P1\textsuperscript{177, 178}; LOE P3\textsuperscript{179-185}).

None of the currently reported clinical decision rules should be used to select ED chest pain patients who can be safely discharged from the ED. Patients less than 40 years with non-classical presentations and lacking significant past medical history, who have normal serial biomarkers and 12-lead ECGs, have a very low short-term event rate.

3) Chest pain observation units

It is suggested that the use of a chest pain observation unit on patients with suspected ACS should increase the accuracy of diagnosis, selection of patients requiring hospital admission, and identification of patients requiring specific treatment for coronary arteriopathy compared with not using a chest pain observation unit. Chest pain units have been developed to assess patients with chest pain and normal initial biomarker and non-ischemic electrocardiogram. The elements that define a chest pain unit vary depending on characteristics of the individual organizations and the clinical context in which the unit is sited (e.g. ED versus inpatient environment versus dedicated site).
Components of the chest pain unit are typically: a protocol or pathway based care strategy; dedicated physical space/infrastructure and staffing; use of an accelerated risk stratification protocol comprising

- Measurement of serial biomarkers of acute infarction (e.g. troponin or CK-MB)
- Serial ECG or continuous ECG monitoring
- A period of observation (6 hours)
- Integrated with more advanced diagnostic testing (e.g. exercise stress test, myocardial perfusion scan)

Eleven studies of patients with chest pain and normal initial biomarkers and non diagnostic ECGs demonstrated that CPUs result in reduced length of stay, hospital admissions quality of life measures and health care costs (LOE 1\textsuperscript{186–196}). One large case-control multi center study showed that chest pain unit care did not reduce the proportion of patients with chest pain admitted to hospital and may have increased ED attendances when implemented across a health care system (LOE 2\textsuperscript{197}). Fifty-five studies from many health care settings demonstrate that CPUs enable evaluation of patients systematically, with a short length of stay, high diagnostic accuracy and a low event rate at follow-up (LOE 4\textsuperscript{198–247}).

In patients with suspicion for ACS, normal initial biomarkers and non-ischemic electrocardiogram, chest pain (observation) protocols may be recommended as a safe and effective strategy for evaluating patients in the ED (Class IIb).

Chest pain observation protocols should include a history and physical examination, a period of observation, serial electrocardiography, serial measurement of serum cardiac markers, and either an evaluation for anatomical coronary disease or for inducible myocardial ischemia at some point after AMI is excluded (Class I). These protocols may be used to improve accuracy in identifying patients requiring inpatient admission or further diagnostic testing, and those who may be discharged (Class IIb).

Chest pain protocols may be recommended as a means to reduce length of stay, reduce hospital admissions, reduce health care costs, improve diagnostic accuracy and improve quality of life (Class IIa). There is no direct evidence demonstrating that CPUs or (observation protocols) reduce adverse cardiovascular outcomes, particularly mortality for patients presenting with possible ACS, normal serum cardiac biomarkers and a non-diagnostic electrocardiogram.

4. Diagnostic Imaging

1) Diagnostic accuracy of imaging

In patients with suspected ACS with a nondiagnostic 12-leads ECG and negative cardiac biomarkers, there are some important reports showing whether the use of specific imaging techniques (eg, CT angiography, MRI, nuclear, echocardiography), compared with not using them, increase accuracy of diagnosis (eg, of ACS).
Data from 1 study (LOE D2) documented a sensitivity of 89% and a specificity of 77% for detection of ACS when myocardial perfusion imaging was used in adults presenting to the ED with chest pain, a nondiagnostic ECG, and negative cardiac biomarkers. Supportive evidence was also provided by 4 other studies (LOE D4) for adults presenting to the ED with chest pain.

Data from 2 studies showed high sensitivity (95%) and specificity (90%) for detection of ACS in adults who received multidetector CT angiography (MDCT, 64-slice scanner) in patients with similar clinical manifestations (LOE D2). This finding was also supported by 4 studies (LOE D4).

Data from 1 study documented sensitivity 93% and specificity 66% when rest echocardiography is used for detection of ACS in patients with similar clinical manifestations (LOE D2). Supportive evidence was also provided by one prospective cohort study (LOE D4). One prospective study provided similar estimates including specificity of 95% and positive predictive value of 81% for exercise stress echo in the same population (LOE D4).

Data from 2 studies documented high sensitivity (85%), specificity (84%), and negative predictive value (95%) for the diagnosis of ACS in adult patients who received MRI within 24 hours of presentation to the ED with chest pain after a nondiagnostic ECG and negative cardiac biomarkers (LOE D4).

A noninvasive test (CT angiography, cardiac MR, myocardial perfusion imaging, and echocardiography) may be considered in selected patients who present to the ED with chest pain and initial nondiagnostic conventional work-ups (Class IIb).

It is reasonable to consider both the exposure to radiation and iodinated contrast when utilizing MDCT and myocardial perfusion imaging (Class IIa).

2) Diagnositic Imaging and Outcome

In patients with suspected ACS, there are some important reports addressing whether the use of specific imaging techniques (eg, CT angiography, MRI, nuclear, or echocardiography), compared with not using them, improve outcome (survival, length of ED stay, hospital admission rate, cost).

Data from 2 studies of low-risk ED patients with an initial negative work-up of ACS with negative cardiac enzymes and non diagnostic ECGs, who received SPECT perfusion imaging, demonstrated low rates of cardiac events, reduced costs, and reduced length of stay (LOE D4).

Data from 3 studies of 64-slice MDCT utilized within 24 hours in adult patients presenting to the ED with chest pain, showed that the procedure decreases time to diagnosis, reduces costs, reduces length of stay, is predictive of major adverse events, and can lead to safe discharge from the ED (LOE 1; LOE 4).

Data from 5 studies of echocardiography performed in adult ED patients presenting with chest pain, negative cardiac enzymes, and non-diagnostic ECG’s demonstrated decreased mean length of stay and reduced costs and predicted a low cardiovascular event rate (LOE 1; LOE 4).
Based on studies which investigated limited numbers of selected individuals, patients presenting to the ED with suspected ACS and having a negative initial work-up, including a nondiagnostic ECG and negative cardiac biomarkers, an evaluation with a noninvasive test (CT angiography, myocardial perfusion imaging, or stress echocardiography) may be considered (Class IIb). In selected groups these noninvasive tests may decrease costs, length of stay, and time to diagnosis and may provide valuable short-term and long-term prognostic information of future major cardiac events. There are insufficient data to assess impact on mortality.

**4 Initial General Therapy**

Few studies have been published that directly address out-of-hospital or ED interventions for ACS. In some situations, extrapolation from in-hospital evidence was needed to provide some guidance for out-of-hospital and early ED management.

1. Oxygen, Nitroglycerin, Analgesics and Sedation

   1) Oxygen

   In suspected ACS patients with normal oxygen saturation levels, whether the oxygen therapy will improve clinical outcomes (e.g., chest pain resolution, infarct size, ECG resolution, survival to discharge, one-month mortality) compared with no oxygen administration, requires extrapolation from limited research data on in-hospital cases.

   One study reported improvement of ST changes if oxygen was given to 17 patients with myocardial infarction (LOE 4266). One LOE 1 trial267 conducted before the introduction of reperfusion therapy reported that the amount of aspartate aminotransferase released in the circulation was higher in patients who received oxygen therapy. Ventricular tachycardia and mortality was not significantly different in the two groups. Another LOE 1 study268 involving myocardial infarction patients treated with streptokinase showed no impact of oxygen on the occurrence of ventricular tachycardia. Severe hypoxemia occurred less often in patients given oxygen therapy. One LOE 1 study269 found that studies were small and lacked statistical power to detect a true influence on clinical outcomes. The review found no definite proof of a harmful effect of oxygen therapy; however, there is absolutely no evidence that oxygen was beneficial to patients with myocardial infarction, unless complicated by hypoxia.

   There is insufficient evidence to support or refute the empiric use of high-flow oxygen therapy in patients with uncomplicated AMI without signs of hypoxemia and/or heart failure.

   Oxygen therapy should be initiated if breathlessness, hypoxemia or signs of heart failure or shock are present (Class I). Non-invasive monitoring of oxygen saturation may be used to decide on the need for oxygen administration (Class IIb).
2) Nitroglycerin

In patients with suspected ACS in the ED and prehospital settings, whether the use of nitroglycerin will improve clinical outcomes (e.g., chest pain resolution, infarct size, ECG resolution, survival to discharge, one-month mortality) compared with no nitroglycerin, needs extrapolation from research data on in-hospital cases. Despite multiple studies performed in the pre-reperfusion era that have shown a benefit of early nitroglycerin administration in patients with a myocardial infarction, no trial specifically evaluated patients in the ED or prehospital settings. The greatest reduction in infarct size was noted in those treated within 3 hours of symptom onset in three studies of patients treated in the ICU (LOE 5\(^{270-272}\)). In addition, two trials suggest that concomitant treatment of nitroglycerin and thrombolytics may impair reperfusion (LOE 2\(^{273, 274}\)). One study of patients with NSTEMI showed a reduction in myocardial infarction size in those treated with diltiazem compared with intravenous glyceryl trinitrate (LOE 1\(^{275}\)). There is insufficient evidence to determine the benefit or harm of initiating nitroglycerin treatment in the prehospital setting or ED.

Although it is reasonable to consider the early administration of nitroglycerin in selected patients without contraindications [hypotension, tachycardia/bradycardia or phosphodeesterase inhibitor] (Class IIa), insufficient evidence exists to support or refute the routine administration of nitroglycerin in the ED or prehospital setting in patients with a suspected ACS. There may be some benefit if nitroglycerin administration results in pain relief (Class IIb).

3) Analgesics and Sedation

There is insufficient evidence to support or refute the use of analgesic and/or sedation, (including NSAIDs, opiates, and benzodiazepines) compared with no analgesia or sedation for patients with suspected ACS/STEMI in the ED and prehospital settings, improve outcome (e.g. chest pain resolution, infarct size, ECG resolution, survival to discharge, 30/60 d mortality).

One study suggested increased mortality and myocardial infarction rates associated with the use of intravenous morphine in patients presenting with high-risk NSTEMI (LOE 4\(^{276}\)). One study demonstrated that the early use of lorazepam with NTG was more effective than NTG alone, and appears to be safe in relieving ocaine-associated chest pain (LOE 1\(^{277}\)). One study was neutral when diazepam was compared with placebo on the endpoints of tachyarrhythmia, self-assessed anxiety, or other symptoms in undifferentiated patients with AMI (LOE 1\(^{278}\)).

One analysis of case control and cohort studies studying patient exposure to NSAIDs (LOE1\(^{279}\)) and a large analysis of clinical trials randomizing patients to Cox inhibitors over placebo (LOE 1\(^{280}\)) revealed an increased risk for developing myocardial infarction with use of NSAIDs. The risk appeared most consistent with rofecoxib, and was less consistently observed with celecoxib, naprosyn, ibuprofen and diclofenac. One study suggests increased harm with the initiation or continuation of NSAID
Morphine should be administered intravenously, and titrated to pain relief, in patients with STEMI (Class I). Morphine may be considered for pain relief in subjects with suspected NSTEMI with extreme caution (Class IIb). Some form of analgesia should be considered for patients with active chest discomfort. While anxiolytics may be administered to patients with ACS to alleviate apprehension and anxiety (Class IIa), there is no evidence that anxiolytics facilitate ECG resolution, reduce infarct size or decrease mortality in undifferentiated patients with suspected ACS. Lorazepam with nitroglycerin may be considered to alleviate pain in patients with cocaine associated chest pain (Class IIb). NSAIDs should not be administered and may be harmful in subjects with suspected ACS (Class III). Patients with suspected ACS who are taking NSAIDs should have them discontinued when feasible (Class I).

2. Aspirin (Acetylsalicylic Acid)
1) Timing of Aspirin Administration

There was no clear evidence to support or refute the use of pre-hospital or EMS dispatch directed (versus hospital administered) aspirin. One study found that aspirin, given before thrombolysis, increased long-term survival (LOE 1282). One study showed a benefit in STEMI patients with a decrease in in-hospital complications and 7 and 30-day mortality when given pre-hospital (LOE 4283). There was clear evidence that aspirin is associated with a reduction in long-term mortality, which is greatest when the aspirin is administered in the first 4 hours of after an event. One study showed no benefit with administration within the first 4 hours of symptoms, compared with later administration (LOE 1284). Two other studies (LOE 1285, 286) showed that the potential benefit from early aspirin administration outweighs potential harm.

In the absence of true allergy or history of recent gastro-intestinal bleeding, aspirin should be administered as soon as possible in patients with suspected ACS (Class I). It is reasonable to consider EMS or dispatcher-guided bystander aspirin administration, despite limited direct evidence to support or refute the practice (Class IIa).

3. Clopidogrel and other Platelet ADP-Receptor Antagonists
1) Clopidogrel

Seven studies (LOE 1287-290; LOE 2291, 292; LOE 3293) documented consistent improvement, and one study (LOE 5294) was neutral in demonstrating benefit in the combined event rate of cardiovascular mortality, non-fatal infarction, non-fatal stroke, and overall mortality. There was a small increase in major bleeding when clopidogrel was administered by providers in the ED and/or hospital to patients with non-ST elevation ACS.

Six studies documented consistent improvement in combined event rate of cardiovascular mortality, nonfatal infarction, and non-fatal stroke, with a resultant small increase
in major bleeding when clopidogrel was administered by providers in the ED or prehospital to patients < 75 years with STEMI managed with fibrinolysis (LOE 1\textsuperscript{295-298}; LOE 3\textsuperscript{299, 300}).

Five studies documented improvement in combined event rate (cardiovascular mortality, nonfatal infarction, and nonfatal stroke) and/or mortality with a resultant small increase in major bleeding when clopidogrel was administered by ED, hospital and/or prehospital providers to patients with STEMI managed with PPCI (LOE 2\textsuperscript{301, 302}; LOE 3\textsuperscript{299, 300}; LOE 5\textsuperscript{306}). There was little evidence on the use of a loading dose of clopidogrel in patients aged ≥ 75 years of age treated by PPCI, and they were excluded from studies if treated with fibrinolysis.

Administration of Clopidogrel in addition to standard care (aspirin, anticoagulants and/or reperfusion) for patients determined to have moderate to high-risk non-ST elevation ACS and STEMI is recommended (Class I). The ideal oral loading dose of clopidogrel in patients < 75 years of age is dependent upon the planned approach: 600 mg in a planned invasive strategy; or 300 mg in a planned non-invasive strategy or together with fibrinolysis. The ideal dose in patients > 75 years of age, has not yet been delineated. For emergency PCI in patients with suspected ACS, a loading dose of 300 mg is approved in Japan. A higher loading dose has not been considered.

2) Prasugrel

There was no direct evidence of use of prasugrel in the ED or prehospital setting for non-ST elevation ACS. Extrapolating evidence from an in-hospital setting, five studies (LOE 5\textsuperscript{303-307}) documented improvement and one study (LOE 1\textsuperscript{308}) documented no benefit in combined event rate (cardiovascular mortality, nonfatal infarction, and nonfatal stroke) or mortality, but with a resultant increase in major bleeding, when prasugrel (compared to clopidogrel) was administered after angiography to patients with non-ST elevation ACS and stenoses suitable for PCI.

There was no direct or indirect evidence of benefit or risk of prasugrel administered by hospital, ED, or prehospital providers to patients with STEMI managed with fibrinolysis. There was no direct evidence of the use of prasugrel in the ED or prehospital setting for patients with STEMI ACS. There was no direct evidence of the use of prasugrel in the ED or prehospital setting for patients with STEMI ACS managed with PCI. Six studies demonstrated small improvements in combined event rate (cardiovascular mortality, nonfatal infarction, and nonfatal stroke) and/or mortality when prasugrel compared with clopidogrel was administered in the hospital setting before, at or after angiography to patients with STEMI managed with PPCI (LOE 5\textsuperscript{300-307,309}).

Post-hoc exploratory analysis of a randomized control trial in STEMI and non-ST-elevation ACS patients treated by PCI identified risk factors associated with a higher rate of bleeding complications with prasugrel: patients aged ≥75 years of age, history of stroke or TIA, and body weight less than 60 kg (LOE 5\textsuperscript{303}).

Prasugrel may be administered after angiography to patients with NSTEMI presenting with stenoses amenable to PCI (Class IIb). ED or prehospital administration of
clopidogrel should be withheld even in patients who are not at high risk for bleeding (age < 75 years, no history of previous stroke or TIA and body weight > 60 kg) pending consideration of prasugrel administration following angiography. In patients who are not at high risk for bleeding with planned PCI, prasugrel (60 mg oral loading dose) may be substituted for clopidogrel for patients determined to have STEMI less than 12 hours after the initial symptoms (Class IIb). Prasugrel is not recommended in STEMI patients receiving fibrinolysis (Class III).

3) Ticagrelor

One study documented improvement in overall mortality and combined event rates (death from vascular causes, MI, or stroke) with a marginal increase in bleeding and an increase in dyspnea when ticagrelor, given by in-hospital providers to patients with high-risk non-ST elevation ACS, was compared with clopidogrel (LOE I10). There was no direct or indirect evidence of benefit or risk of ticagrelor administered by hospital, ED, or prehospital providers to patients with STEMI managed with fibrinolysis. One study documented improvement in overall mortality and combined event rates (death from vascular causes, MI, or stroke) with a marginal increase in bleeding and an increase in dyspnea when ticagrelor was administered compared to clopidogrel by in-hospital providers to patients with STEMI managed by PPCI (LOE I10).

Administration of ticagrelor (180 mg oral loading dose) in addition to standard care (aspirin, anticoagulants and/or reperfusion) determined to have non-ST elevation ACS or STEMI managed with early invasive strategy by hospital personnel may be an option instead of clopidogrel. The risks and/or benefits of ticagrelor in STEMI patients managed with fibrinolysis is unknown.

4) Combination

The risks and/or benefits of combining these agents (clopidogrel, prasugrel and/or ticagrelor) for loading and maintenance dosing has not been sufficiently determined.

4. Heparins

At present in Japan, unfractionated heparin (UFH) is the only anticoagulant with approved indication for ACS and low-molecular-weight heparin (LMWH) and selective Xa inhibitor have no indication for ACS. This part of guideline contains consensus of science and treatment recommendation based on the evidence from areas other than Japan. Because UFH has disadvantages such as the requirements for frequent monitoring of the activated partial thromboplastin time (aPTT) and cause of thrombocytopenia, we need to discuss indication of LMWH, Xa inhibitor, and other thrombin inhibitors for ACS in Japan in future.

1) Anticoagulants and Non-ST-Elevation ACS
Many studies demonstrated improved combined end points (death, MI, revascularization) with an increase in the proportion of patients with bleeding complications when enoxaparin was administered in-hospital rather than UFH in patients with AMI (LOE131-321; LOE2322-327; LOE5328-335). Randomized, controlled trials (LOE1331-334), meta-analyses (LOE1335-337), nonrandomized control trials (LOE2-4338-345), and additional studies (LOE4-5346-356) did not demonstrate a difference for outcomes among in-hospital patients given enoxaparin compared with UFH. One RCT (LOE1351), nonrandomized control studies (LOE2352-354), additional studies (LOE5355, 356) demonstrated improved combined end points (death, MI, revascularization) without increased bleeding when fondaparinux, compared with UFH, was administered in-hospital in patients with AMI. Several studies (LOE2357, 358; LOE5359) did not demonstrate a difference in outcomes for fondaparinux compared with UFH when given in-hospital. One RCT (LOE1351) indicated fondaparinux may lead to excess catheter thrombosis when used as part of an invasive approach without the use of adjunctive medications. Many studies (LOE1360-365; LOE2-4366-376; LOE5377-387) did not demonstrate a difference in combined outcomes for major adverse cardiac events but did demonstrate less bleeding for bivalirudin administered in-hospital compared with UFH.

For patients with non-ST-elevation ACS managed with a planned initial conservative approach, either fondaparinux or enoxaparin are reasonable alternatives to UFH (Class IIa). For patients with non-ST-elevation ACS managed with a planned invasive approach, either enoxaparin or UFH are reasonable choices (Class IIa). Bivalirudin may be considered as an alternative, but does not appear to offer an advantage over UFH (Class IIb). Fondaparinux may be used in the setting of PCI, but requires co-administration of UFH and does not appear to offer an advantage over UFH alone (Class IIb).

For patients with non-ST-elevation ACS and renal insufficiency, bivalirudin or UFH may be considered (Class IIb). For patients with non-ST-elevation ACS and increased bleeding risk, where anticoagulant therapy is not contraindicated, fondaparinux or bivalirudin are reasonable (Class IIa), and UFH may be considered (Class IIb). There is no specific evidence for or against anticoagulant use in non-ST-elevation ACS in the prehospital setting.

2) Anticoagulants and STEMI Treated With Fibrinolysis

(1) Enoxaparin

For patients with STEMI to be treated with fibrinolysis, many studies supported enoxaparin over UFH (LOE1387, 388-394; LOE2395-397; LOE4398; LOE5394, 395, 399-402). Other studies were neutral comparing enoxaparin and UFH (LOE1403-406; LOE5407-412). For patients with STEMI managed with fibrinolysis, it is reasonable to administer enoxaparin instead of UFH (Class IIa). For prehospital patients with STEMI managed with fibrinolysis, adjunctive enoxaparin instead of UFH may be considered (Class IIb). Patients initially treated with enoxaparin should not be switched to UFH and vice versa to avoid increased bleeding risk (Class III).

(2) Reviparin.
One study demonstrated improved clinical outcome with reviparin compared with UFH in STEMI patients treated with fibrinolysis (LOE 1\textsuperscript{415}).

(3) Other LMWH
There were neutral meta-analyses of dalteparin, nadroparin, reviparin, parnaparin (LOE 5\textsuperscript{414, 415}), dalteparin supporting study using a surrogate end point (LOE 1\textsuperscript{416}) and neutral studies for nadroparin and parniparin (LOE 1\textsuperscript{417-419}).

(4) Fondaparinux
One study demonstrated superiority in clinical outcomes when fondaparinux was compared with UFH in patients treated with fibrinolysis (LOE 1\textsuperscript{420}). Other studies did not demonstrate a significant difference in outcomes (LOE 1\textsuperscript{421}; LOE 2\textsuperscript{422}). Fondaparinux may be considered in the hospital for patients treated specifically with non-fibrin-specific thrombolytics (ie, streptokinase), provided the creatinine level is < 3 mg/dL (Class IIb).

(5) Bivalirudin
Two studies did not demonstrate a significant difference in outcomes with bivalirudin (LOE 1\textsuperscript{423}; LOE 2\textsuperscript{424}). There are insufficient data to recommend other LMWH or bivalirudin over UFH in patients treated with fibrinolysis in STEMI (Class IIb).

3) Anticoagulants and STEMI Treated With PCI
(1) Bivalirudin.
Two studies resulted in less bleeding and a short- and long-term reduction in cardiac events and overall mortality with bivalirudin compared with UFH plus a glycoprotein inhibitor in patients with STEMI and planned PCI (LOE 1\textsuperscript{425, 426}). Other case series also resulted in fewer cardiac events and less bleeding (LOE 4\textsuperscript{427, 428}). One study demonstrated better outcome of patients with cardiogenic shock if treated with or without a glycoprotein IIb/IIIa inhibitor, compared with UFH plus a glycoprotein IIb/IIIa inhibitor (LOE 4\textsuperscript{429}). One study with prehospital initiation of bivalirudin versus UFH showed no difference (LOE 3\textsuperscript{430}). One analysis showed no difference when bivalirudin and UFH were compared for PCI (LOE 5\textsuperscript{431}). In studies of bivalirudin versus UFH, outcomes were similar (LOE 2\textsuperscript{432}; LOE 4\textsuperscript{433}).

Bivalirudin may be superior to UFH plus glycoprotein IIb/IIIa inhibitors with respect to bleeding and reduces adverse cardiac events and mortality in STEMI patients undergoing PCI. An increased rate of stent thromboses has been observed with bivalirudin within the first 24 hours after PCI.

(2) Enoxaparin.
Several studies of PCI after fibrinolysis resulted in favorable outcome when enoxaparin was compared with UFH (LOE 4\textsuperscript{434, 435}; LOE 5\textsuperscript{435}). Other studies showed no benefit
using enoxaparin compared with UFH (LOE 2\textsuperscript{343, 434, 435}; LOE 4 \textsuperscript{407, 410, 436, 437}; LOE 5 \textsuperscript{414}).

For patients with STEMI undergoing contemporary PCI, enoxaparin may be considered a safe and effective alternative to UFH (Class IIb). To avoid increased bleeding risk, patients initially treated with enoxaparin should not be switched to UFH and vice versa (Class III). There are insufficient data to recommend other LMWH than enoxaparin for antithrombin treatment in STEMI patients undergoing PCI.

(3) Fondaparinux.
One clinical trial comparing fondaparinux with UFH documented similar rates of cardiovascular events but a lower rate of bleeding (LOE 1\textsuperscript{420}). One trial, which included patients with NSTEMI and patients undergoing elective PCI, was neutral in outcomes (LOE 5\textsuperscript{409}). One analysis of NSTEMI patients documented fewer acute cardiac events and less bleeding using fondaparinux and PCI compared with other antithrombins (LOE 5\textsuperscript{435}). Thrombus formation on catheter material in patients on fondaparinux required the addition of UFH during PCI.

In comparison with UFH, fondaparinux reduces the bleeding risk in STEMI patients undergoing PCI. There is an increased risk of catheter thrombi with fondaparinux alone; additional UFH (50 to 100 U/kg BW bolus) may help to avoid this complication, but using these 2 agents is not recommended over UFH alone. The dose of fondaparinux and enoxaparin requires adjustment in patients with renal impairment.

(4) Other LMWH
One nonrandomized study compared dalteparin with UFH in STEMI patients undergoing PCI and showed a neutral result (LOE 2\textsuperscript{458}).

5. Glycoprotein IIb/IIIa Inhibitors
Twelve larger randomized studies and metaanalyses (LOE1\textsuperscript{379-459}) and 2 smaller randomized studies\textsuperscript{451, 452} consistently reported better clinical outcome with use of Glycoprotein IIb/IIIa receptor blockers compared with placebo. This result was supported by many studies which consistently reported better outcome with upstream or early use of Glycoprotein IIb/IIIa inhibitor compared with deferred treatment or other strategies (LOE 1\textsuperscript{453-468}; LOE 2\textsuperscript{469-474}; LOE 3\textsuperscript{475}; LOE 4\textsuperscript{476-478}; LOE 5\textsuperscript{480}). There were 12 studies with neutral outcomes/evidence (LOE 1\textsuperscript{274, 481-488}; LOE 2\textsuperscript{489, 490}; LOE 5\textsuperscript{491}). Seven LOE 1 studies\textsuperscript{373, 425, 492-496} showed worse outcome, or at least more bleeding and need for transfusion without clinical advantage, with Glycoprotein IIb/IIIa blockers compared with standard/alternative procedures. In most of the supporting, as well as neutral and opposing, studies a higher rate of (major) bleedings has been observed. In a study (J–LOE 1\textsuperscript{497}) conducted in Japan with 973 patients with STEMI/UA aged younger than 75 years and weighing less than 100kg, patients were compared between a group with an initial dose of 0.2mg/kg of Abciximab followed by continuous dosing of 10µg/min or 0.125µg/kg/min, another group with an initial dose of 0.25mg/kg of Abciximab followed by continuous
dosing of 10µg/min or 0.125µg/kg/min, and the placebo group. There was no significant difference in the primary end point of 30-day mortality, AMI, and emergency revascularization among the three groups. Hemorrhagic complications increased in a dose-independent manner.

There were insufficient data to support the routine use of Glycoprotein IIb/IIIa inhibitors in patients with suspected STEMI or NSTE-ACS in the prehospital or ED settings. For selected high-risk patients with NSTE-ACS, abciximab, eptifibatide or tirofiban administration may be acceptable, provided PCI is planned (Class IIb). There is an increased bleeding risk with routine Glycoprotein IIb/IIIa blockers when used with heparins. Alternatives for anticoagulation and antiplatelet treatment might be considered instead (Class IIb).

5 Reperfusion Strategies

In the majority of patients, STEMI occurs as the result of a recent acute occlusion of a major epicardial coronary artery due to the disruption of atherosclerotic plaque and thrombus formation. Strategies aimed at restoring myocardial perfusion are an important part of the management of these patients. Restoring coronary blood flow and myocardial perfusion either by pharmacological (fibrinolytics) and/or mechanical therapy (PCI) has been demonstrated to improve outcomes in patients presenting within 12 hours of symptom onset and later other patients group such as those with cardiogenic shock. There is evidence that prehospital fibrinolysis reduces delay to treatment especially in rural areas with long transit times. In these settings prehospital fibrinolysis is a reasonable treatment strategy.

1. Prehospital Fibrinolysis
1) Prehospital Fibrinolysis for STEMI

STEMI is caused by occlusive coronary thrombus, and the early reperfusion strategy is considered important. It can be easily imagined that delay in treatment in cases where patient transportation takes time affects clinical results. In this section, clinical results (e.g., chest pain resolution, infarct size, ECG resolution, survival to discharge, 30/60 days mortality) from one group in which fibrinolytics were administered in the prehospital setting, and the other group in which fibrinolytics were administered on arrival at hospital, are examined in the context of the current evidence to evaluate the validity.

Nineteen studies demonstrated significantly reduced time to treatment when fibrinolytics were given to patients with STEMI in the prehospital setting by either physicians, nurses or paramedics (LOE 1498-503; LOE 2125, 504-512; LOE 3513-515). Eleven studies showed that a greater proportion of the patients treated with prehospital fibrinolysis had shorter duration and increased frequency of total resolution of chest pain by the time of admission, ECG resolution, and decreased mortality (LOE 1498, 501, 502, 516-518; LOE
And, the sooner the thrombolytic agents subscription, the better clinical outcomes, especially, most effective within 2 hours from the onset

In patients with STEMI diagnosed in the prehospital setting, reperfusion may be achieved by administration of fibrinolytics by health care providers in the field (Class IIb). Alternately, fibrinolytic therapy may be administered on arrival at hospital (Class IIb). If fibrinolysis is chosen as the reperfusion strategy, it should be started as soon as possible, ideally in the prehospital setting, and should be administered by paramedics, nurses or doctors using well-established protocols, competency training programs, and quality assurance programs, under medical oversight. However, in Japan, paramedics and nurses are not allowed to administer these drugs.

2. Choice of Reperfusion Strategy in the Hospital
1) PCI versus Fibrinolytic Therapy for STEMI

In patients with suspected STEMI presenting to the ED, whether to perform fibrinolytic therapy or PCI requires examination of treatment outcomes such as arrhythmias, infarct size, ECG resolution, survival to discharge, and 30/60 days mortality.

Application of PPCI has been limited by access to catheter laboratory facilities and appropriately skilled clinicians. Fibrinolytic therapy is a widely available reperfusion strategy, and may be used if delays to PPCI are anticipated. Both treatment strategies are well established and have been the subject of large randomized multicenter trials been over the last two decades.

Early reperfusion therapy for the patients with STEMI, thrombolysis, or primary PCI, benefits short and long term prognosis (J-LOE 157, 520, 521). For patients admitted to hospital with PCI facilities, evidence from two studies demonstrated that PPCI conferred clinical benefit compared with fibrinolysis both in terms of mortality and morbidity (reinfarction/stroke) for the majority of patients (LOE 1522, 523).

Table 1. Contraindications and Cautions for Fibrinolysis in STEMI

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
<th>Relative contraindications</th>
</tr>
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<tbody>
<tr>
<td>• Any prior ICH</td>
<td>• History of chronic, severe, poorly controlled hypertension</td>
</tr>
<tr>
<td>• Known structural cerebral vascular lesion (e.g., arteriovenous malformation)</td>
<td>• Severe uncontrolled hypertension on presentation (SBP greater than 180 mm Hg or DBP greater than 110 mm Hg)†</td>
</tr>
<tr>
<td>• Known malignant intracranial neoplasm (primary or metastatic)</td>
<td>• History of prior ischemic stroke greater than 3 months, dementia, or known intracranial pathology not covered in contraindications</td>
</tr>
<tr>
<td>• Ischemic stroke within 3 months EXCEPT acute ischemic stroke within 3 hours</td>
<td>• Traumatic or prolonged (greater than 10 minutes) CPR or major surgery (less than 3 weeks)</td>
</tr>
<tr>
<td>• Suspected aortic dissection Active bleeding or bleeding diathesis (excluding menses)</td>
<td>• Recent (within 2-4 weeks) internal bleeding Noncompressible vascular punctures For streptokinase/anistreplase: prior exposure (more than 5 days ago) or prior allergic reaction to these agents</td>
</tr>
<tr>
<td>• Significant closed-head or facial trauma within 3 months</td>
<td>• Pregnancy</td>
</tr>
<tr>
<td></td>
<td>• Active peptic ulcer</td>
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<tr>
<td></td>
<td>• Current use of anticoagulants: the higher the INR, the higher the risk of bleeding</td>
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</tbody>
</table>

Primary PCI confers clinical benefit as compared to fibrinolysis in early restoring infarct-related artery flow, early resolution of ST elevation, limiting the infarct
size, preservation of left ventricular function, improving the short (LOE 1\textsuperscript{522, 523}; J-LOE 2\textsuperscript{424}) and long-term (LOE 1\textsuperscript{522, 523}; J-LOE 2\textsuperscript{525}) mortality. The rate of stroke especially intracranial hemorrhage, was dramatically decreased in primary PCI, respectively (LOE 1\textsuperscript{529}). The incidences of mechanical complication in STEMI, such as, cardiac rupture, ventricular septal perforation and acute mitral regurgitation occurred 22% in thrombolytic therapy era, on the other hands, the rate of mechanical complication improved to 0.31% in PPCI era (J-LOE 3\textsuperscript{526}).

Thrombolytic therapy administered within the first 2 hours dramatically reduces mortality (LOE 1\textsuperscript{502}), however, time-dependent decrease in efficacy of thrombolytic therapy (J-LOE 2\textsuperscript{527}). As PPCI is also reported to be time-dependent decrease in efficacy (J-LOE 1\textsuperscript{528}), it is recommended to achieve door to balloon time within 90 minutes in STEMI in AHA/ACC guideline (J-LOE 1\textsuperscript{519}). Compared with thrombolytic therapy, less influence of time delay on efficacy within 6 hours in PPCI (LOE 1\textsuperscript{523}). The evidence from two studies was scant for additional benefit of PCI over fibrinolysis for specific subgroups such as post CABG patients or patients with renal failure (LOE 1\textsuperscript{529}; LOE 3\textsuperscript{530}).

For patients admitted to hospital without PCI facilities, two studies showed benefit associated with transferring patients for PPCI versus on-site fibrinolysis in terms of reinfarction and stroke and a trend to a lower mortality in the PPCI group (LOE 2\textsuperscript{531, 532}). The average time from randomization to PCI varied among the separate trials in this meta-analysis and ranged between 82 and 122 minutes. The benefit was correlated directly to risk status of the patient with those at high risk benefiting more from transfer.

For patients with cardiogenic shock, evidence from one randomized trial demonstrated that early revascularization improves survival at six months (LOE 1\textsuperscript{533}). The survival benefit was seen mainly in patients less than 75 years of age. However, PPCI improved the survival in patients of age more than 75 with cardiogenic shock, therefore, any STEMI patients complicated by cardiogenic shock should be transferred to a PCI-capable center (J-LOE 2\textsuperscript{534}). Furthermore, PCI for the patients with myocardial infarction with heart failure (more than Killip II) was reported to be superior to thrombolysis (J-LOE 2\textsuperscript{535}). As a rule, hemodynamic compromised patients are recommended to be transferred to PCI capable centers.

Data from registries (LOE 3\textsuperscript{536}) and a meta-regression from previously published studies (LOE 1\textsuperscript{537}) highlight that the PCI-related time delay varied between 40 and 179 min, which mitigates the benefit of mechanical intervention over fibrinolysis.

This variability is influenced by several factors including age, symptom duration, location of infarction. Similarly, one study showed that the benefit of PCI over TT is offset when PCI is carried out in low volume PCI centers (LOE 1\textsuperscript{538}).

Operator and institutional experiences were one of the key for determinant of long term prognosis of the patients underwent PPCI. One report compared outcomes of reperfusion of acute myocardial infarction at hospitals with different volumes of primary PCI, and concluded that the patients with AMI treated at hospitals with high or intermediate volumes of PPCI had lower mortality and had shorter door to balloon
time compared with low volumes of PPCI (LOE 1\textsuperscript{538}). On the other hands, recent report of STEMI concluded that high-volume centers were associated with shortest door to balloon time (98min vs. 90min vs. 88min) among low and medium-volume centers, however, not with in-hospital mortality or length of hospital stay among the three groups (J-LOE 2\textsuperscript{539}). In Japan, PCI can be performed at many hospitals and the predominant strategy for reperfusion therapy for acute myocardial infarction is PPCI. Nakayama, et al. (J-LOE 3\textsuperscript{540}) reported the comparison between tertiary emergency center (TEC) and community hospitals in achievement of rapid reperfusion therapy (door to balloon time within 90 min.). There were no significant differences in 30 days mortality among the institutions; however, door to balloon time was significantly shorter in TEC compared with community hospitals (63 min vs. 104min), almost all of the patients treated at TEC underwent PPCI with door to balloon time within 90 min (96%). Furthermore, multiple logistic regression analysis demonstrated that prolonged door to balloon time was an independent predictors of 30 days mortality. Terkelsen reported that not door to balloon delay, but the time first contact with health care system to the initiation of reperfusion therapy (system delay) was associated with mortality in patients with STEMI treated with PPCI (J-LOE 2\textsuperscript{541}). Therefore, it is important to improve the mortality in the patients with STEMI was to establish the emergency care systems including pre-hospital settings.

Programs should be implemented to reduce the time to PCI (Class I). Shorter intervals to reperfusion increase myocardial salvage, whereas delays to reperfusion increase morbidity and mortality. The precise threshold of PPCI-related delays that should trigger the decision for fibrinolysis has not been definitively established, but time to PCI should be as short as possible (Class I). Individual Councils will determine the acceptable limit or target interval from first medical contact to PCI in light of likely patient factors and available healthcare system resources, and the reader is referred to those Council-specific guidelines for more detailed information.

For patients presenting within 12 hours of symptom onset and with ECG findings consistent with STEMI, reperfusion should be initiated as soon as possible independently of the method chosen (Class I). The benefit of mechanical intervention over fibrinolysis varies considerably depending on the patient’s condition and the duration of PPCI-related delays. The precise threshold of PPCI-related delays that should trigger the decision for fibrinolysis has not been definitively established, PPCI should be initiated as soon as possible (Class undetermined).

Japanese guideline (Fig 2) recommended that
1) initiation of reperfusion within 120 min from onset
2) initiation of thrombolysis within 30 min from first medical contact
3) achievement of first medical contact to balloon time within 90 min.

For those patients with a contraindication to fibrinolysis, PCI should still be pursued despite the delay, rather than offering no reperfusion therapy (Class I).

For those STEMI patients presenting in shock, PCI (or coronary artery bypass surgery) is the preferred reperfusion treatment. Fibrinolysis should only be considered if there
is a substantial delay to PCI (Class I).

Reperfusion goals:
- Symptom onset-to-reperfusion < 120 min
- EMS-to-drug < 30 min
- EMS-to-balloon < 90 min

(1) Prehospital ECG interpreted by EMS or transmitted by cell phone to hospital
(2) Pre-arrival activation of catheterization laboratory

Symptom onset | EMS Arrival | Field Triage | Hospital Arrival | Cardiologists
---|---|---|---|---
Patient delay | Transportation delay | Door-to-balloon delay
---|---|---
Prehospital system delay | System delay | Treatment delay

Increasing loss of myocytes

Figure 2. Reperfusion goals for STEMI

The overarching goal is to achieve reperfusion within 120 minutes from symptom onset. Rapid activation of the EMS system is necessary. The medical first-contact providers (EMS personnel) should aim to deliver intravenous administration of fibrinolysis within 30 minutes or start PCI within 90 minutes of their arrival on the scene. It is recommended that the EMS personnel should acquire the prehospital 12-lead-ECG and describe the findings or transmit them to the medical facility, which will help expedite the process from symptom onset to reperfusion treatment by two steps. That means it is possible to reduce the time both for the EMS personnel to select a medical facility and for medical providers to decide on a treatment course. (Cited and adapted from reference \(^{541-543}\))

3. Combined PCI and Fibrinolysis
1) Fibrinolysis and immediate PCI (Facilitated PCI) versus immediate PCI
Fibrinolysis and PCI may be used in a variety of combinations to restore coronary blood flow and myocardial perfusion. There are several ways in which the two therapies can be combined. There is some lack of uniformity in the nomenclature used to describe these regimes.
In this analysis, facilitated PCI is used to describe PCI performed immediately after fibrinolysis, a pharmaco-invasive strategy refers to PCI performed routinely 2 to 6 hours after fibrinolysis, and rescue PCI is defined as PCI performed for a failed reperfusion (as evidenced by <50% resolution of ST segment elevation at 60 to 90 minutes post lytic). These strategies are distinct from a routine PCI approach where the angiography and intervention is performed more than 12 hours after successful fibrinolysis.

Twelve studies demonstrated poorer outcome with routine PCI shortly after fibrinolysis (LOE 1 482, 544-549; LOE 2 550; LOE 5 551-554). Most of these studies have been performed in recent years. Meta-analysis from 17 randomized control trials demonstrated that facilitated approach (administration of GpIIb/IIIa antagonist regimens or thrombolytic therapy regimens prior to PCI) resulted in a greater than two-fold increase in the number of patients with initial TIMI-3 flow compared with PPCI groups, however, the incidences of adverse events; death, non-fatal reinfarction, urgent target vessel revascularization, major bleeding, and hemorrhagic stroke were significantly higher in facilitated group, especially thrombolytic-therapy-containing facilitated regimens (LOE 1 482).

The routine use of fibrinolysis-facilitated PPCI, compared with PPCI, is not recommended in patients with suspected STEMI (Class III). It is reasonable to perform angiography and possible PCI in patients with failed fibrinolysis according to clinical signs and/or insufficient ST-segment resolution (Class IIa).

### 6 Additional Medical Therapy

Several additional medical therapies have been proposed for ACS patients with the goal of reducing complications from myocardial ischemia, major adverse cardiac events, and ultimately long-term survival. Therapeutic options include antiarrhythmics, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, and HMG-CoA reductase inhibitors (statins). The bulk of data available to determine the usefulness of these therapies has not been derived from patients in the prehospital or ED settings. Traditional preventive interventions usually start with the first admission with a confirmed diagnosis of ACS. The current evidence indicates that none play a significant role in the out-of-hospital and ED management of ACS.

1. **Prophylactic Antiarrhythmics**

   Evidence from 3 studies suggested a reduction in ventricular fibrillation (VF), which was not statistically significant; however, there was no improvement in survival to hospital discharge (LOE 1 492-494; LOE 4 596). The studies had heterogeneous clinical
protocols, and most were underpowered. Twelve studies showed no improvement in suppression of ventricular arrhythmias (LOE 1\textsuperscript{596-605}; LOE 2\textsuperscript{606}; LOE 4\textsuperscript{607}). The studies showed no improvement in survival to hospital discharge. Four studies showed worsening of arrhythmias and the potential for harm (LOE 1\textsuperscript{603, 608, 609}; LOE 2\textsuperscript{610}). Lidocaine is the antiarrhythmic drug that has been studied most extensively in this clinical setting. The majority of the evidence suggests lidocaine is not associated with improved clinical outcomes. There were 3 studies supporting arrhythmia suppression with lidocaine; however, no clinical benefit was shown (LOE 1\textsuperscript{602-594}; LOE 4\textsuperscript{595}). There were 8 studies that were neutral for demonstrating arrhythmia suppression with lidocaine (LOE 1\textsuperscript{598, 600, 603-605}; LOE 2\textsuperscript{606, 618}; LOE 4\textsuperscript{607}). There were 2 studies that showed harm (LOE 1\textsuperscript{597, 600}). One trial showed a statistically significant benefit in decreasing the incidence of VT using sotalol (LOE 1\textsuperscript{611}). Three studies were neutral with respect to tocainide and disopyramide (LOE 1\textsuperscript{599}), mexiletine (LOE 1\textsuperscript{608}) and tocainamide (LOE 1\textsuperscript{605}). One study showed harm with amiodarone (LOE 1\textsuperscript{601}) and 1 trial (LOE 1\textsuperscript{608}) showed harm with a variety of drugs, including \( \beta \)-blockers.

Prophylactic antiarrhythmics are not recommended for patients with suspected ACS or myocardial infarction (Class III).

2. \( \beta \)-blockers

Studies of \( \beta \)-blockers are heterogenous with respect to the time of \( \beta \)-blocker administration. There is a paucity of data on the administration of \( \beta \)-blockers in the prehospital or early ED settings (ie, within the first hour of a suspected ACS). Eight studies showed no advantage for IV \( \beta \)-blockers on mortality, infarct size, prevention of arrhythmias, or reinfarction (LOE 1\textsuperscript{612-618}). None of the papers reviewed showed that \( \beta \)-blockers caused irreversible harm when given early in the development of suspected ACS. One study showed a statistically significant reduction in 6-week mortality in a subgroup of low-risk (ie, Killip Class 1) patients (LOE 1\textsuperscript{613}). Other studies (LOE 1\textsuperscript{620, 621}) have shown reduced mortality and decreased infarct size (LOE 1\textsuperscript{622-624}) with early IV \( \beta \)-blocker use. Four studies showed that early \( \beta \)-blocker administration helped prevent dangerous arrhythmias, (LOE 1\textsuperscript{621, 622, 625, 626}) while 2 studies showed a prevention of reinfarction but increased incidence of cardiogenic shock (LOE 1\textsuperscript{621, 625}). Many of the \( \beta \)-blocker trials in the early 1980s were small and had wide confidence intervals. One study suggested that the earlier IV \( \beta \)-blockers were administered, the greater the reduction in infarct size and mortality (LOE 3\textsuperscript{627}).

For patients with ACS, there is no evidence to support the routine administration of IV \( \beta \)-blockers in the prehospital setting or during initial assessment in the ED (Class III). It may be reasonable to administer IV \( \beta \)-blockers in specific situations, such as severe hypertension or tachycardia, in patients without contraindications (Class IIb). Starting oral \( \beta \)-blockers at low doses is recommended once the patient’s condition has been stabilized (Class I).
3. Angiotensin Converting Enzyme Inhibitors (ACEIs) and Angiotensin Receptor Blockers (ARBs)

While multiple studies have shown that ACEIs and ARBs have beneficial effects in patients with myocardial infarction (MI), no trial has specifically evaluated patients in a prehospital or emergency department setting. One randomized trial showed a reduction in mortality in patients who were treated with ACEIs soon after the presentation of ACS, although it also caused some hypotension (LOE 1\textsuperscript{629-631}). Three randomized trials showed a reduction in the rate of heart failure and mortality in patients treated with ACEIs and ARBs soon after fibrinolysis (LOE 1\textsuperscript{629-631}). In one study (LOE 1\textsuperscript{630}), there was no benefit associated with the use of ACEI within 1 hour of reperfusion, and two meta-analyses (LOE 1\textsuperscript{632, 633}) showed that ACEI administration conferred no benefit. In a Japanese trial, early ARBs administration (within 24hr) decreased the rate of target lesion revascularization and restenosis 6 months after stenting in patients with MI (J-LOE 1\textsuperscript{635}). While ACEIs/ARBs reduce mortality in patients with acute myocardial infarction, there is insufficient evidence to support the routine initiation of ACEIs and ARBs in the prehospital or emergency department setting in patients with myocardial infarction.

4. HMG CoA Reductase Inhibitors (Statins)

There are no data available on whether the use of statins, when compared with standard management, improves clinical outcomes (e.g., infarct size, ECG resolution, survival to discharge, 30/60 d mortality) in patients with suspected ACS/MI in the prehospital and emergency department setting. Nineteen studies have documented a reduction in both short- and long-term major adverse cardiovascular events after intensive treatment with statins within the first 24 hours after hospital admission for patients with ACS (LOE 1\textsuperscript{635-640}, LOE 2\textsuperscript{641-653}). Multiple studies have consistently reported reduced short-term mortality and a reduced incidence of death and nonfatal myocardial infarction during a 30-day follow-up with continued statin treatment or the early initiation of this treatment compared with the discontinuation of statins at hospital admission in ACS patients (LOE 3\textsuperscript{654}, LOE 4\textsuperscript{655-663}). Some studies have also reported a reduction in markers of myocardial necrosis or inflammation under statin treatment in patients undergoing PCI. One meta-analysis (LOE 1\textsuperscript{664}) and two other studies (LOE 4\textsuperscript{665, 666}) were neutral with regard to death and nonfatal myocardial infarction during a 30-day follow-up. There have been no reports on risks or safety considerations regarding the early initiation of statin treatment in ACS. In Japanese trials, the early administration of statins reduced plaque volume (J-LOE 1\textsuperscript{667}) and % coronary diameter stenosis (J-LOE 2\textsuperscript{668}), and improved long-term clinical outcomes (J-LOE 2\textsuperscript{669}) in patients with ACS.

Intensive statin treatment should be considered early after the onset of an ACS event (e.g., immediately after hospital admission) in patients who present with ACS unless contraindicated (e.g. by proven intolerance) (Class I). Pre-existing statin therapy should be continued in patients who present with ACS (Class I).
Several systems-related strategies have been developed to improve quality of care for patients with ACS and reduce reperfusion delays for patients with STEMI. Strategies exist for patients identified in the prehospital setting and in the ED. These strategies focus on the use of prehospital 12-lead ECG and time-saving strategies to facilitate early diagnosis and rapid treatment for patients with STEMI (Figure 2541–543).

1. Prehospital 12-lead ECG and Advanced ED Notification

1) Prehospital 12-lead ECG

Eight studies demonstrated a reduction in the door-to-needle time interval ranging from 20 to 60 minutes when physician- or paramedic-interpreted prehospital 12-lead ECG was used to evaluate patients with suspected AMI who are then treated with a fibrinolytic (LOE 1670–677; LOE 2117, 118, 674, 675). Eight studies demonstrated a reduction in the reperfusion delay (with varied time interval definitions) ranging from 15 to 65 minutes in patients treated with PCI (LOE 2676–679; LOE 3113, 680, 681; LOE 4682). Two studies suggested that the time saved by using prehospital ECGs was dependent on advanced hospital notification of an incoming STEMI patient and activation of the catheterization team before the patient’s arrival (LOE 2676, 681). When comparing the door-to-reperfusion time for patients with a prehospital ECG and prehospital activation to patients with no prehospital ECG, the mean door-to-reperfusion interval was reduced by more than 30 minutes.681 Two nonrandomized trials reported no significant reductions in mortality with the use of prehospital ECGs (LOE 2118, 678). In one of these studies in-hospital all-cause mortality was 15.6% in a group of STEMI patients brought by EMS to the ED without prehospital ECGs, and 8.4% for patients who had a prehospital ECG and were brought directly to the critical care unit for fibrinolysis.678 The study was not powered to detect a mortality difference. The second study reported an 11% in-hospital mortality for STEMI patients brought by EMS without a prehospital ECG versus 5% in those with a prehospital ECG.678

Prehospital 12-lead ECGs facilitate earlier diagnosis of STEMI and provide the opportunity for rapid prehospital reperfusion or for rapid triage of patients to awaiting institutions able to provide such reperfusion. EMS personnel should acquire a prehospital 12-lead ECG on all patients exhibiting signs and symptoms of ACS and provide advance notification to receiving institutions for patients diagnosed with STEMI (Class I). It is recommended that the widespread implementation of prehospital 12-lead ECG is performed in Japan. Advance notification may be achieved with direct transmission of the ECG or with interpretation of the ECG by prehospital personnel (Class IIb). Advance notification should prompt preparations at the receiving institution for rapid reperfusion of the arriving STEMI patient (Class I).
2. Improving Systems of Care for ACS

1) Emergency Physician or Prehospital Activation of the Catheterization Laboratory Team.
   Two studies suggested an association between the ability of emergency physicians to activate the catheterization laboratory team and decreased door-to-balloon time interval (LOE 583, 684). Twelve studies demonstrated that emergency physician activation of the catheterization laboratory was associated with significant reductions in door-to-balloon time intervals (20 to 68 minutes) (LOE 2685-687; LOE 3688-694; LOE 5684, 695). False-positive activation rate in these studies ranged from 0% to 15% (LOE 2685-687; LOE 3688-694; LOE 5684, 695).

2) Prehospital Activation of the Catheterization Laboratory
   Seven studies demonstrated the effectiveness of prehospital activation on reducing door-to-balloon time intervals (22 to 69 minutes) (LOE 2677, 696; LOE 3697, 698; LOE 4681, 699). The studies were variable in their implementation and all had significant limitations. False-positive activation of the catheterization laboratory was not assessed by any of the studies.

3) Single Call to a Central Page Operator
   One qualitative survey suggested an association between single call to a central page operator and reduced reperfusion delay (LOE 5700). There were no studies that investigated the effect of this specific technique in isolation.

4) Real-Time Data Feedback
   Four studies demonstrated a positive impact of feedback on reducing the door-to-balloon interval (10 to 54 minutes) (LOE 3688, 692; LOE 5700, 701). These studies were heterogeneous and had significant limitations.

5) Institutional Commitment
   Two qualitative studies suggested that senior management commitment and leadership was crucial to improving treatment of STEMI. However, no other studies proved this relationship (LOE 5702, 705).

6) Team Based Approach.
   One qualitative study suggested a team-based approach led to improvements in STEMI systems of care (LOE 5706). However, no other studies proved this relationship empirically.

7) Expecting the Catheterization Laboratory Staff to Arrive in 20 Minutes.
   One study established an association between hospitals that expect the catheterization team to arrive in 20 minutes and having decreased door-to-balloon time (LOE 5706). However,
no studies have investigated the impact of implementing this specific technique in isolation. One study used this specific expectation of arrival of catheterization laboratory staff along with other methods as part of a quality improvement initiative (LOE 3989). Another study evaluated the outcomes of patients that presented during peak hours compared with off-peak hours and found decreased door-to-balloon time intervals among patients who presented when the catheterization laboratory team was in house (LOE 5704).

8) Having an Interventional Cardiologist Immediately Available at the Hospital

One study demonstrated an association between having an interventional cardiologist always at the hospital and decreased door to balloon times of 8.2 minutes (LOE 5708). No studies have investigated the impact of implementing this specific technique on reperfusion delay. No studies demonstrated direct effect on mortality or other outcomes data.

Hospitals should implement prehospital activation of the catheterization laboratory for patients with suspected STEMI who arrive by EMS and should implement first-physician-contact activation of the catheterization laboratory for patients suspected of having STEMI arriving by other means (Class I). Hospitals may implement additional institution-specific techniques to improve STEMI systems of care; however there is little evidence to support their widespread implementation (Class IIb).

These techniques include:
- Arranging single-call activation of the catheterization laboratory
- Requiring the catheterization laboratory to be ready in 20 minutes
- Having the interventional cardiologist immediately available at the hospital
- Providing real-time data feedback
- Fostering the commitment of senior management
- Encouraging a team-based approach

3. Prehospital Triage

Two studies suggested that transportation of STEMI patients diagnosed by paramedics directly to PCI centers for PPCI as part of a coordinated regional response to STEMI reduced in-hospital mortality when compared with historical controls with a strategy of transportation to the closest hospital for fibrinolysis (LOE 3705; LOE 5706). Four studies failed to show that a strategy of prehospital diagnosis and direct transportation for PCI was any better than prehospital fibrinolysis followed by early PCI in patients with STEMI (in systems involving the presence of physicians in mobile intensive care units) in reducing the composite outcome of death, nonfatal reinfarction, and nonfatal stroke at 30 days (LOE 1579, 707, 708; LOE 4572). Three studies suggested a benefit of prehospital fibrinolysis (when coupled with an early invasive strategy) over that
of PCI for patients presenting early after the onset of chest pain (less than 2 hours) and in certain clinical subsets (<65 years-of-age, anterior STEMI) in reduction of mortality (LOE 1709; LOE 4530, 710). Six studies comparing interfacility transfer for PPCI with on-site ED fibrinolysis in STEMI patients diagnosed in the ED demonstrated improved outcomes, including the triple end point of death, reinfarction, and stroke at 30 days; and outcomes for 30-day survival alone and reinfarction alone supported the strategy of direct transport for PPCI over fibrinolysis (LOE 5531, 547, 711-714). Eleven studies demonstrated improved outcomes for patients diagnosed with STEMI in the prehospital setting and brought directly to PCI centers for PPCI compared with STEMI patients diagnosed in the ED of a non-PCI hospital who were transferred for PPCI (LOE 4116, 697, 699, 715-721; LOE 5700). Thirteen studies also suggested equivalent outcomes between a strategy of transfer for PPCI and of fibrinolysis in the prehospital or hospital setting (LOE 2678, 698; LOE 4116, 697, 699, 715-721; LOE 5536).

It is reasonable to consider direct transport to PCI capable facilities for PPCI for patients diagnosed with STEMI by EMS in the prehospital setting, bypassing closer EDs as necessary, in systems where time intervals between first medical contact and balloon time are <90 minutes (Class IIa).

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**8 PCI Following ROSC**

There is evidence of underlying ischemic heart disease in the majority of patients who have an out-of-hospital cardiac arrest (OHCA). Acute coronary artery occlusion is known to be the precipitating factor in many of these patients. While coronary artery occlusion after cardiac arrest is associated with ECG ST-elevation or left bundle branch block (LBBB), it can also occur in the absence of these findings. Fibrinolysis in setting of OHCA is addressed in Chapter 2: "Adult Advanced Life Support."

One study suggested that cardiac angiography and PCI, when used as part of a standardized advanced post-cardiac arrest protocol, may be associated with improved survival to hospital discharge when compared with no standardized protocol (LOE 3728). Sixteen studies suggested that percutaneous intervention (PCI) was feasible following ROSC (LOE 3729; LOE 4730-745). These studies demonstrated that successful PCI versus no PCI may be associated with improved cardiac ejection fraction and survival,745 and coronary angiography may be favorably associated with neurologically intact survival.744 In most of the patients in these studies, immediate angiography and PPCI were performed. Evidence from 2 studies suggested that outcomes after angiography and PCI vary considerably depending on patient-related factors (LOE 4730,725). The survival in patients who had witnessed VF-arrests of short durations, STEMI, and recovery of consciousness was as high as 95% to 100%. One study showed that therapeutic hypothermia in combination with PPCI was feasible and safe in patients resuscitated after cardiac arrest (LOE 4746). One study compared PCI with fibrinolysis and demonstrated no difference in functional
neurologic recovery or survival at 6 months in patients with ROSC after cardiac arrest (LOE 4).\textsuperscript{747}

Two additional retrospective case series (LOE 4\textsuperscript{747,748}) compared outcomes of PCI in patients with and without cardiac arrest. One study compared 20 post-cardiac arrest patients who underwent PCI and mild hypothermia with a control group of 70 patients who underwent mild hypothermia without PCI. There was no difference in the rate of arrhythmias (the primary end point) or other adverse events between the 2 groups.\textsuperscript{748}

In the other retrospective study\textsuperscript{749} of 948 STEMI patients without cardiogenic shock treated by PPCI, 20 were post-cardiac arrest. There was no difference in one-month mortality between the non-arrest (cardiogenic shock) group and the post-cardiac arrest group, but non-cardiac mortality was higher in the post-cardiac arrest group.\textsuperscript{749}

Recent publications provide additional information about the survival and functional outcome of patients who have PCI following ROSC after cardiac arrest. One retrospective series (LOE 4\textsuperscript{750}) of 98 post-cardiac arrest patients who had ECG evidence of STEMI and underwent emergent angiography included 59 patients who were unresponsive. The survival rate to discharge (and proportion of these with full neurological recovery) was 64% (92%) overall and 44% (88%) among the initially unresponsive patients.\textsuperscript{750} In a prospective observational registry (LOE 3\textsuperscript{751}) of out-of-hospital cardiac arrest patients, (the Parisian Regional Out of hospital Cardiac Arrest Trial [PROCAT]), 435 patients had no obvious extracardiac cause and all underwent immediate coronary angiography, followed by PCI if indicated. At least one significant coronary artery lesion was found in 128 (96%) of 134 patients with STEMI on the ECG and in 176 (58%) of 301 patients without STEMI. In patients with a significant coronary lesion, PCI was successful in 99 of the 128 STEMI patients and in 78 of the 176 patients with other ECG patterns. Hospital survival was 40%. Multivariate analysis showed successful PCI to be an independent predictor of survival, regardless of the post-resuscitation ECG (odds ratio 2.06; 95% CI 1.16–3.66).\textsuperscript{751}

In OHCA patients with STEMI or new LBBB on ECG following ROSC, early angiography and PPCI should be considered (Class I). It is reasonable to perform early angiography and PPCI in selected patients despite the absence of ST-segment elevation on the ECG or prior clinical findings, such as chest pain, if coronary ischemia is considered the likely cause on clinical grounds (Class IIa). Out-of-hospital cardiac arrest patient are often initially comatose but this should not be a contraindication to consider immediate angiography and PCI (Class I). It may be reasonable to include cardiac catheterization in a standardized post-cardiac-arrest protocol as part of an overall strategy to improve neurologically intact survival in this patient group (Class IIb). Therapeutic hypothermia is recommended in combination with primary PCI, and should be started as early as possible, preferably before initiation of PCI (Class IIa).
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