Part 5: Acute Coronary Syndromes

2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

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Introduction

Since 2000, the International Liaison Committee on Resuscitation (ILCOR) has published the *International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations* (CoSTR) every 5 years based on review of cardiopulmonary resuscitation (CPR) science. Seven task forces with representatives from the 7 member resuscitation organizations create the CoSTR that enables regional resuscitation organizations to create their individual guidelines. The different guidelines are based on the scientific evidence and incorporate or adjust for regional considerations.

Why Acute Coronary Syndromes?

Coronary heart disease remains among the leading causes of mortality globally. There is considerable research focus worldwide on improving outcomes in patients with acute coronary syndromes (ACS). Undoubtedly, this has led to improved health and dramatically improved morbidity and mortality in much of the world. Indeed, timely and appropriate care of ACS can reduce and prevent cardiac arrest. Some of the recommended interventions for ACS, however, are considered resource intensive and/or require significant infrastructure, such as well-trained emergency medical services personnel to administer fibrinolysis, and cardiac catheterization laboratories that require capital and experienced staff. These regional disparities present challenges to regional and national health authorities as guidelines evolve and become more complex.

The American College of Cardiology with the American Heart Association, European Society of Cardiology, and other organizations have developed guidelines for treatment and management of patients with ST-segment elevation myocardial infarction (STEMI) and non-STEMI ACS. These guidelines primarily focus on the hospital setting, and, for many years, the prehospital and emergency department (ED) management of patients was based on extrapolation of in-hospital evidence. There is now increasing interest and evidence on the prehospital decisions and management of ACS. The time-sensitive nature of ACS forces us to scrutinize not only the time goals to deliver the interventions but also the proper sequencing of them. For these reasons, the ACS Task Force emphasized the evidence review for 2015 on the management of ACS before the patient is admitted.

There has been renewed interest of late in focusing less on the individual aspects of STEMI care and more on the systems of care. This is in recognition that the system may be more than the sum of its parts. In STEMI care, this system integrates awareness and prevention, prehospital care, in-hospital care, specialty centers, and rehabilitation and secondary prevention. The ACS Task Force concentrated on the questions that will inform regional systems-of-care decisions. If a patient with ACS or STEMI presents to prehospital care, a local hospital, or a specialty center, there needs to be a common but nuanced approach to diagnosis and treatment. However, the specifics of that treatment may depend on local resources. The questions covered were intentionally focused to answer questions based on different community resources.

Evidence Evaluation and GRADE Process

Each task force performed a detailed systematic review based on the recommendations of the Institute of Medicine of the National Academies[1] and using the methodological approach proposed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group.[2] After identification and prioritization of the questions to be addressed (using the PICO [population, intervention, comparator, outcome] format),[3] with the assistance of information specialists, a detailed search for relevant articles was performed in each of 3 online databases (PubMed, Embase, and the Cochrane Library).

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By using detailed inclusion and exclusion criteria, articles were screened for further evaluation. The reviewers for each question created a reconciled risk of bias assessment for each of the included studies, using state-of-the-art tools: Cochrane for randomized controlled trials (RCTs),[4] Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 for studies of diagnostic accuracy,[5] and GRADE for observational studies that inform both therapy and prognosis questions.[6]

GRADE evidence profile tables[7] were then created to facilitate an evaluation of the evidence in support of each of the critical and important outcomes. The quality of the evidence (or confidence in the estimate of the effect) was categorized as high, moderate, low, or very low,[8] based on the study methodologies and the 5 core GRADE domains of risk of bias, inconsistency, indirectness, imprecision, and other considerations (including publication bias).[9]

These evidence profile tables were then used to create a written summary of evidence for each outcome (the consensus on science statements). Whenever possible, consensus-based treatment recommendations were then created. These recommendations (designated as strong or weak) were accompanied by an overall assessment of the evidence and a statement from the task force about the values and preferences that underlie the recommendations.

Further details of the methodology that underpinned the evidence evaluation process are found in "Part 2: Evidence Evaluation and Management of Conflicts of Interest."

The ILCOR ACS Task Force Process

The 2015 ILCOR ACS Task Force included expert cardiology, emergency, and prehospital physicians from Singapore, Japan, Australia, New Zealand, Greece, Belgium, France, the United States, Canada, and Panama. These 12 experts, along with an additional 5 expert evaluators (paramedics and residents/fellows), reviewed 18 topics related to the acute initial management of ACS and STEMI. The task force reviewed the evidence specifically related to diagnosis and treatment of STEMI (and ACS) in the out-of-hospital setting and the first hours of care in the in-hospital setting, typically in the ED. The evidence evaluation took place over 3 years leading up to the ILCOR 2015 International Consensus on CPR and ECC Science With Treatment Recommendations (C2015) meeting, with ongoing refinement of recommendations being made as new evidence was published. The purpose of the review was to generate current, evidence-based consensus on science and treatment recommendations for healthcare providers who serve as the initial point of contact for patients with signs and symptoms suggestive of ACS.

The ACS Task Force spent considerable time preparing for the introduction of the GRADE process through group in-person, online, and self-directed educational sessions. The ACS Task Force had 5 in-person meetings (Vienna, Austria, October 2012; Melbourne, Australia, April 2013; Banff, Canada, April 2014; Chicago, United States, November 2014; Dallas, United States, January/February 2015) plus 9 webinars (June 2014 to January 2015). Use of the Scientific Evidence Evaluation and Review System (SEERS) website facilitated offline evidence review and online repository of progress and findings. This enabled periodic review and approval by task force members (TFMs), task force co-chairs, evidence evaluation experts, and senior editors.

The major steps from selection of review topics to the final CoSTR were:

- Topics prioritized for review
- 20 topics assigned to lead TFM. Two deferred after scant new research found
- PICO questions formed for each topic
- Importance of potential outcomes graded according to GRADE methodology
- Comprehensive search strategies run, search results uploaded online (SEERS)
- ACS TFMs, along with 5 additional external evidence reviewers paired to perform the following blinded duplicate processes:
  - Study inclusion/exclusion (non-RCTs excluded when there was evidence from several RCTs)
  - Data extraction
  - Bias assessments
- GRADE evidence profile tables formed
- Formal meta-analysis performed if appropriate
- Consensus on science reported according to evidence profile tables
- Quality of evidence determined across all outcomes
- Strength of recommendations determined
- Values, preferences, and resource implications, reported
- Additional commentary
- Potential gaps in the literature related to the systematic reviews identified
- Systematic reviews posted for public comments
- Comments accessed and distributed to the TFMs electronically
- Comments considered in the context of the draft recommendations; if necessary, amendments made by the TF co-chairs
- Systematic reviews presented at the C2015 conference—invited topic matter experts provided critical commentary. Feedback from public commentary and invited experts was reviewed and incorporated where needed.
- Key new evidence reviewed and incorporated
- The CoSTR Editorial Board signs off on final CoSTR

An iterative process was used in which TFMs presented their interim evidence evaluation and gained input from the task force, evidence evaluation experts, public, and invited topic matter experts. They presented the key articles and findings to the task force at face-to-face meetings or webinars to enable discussion, refinement, and expert input. Additionally, evidence evaluation experts acted as methodological support advisors for GRADE and other aspects of systematic review development. These were discussed during face-to-face and webinar meetings and were collated for consideration into this final document.

Regional resuscitation organizations will need to determine where the interventions are applicable in their systems and thus how to implement the evidence into practice.

ACS Task Force Summary

The ACS Task Force ultimately completed 18 systematic reviews (14 based on meta-analyses) on more than 110 relevant studies spanning 40 years. The treatment recommendations were grouped by major topics as outlined below:

Diagnostic Interventions in ACS

- Prehospital electrocardiography (ECG) (ACS 336)
- Computer-assisted ECG STEMI interpretation (ACS 559)
- Nonphysician ECG STEMI interpretation (ACS 884)
- Prehospital STEMI activation of the catheterization laboratory (ACS 873)
- Biomarkers to rule out ACS (ACS 737)

Therapeutic Interventions in ACS

- Prehospital adenosine diphosphate (ADP)-receptor antagonists in STEMI (ACS 335)
- Prehospital anticoagulants versus none in STEMI (ACS 562)
- Prehospital anticoagulants versus unfractionated heparin (UFH) in STEMI (ACS 568)
- Supplementary oxygen in ACS (ACS 887)

Reperfusion Decisions in STEMI

- Prehospital fibrinolysis versus ED fibrinolysis (ACS 338)
- Prehospital triage to percutaneous coronary intervention (PCI) center versus prehospital fibrinolysis (ACS 341)
- ED fibrinolysis and immediate PCI versus immediate PCI alone (ACS 882)
- Delayed PCI versus fibrinolysis stratified by time from symptoms (ACS 337)
- Transport for PCI versus ED fibrinolysis and transport only for rescue PCI (ACS 332)
- ED fibrinolysis and routine early angiography versus transport for PCI (ACS 779)
- ED fibrinolysis and then routine early angiography versus only rescue PCI (ACS 334)

Hospital Reperfusion Decisions After Return of Spontaneous Circulation (ROSC)

- PCI after ROSC with ST elevation (ACS 340)
- PCI after ROSC without ST elevation (ACS 885)

Some topics were not prioritized for review in the 2015 ILCOR process. Those topics not reviewed from 2005 and 2010 and/or not yet reviewed are

- History and physical examination in the diagnosis of ACS
- Chest pain observation units and protocols
- Institutional requirements for performing interventions in ACS
- Use of new biomarkers or other imaging tests for the diagnosis of ACS (rule-in)
- Use and timing of nitrates, β-blockers, ACE inhibitors, morphine, statins, glycoprotein IIb-IIIa antagonists, antiarrhythmics, analgesics, and anxiolytics in the prehospital, ED, and in-hospital settings
- Use of antiplatelet and anticoagulant medications in-hospital
- Administration of aspirin (early aspirin use was reviewed by the First Aid Task Force for 2015; see FA 871 and FA 586 in "Part 9: First Aid")
- Optimal metrics of system performance/comparison regarding prompt revascularization in STEMI

Summary of New Treatment Recommendations

The following is a summary of the most important new reviews or changes in recommendations for diagnosis and treatment of ACS since the last ILCOR review in 2010:

Diagnostic Interventions in ACS

- The role of prehospital ECG was reemphasized. Newer evidence suggests that prehospital ECG may not only facilitate earlier diagnosis of STEMI and provide the opportunity for rapid prehospital and in-hospital reperfusion, but there is evidence of a substantial mortality benefit. This is relevant to patients that will undergo primary percutaneous coronary intervention (PPCI) or fibrinolysis.
- Computer-assisted ECG STEMI interpretation is still suggested as an adjunct to recognize STEMI, given the high specificity of the computer algorithms evaluated. The strength of recommendation is reduced to a weak recommendation, because there was very low confidence in the effect size provided by the existing literature.
- Nonphysician ECG STEMI interpretation is suggested if adequate diagnostic performance can be maintained through carefully monitored programs.
- For prehospital STEMI activation of the catheterization laboratory, newer evidence suggests that it can not only reduce treatment delays but also improve patient mortality.
- The use of troponins at 0 and 2 hours as a stand-alone measure for excluding the diagnosis of ACS is strongly discouraged. Excluding the diagnosis of ACS (defined as less than 1% 30-day major adverse cardiac event [MACE]) can be accomplished by combining negative* high-sensitivity cardiac troponin (hs-cTnI) measured at 0 and 2 hours with low-risk stratification or by combining negative* cardiac troponin I (cTnI) or cardiac troponin T (cTnT) measured at 0 and 3 to 6 hours with very low risk stratification.

Therapeutic Interventions in ACS

- ADP-receptor antagonists can be given either prehospital or in-hospital for suspected STEMI patients with a planned primary PCI approach.
- UFH can be administered in either the prehospital or in-hospital setting in suspected STEMI patients with a planned primary PCI approach.
- Prehospital enoxaparin may be used as an alternative to prehospital UFH as an adjunct for primary PCI for STEMI. We have insufficient confidence in the treatment effect for prehospital administration of bivalirudin compared with prehospital administration of UFH in prehospital-identified STEMI patients to recommend a change in existing practice.

*Negative troponin value is less than 99th percentile.

- We suggest withholding oxygen in comparison with routine oxygen supplementation in normoxic patients with ACS.

Reperfusion Decisions in STEMI

- When fibrinolysis is the planned treatment strategy, we recommend using prehospital fibrinolysis in comparison with in-hospital fibrinolysis for STEMI where transport times are greater than 30 minutes and prehospital personnel are well trained.
- Where PCI facilities exist and are available in a geographic region we suggest that direct triage and transport for PCI is preferred to prehospital fibrinolysis for STEMI.
- We recommend against the routine use of fibrinolytic administration combined with immediate PCI, compared with immediate PCI alone in patients with STEMI.
- We provide recommendations on PCI versus fibrinolysis based on time from symptom onset and potential delay to PCI.
- After fibrinolysis of STEMI patients in the ED (when primary PCI is not available on-site), we suggest transport for early routine angiography in the first 3 to 6 hours (or up to 24 hours) rather than only transport for ischemia-guided angiography.
- For adult patients presenting with STEMI in the ED of a non–PCI-capable hospital, we recommend emergency transfer without fibrinolysis to a PCI center as opposed to immediate in-hospital fibrinolysis and transfer only for rescue PCI.
- For patients presenting with STEMI in the ED of a non-PCI hospital, we suggest fibrinolytic therapy with routine transfer for angiography within 3 to 6 and up to 24 hours as an alternative to immediate transfer to PPCI.

Hospital Reperfusion Decisions After ROSC

- We recommend emergency cardiac catheterization laboratory evaluation in comparison with cardiac catheterization later in the hospital stay or no catheterization in select adult patients with ROSC after out-of-hospital cardiac arrest (OHCA) of suspected cardiac origin with ST elevation on ECG.
- We suggest emergency cardiac catheterization laboratory evaluation in comparison with cardiac catheterization later in the hospital stay or no catheterization in select adult patients who are comatose with ROSC after OHCA of suspected cardiac origin without ST elevation on ECG.

Diagnostic Interventions in ACS

Acute coronary syndromes refers to a spectrum of clinical disorders that include acute myocardial infarction (AMI) with and without ST elevation and unstable angina pectoris. The term *myocardial infarction*, as defined by the World Health Organization, is used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia (no evidence of a cause other than ischemia). Criteria for diagnosis of AMI include[10]

- Detection of increase and/or decrease of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit
- Evidence of myocardial ischemia with at least 1 of the following: symptoms, ECG changes, or supportive imaging

Symptoms of ischemia include various combinations of chest, upper extremity, jaw, or epigastric discomfort with exertion or at rest. The discomfort usually lasts 20 minutes or less (may have any duration, but if it is greater than 20 minutes, then it is more likely an infarction); often is diffuse, not localized, not positional, and not affected by movement of the region; and may be accompanied by dyspnea, diaphoresis, nausea, or syncope. ECG changes indicative of new ischemia include new ST-T changes, new left bundle branch block, or development of pathological Q waves in the ECG. Imaging may show evidence of new loss of viable myocardium or new regional wall motion abnormality.

This diagnostic interventions section will focus on the value of the prehospital ECG in recognizing or "ruling in" STEMI, and on the use of diagnostic tests including biomarkers to identify low-risk chest pain and thus "rule out" ACS.

The ECG

In the ED and out-of-hospital settings, the ECG is essential for the initial triage and initiation of management of patients with possible ACS. It is well recognized that signs and symptoms alone may not be sufficiently sensitive to diagnose AMI or ischemia in the prehospital or ED setting. Prehospital ECG acquisition and interpretation is critical in early recognition of STEMI and other high-risk ACS patients. The ACS Task Force focused its attention on the use of the prehospital ECG for recognition of STEMI patients. Accurate recognition and advance notification of the hospital has the potential of minimizing in-hospital treatment delays, thus improving patient outcomes.

In many studies of prehospital ECG STEMI recognition, physician interpretation is considered to be the gold standard. This approach, however, is limited by the fact that physicians are not always available on scene, which increases the possibility of false ECG readings. The prehospital ECG can be interpreted in 4 ways: on-scene interpretation by a physician, nonphysician, or computer, or transmission off-site to a physician or other experienced healthcare provider.

This section will review the evidence for the use of the prehospital ECG in STEMI recognition, its value when used to notify the hospital and/or activate the catheterization laboratory, and the evidence for use of adjunctive computer interpretation and/or interpretation by nonphysicians in the prehospital setting.

This science review has focused on the ability of prehospital ECG recording with advance notification to affect not only patient treatment delays but also patient outcomes. We have also addressed accuracy of ECG interpretation by nonphysicians with or without the aid of computer interpretation. In the latter 2 analyses, it was impossible to provide pooled estimates for diagnostic performance because of considerable heterogeneity among the included studies. Rather,

ranges for observed sensitivity and specificity across studies are provided. Based on these values, we have calculated false-positive (FP) and false-negative (FN) results over an arbitrarily chosen spectrum of disease prevalence from 5% to 20%. Large variations within the existing evidence preclude extrapolation from these data to other situations and recommendations with general applicability to all systems of care that might be considering implementation of the reviewed diagnostic strategies. Each system should make every effort to achieve optimal diagnostic performance for prehospital ECG interpretation and STEMI recognition regardless of the diagnostic strategy they are using. The sensitivity and specificity of the diagnostic performance should be considered in conjunction with local prevalence of STEMI among transferred patients to determine the expected FP and FN rates for a particular system. This is highly important for effective balancing between patient risk for undue treatment delays in those with FN ECG readings and inappropriate resource allocation from false system alarms in case of FP ECG interpretations.

Prehospital ECG (ACS 336)

Among adult patients with suspected STEMI outside of a hospital (P), does prehospital 12-lead ECG with transmission or notification (I), compared with no ECG or no transmission/notification (C), change death, or time to treatment (first medical contact–to–balloon time, first medical contact–to–needle time, door-to-balloon time, door-to-needle time) (O)?

Consensus on Science

For the critical outcome of **30-day mortality in STEMI patients who receive PCI**, we have identified low-quality evidence (downgraded for bias, upgraded for treatment effect) from 9 observational studies[11–19] enrolling 20 402 patients showing benefit of prehospital 12-lead ECG and hospital notification compared with no ECG or no notification (relative risk [RR], 0.68; 95% confidence interval [CI], 0.51–0.91) (Figure 1). This is a 32% relative reduction in mortality.

For the critical outcome of **30-day mortality in STEMI patients who receive fibrinolysis**, we have identified low-quality evidence (downgraded for bias, upgraded for treatment effect) from 2 observational studies[11,19] enrolling 59 631 patients showing benefit of prehospital ECG and hospital notification compared with no 12-lead ECG or no notification (RR, 0.76; 95% CI, 0.71–0.82) (Figure 2). This is a 24% relative reduction in mortality.

For the important outcomes of **first medical contact–to–reperfusion, door-to-balloon, and door-to-needle time in STEMI patients**, we have identified very-low-quality evidence (downgraded for serious risk of bias) in 7 observational studies,[12,15–17,20–22] 14 observational studies,[11–14,16–18,20–26] and 3 observational studies,[11,26,27] respectively, of consistent reduction in times to reperfusion with prehospital 12-lead ECG and hospital notification. The time to treatment results could not be pooled because of heterogeneity in estimate of effect size.

Treatment Recommendation

We recommend prehospital 12-lead ECG acquisition with hospital notification for adult patients with suspected STEMI (strong recommendation, low-quality evidence).

Values, Preferences, and Task Force Insights

In making this recommendation, we are placing a higher value on the consistent mortality-benefit and consistent reduction-in-reperfusion times in a large number of patients (greater than 80 000) over the risk of bias inherent in observational studies.

Knowledge Gaps

- This question did not specifically address the method for ECG interpretation. We did not find direct comparison of different systems of ECG STEMI recognition (with and without adjunctive computer algorithm).

Computer-Assisted ECG STEMI Interpretation (ACS 559)

Among adult patients with suspected STEMI outside of a hospital (P), does the use of computer-assisted ECG interpretation (I), compared with physician ECG interpretation and/or clinical diagnosis of STEMI (C), change identification of STEMI on an ECG with acceptable rates of FNs to allow earlier identification and FPs, minimizing unnecessary intervention (O)?

Consensus on Science

For the important outcomes of **FP and FN**, we have identified very-low-quality evidence (downgraded for risk of bias, inconsistency, and imprecision) from 2 cohort studies[28,29] enrolling 1112 patients/ECGs of FP for STEMI recognition ranging from 0% to 8.7% (assuming STEMI prevalence of 5% [highest expected FP results]) and FN ranging from 4.4% to 8.4% (assuming STEMI prevalence of 20% [highest expected FN results]). Note that sensitivity ranged from 0.58 to 0.78, and specificity ranged from 0.91 to 1.

For the important outcome of **FP/all positive results**, we identified very-low-quality evidence (downgraded for risk of bias, inconsistency, and imprecision) from 6 observational studies[14,30–33] enrolling 1949 ECGs of FP/all positive results for STEMI recognition ranging from 0% to 42.9%.

Treatment Recommendations

We suggest computer-assisted ECG interpretation can be used as an adjunct* to recognize STEMI, given the high specificity of the computer algorithms evaluated (weak recommendation, very-low-quality evidence).

We suggest computer-assisted ECG interpretation not be used alone to rule out STEMI, because of the poor sensitivity and thus the considerable risk for FN results of the computer algorithms evaluated (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

In making this recommendation, we put a higher value on minimizing treatment delays of patients with STEMI over possible wasted resources resulting from FP system activation.

Recognition of STEMI on ECG may achieve highest accuracy if computer-assisted interpretation is implemented as an adjunct to on-site healthcare provider interpretation in the

*The computer-assisted ECG interpretation can be used as an adjunct or in conjunction with the interpretation of a physician or other trained professional. In this way, recognition of STEMI by the computer interpretation can be verified by individual interpretation, and lack of recognition by the computer would not be used solely to rule out STEMI.

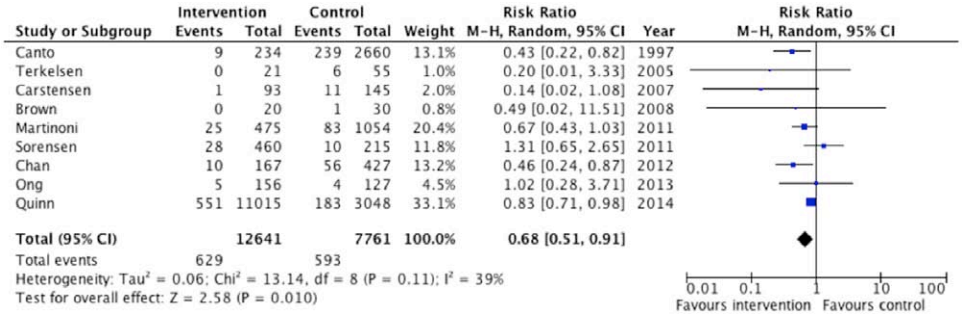

Figure 1. Thirty-day mortality in STEMI patients undergoing PPCI with and without prehospital ECG and hospital notification (random effects model). Intervention = prehospital ECG; control = without prehospital ECG.

context of strong initial education programs, quality assurance programs, and ongoing oversight.

As was pointed out in the public comments, it is difficult to perform head-to-head comparisons or combine data from these studies, because they have used different proprietary computer interpretation algorithms and different gold standards. It is likely that different algorithms perform differently. Computer interpretation algorithms can be updated periodically, which may change their effectiveness, making previous studies less relevant unless the algorithm and version are the same as is used in your setting. Last, some of the algorithms can now be adjusted to favor either lower FP results or lower FN results, depending on the needs or how it is used. Therefore, in choosing to use such a computer algorithm as an adjunct, careful consideration of the individual algorithm's reported performance and evaluation of this in your own setting are key.

The use of computer ECG interpretation did not yield equally effective performances across the various systems of care where it has been used with observed sensitivities ranging from 0.58 to 0.78 and specificity ranging from 0.91 to 1. This may be due to the algorithm performance (different performance with different types of STEMI), but it may also be related to the quality of obtained ECG and the level of training and individual expertise in acquiring the ECG. It is possible that the performance characteristics of a computer algorithm are different in controlled, in-hospital settings in stable patients compared with prehospital settings. Therefore, each system of care has to evaluate performance of any specific algorithm in the particular context where the algorithm is used. Diagnostic performance should always be considered in conjunction with local STEMI prevalence, because very high or low prevalence rates may lead to unacceptable FP and/or FN rates despite sensitivity and specificity rates that may seem satisfactory as stand-alone values. This approach may give important clues as to whether this method fits best in comparison with other existing options of ECG interpretation such as transmission of ECG for interpretation by an experienced provider.

Knowledge Gaps

- Different computer algorithms have not been compared. The optimal ECG computer algorithm for implementation with adjunctive nonexpert interpretation has not been determined.

Nonphysician STEMI ECG Interpretation (ACS 884)

Among adult patients with suspected STEMI outside of a hospital (P), do nonphysicians (eg, nurses and paramedics) (I), compared with physicians (C), change identification of STEMI on an ECG with acceptable rates of FNs to allow earlier identification and FPs, minimizing unnecessary angiography (O)?

Consensus on Science

For the important outcomes of **FP and FN results**, we have identified very-low-quality evidence (downgraded for risk of bias, inconsistency, and publication bias) from 3 studies[34–36] including 1360 ECGs of FP results of STEMI recognition ranging from 0.3% to 30.5% (under the assumption of a disease prevalence of 5% [highest expected FP results]), and FN results did not exceed 4% (under the assumption of 20% prevalence [highest expected FN results]). Sensitivity ranged from 80% to 99.6%, and specificity ranged from 68% to 96.8%.

For the important outcome of **FP/all positive tests**, we have identified very-low-quality studies (downgraded for risk of bias and inconsistency) from 9 observational studies[34–41] including 900 ECGs of FP/all positive tests for STEMI recognition ranging from 8% to 40%.

Treatment Recommendation

We suggest that in adult patients with suspected STEMI outside of a hospital, nonphysicians may perform ECG interpretation to recognize STEMI in a system where the FP and FN rates are low (weak recommendation, very-low-quality evidence).

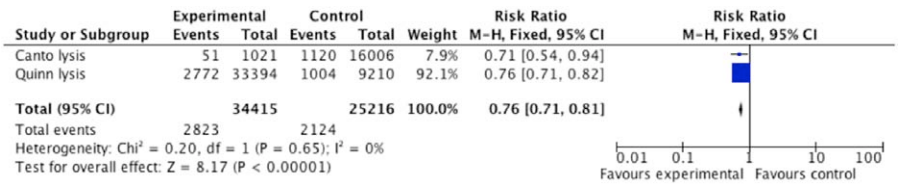

Figure 2. Thirty-day mortality in STEMI patients undergoing fibrinolysis with and without prehospital ECG and hospital notification (fixed effects model). Experimental = prehospital ECG; control = without prehospital ECG.

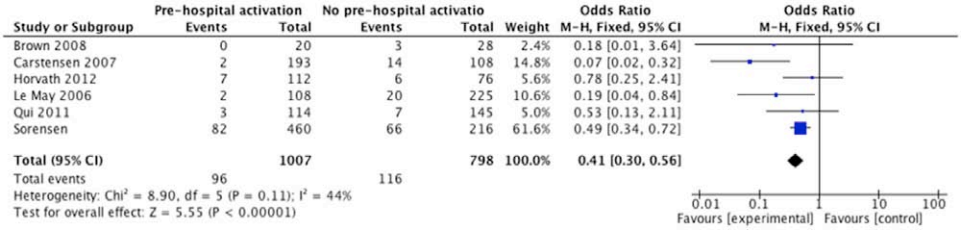

Figure 3. Thirty-day mortality for prehospital STEMI activation of the catheterization laboratory versus no prehospital activation. Experimental = prehospital STEMI activation of the catheterization laboratory; control = no prehospital STEMI activation of the catheterization laboratory.

Values, Preferences, and Task Force Insights

In making this recommendation, we adopt a balanced approach in between minimizing treatment delays of patients with STEMI and avoiding excess waste of resources resulting from FP system activations.

It is recognized that in many prehospital systems, physicians will not be available on-site, and the evidence indicates that highly trained paramedics and nurses can reliably recognize STEMI. This should occur in an organized system of prehospital care where there is a strong initial education program, ongoing oversight, possible adjunctive computer interpretation, and a quality assurance program.

It is impossible to provide pooled estimates from the reviewed data, because different study methods and/or gold standards have been used. Nonphysician STEMI ECG recognition was not equally reliable across the various reporting systems of care. This may be relevant to the quality of the ECG obtained and the ECG findings but also to the level of training and individual expertise of healthcare providers. Therefore, each system of care should make every effort to assure optimal diagnostic accuracy from healthcare providers by maintaining adequate training programs and meticulous care for quality control. Timely feedback from STEMI receiving centers, including performance benchmarks, prehospital and in-hospital ECGs, and catheterization findings, may be essential in this regard. Diagnostic performance should always be considered in conjunction with local STEMI prevalence as very high or low prevalence rates may lead to unacceptable FP and/or FN rates despite sensitivity and specificity rates that may seem satisfactory as stand-alone values. This may give important clues as to whether nonphysician STEMI interpretation fits best in the setting of a particular system of care in comparison with other existing options of on-site ECG interpretation such as transmission of ECG for interpretation by an experienced provider or computer-assisted interpretation.

Knowledge Gaps

- We did not find evaluation of nonphysician ECG interpretation initial and maintenance training programs or measurement of ECG interpretation performance based on specific education or experience.

Prehospital STEMI Activation of the Catheterization Laboratory (ACS 873)

Among adult patients with suspected STEMI outside of a hospital (P), does prehospital activation of catheterization laboratory (I), compared with no prehospital activation of the catheterization laboratory (C), change mortality, major bleeding, stroke, reinfarction (O)?

Introduction

Prompt restoration of coronary flow in the affected area is key to treatment of STEMI. Several system-related strategies have been developed to minimize system-related delays to reperfusion. For patients with suspected STEMI in the prehospital setting, the above strategies for ECG interpretation are used to ensure prehospital STEMI recognition. Where prehospital fibrinolysis is not possible or appropriate, the focus should then be on prompt patient triage for transfer to the medical institution where the most appropriate treatment would be offered in a timely manner. Advance hospital notification and early activation of the catheterization laboratory can expedite invasive revascularization. This review has focused on the potential of prehospital STEMI activation of the catheterization laboratory to improve patient safety and efficacy outcomes.

Consensus on Science

For the critical outcome of **30-day mortality**, we have identified moderate-quality evidence (upgraded for large effect size) from 6 observational studies[13,14,16,42–44] enrolling 1805 patients in favor of prehospital activation of the catheterization laboratory over no activation of catheterization laboratory (odds ratio [OR], 0.41; 95% CI, 0.30–0.56) (Figure 3).

For the important outcome of **major bleeding**, we have identified very-low-quality evidence (downgraded for imprecision) from 1 observational study[43] enrolling 188 patients showing no benefit of prehospital activation of catheterization laboratory over no activation of catheterization laboratory (OR, 0.68; 95% CI, 0.04–10.68).

For the important outcome of **nonfatal stroke**, we have identified very-low-quality evidence (downgraded for imprecision) from 1 observational study[13] enrolling 301 patients showing no benefit of prehospital activation of catheterization laboratory over no activation of catheterization laboratory (OR, 0.06; 95% CI, 0.00–1.13).

For the important outcome of **nonfatal reinfarction**, we have identified very-low-quality evidence (downgraded for imprecision) from 3 observational studies[13,43,44] enrolling 748 patients showing no benefit of prehospital activation of catheterization laboratory over no activation of catheterization laboratory (OR, 0.48; 95% CI, 0.22–1.03).

Treatment Recommendation

We recommend that when primary PCI is the planned strategy, that prehospital activation of catheterization laboratory for

PPCI is preferred (strong recommendation, very-low-quality evidence) over no prehospital activation.

Values, Preferences, and Task Force Insights

In making this recommendation, we place higher value of benefit to patient outcomes over the potential increased resource utilization.

Biomarkers to Rule Out ACS (ACS 737)

In patients presenting to the ED with chest pain suspected to be of cardiac etiology (P), does a negative troponin test at presentation and 1, 2, 3, and 6 hours (I), compared with a positive test (C), exclude the diagnosis of ACS (O)?

Introduction

Troponin has become the most widely used and well-validated diagnostic laboratory test for the diagnosis of myocardial ischemia and is the preferred biomarker for the international definition of myocardial infarction.[45] There have been a variety of biomarkers proposed for the diagnosis of myocardial infarction, including myoglobin, brain natriuretic peptide (BNP), NT-proBNP, D-dimer, C-reactive protein, ischemia-modified albumin pregnancy-associated plasma protein A (PAPP-A), and/or interleukin-6. There is insufficient evidence to support the use of many of these in isolation as primary tests to evaluate patients with symptoms suspicious for cardiac ischemia.[46,47]

The diagnosis of AMI includes the increase and/or decrease in the biomarker troponin; therefore, numerous studies have evaluated the effectiveness of different timelines for ruling in an AMI by using various troponin assays. Many cardiology guidelines have recommended timelines for ruling in AMI. The accuracy and test characteristics of troponins for ruling out an AMI is an area of interest, given the relatively new high-sensitivity troponin tests available.

This evidence review is confined to the use of troponin in the rule out of ACS. Although troponin use to rule out AMI is feasible, non-AMI ACS may not have a rise of troponin, and thus ruling out ACS with only troponin may not be possible. However, troponin in combination with other investigations may be able to identify a group of patients with very low frequency (defined as less than 1%) of MACE in the next 30 days, thus virtually able to rule out or exclude the diagnosis of ACS.

In chest pain patients in the ED, early identification of a group of patients with very low risk of 30-day MACE could substantially decrease the number of chest pain patients admitted to hospital. This use of troponin at specific time intervals with or without other tools may identify the very low risk of patients that can be safely discharged home. These very-low-risk patients may still need additional diagnostic workup for coronary artery disease, but this could be accomplished as outpatients.

This body of evidence reviewed consisted entirely of observational data, because no RCTs were found. In most of these studies, the gold standard for the diagnosis of acute coronary ischemia frequently was a diagnosis of a documented MACE in a given time frame (30 days, 6 months, or 1 year). In the ED setting, one of the most important imperatives is to identify patients in whom ACS can be safely excluded to facilitate timely discharge. Hence, the critical measure of the value of the diagnostic tests is the FN rate, which is the proportion of FNs relative to all patients with ACS (FN/(FN+TP)). The incidence of FN is determined by the prevalence of the relevant disease in the population. So, in patients with ACS, we sought to review the evidence for combining clinical risk stratification tools with the troponin assay to improve the accuracy of ACS identification. This is important, given the many patients who present with chest pain to emergency healthcare providers and the adverse consequences for patients in whom the diagnosis of ACS is missed.

Consensus on Science

High-Sensitivity Cardiac Troponin T (Table 1)

For the critical outcome of **excluding the diagnosis of ACS***, we have identified very-low-quality evidence (downgraded for selection bias and imprecision) from 1 observational study[48] enrolling 939 patients presenting to the ED with chest pain showing an FN rate (FN/(FN+TP)) of 2.5% if both 0- and 2-hour high-sensitivity cardiac troponin T (hs-cTnT) were less than 99th percentile and the increase was less than 20% without the use of clinical scoring, using the outcome of adjudicated 1-year events.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias and imprecision) from 1 observational study[49] enrolling 764 patients presenting to the ED with chest pain showing an FN rate (FN/(FN+TP)) of 3.6% if both 0- and 2-hour hs-cTnT were less than 14 ng/L without the use of clinical scoring, using the outcome of 30-day MACE.

High-Sensitivity Cardiac Troponin I

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias and imprecision) from 1 observational study[49a] enrolling 1635 patients presenting to the ED with symptoms suggestive of ACS showing an FN rate (FN/(FN+TP)) of 0.9% if both 0- and 2-hour hs-cTnI were less than 99th percentile and met the Vancouver Rule, using the outcome of 30-day MACE.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias, inconsistency, and imprecision) from 1 observational study[50] enrolling 909 patients presenting to the ED with symptoms suggestive of ACS, finding an FN rate (FN/(FN+TP)) of 0.8% if both 0- and 2-hour hs-cTnI were less than 99th percentile and a Thrombolysis in Myocardial Infarction (TIMI) score of 0 or 1, using the outcome of 30-day MACE.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias and imprecision) from 1 observational study[50] enrolling 1635 patients presenting to the ED with greater than 5 minutes of chest pressure showing an FN rate of 0.8% if both 0- and 2-hour hs-cTnI were less than 99th percentile and a TIMI score of 0 or 1, using the outcome of 30-day MACE.

*Exclude the diagnosis of ACS defined as less than 1% 30-day MACE.

Table 1. Troponin and Risk Stratification to Rule Out MACE

Reference	Inclusion Criteria	n	Measurement	Clinical Score	FN/(FN+TP), %	Outcome
Marker: high-sensitivity cardiac troponin T (hs-cTnT)						
Aldous,[48] 2011	Chest pain	939	0- and 2-hour hs-cTnT <99th percentile and delta <20%	None	2.5	Adjudicated 1-year cardiac event
Parsonage,[49] 2014	Chest pain	764	0- and 2-hour hs-cTnT <14 ng/L	None	3.6	30-day MACE
Marker: high-sensitivity cardiac troponin I (hs-cTnI)						
Cullen,[49a] 2014	Symptoms suggestive of ACS	1635	0- and 2-hour hs-cTnI <99th percentile	Vancouver	0.9	30-day MACE
Cullen,[50] 2013	<12 hours of symptoms suggestive of ACS	909	0- and 2-hour hs-cTnI <99th percentile	TIMI score 0 or 1	0.8	30-day MACE
Cullen,[50] 2013	>5 minutes of chest pressure	1635	0- and 2-hour hs-cTnI <99th percentile	TIMI score 0 or 1	0.8	30-day MACE
Cullen,[50] 2013	<12 hours of symptoms suggestive of ACS	909	0- and 2-hour hs-cTnI <99th percentile	TIMI score 0	0	30-day MACE
Cullen,[50] 2013	>5 minutes of chest pressure	1635	0- and 2-hour hs-cTnI <99th percentile	TIMI score 0	0	30-day MACE
Markers: cardiac troponin I and troponin T (cTnI and cTnT)						
Aldous,[48] 2011	Chest pain	939	0- and 2-hour cTnI <0.056 mcg/L	None	7.8	Adjudicated 1-year cardiac event
Cullen,[49a] 2014	Symptoms suggestive of ACS	1635	0- and 2-hour cTnI <99th percentile	Vancouver	1.2	30-day MACE
Xavier Scheuermeyer,[51] 2014	Symptoms suggestive of ACS	906	0- and 2-hour cTnT <99th percentile	Vancouver	0.8	30-day MACE
Kelly,[52] 2014	>10 minutes of chest pain	840	0- and 2-hour cTnI <99th percentile	TIMI score 0	0	30-day MACE
Mahler,[53] 2013	Anterior chest pain	1002	0- and 3-hour cTnI <99th percentile	Low risk using an unstructured risk assessment	2.3	30-day MACE
Mahler,[53] 2013	Anterior chest pain	1002	0- and 3-hour cTnI <99th percentile	Low-risk HEART score	0.9	30-day MACE
Mahler,[53] 2013	Anterior chest pain	1002	0- and 3-hour cTnI <99th percentile	Low-risk North American CP score	0	30-day MACE
Hess,[54] 2013	Anterior chest pain	2718	0- and 3- to 6-hour cTnI or cTnT <99th percentile	North American CP score of 0 and age <60 years	1.1	30-day MACE
Hess,[54] 2013	Anterior chest pain	2718	0- and 3- to 6-hour cTnI or cTnT <99th percentile	North American CP score of 0 and age <50 years	0	30-day MACE

ACS indicates acute coronary syndromes; CP, chest pain; FN, false negative; MACE, major adverse cardiac event; TIMI, Thrombolysis in Myocardial Infarction; and TP, true positive.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias, inconsistency, and imprecision) from 1 observational study[50] enrolling 909 patients presenting to the ED with symptoms suggestive of ACS showing an FN rate of 0% if both 0- and 2-hour hs-cTnI were less than 99th percentile and a TIMI score of 0, using the outcome of 30-day MACE.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias and imprecision) from 1 observational study[50] enrolling 1635 patients presenting to the ED with greater than 5 minutes of chest pressure showing an FN rate of 0% if both 0- and 2-hour hs-cTnI were less than 99th percentile and a TIMI score of 0, using the outcome of 30-day MACE.

Cardiac Troponin I and T

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias and imprecision) from 1 observational study[48] enrolling 939 patients presenting to the ED with chest pain showing an FN rate (FN/(FN+TP)) of 7.8% if both 0- and 2-hour cTnI were less than 0.056 mcg/L without the use of clinical scoring, using the outcome of adjudicated 1-year cardiac events.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias and imprecision) from 1 observational study[49a] enrolling 1635 patients presenting to the ED with symptoms suggestive of ACS showing an FN rate (FN/(FN+TP)) of 1.2% if both 0- and 2-hour cTnI were less than 99th percentile and met the Vancouver rule, using the outcome of 30-day MACE.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias) from 1 observational study[51] enrolling 906 patients presenting to the ED with symptoms suggestive of ACS showing an FN rate of 0.8% if 0- and 2-hour cTnT were less than 99th percentile and met the Vancouver rule, using the outcome of 30-day MACE.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias) from 1 observational study[52] enrolling 840 patients presenting to the ED with greater than 10 minutes of chest pain showing an FN rate of 0% if 0- and 2-hour cTnI were less than 99th percentile and TIMI risk score of 0, using the outcome of 30-day MACE.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias) from 1 observational study[53] enrolling 1002 patients presenting to the ED with anterior chest pain showing an FN rate of 0.8% if 0- and 3-hour cTnI were less than 99th percentile and a low-risk unstructured risk assessment, using the outcome of 30-day MACE.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias) from 1 observational study[53] enrolling 1002 patients presenting to the ED with anterior chest pain showing an FN rate of 0.8% if 0- and 3-hour cTnI were less than 99th percentile and a low-risk HEART score, using the outcome of 30-day MACE.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias) from 1 observational study[53] enrolling 1002 patients presenting to the ED with anterior chest pain showing an FN rate of 0.8% if 0- and 3-hour cTnI were less than 99th percentile and a low-risk North American CP score, using the outcome of 30-day MACE.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias) from 1 observational study[54] enrolling 2718 patients presenting to the ED with anterior chest pain and had a troponin ordered showing an FN rate of 1.1% if both 0- and 3–6 hour cTnI or cTnT were less than 99th percentile, a North American CP score of 0, and age was less than 60 years, using the outcome of 30-day MACE.

For the critical outcome of **excluding the diagnosis of ACS**, we have identified very-low-quality evidence (downgraded for selection bias) from 1 observational study[54] enrolling 2718 patients presenting to the ED with anterior chest pain and had a troponin ordered showing an FN rate of 0% if both 0- and 3–6 hour cTnI or cTnT were less than 99th percentile, a North American CP score of 0, and age was less than 50 years, using the outcome of 30-day MACE.

Treatment Recommendations

We recommend against using hs-cTnT and cTnI alone measured at 0 and 2 hours to exclude the diagnosis of ACS* (strong recommendation, very-low-quality evidence).

There is no evidence of using hs-cTnI and cTnT alone to exclude the diagnosis of ACS.

We suggest that negative† hs-cTnI measured at 0 and 2 hours may be used together with low-risk patients (low risk defined by Vancouver rule or TIMI score of 0 or 1) to exclude the diagnosis of ACS* (weak recommendation, low-quality evidence).

We suggest negative† cTnI or cTnT measured at 0 and 3 to 6 hours may be used together with very-low-risk patients (low risk defined by Vancouver rule, TIMI score of 0, low-risk HEART score, low-risk North American CP rule) to exclude the diagnosis of ACS* (weak recommendation, low-quality evidence).

Values, Preferences, and Task Force Insights

In making these recommendations, we place higher value on reducing resource utilization by avoiding hospitalization, only if these patients have a very low likelihood of subsequent MACE. We defined the acceptable risk as less than 1% risk of ACS, MACE, or death at 30-day or longer follow-up.

Knowledge Gaps

- We encourage further studies to evaluate the combination of troponin and clinical risk scores to determine which patients with chest pain may be safely discharged from the ED.

Therapeutic Interventions in ACS

Myocardial reperfusion therapy, by fibrinolysis or primary PCI, is the pivotal treatment of STEMI. The development of STEMI networks during the past decade has improved quick access to reperfusion therapy and led to a reduction of mortality in this setting.[55]

Reperfusion therapy benefits from adjunctive antithrombotic therapy, which, depending on the logistics and organization of emergency medical services, may be provided in the prehospital setting by physicians or in some regions by nurses and paramedics under medical authority. Such therapy includes antiplatelet agents (eg, aspirin, ADP inhibitors) and anticoagulants (eg, UFH, enoxaparin, bivalirudin).

The benefit of aspirin administration in STEMI patients is strong, and as there was no significant new research in this area, this question was not prioritized for update in 2015. The administration of aspirin by first aid providers was reviewed in 2015 (see FA 871 and FA 586 in "Part 9: First Aid").

Although the administration of ADP-receptor inhibitors is strongly recommended in STEMI (and other) patients, the in-hospital use of these drugs was not addressed in this 2015 publication; however, their prehospital use was reviewed. There were very few studies that evaluated the prehospital versus in-hospital administration of these drugs, and this is

*Exclude the diagnosis of ACS defined as less than 1% 30-day MACE.
†Negative value is less than 99th percentile.

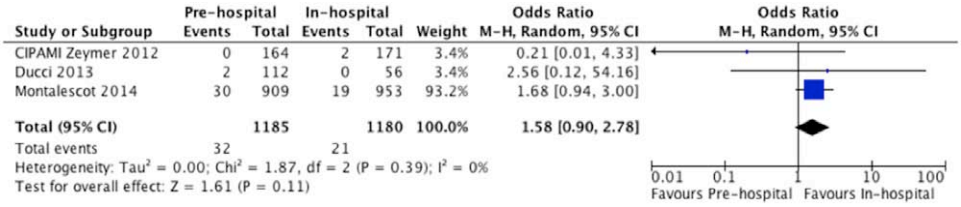

Figure 4. Thirty-day mortality for prehospital versus in-hospital ADP-antagonist administration. Experimental = prehospital ADP-antagonist administration; control = in-hospital ADP-antagonist administration.

a topic requiring further research. Our a priori outcomes did not include stent thrombosis; thus, this was not included in the 2015 consensus on science. However, where post hoc evidence of increased stent thrombosis rates were available, inclusion in treatment recommendations was considered.

The concomitant administration of adjunctive antithrombotic therapy in association with reperfusion therapy is recommended widely based on consistent evidence in international specialty guidelines.[56,57] Nevertheless, whether effort should be undertaken to include such additional therapy in the prehospital management of STEMI patients, particularly in a planned primary PCI strategy, remains to be evaluated and is the subject of this section. Two related questions reviewed the evidence for administration of anticoagulants in the prehospital setting. One reviewed prehospital versus in-hospital use, and the other reviewed prehospital administration of different agents. Interestingly, only UFH has been evaluated directly in a comparison of prehospital versus in-hospital use despite other agents being used in the prehospital setting. We encourage prospective RCTs on the relative benefits of prehospital versus in-hospital administration of anticoagulants. While stent thrombosis was not an a priori outcome in our evaluations, it remains a major complication of PCI, and, thus, where post hoc evidence of increased stent thrombosis rates were available, this was considered for the treatment recommendations and is discussed further in the comments section.

In addition to the prehospital antiplatelet and anticoagulant treatments for STEMI patients above, this section also includes oxygen supplementation in ACS patients. Although the use of supplementary oxygen (regardless of oxygen saturation) had previously been considered standard of care, its routine use for ACS patients (and postarrest patients, patients with chronic obstructive pulmonary disease, etc) has more recently been questioned. Most of the literature on this topic is relatively old, some before reperfusion therapy for STEMI (1970s) and, thus, this limits its generalizability. These studies also used different nonstandardized outcomes, which limits the ability to combine the studies. Despite these numerous methodological concerns, in 2010 the ILCOR ACS Task Force stated that the routine use of supplementary oxygen in ACS was not recommended. The review did cite gaps in prospective studies of oxygen use in ACS in the modern era. Since 2010, 3 prospective research studies on the use of supplementary oxygen use in STEMI were started. Therefore, this topic was reviewed for 2015 to update the review with the use of the new GRADE methodology and in anticipation of additional evidence in the near future. At the time of final manuscript preparation, the published results were available for only 1 of these trials. The other 2 studies were not yet published.

Prehospital ADP-Receptor Antagonists in STEMI (ACS 335)

Among adult patients with suspected STEMI outside of the hospital (P), does prehospital administration of an ADP-receptor antagonist (clopidogrel, prasugrel, or ticagrelor) in addition to usual therapy (I), compared with administration of an ADP-receptor antagonist in-hospital (C), change death, intracranial hemorrhage, revascularization, stroke, major bleeding, reinfarction (O)?

Consensus on Science

For the critical outcome of **30-day mortality**, we have identified very-low-quality evidence (downgraded for imprecision and reporting bias) from 3 RCTs[58–60] enrolling 2365 patients showing no additional benefit with prehospital administration of an ADP-receptor antagonist compared with in-hospital administration (OR, 1.58; 95% CI, 0.90–2.78) (Figure 4).

For the important outcome of **major bleeding**, we have identified very-low-quality evidence (downgraded for imprecision and reporting bias) from 3 RCTs[58–60] enrolling 2365 patients showing no additional benefit with prehospital administration of an ADP-receptor antagonist compared with in-hospital administration (OR, 1.12; 95% CI, 0.72–1.74).

Treatment Recommendation

We suggest that when ADP-receptor antagonists are given to suspected STEMI patients with a planned primary PCI approach, administration can occur in either the prehospital or in-hospital setting, but there is insufficient evidence to change existing practice (very-low-quality evidence, weak recommendation).

Values, Preferences, and Task Force Insights

In making this recommendation we place a higher value on not recommending adding complexity to prehospital treatment regimens over uncertain benefits.

There was no difference in mortality or major bleeding with either prehospital or in-hospital administration. We acknowledge, however, that although stent thrombosis was not considered as an outcome a priori, 1 study did report lower early (≤24 hours) stent thrombosis rates with prehospital (0.8%) versus in-hospital administration (0%).[60] However, there were no differences in mortality, or their composite ischemic end points in this trial. The relevance of this very rare occurrence of early stent thrombosis in balance with the rare occurrence of additional bleeding if the patient underwent an emergency surgical strategy rather than PCI will need to

be elucidated in further studies. Therefore, we find that the relative benefit to administering these agents prehospital versus in-hospital is marginal at best and may be offset by additional harms that could only be evaluated by larger RCTs that include these additional patient-oriented outcomes.

Prehospital Anticoagulants Versus None in STEMI (ACS 562)

Among adult patients with suspected STEMI outside of hospital transferred for primary PCI (P), does any anticoagulant administered prehospital (eg, bivalirudin, dalteparin, enoxaparin, fondaparinux, UFH) (I), compared with no anticoagulant administered prehospital (C), change death, intracranial hemorrhage, revascularization, major bleeding, stroke, reinfarction (O)?

Consensus on Science

For the critical outcome of **30-day mortality**, we have identified very-low-quality evidence (downgraded for indirectness and imprecision) from 1 non-RCT[61] enrolling 1702 patients undergoing PPCI for STEMI showing no benefit of prehospital UFH versus in-hospital UFH (OR, 1.07; 95% CI, 0.595–1.924).

For the important outcome of **stroke**, we have identified very-low-quality evidence (downgraded for indirectness and imprecision) from 1 non-RCT[61] enrolling 1702 patients undergoing PPCI for STEMI showing no benefit of prehospital UFH over in-hospital UFH (OR, 0.25; 95% CI, 0.034–3.136).

For the important outcome of **myocardial infarction**, we have identified very-low-quality evidence (downgraded for indirectness and imprecision) from 1 non-RCT[61] enrolling 1702 patients undergoing PPCI for STEMI showing no benefit of prehospital UFH over in-hospital UFH (OR, 0.979; 95% CI, 0.366–2.62).

For the important outcome of **major bleeding**, we have identified very-low-quality evidence (downgraded for indirectness and imprecision) from 1 non-RCT[61] enrolling 1702 patients undergoing PPCI for STEMI showing no benefit of prehospital UFH over in-hospital UFH (OR, 0.699; 95% CI, 0.466–1.047).

There was no direct evidence of other anticoagulant medications administered in the prehospital setting compared with in-hospital setting for STEMI patients.

Treatment Recommendation

We suggest that when UFH is given in suspected STEMI patients with a planned primary PCI approach, administration can occur in either the prehospital or in-hospital setting, and there is insufficient evidence to change existing practice (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

In making this recommendation, we place a higher value on not recommending adding complexity to prehospital treatment regimens over uncertain additional benefit.

Prehospital Anticoagulants Versus UFH in STEMI (ACS 568)

Among adult patients with suspected STEMI outside of a hospital transferred for primary PCI (P), does any anticoagulant prehospital (eg, bivalirudin, dalteparin, enoxaparin, fondaparinux) (I), compared with UFH prehospital (C), change death, intracranial hemorrhage, revascularization, major bleeding, stroke, reinfarction (O)?

Consensus on Science

Bivalirudin Versus UFH RCTs

For the critical outcome of **30-day mortality**, we have identified very-low-quality evidence (downgraded for risk of bias, indirectness, and imprecision) from 1 RCT[62] enrolling 2218 patients transferred for PPCI for STEMI showing no benefit of prehospital bivalirudin compared with prehospital UFH (OR, 0.96; 95% CI, 0.59–1.56).

For the important outcome of **stroke**, we have identified very-low-quality evidence (downgraded for risk of bias, indirectness, and imprecision) from 1 RCT[62] enrolling 2218 patients transferred for PPCI for STEMI showing no benefit of prehospital bivalirudin compared with prehospital UFH (OR, 0.55; 95% CI, 0.2–1.5).

For the important outcome of **reinfarction**, we have identified very-low-quality evidence (downgraded for risk of bias, indirectness, and imprecision) from 1 RCT[62] enrolling 2218 patients transferred for PPCI for STEMI showing no benefit of prehospital bivalirudin compared with prehospital UFH (OR, 1.95; 95% CI, 0.90–4.22).

For the important outcome of **major bleeding**, we have identified very-low-quality evidence (downgraded for risk of bias, indirectness, and imprecision) from 1 RCT[62] enrolling 2218 patients transferred for PPCI for STEMI showing a benefit of prehospital bivalirudin compared with prehospital UFH (OR, 0.5; 95% CI, 0.26–0.96).

Bivalirudin Non-RCTs

For the critical outcome of **30-day mortality**, we have identified very-low-quality evidence (downgraded for inconsistency, indirectness, and imprecision) from 2 non-RCTs[63,64] enrolling 543 patients transferred for PPCI for STEMI showing no benefit of prehospital bivalirudin compared with prehospital UFH (OR, 0.78; 95% CI, 0.39–1.56).

For the important outcomes of **stroke and reinfarction**, we have identified very-low-quality evidence (downgraded for indirectness and imprecision) from 1 non-RCT[64] enrolling 369 patients transferred for PPCI for STEMI showing no benefit of prehospital bivalirudin over prehospital UFH for stroke (OR, 0.86; 95% CI, 0.12–6.19) or reinfarction (OR, 0.86; 95% CI, 0.17–4.33).

For the important outcome of **major bleeding**, we have identified very-low-quality evidence (downgraded for indirectness and imprecision) from 2 non-RCTs[63,64] enrolling 543 patients transferred for PPCI for STEMI showing a benefit of prehospital bivalirudin compared with UFH (OR, 0.39; 95% CI, 0.2–0.76).

Enoxaparin Versus UFH

For the critical outcome of **30-day mortality**, we have identified low-quality evidence (downgraded for risk of bias and imprecision) from 1 RCT[65] enrolling 910 patients transferred for PPCI for STEMI showing no benefit of prehospital enoxaparin compared with prehospital UFH (OR, 0.58; 95% CI, 0.32–1.08).

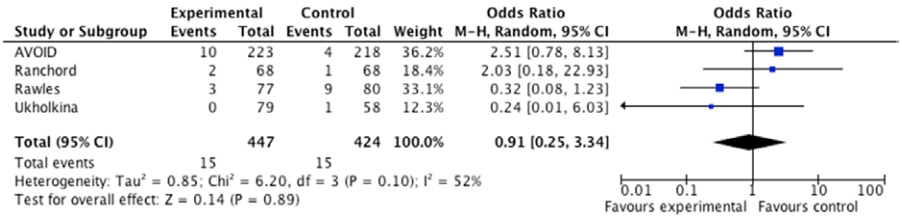

Figure 5. Mortality in AMI patients when oxygen is withheld compared with routine administration. Experimental = oxygen withholding; control = routine supplementary oxygen.

For the important outcome of **stroke**, we have identified low-quality evidence (downgraded for risk of bias and imprecision) from 1 RCT[65] enrolling 910 patients transferred for PPCI for STEMI showing no benefit of prehospital enoxaparin compared with prehospital UFH (OR, 3.08; 95% CI, 0.32–29.73).

For the important outcome of **reinfarction**, we have identified low-quality evidence (downgraded for risk of bias and imprecision) from 1 RCT[65] enrolling 910 patients transferred for PPCI for STEMI showing no benefit of prehospital enoxaparin compared with prehospital UFH (OR, 0.5; 95% CI, 0.90–4.22).

For the important outcome of **major bleeding**, we have identified low-quality evidence (downgraded for risk of bias and imprecision) from 1 RCT[65] enrolling 910 patients transferred for PPCI for STEMI showing no benefit of prehospital enoxaparin compared with prehospital UFH (OR, 0.61; 95% CI, 0.31–1.20).

Treatment Recommendations

We have insufficient confidence in the treatment effect for prehospital administration of bivalirudin compared with prehospital administration of UFH in prehospital-identified STEMI patients to recommend a change in existing practice (weak recommendation, very-low-quality evidence).

We suggest that prehospital enoxaparin may be used as an alternative to prehospital UFH as an adjunct for primary PCI for STEMI (weak recommendation, low-quality evidence).

Values, Preferences, and Task Force Insights

In making this recommendation regarding bivalirudin, we place a higher value on not recommending new resource allocation for an intervention where the relative benefit is unclear.

In making this recommendation regarding enoxaparin, we place a higher value on recommending agents that may provide benefit with regard to the ease of administration and lack of need for monitoring.

In making these recommendations, it is important to also consider the related review on anticoagulants given to STEMI patients in the prehospital versus in-hospital setting. Only UFH has been evaluated directly in this setting without clear evidence of benefit. We are not recommending that systems implement anticoagulant administration in the prehospital setting. However, in recognizing that some systems are doing this routinely, we conducted this review to look at the relative benefit of one agent over another.

Although stent thrombosis was not considered as an a priori outcome, bivalirudin was strongly associated with the risk of acute stent thrombosis (RR, 6.11; 95% CI, 1.37–27.24).[62] Such association is also consistently reported in other published in-hospital studies and meta-analyses of this agent in patients undergoing PCI.[66,67] While the benefit of bivalirudin over UFH alone in reducing bleeding complications has been shown, this benefit has been challenged by the additional consistent risk of stent thrombosis. This stent thrombosis risk was considered by the task force in making its treatment recommendations.

Supplementary Oxygen in ACS (ACS 887)

Among adult patients with suspected ACS and normal oxygen saturation in any setting (prehospital, emergency, or in-hospital) (P), does withholding oxygen (I), compared with routine supplementary oxygen (C), change death, infarct size, chest pain resolution, ECG resolution (O)?

Consensus on Science

For the critical outcome of **mortality**, we have identified very-low-quality evidence (downgraded for indirectness, heterogeneity, and bias) from 4 RCTs[68–71] enrolling 871 patients showing no benefit (OR, 0.91; 95% CI, 0.25–3.34) when oxygen is withheld compared with routine supplementary oxygen administration (Figure 5).

For the important outcome of **infarct size**, we have identified very-low-quality evidence (downgraded for bias, inconsistency, indirectness, and imprecision) from 3 RCTs[68,70,71] enrolling 713 patients showing a small reduction in infarct size when oxygen is withheld compared with routine supplementary oxygen administration. Data from a fourth RCT suggesting increased infarct size when oxygen is withheld could not be used because of incomplete reporting and unvalidated methods.[69] The trial data generated for infarct size are too heterogeneous to enable combined assessment.

For the important outcome of **chest pain resolution**, we have identified very-low-quality evidence (downgraded for bias, inconsistency, indirectness, and imprecision) from 2 RCTs[68,72] enrolling 199 patients showing no difference when oxygen is withheld compared with routine supplementary oxygen administration.

For the important outcome of **ECG resolution**, no evidence has been identified in RCTs.

Treatment Recommendation

We suggest withholding oxygen in comparison with routine oxygen supplementation in normoxic patients* with ACS† (weak recommendation, very-low-quality evidence).

*Two later studies of Spo_2 greater than 93% or 93% to 96%.

†Patients with AMI, excluded previous myocardial infarction, severe chronic obstructive pulmonary disease, respiratory failure, cardiogenic shock, central cyanosis, Spo_2 less than 85%, dyspnea from any other cause.

Table 2. Reperfusion Decisions in STEMI: 2015 Topics

	Decision Setting	Intervention	Comparator
Prehospital fibrinolysis versus ED fibrinolysis[338]	Prehospital	Prehospital FL	ED FL
Prehospital triage to PCI center versus prehospital fibrinolysis[341]	Prehospital	Transfer to PPCI	Prehospital FL
ED fibrinolysis and immediate PCI versus immediate PCI alone[882]	ED	FL + immediate PCI (within 1–4 hours)	PPCI
Delayed PCI versus fibrinolysis stratified by time from symptoms[337]	Any setting	PPCI	FL (time dependent)
Transport for PCI versus ED fibrinolysis and transport only for rescue PCI[332]	ED	Transport to PPCI	FL+transport only for rescue PCI
ED fibrinolysis and routine early angiography versus transport for PCI[779]	ED	FL + routine transport to PCI	Transport to PCI
ED fibrinolysis and then transport for early angiography versus only rescue PCI[334]	ED	FL + routine transport to PCI	FL + transport only for rescue PCI

ED indicates emergency department; FL, fibrinolysis; PCI, percutaneous coronary intervention; and PPCI, primary percutaneous coronary intervention.

Values, Preferences, and Task Force Insights

In making this recommendation, we place a higher value on avoiding possible harm when the evidence available suggests no mortality benefit and possible harm in providing routine oxygen supplementation.

We acknowledge the pending results of 2 additional trials addressing this topic. No data were identified for routine administration of oxygen with lower concentrations than those used in the reviewed trials (4–8 L/min via mask or nasal prongs). Oxygen saturation readings from pulse oximetry should be interpreted with caution, and every effort should be made to recognize and correct patient- or equipment-related factors that might lead to inaccurate results.

Knowledge Gaps

- We await the pending results of 2 trials addressing the benefit and safety of administration of supplementary oxygen in ACS patients.

Reperfusion Decisions in STEMI

This section addresses the questions of which reperfusion strategy is best under specific circumstances. Which options are available for reperfusion will depend on the local prehospital system and availability of PCI centers. Some prehospital systems include physicians or highly trained personnel that can safely administer prehospital fibrinolysis. Some regions have short transport times to PCI, and STEMI patients can be triaged and transported directly to PCI. The questions in this section consider reperfusion decisions in relation to regional availability (eg, prehospital fibrinolysis versus ED fibrinolysis or prehospital fibrinolysis versus transport direct for PCI). Table 2 outlines the systematic reviews in this section including the setting where the reperfusion is being made and the intervention versus comparator.

Where there are strong recommendations, regions should consider if these could be implemented safely to provide the same benefits found in the studies. Alternatively, where there are weak recommendations, the current resources and system may determine what option would work best. When reperfusion is the planned strategy, this should occur as soon as possible after diagnosis.

Prehospital fibrinolysis may have advantages when there are long transport times. As the transport time shortens, any expected advantage is lost. These advantages need to be weighed against the resources required to implement this and the alternatives available. Thus, if PCI is available, time to transport to PCI is a more important determinant of the decision. Several of the systematic reviews focused on specific decisions of fibrinolysis versus PCI based on the regional resources or "system."

As fibrinolysis is still a viable option in many systems, some of the reviews addressed whether routine angiography (with PCI if indicated) should be undertaken when fibrinolysis has been administered versus only ischemia-guided (rescue) angiography and in what time frame. These decisions may be dependent on whether PCI is available on-site or via transport.

Although the 2010 CoSTR recommended PCI as the preferred reperfusion strategy for STEMI, the benefit is mostly reflected in lower reinfarction rates, such that fibrinolysis and early transfer for angiography may be a reasonable alternative in settings where access to PCI may be limited or delayed (geographic, resources, time of day).[46] Benefit is less clear if PCI is not performed in high-volume centers by experienced operators. Patient transfer should be within a well-organized system of care including adequate patient surveillance and capability of treating complications such as cardiac arrest.

One of the reviews specifically addressed PCI versus fibrinolysis based on the time from symptoms to provide a summary of the evidence for early presenters versus other time frames. The recommendations depend on any associated delays to PCI and can be used to provide a framework to make decisions for individual systems. Because the other questions did not separately address early presenters or time from symptom onset, this review is key to providing context that can be incorporated into the specific system decisions. These recommendations must be considered in the context of specific patients (gender, age, comorbidities, vascular territory of infarct); some patients have relative

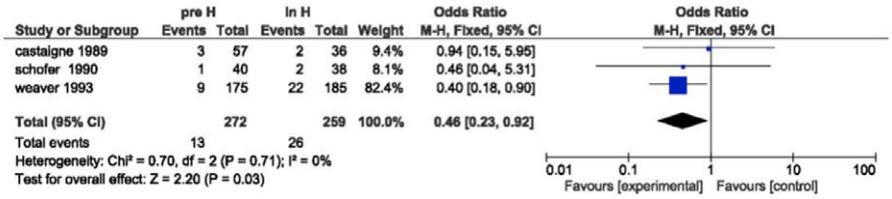

Figure 6. Hospital mortality for prehospital fibrinolysis versus in-hospital fibrinolysis. Experimental = prehospital fibrinolysis; control = in-hospital fibrinolysis.

contraindications to fibrinolysis and/or may have such little additional benefit from reperfusion that only a low-risk option is beneficial.

The PCI trials excluded patients with contraindications to thrombolysis, high-risk patients who presented with cardiogenic shock, and those in whom femoral vascular access was unobtainable. Patients who were excluded for contraindication to thrombolysis or were in shock usually underwent primary PCI. Fibrinolysis may be relatively or absolutely contraindicated in some patients, making PPCI necessary regardless of the time frame.

Prehospital Fibrinolysis Versus ED Fibrinolysis (ACS 338)

Among adults who are suspected of having STEMI outside of a hospital (P), does prehospital fibrinolysis (I), compared with in-hospital fibrinolysis (C), change death, intracranial hemorrhage, revascularization, major bleeding, stroke, reinfarction (O)?

Consensus on Science

For the critical outcome of **hospital mortality**, we have identified moderate-quality evidence (downgraded for imprecision) from 3 RCTs[73–75] enrolling 531 patients showing benefit for prehospital fibrinolysis compared with in-hospital fibrinolysis (OR, 0.46; 95% CI, 0.23–0.93) (Figure 6).

For the critical outcome of **intracranial hemorrhage**, we have identified low-quality evidence (downgraded for risk of bias and imprecision) from 2 RCTs[74,75] enrolling 438 patients showing no additional harm from prehospital fibrinolysis compared with in-hospital fibrinolysis (OR, 2.14; 95% CI, 0.39–11.84).

For the important outcome of **bleeding**, we have identified low-quality evidence (downgraded for imprecision) from 2 RCTS[74,75] enrolling 438 patients showing no additional harm from prehospital fibrinolysis compared with in-hospital fibrinolysis (OR, 0.96; 95% CI, 0.40–2.32).

For other outcomes (**revascularization, reinfarction, and ischemic stroke**), no evidence from RCTs was found.

Treatment Recommendation

When fibrinolysis is the planned treatment strategy, we recommend using prehospital fibrinolysis in comparison with in-hospital fibrinolysis for STEMI in systems where the transport times are commonly greater than 30 minutes and can be accomplished by prehospital personnel using well-established protocols, comprehensive training programs, and quality assurance programs under medical oversight (strong recommendation, moderate-quality evidence).

Values, Preferences, and Task Force Insights

In making this recommendation, we place a higher value on the reduction of mortality compared with no increased evidence of complications and consideration of the significant resource implications to implement a prehospital fibrinolysis program.

With the advent of more PPCI availability, in some areas the comparison of prehospital fibrinolysis to PPCI is more relevant (see the next systematic review on this topic).

The 3 studies that formed this evidence were all conducted more than 20 years ago. Since those studies showed combined benefit in mortality, no further RCTs have directly addressed this same question. To determine if there was more recent non-RCT evidence that might support or refute these early studies, a post hoc review was done and 1 relevant non-RCT was found from the last 5 years.[76] The review of this study confirmed the inherent risk of bias of a non-RCT. However, the study had similar findings of no greater harm from prehospital fibrinolysis, although it did not show the same potential mortality benefit.

The real advantage of prehospital fibrinolysis is where transport times are greater than 30 minutes. These RCTs were conducted in healthcare settings with a difference in time between prehospital treatment and in-hospital treatment of 33 to 52 minutes. Transport times to hospital were 38 to 60 minutes. As the transport time shortens, any expected advantage is lost.

The systems in the included studies included physician and other prehospital professionals who administered fibrinolysis by using well-established protocols, comprehensive training programs, and quality assurance programs under medical oversight.

Prehospital Triage to PCI Center Versus Prehospital Fibrinolysis (ACS 341)

Among adult patients with suspected STEMI outside of a hospital (P), does direct triage and transport to a PCI center (I), compared with prehospital fibrinolysis (C), change death, intracranial hemorrhage, major bleeding (O)?

Consensus on Science

For the critical outcome of **30-day mortality**, we have identified moderate-quality evidence (downgraded for imprecision) from 4 RCTs[77–80] enrolling 2887 STEMI patients showing no differential benefit to either therapy (direct triage and transport to a PCI center compared with prehospital fibrinolysis) (OR, 1.03; 95% CI, 0.72–1.46) (Figure 7).

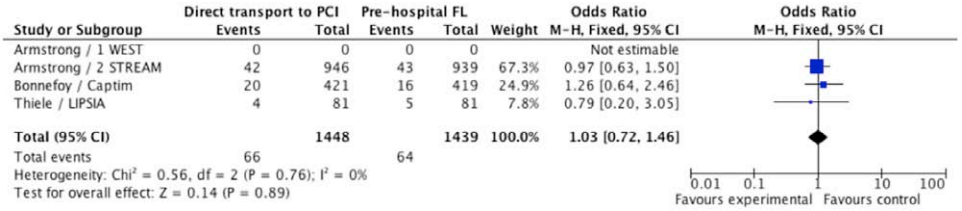

Figure 7. Thirty-day mortality for prehospital triage to PCI center versus prehospital fibrinolysis. Experimental = prehospital triage to PCI center; control = prehospital fibrinolysis.

For the critical outcome of **1-year mortality**, we have identified moderate-quality evidence (downgraded for imprecision) from 2 RCTs[80,81] enrolling 1877 STEMI patients showing no difference between direct triage and transport to a PCI center compared with prehospital fibrinolysis (OR, 0.88; 95% CI, 0.60–1.27).

For the critical outcome of **intracranial hemorrhage**, we have identified moderate-quality evidence (downgraded for imprecision) from 4 RCTs[77–80] enrolling 2887 STEMI patients showing less harm with direct triage and transport to a PCI center compared with prehospital fibrinolysis (OR, 0.21; 95% CI, 0.05–0.84).

Treatment Recommendations

We suggest that where PCI facilities are available in a geographic region, that direct triage and transport for PCI is preferred (weak recommendation, low-quality evidence). There is moderate evidence that mortality is not reduced and low-quality evidence of harm from fibrinolysis.

We suggest that where PCI facilities are not available in a geographic region, that prehospital fibrinolysis is a reasonable alternative to triage and transport directly to PCI.

Values, Preferences, and Task Force Insights

In making this recommendation, we are placing a higher value on avoiding iatrogenic harm and a lower value on uncertain benefits on survival. Given the lack of mortality benefit, we are not suggesting the addition of new PCI facilities for this indication and recognize that concentration in fewer high-volume centers may provide better outcomes.

ED Fibrinolysis and Immediate PCI Versus Immediate PCI Alone (ACS 882)

Among adults who are having STEMI in the ED (P), does fibrinolytic administration combined with immediate PCI (I), compared with immediate PCI alone (C), change death, intracranial hemorrhage, reinfarction, urgent target vessel revascularization, major bleeding (O)?

Consensus on Science

For the critical outcome of **30-day mortality**, we have identified moderate-quality evidence (downgraded for imprecision) from 5 RCTs[82–86] enrolling 3533 patients showing no benefit when fibrinolytic administration is combined with immediate PCI versus immediate PCI alone (OR, 1.29; 95% CI, 0.96–1.74) (Figure 8).

For the critical outcome of **intracranial hemorrhage**, we have identified moderate-quality evidence (downgraded for imprecision) from 3 RCTs[82,83,86] enrolling 3342 patients showing harm when fibrinolytic administration is combined with immediate PCI versus immediate PCI alone (OR, 7.75; 95% CI, 1.39–43.15) (Figure 9).

For the important outcome of **nonfatal myocardial infarction**, we have identified low-quality evidence (downgraded for bias, inconsistency, and imprecision) from 5 RCTs[82–86] enrolling 3498 patients showing no benefit when fibrinolytic administration is combined with immediate PCI versus immediate PCI alone (OR, 1.15; 95% CI, 0.73–1.81).

For the important outcome of **target vessel revascularization**, we have identified low-quality evidence (downgraded for inconsistency and imprecision) from 4 RCTs[82–84,86] enrolling 3360 patients showing no benefit when fibrinolytic administration is combined with immediate PCI versus immediate PCI alone (OR, 1.16; 95% CI, 0.91–1.47).

For the important outcome of **major bleeding**, we have identified high-quality evidence from 5 RCTs[82–86] enrolling 3543 patients showing harm when fibrinolytic administration is combined with immediate PCI versus immediate PCI alone (OR, 1.52; 95% CI, 1.05–2.20).

Treatment Recommendation

We recommend against the routine use of fibrinolytic administration combined with immediate* PCI, compared with immediate PCI alone in patients with STEMI (strong recommendation, moderate-quality evidence).

Values, Preferences, and Task Force Insights

In making this recommendation, we place a higher value on avoiding harm (intracranial hemorrhage and major bleeding), given that the evidence suggests no mortality benefit for fibrinolytic administration combined with immediate PCI.

Delayed PCI Versus Fibrinolysis Stratified by Time From Symptoms (ACS 337)

Among patients with STEMI stratified by time from symptom onset to presentation when fibrinolysis is readily available (P), does delayed PCI (I), compared with fibrinolysis (C), change mortality, reinfarction, major bleeding, intracranial hemorrhage (O)?

Consensus on Science

In STEMI Patients Presenting Less Than 2 Hours After Symptom Onset in Whom Immediate PPCI Will Delay Treatment 60 to 160 Minutes Compared With Fibrinolysis

For the critical outcome of **30-day mortality**, we have identified low-quality evidence (downgraded for indirectness and

*In these studies, the time frame from fibrinolysis to PCI ranged from 1 to 4 hours.

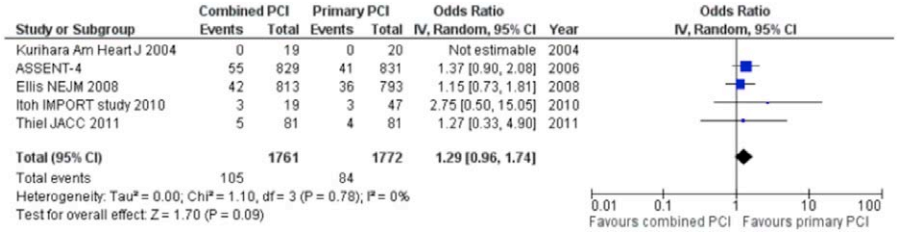

Figure 8. Thirty-day mortality for ED fibrinolysis and immediate PCI versus immediate PCI alone. Experimental = combined PCI; control = primary PCI.

imprecision) from a combined analysis of 2 RCTs[87] enrolling 646 patients showing greater harm with delayed PPCI compared with fibrinolysis (OR, 2.6; 95% CI, 1.2–5.64).

For the critical outcome of **5-year mortality**, we have identified low-quality evidence (downgraded for indirectness and imprecision) from 1 RCT[88] enrolling 449 patients showing greater harm with delayed PPCI compared with fibrinolysis (OR, 2.03; 95% CI, 1.1–4.08).

For the important outcome of **reinfarction**, we have identified low-quality evidence (downgraded for indirectness and imprecision) from a combined analysis of 2 RCTs[87] enrolling 657 patients showing no difference between delayed PPCI compared with fibrinolysis (OR, 0.43; 95% CI, 0.17–1.1).

For the important outcome of **severe bleeding** we have identified low-quality evidence (downgraded for indirectness and imprecision) from 1 RCT[89] enrolling 455 patients showing no difference in delayed PPCI compared with fibrinolysis (OR, 0.33; 95% CI, 0.01–8.15).

In STEMI Patients Presenting 2 to 6 Hours After Symptom Onset in Whom PPCI Will Delay Treatment 60 to 160 Minutes Compared With Fibrinolysis

For the critical outcome of **30-day mortality**, we have identified low-quality evidence (downgraded for indirectness and imprecision) from a combined analysis of 2 RCTs[87] enrolling 508 patients showing no benefit of delayed PPCI over fibrinolysis (1-year mortality OR, 0.85; 95% CI, 0.42–1.74).

For the critical outcome of **5-year mortality**, we have found low-quality evidence (downgraded for indirectness and imprecision) from 1 RCT[88] enrolling 367 patients showing no benefit of fibrinolysis over delayed PPCI (OR, 0.99; 95% CI, 0.55–1.77).

For the important outcome of **reinfarction**, we have identified low-quality evidence (downgraded for indirectness and imprecision) from a combined analysis of 2 RCTs[87] enrolling 511 patients showing no difference (OR, 0.4; 95% CI, 0.13–1.22).

For the important outcome of **severe bleeding**, we have identified low-quality evidence (downgraded for indirectness and imprecision) from 1 RCT[89] enrolling 375 patients showing greater harm from delayed PPCI compared with fibrinolysis (OR, 8.18; 95% CI, 1.01–66.04).

In STEMI Patients Presenting 3 to 12 Hours After Symptom Onset in Whom PPCI Will Delay Treatment 60 to 140 Minutes Compared With Fibrinolysis

For the critical outcome of **30-day mortality**, we have identified very-low-quality evidence (downgraded for bias, indirectness, and imprecision) from 1 RCT[90] enrolling 295 patients showing benefit of delayed PPCI (mean fibrinolysis-to-balloon delay of 85 ± 28 minutes) over immediate fibrinolysis (OR, 0.35; 95% CI, 0.16–0.79).

Other Analyses

A reanalysis of the raw data from 16 RCTs comparing 30-day mortality between fibrin-specific fibrinolysis and PPCI[91] has suggested that the acceptable fibrinolysis to PPCI delay varies depending on the patient's baseline risk and presentation delay (low-quality evidence, downgraded for inconsistency and indirectness). Patients with higher risk including Killip class >1, may benefit from PPCI even when there are treatment delays up to 120 minutes. The acceptable delay may range from 35 minutes when the risk is low (4%) through to greater than 5 hours for high risk (18%). A pragmatic simplification of the formula derived in the analysis has been suggested in the associated editorial: Patients over 65 years of age, and all patients in Killip class greater than 1, should be treated with PPCI.[92] Patients less than 65 years of age in Killip class 1 should have PPCI unless delay is greater than 35 minutes.

Two observational studies[93,94] used propensity-matched analysis of the National Registry of Myocardial Infarction registry, so they were not included in the original search strategy of RCTs only. The findings suggest an upper time limit for delay of 120 minutes overall.

Treatment Recommendations (Table 3)

In patients with STEMI presenting less than 2 hours after symptom onset, when PPCI will result in a delay of greater than 60 minutes, we suggest fibrinolysis in comparison with PPCI (weak recommendation, low-quality evidence).

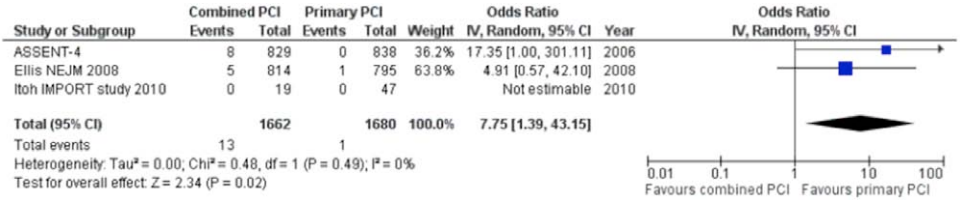

Figure 9. Intracranial hemorrhage for ED fibrinolysis and immediate PCI versus immediate PCI alone. Experimental = combined PCI; control = primary PCI.

Table 3. Most Appropriate Reperfusion Strategy According to Time From Symptom Onset and Anticipated Treatment Delays

Treatment delays, minutes	Time From Symptom Onset		
	<2 Hours	2–3 Hours	3–6 Hours*
<60	PPCI	PPCI or FL†	PPCI
60 to 120	FL†	PPCI or FL†	PPCI
>120	FL†	FL†	FL†

Patients with higher risk, including Killip class >1, may benefit from PPCI even when there are treatment delays up to 120 minutes.

*If time from symptom onset is greater than 6 hours, PPCI is appropriate regardless of treatment delays.

†In case of fibrinolytic therapy, immediate transfer to a percutaneous coronary intervention center after fibrinolysis should be considered for cardiac angiography within 3 to 24 hours.

FL indicates fibrinolysis; and PPCI, primary percutaneous coronary intervention.

In patients with STEMI presenting 2 to 3 hours after symptom onset, when PPCI will result in a delay of 60 to 120 minutes, we suggest either fibrinolysis or PPCI (weak recommendation, low-quality evidence).

In patients with STEMI presenting 3 to 12 hours after symptom onset, when PPCI will result in a delay of up to 120 minutes, we suggest PPCI in comparison with fibrinolysis (weak recommendation, very-low-quality evidence).

The evidence does not differentiate the late presenters with long delays to PCI. It is acknowledged that fibrinolysis becomes significantly less effective more than 6 hours after symptom onset and, thus, a PPCI may be the ideal option in patients more than 6 hours after symptom onset, even if this can only be accomplished with a long delay to PPCI (eg, more than 120 minutes).

When long delays to PPCI are anticipated (more than 120 minutes), a strategy of immediate fibrinolysis followed by routine early (within 3–24 hours) angiography and PCI, if indicated, is reasonable (ACS 334).

Values, Preferences, and Task Force Insights

In making this recommendation, we place a high priority on the evidence of mortality benefit; however, we acknowledge that geographic and resource factors may limit the availability of PPCI.

Knowledge Gaps

- Further evidence is required on the maximal treatment delay for PCI versus fibrinolytic therapy by patient characteristics.

ED Fibrinolysis and Transport Only for Rescue PCI Versus Transport for PCI (ACS 332)

Among adult patients with STEMI in the ED (of a non–PCI-capable hospital) (P), does transfer to a PCI center (I), compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI (rescue PCI) in first 24 hours (C), change short-term survival, stroke, major bleeding, reinfarction (O)?

Consensus on Science

For the critical outcome of **30-day mortality**, we have identified moderate-quality evidence (downgraded for serious risk of bias) from 8 RCTs[90,95–101] enrolling 3119 patients showing benefit of transfer without fibrinolysis to a PCI center compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI in the first 24 hours (OR, 0.66; 95% CI, 0.50–0.86) (Figure 10).

For the important outcome of **reinfarction**, we have identified moderate-quality evidence (downgraded for serious risk of bias) from the same 8 RCTs[90,95–101] enrolling 3119 patients showing benefit of transfer without fibrinolysis to a PCI center compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI in the first 24 hours (OR, 0.33; 95% CI, 0.21–0.51).

For the important outcome of **stroke**, we have identified moderate-quality evidence (downgraded for serious risk of bias) from the same 8 RCTs[90,95–101] enrolling 3119 patients showing benefit of transfer without fibrinolysis to a PCI center compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI in the first 24 hours (OR, 0.41; 95% CI, 0.22–0.76).

For the important outcome of **major hemorrhage**, we have identified very-low-quality evidence (downgraded for serious risk of bias, imprecision, and publication bias) from 2 RCTs[97,100] enrolling 550 patients showing no benefit of transfer without fibrinolysis to a PCI center compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI in the first 24 hours (OR, 0.68; 95% CI, 0.20–2.29).

Treatment Recommendation

For adult patients presenting with STEMI in the ED of a non–PCI-capable hospital, we recommend emergency transfer without fibrinolysis to a PCI center as opposed to immediate in-hospital fibrinolysis and transfer only for rescue PCI (strong recommendation, moderate-quality evidence).

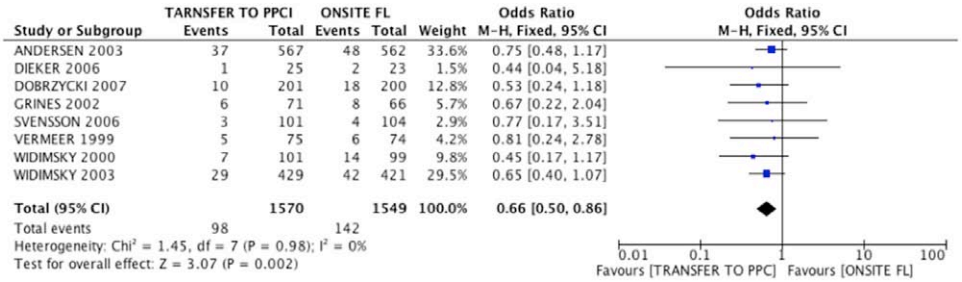

Figure 10. Thirty-day mortality for ED transport for PCI versus fibrinolysis and transport only for rescue PCI. Experimental = transfer to PCI; control = onsite fibrinolysis. FL indicates fibrinolysis.

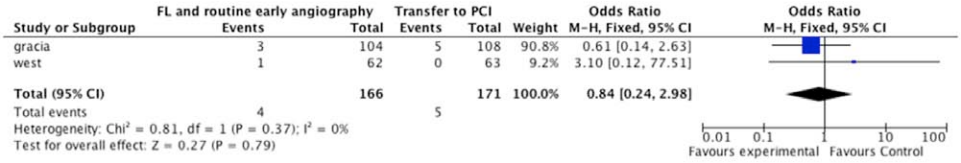

Figure 11. Thirty-day mortality for ED fibrinolysis and routine early angiography versus transport for PCI. Experimental = ED fibrinolysis and routine early angiography; control = transport for PCI. FL indicates fibrinolysis.

Values, Preferences, and Task Force Insights

In making this recommendation, we put great weight on the patient benefits of mortality, reinfarction, and stroke with no additional harm in terms of major hemorrhage.

ED Fibrinolysis and Routine Early Angiography Versus Transport for PCI (ACS 779)

Among adult patients with STEMI in the ED of a non–PCI-capable hospital (P), does immediate in-hospital fibrinolysis and routine transfer for angiography at 3 to 6 hours (or up to 24 hours) (I), compared with transfer to a PCI center (C), change 30-day mortality, stroke, major bleeding, reinfarction (O)?

Consensus on Science

For the critical outcome of **30-day mortality**, we have identified very-low-quality evidence (downgraded for risk of bias, imprecision, and indirectness) from 2 RCTs[80,102] enrolling 337 patients with STEMI showing no differential benefit of immediate in-hospital fibrinolysis and routine transfer for angiography compared with transfer to a PCI center (OR, 0.84; 95% CI, 0.24–2.98) (Figure 11).

For the critical outcome of **30-day mortality**, we have also identified 1 non-RCT enrolling 1714 patients[103] of very-low-quality evidence (downgraded for risk of bias and imprecision), showing no differential benefit of immediate in-hospital fibrinolysis and routine transfer for angiography compared with transfer to a PCI center (OR, 0.86; 95% CI, 0.48–1.55).

For the critical outcome of **intracranial hemorrhage**, we have identified very-low-quality evidence (downgraded for risk of bias, imprecision, and indirectness) from the same 2 RCTs[80,102] enrolling 337 patients with STEMI showing no differential benefit of immediate in-hospital fibrinolysis and routine transfer for angiography compared with transfer to a PCI center (OR, 3.14; 95% CI, 0.13–78.08).

For the important outcome of **reinfarction**, we have identified very-low-quality evidence (downgraded for risk of bias, imprecision, and indirectness) from the same 2 RCTs[80,102] enrolling 337 patients with STEMI showing no differential benefit of immediate in-hospital fibrinolysis and routine transfer for angiography compared with transfer to a PCI center (OR, 2.11; 95% CI, 0.51–8.64).

For the important outcome of **reinfarction**, we also identified very-low-quality evidence (downgraded for risk of bias and imprecision) from 1 non-RCT enrolling 1714 patients[103] showing no differential benefit of immediate in-hospital fibrinolysis and routine transfer for angiography compared with transfer to a PCI center (OR, 2.2; 95% CI, 0.73–6.61).

For the important outcome of **stroke**, we have identified very-low-quality evidence (downgraded for risk of bias, imprecision, and indirectness) from the same 2 RCTs[80,102] enrolling 416 patients with STEMI showing no differential benefit of immediate in-hospital fibrinolysis and routine transfer for angiography compared with transfer to a PCI center (OR, 0.96; 95% CI, 0.06–15.58).

For the important outcome of **stroke**, we also identified 1 non-RCT enrolling 1714 patients[103] of very-low-quality evidence (downgraded for risk of bias and imprecision) showing no differential benefit of immediate in-hospital fibrinolysis and routine transfer for angiography compared with transfer to a PCI center (OR, 1.52; 95% CI, 0.41–5.67).

For the important outcome of **major bleeding**, we have identified very-low-quality evidence (downgraded for risk of bias, imprecision, and indirectness) from the same 2 RCTs[80,102] enrolling 337 patients with STEMI showing no differential benefit of immediate in-hospital fibrinolysis and routine transfer for angiography compared with transfer to a PCI center (OR, 1.33; 95% CI, 0.32–5.47).

For the important outcome of **major bleeding**, we also identified very-low-quality evidence (downgraded for risk of bias and imprecision) from 1 non-RCT[103] enrolling 1714 patients with STEMI showing no differential benefit of immediate in-hospital fibrinolysis and routine transfer for angiography compared with transfer to a PCI center (OR, 0.65; 95% CI, 0.26–1.63).

Treatment Recommendation

We suggest fibrinolytic therapy with routine transfer for angiography as an alternative to immediate transfer to PCI for patients presenting with STEMI in the ED of a non–PCI-capable hospital (weak recommendation, very-low-quality evidence).

Values, Preferences, and Task Force Insights

This recommendation indicates that either therapy would be appropriate according to the evidence. Fibrinolysis and routine transfer may be appropriate where patients cannot be transferred to a PCI-capable center in a timely manner. Alternatively, transfer to PCI may be appropriate when this can be accomplished quickly or the patient has greater risks with fibrinolysis. Given the lack of mortality benefit, if transport directly to PCI is delayed, fibrinolysis before transport for routine early angiography is a reasonable option. We are not suggesting the addition of new PCI facilities for this indication and recognize that fewer high-volume centers may provide better outcomes.

ED Fibrinolysis and Then Routine Early Angiography Versus Only Rescue PCI (ACS 334)

Among adult patients with STEMI in the ED (of a non–PCI-capable hospital) who have received immediate in-hospital fibrinolysis (P), does routine transport for angiography at 3 to 6 hours (or up to 24 hours) (I), compared with only transfer for ischemia-driven PCI (rescue PCI) in first 24 hours (C), change death, intracranial hemorrhage, major bleeding, stroke, reinfarction (O)?

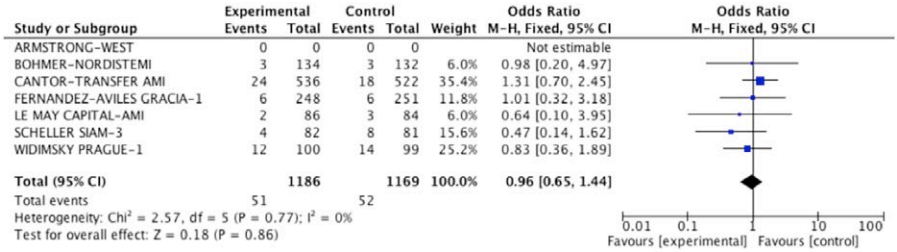

Figure 12. Thirty-day mortality for ED fibrinolysis and then routine early angiography versus only rescue PCI. Experimental = ED fibrinolysis and then routine early angiography; control = fibrinolysis and only rescue PCI.

Consensus on Science

For the critical outcome of **30-day mortality**, we have identified moderate-quality evidence (downgraded for imprecision) from 7 RCTs[80,101,104–108] enrolling 2355 patients showing no differential benefit to either therapy (immediate in-hospital fibrinolysis and routine transfer for angiography at 3 to 6 hours [or up to 24 hours], compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI [rescue PCI] in first 24 hours) (OR, 0.96; 95% CI, 0.64–1.44) (Figure 12).

For the critical outcome of **1-year mortality**, we have identified moderate-quality evidence (downgraded for imprecision) from 6 RCTs[80,104,105,108–110] enrolling 2275 STEMI patients showing no benefit to either therapy (immediate in-hospital fibrinolysis and routine transfer for angiography at 3 to 6 hours [or up to 24 hours], compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI [rescue PCI] in first 24 hours) (OR, 0.54; 95% CI, 0.16–1.89).

For the critical outcome of **intracranial hemorrhage**, we have identified moderate-quality evidence (downgraded for imprecision) from 6 RCTs[80,104–108] enrolling 2156 STEMI patients, showing no differential harm from either therapy (immediate in-hospital fibrinolysis and routine transfer for angiography at 3 to 6 hours [or up to 24 hours], compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI [rescue PCI] in first 24 hours) (OR, 0.71; 95% CI, 0.34–1.44).

For the important outcome of **major bleeding**, we have identified moderate-quality evidence (downgraded for imprecision) from 6 RCTs[80,104–108] enrolling 2156 STEMI patients showing no differential harm from either therapy (immediate in-hospital fibrinolysis and routine transfer for angiography at 3 to 6 hours [or up to 24 hours], compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI [rescue PCI] in first 24 hours) (OR, 0.88; 95% CI, 0.61–1.27).

For the important outcome of **stroke** we have identified moderate-quality evidence (downgraded for imprecision) from 4 RCTs[101,104,106,108] enrolling 798 STEMI patients showing no differential harm from either therapy (immediate in-hospital fibrinolysis and routine transfer for angiography at 3 to 6 hours [or up to 24 hours], compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI [rescue PCI] in first 24 hours) (OR, 0.99; 95% CI, 0.39–2.51).

For the important outcome of **reinfarction**, we have identified moderate-quality evidence (downgraded for risk of bias) from 7 RCTs[80,101,104–108] in 2355 patients of benefit of immediate in-hospital fibrinolysis and routine transfer for angiography at 3 to 6 hours (or up to 24 hours), compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI (rescue PCI) in first 24 hours (OR, 0.57; 95% CI, 0.38–0.85).

Treatment Recommendation

After fibrinolysis of STEMI patients in the ED (when primary PCI is not available on-site), we suggest transport for early routine angiography in the first 3 to 6 hours (or up to 24 hours) rather than only transport for ischemia-guided angiography (weak recommendation, moderate-quality evidence).

Values, Preferences, and Task Force Insights

In making this suggestion, we place a higher value on a measurable benefit in the important outcome of reinfarction despite no apparent benefit in 30-day or 1-year mortality and with no harm from bleeding or stroke. However, there may be circumstances or geography where transfer for angiography within 24 hours is particularly difficult or not available. In these cases, the small measurable benefit in reinfarction only may not outweigh any prolonged or difficult transfer.

Knowledge Gaps

- The current evidence indicates that PCI at 3 to 24 hours after fibrinolysis reduces reinfarction. The optimal timing within this time window has not been elucidated. Similarly, the optimal management is unclear for patients after fibrinolysis in remote areas where transport to PCI is difficult or prolonged.

Hospital Reperfusion Decisions After ROSC

There are widely accepted published guidelines surrounding the treatment of STEMI and NSTEMI in the general adult population that are endorsed by the ILCOR community. The evidence used to generate these guidelines did not specifically address patient populations who experienced OHCA and subsequently had ROSC. The management of this patient group, particularly patients having prolonged resuscitation and nonspecific ECG changes, has been controversial because of the lack of specific evidence and significant implications on use of resources.

The majority of patients who have an OHCA have underlying ischemic heart disease. Acute coronary artery occlusion is known to be the precipitating factor in many of these patients. While coronary artery occlusion after cardiac arrest is frequently associated with ECG ST elevation or left bundle branch block, it can also occur in the absence of these findings. In fact, it has been recognized from several large observational series that absence of ST elevation may be associated with acute coronary occlusion in patients with ROSC after OHCA.[111] Similarly, ST

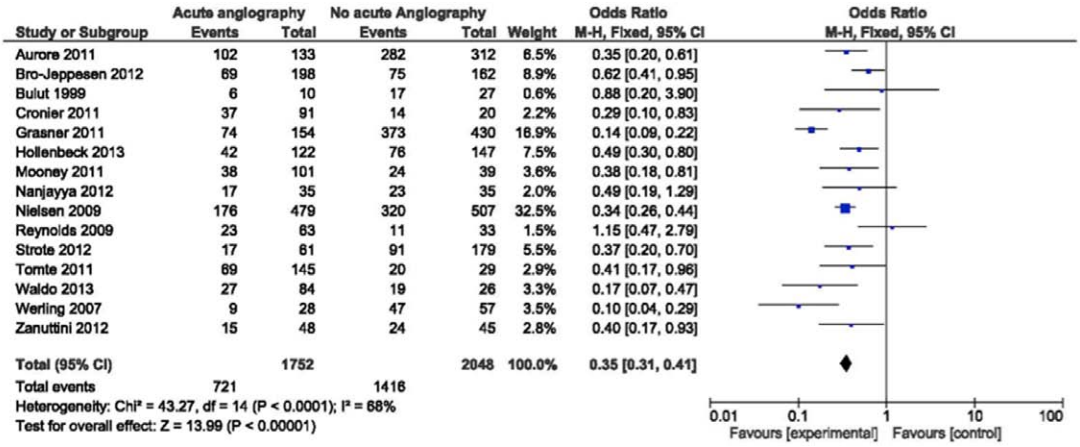

Figure 13. Hospital mortality for patients with ROSC after cardiac arrest with ST elevation: emergency cardiac catheterization versus delayed or no cardiac catheterization. Experimental = emergency cardiac catheterization; control = delayed or no cardiac catheterization.

elevation after OHCA may be temporary and does not always correlate with an acute coronary artery occlusion.

In 2010, ILCOR completed a single evidence review to examine all adult patients with OHCA and ROSC, inclusive of patients with and without ST elevation. In clinical practice, ACS with and without ST elevation are clinically distinct syndromes that are managed with guidelines that promote specific time to intervention targets for STEMI, while less time-sensitive strategies are recommended for non–ST elevation ACS. For this reason, the evidence review of this topic has been stratified to reflect the need to give guidance specific to each subset (ST elevation and no ST elevation) of the post-OHCA population.

PCI After ROSC With ST Elevation (ACS 340)

Among adult patients with ROSC after cardiac arrest with evidence of ST elevation on ECG (P), does emergency cardiac catheterization laboratory evaluation* (I), compared with cardiac catheterization later in the hospital stay or no catheterization (C), change hospital mortality and neurologically favorable survival (O)?

Consensus on Science

For the critical outcome of **hospital mortality in patients with ROSC after cardiac arrest with ST elevation on ECG**, we have identified very-low-quality evidence (downgraded for serious risk of bias and inconsistency and upgraded for large treatment effect) from 15 observational studies[112–126] enrolling 3800 patients showing benefit of emergency cardiac catheterization versus cardiac catheterization later in the hospital stay or no catheterization (OR, 0.35; 95% CI, 0.31–0.41) (Figure 13).

For the critical outcome of **neurologically favorable survival in patients with ROSC after cardiac arrest with ST elevation on ECG**, we have identified very-low-quality evidence (downgraded for serious risk of bias and inconsistency and upgraded for large treatment effect) from 9 observational studies,[112–114,117,119–122,124] enrolling 2919 patients showing benefit of emergency cardiac catheterization versus cardiac catheterization later in the hospital stay or no catheterization (OR, 2.54; 95% CI, 2.17–2.99).

Treatment Recommendation

We recommend emergency† cardiac catheterization laboratory evaluation in comparison with cardiac catheterization later in the hospital stay or no catheterization in select†† adult patients with ROSC after OHCA of suspected cardiac origin with ST elevation on ECG (strong recommendation, low-quality evidence).

†Time Frame for Treatment

The time frame for emergency catheterization has been variably defined in the evidence reviewed. In general, patients were managed to minimize door-to-reperfusion times in a manner similar to the general STEMI patient population. The complexity and heterogeneity of this patient group may delay their resuscitation and management.

††Patient Selection

The evidence base was nonrandomized case-control studies that were subject to a high level of selection bias. The decision to undertake emergency cardiac catheterization was frequently made at the discretion of the treating physician, and the patient's likelihood of survival is likely to have influenced the decision to undertake the intervention. A variety of factors were more likely to be associated with cardiac catheterization (Table 4): male gender, younger age, ventricular fibrillation as the presenting cardiac arrest rhythm; witnessed arrest; and bystander CPR, being supported with vasopressors or left ventricular assist devices. Those patient characteristics that were less likely to be associated with angiography were diabetes mellitus, renal failure, and heart failure.

Values, Preferences, and Task Force Insights

In making this recommendation, we placed a higher value on survival and good neurologic outcome over resource utilization. Although the evidence was low-quality because it involved observational studies of selected patients, the strength of the benefit was large and consistent in numerous studies. Given that the evidence derives from selected patients, this recommendation is not intended to apply to all post-ROSC patients with ST

*Catheterization laboratory evaluation included coronary angiography and early revascularization of acute coronary occlusions or significant stenosis as indicated.

Table 4. Patient Characteristics and Confounding Variables in Studies of Patients Selected for Angiography After ROSC With ST Elevation

	Number of Studies	Number of Patients	CAG	No/Delayed CAG	Risk Difference (95% CI)	*P* Value
1.2 Male gender	8	1828	0.76	0.64	0.12 (0.0 to 0.19)	0.0002
1.3 Diabetes mellitus	5	870	0.13	0.18	−0.05 (−0.1 to 0.00)	0.05
1.4 Hypertension	5	817	0.37	0.43	−0.06 (−0.12 to 0.01)	0.09
1.5 Renal failure	2	600	0.01	0.06	−0.04 (−0.08 to 0.00)	0.007
1.6 Stroke	2	600	0.05	0.13	−0.8 (−0.18 to 0.02)	0.12
1.7 VF rhythm	7	1472	0.78	0.47	0.31 (0.26 to 0.35)	0.0001
1.8 Witnessed CA	5	1026	0.88	0.83	0.05 (0.01 to 0.09)	0.02
1.9 Bystander CPR	6	1361	0.48	0.44	0.05 (−0.01 to 0.12)	0.10
1.10 Therapeutic hypothermia	3	711	0.66	0.56	0.09 (0.02 to 0.17)	0.01
1.11 LVSD	2	339	0.25	0.01	0.25 (0.18 to 0.31)	<0.0001
1.12 Vasopressors	3	771	0.31	0.13	0.18 (0.12 to 0.25)	<0.0001
1.13 Heart failure	3	739	0.20	0.39	−0.18 (−0.24 to −0.12)	<0.0001

Confounders found in the group that received cardiac angiography (CAG) and no/delayed CAG are reported as frequencies with 95% confidence intervals (CIs) and *P* values. A positive risk difference indicates a higher frequency of confounder variable in patient cohort undergoing early coronary angiography.

CA indicates cardiac arrest; CPR, cardiopulmonary resuscitation; LVSD, left ventricular support device, including aortic balloon pump; and VF, ventricular fibrillation as presenting arrest rhythm.

elevation; however, a systematic emergency assessment and consideration of all of these patients is warranted.

We recognize that the capacity to deliver emergency cardiac catheterization is not readily available in all healthcare settings. These recommendations are particularly relevant where primary PCI is available as part of the system of care. We suggest that emergency cardiac catheterization be incorporated in a standardized post–cardiac arrest protocol as part of an overall strategy to improve neurologically intact survival in this patient group. Targeted temperature management is now recommended in patients with ROSC after OHCA. The evidence reviewed demonstrated the feasibility of combining emergency cardiac catheterization and PCI with the early implementation of targeted temperature management.

PCI After ROSC Without ST Elevation (ACS 885)

Among adult patients with ROSC after cardiac arrest without evidence of ST elevation on ECG (P), does emergency cardiac catheterization laboratory evaluation (I), compared with cardiac catheterization later in the hospital stay or no catheterization (C), change hospital mortality and neurologically favorable survival (O)?

Consensus on Science

For the critical outcome of **hospital mortality in patients with ROSC after cardiac arrest without ST elevation on ECG**, we have identified very-low-quality evidence (downgraded for risk of bias) from 2 observational studies[112,117] enrolling 513 patients showing benefit from emergency cardiac catheterization laboratory evaluation compared with catheterization laboratory evaluation later in the hospital stay or no catheterization (OR, 0.51; 95% CI, 0.35–0.73) (Figure 14).

For the critical outcome of **neurologically favorable survival (CPC 1 or 2) in patients with ROSC after cardiac arrest without ST elevation on ECG**, we have identified very-low-quality evidence (downgraded for risk of bias) from 2 observational studies[112,117] enrolling 513 patients showing benefit from emergency cardiac catheterization laboratory evaluation compared with catheterization laboratory evaluation later in the hospital stay or no catheterization (OR, 1.96; 95% CI, 1.35–2.85).

Treatment Recommendation

We suggest emergency* cardiac catheterization laboratory evaluation in comparison with cardiac catheterization later in the hospital stay or no catheterization in select† adult patients who are comatose with ROSC after OHCA of suspected cardiac origin without ST elevation on ECG (weak recommendation, very-low-quality evidence).

**Time Frame for Treatment*

In the evidence reviewed, the time frame was variably defined, but patients were managed to minimize door-to-reperfusion times in a manner similar to the general STEMI patient population. The complexity and heterogeneity of this patient group may delay their resuscitation and management.

†Patient Selection

The evidence base was nonrandomized case-control studies that were subject to a high level of selection bias. Unlike the review pertaining to ST elevation, all of the studies without ST elevation enrolled comatose patients exclusively. The decision to undertake emergency catheterization was frequently made at the discretion of the treating physician. A variety of factors such as patient age, duration of CPR, hemodynamic instability, presenting cardiac rhythm, neurologic status upon hospital arrival, and perceived likelihood of cardiac etiology influenced the decision to undertake the intervention.

Values, Preferences, and Task Force Insights

In making this recommendation, we are emphasizing similar values to those outlined above for STEMI. There is a smaller

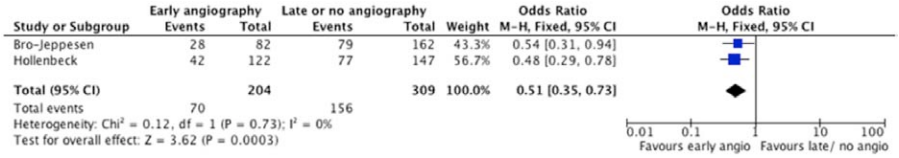

Figure 14. Hospital mortality for patients with ROSC after cardiac arrest without ST elevation: emergency cardiac catheterization versus delayed or no cardiac catheterization. Experimental = emergency cardiac catheterization; control = delayed or no cardiac catheterization.

body of evidence for emergency intervention in patients without ST elevation after OHCA with ROSC in comparison to those with ST elevation: The population studied was smaller, the magnitude of the effect was slightly smaller, and the proportion of patients that went on to have PCI was smaller. Therefore, we believed that a weak recommendation was appropriate. We understand that this recommendation represents a departure from most existing guidelines for the treatment of the general population of non–ST elevation ACS patients without OHCA.

Catheterization laboratory evaluation included coronary angiography and early revascularization of acute coronary occlusions or significant stenosis as indicated.

Knowledge Gaps

- Further investigation is needed to confirm the benefit seen in the initial 2 observational studies. Ideally, randomized studies would help identify if there are certain subgroups of patients that would benefit most or least from angiography after ROSC.

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Disclosures

2015 CoSTR Part 5: Acute Coronary Syndromes: Writing Group Disclosures

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Hiroshi Nonogi	Hospital Deputy, Shizuoka General Hospital	None	None	None	None	None	None	None
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Karen G. H. Woolfrey	University of Toronto	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10,000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10,000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Appendix

CoSTR Part 5: PICO Appendix

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 5	ACS	ACS 332	ED Fibrinolysis and Transport Only for Rescue PCI Versus Transport for PCI	Among adult patients with STEMI in the ED (of a non–PCI-capable hospital) (P), does transfer to a PCI center (I), compared with immediate in-hospital fibrinolysis and only transfer for ischemia-driven PCI (rescue PCI) in first 24 hours (C), change short-term survival, stroke, major bleeding, reinfarction (O)?	Nikolaos Nikolaou, Abdulaziz S. Ali
Part 5	ACS	ACS 334	ED Fibrinolysis and Then Routine Early Angiography Versus Only Rescue PCI	Among adult patients with STEMI in the ED (of a non–PCI-capable hospital) who have received immediate in-hospital fibrinolysis (P), does routine transport for angiography at 3 to 6 hours (or up to 24 hours) (I), compared with only transfer for ischemia-driven PCI (rescue PCI) in first 24 hours (C), change death, intracranial hemorrhage, major bleeding, stroke, reinfarction (O)?	Michelle Welsford, Robert O'Connor
Part 5	ACS	ACS 335	Prehospital ADP-Receptor Antagonists in STEMI	Among adult patients with suspected STEMI outside of the hospital (P), does prehospital administration of an ADP-receptor antagonist (clopidogrel, prasugrel, or ticagrelor) in addition to usual therapy (I), compared with administration of an ADP-receptor antagonist in-hospital (C), change death, intracranial hemorrhage, revascularization, stroke, major bleeding, reinfarction (O)?	Karen Woolfrey, Daniel Pichel
Part 5	ACS	ACS 336	Prehospital ECG	Among adult patients with suspected STEMI outside of a hospital (P), does prehospital 12-lead ECG with transmission or notification (I), compared with no ECG or no transmission/notification (C), change death, or time to treatment (first medical contact–to–balloon time, first medical contact–to–needle time, door-to-balloon time, door-to-needle time) (O)?	Michelle Welsford, Abdulaziz S. Ali
Part 5	ACS	ACS 337	Delayed PCI Versus Fibrinolysis Stratified by Time From Symptoms	Among patients with STEMI stratified by time from symptom onset to presentation when fibrinolysis is readily available (P), does delayed PCI (I), compared with fibrinolysis (C), change mortality, reinfarction, major bleeding, intracranial hemorrhage (O)?	Anthony Scott, Hiroshi Nonogi
Part 5	ACS	ACS 338	Prehospital Fibrinolysis Versus ED Fibrinolysis	Among adults who are suspected of having STEMI outside of a hospital (P), does prehospital fibrinolysis (I), compared with in-hospital fibrinolysis(C), change death, intracranial hemorrhage, revascularization, major bleeding, stroke, reinfarction (O)?	Chris Ghaemmaghami, Darren Walters
Part 5	ACS	ACS 340	PCI After ROSC With ST Elevation	Among adult patients with ROSC after cardiac arrest with evidence of ST elevation on ECG (P), does emergency cardiac catheterization laboratory evaluation* (I), compared with cardiac catheterization later in the hospital stay or no catheterization (C), change hospital mortality and neurologically favorable survival (O)?	Darren Walters, Chris Ghaemmaghami
Part 5	ACS	ACS 341	Prehospital Triage to PCI Center Versus Prehospital Fibrinolysis	Among adult patients with suspected STEMI outside of a hospital (P), does direct triage and transport to a PCI center (I), compared with prehospital fibrinolysis (C), change death, intracranial hemorrhage, major bleeding (O)?	Michelle Welsford, Michael Longeway
Part 5	ACS	ACS 559	Computer-Assisted ECG STEMI Interpretation	Among adult patients with suspected STEMI outside of a hospital (P), does the use of computer-assisted ECG interpretation (I), compared with physician ECG interpretation and/or clinical diagnosis of STEMI (C), change identification of STEMI on an ECG with acceptable rates of FNs to allow earlier identification and FPs, minimizing unnecessary intervention (O)?	Chi Keong Ching, Catherine Patocka
Part 5	ACS	ACS 562	Prehospital Anticoagulants Versus None in STEMI	Among adult patients with suspected STEMI outside of hospital transferred for primary PCI (P), does any anticoagulant administered prehospital (eg, bivalirudin, dalteparin, enoxaparin, fondaparinux, UFH) (I), compared with no anticoagulant administered prehospital (C), change death, intracranial hemorrhage, revascularization, major bleeding, stroke, reinfarction (O)?	Farzin Beygui, Vincent Roule
Part 5	ACS	ACS 568	Prehospital Anticoagulants vs UFH for STEMI	Among adult patients with suspected STEMI outside of a hospital transferred for primary PCI (P), does any anticoagulants prehospital (eg: bivalirudin, dalteparin, enoxaparin, fondaparinux) (I), compared with UFH prehospital (C), change death, ICH, revascularization, major bleeding, stroke, reinfarction (O)?	Farzin Beygui, Vincent Roule

(*Continued*)

CoSTR Part 5: PICO Appendix, *Continued*

Part	Task Force	PICO ID	Short Title	PICO Question	Evidence Reviewers
Part 5	ACS	ACS 737	Biomarkers to Rule Out ACS	In patients presenting to the ED with chest pain suspected to be of cardiac etiology (P), does a negative troponin test at presentation and 1, 2, 3, and 6 hours (I), compared with a positive test (C), exclude the diagnosis of ACS (O)?	Robert O'Connor, Michelle Welsford
Part 5	ACS	ACS 779	ED Fibrinolysis and Routine Early Angiography Versus Transport for PCI	Among adult patients with STEMI in the ED of a non–PCI-capable hospital (P), does immediate in-hospital fibrinolysis and routine transfer for angiography at 3 to 6 hours (or up to 24 hours) (I), compared with transfer to a PCI center (C), change 30-day mortality, stroke, major bleeding, reinfarction (O)?	Nikolaos Nikolaou, Farzin Beygui
Part 5	ACS	ACS 873	Prehospital STEMI Activation of the Catheterization Laboratory	Among adult patients with suspected STEMI outside of a hospital (P), does prehospital activation of catheterization laboratory (I), compared with no prehospital activation of the catheterization laboratory (C), change mortality, major bleeding, stroke, reinfarction (O)?	Karen Woolfrey, Daniel Pichel
Part 5	ACS	ACS 882	ED Fibrinolysis and Immediate PCI Versus Immediate PCI Alone	Among adults who are having STEMI in the ED (P), does fibrinolytic administration combined with immediate PCI (I), compared with immediate PCI alone (C), change death, intracranial hemorrhage, reinfarction, urgent target vessel revascularization, major bleeding (O)?	Hiroshi Nonogi, Anthony Scott
Part 5	ACS	ACS 884	Non-physician STEMI ECG interpretation	Among adult patients with suspected STEMI outside of a hospital (P), do nonphysicians (eg, nurses and paramedics) (I), compared with physicians (C), change identification of STEMI on an ECG with acceptable rates of FNs to allow earlier identification and FPs, minimizing unnecessary angiography (O)?	Chi Keong Ching, Catherine Patocka
Part 5	ACS	ACS 885	PCI After ROSC Without ST Elevation	Among adult patients with ROSC after cardiac arrest without evidence of ST elevation on ECG (P), does emergency cardiac catheterization laboratory evaluation (I), compared with cardiac catheterization later in the hospital stay or no catheterization (C), change hospital mortality and neurologically favorable survival (O)?	Chris Ghaemmaghami, Darren Walters
Part 5	ACS	ACS 887	Supplementary Oxygen in ACS	Among adult patients with suspected ACS and normal oxygen saturation in any setting (prehospital, emergency, or in-hospital) (P), does withholding oxygen (I), compared with routine supplementary oxygen (C), change death, infarct size, chest pain resolution, ECG resolution (O)?	Anthony Scott, Anthony Seto

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Part 5: Acute Coronary Syndromes: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

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