Clinical Policy: Emergency Department Management of Patients Needing Reperfusion Therapy for Acute ST-Segment Elevation Myocardial Infarction

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Approved by the ACEP Board of Directors June 28, 2017

Endorsed by the Emergency Nurses Association August 22, 2017

0196-0644/$-see front matter

https://doi.org/10.1016/j.annemergmed.2017.09.035

[Ann Emerg Med. 2017;70:724-739.]

ABSTRACT

Ischemic heart disease is the leading cause of death in the world. More than half a million patients present to emergency departments across the United States each year with ST-segment elevation myocardial infarctions.[1] Timely reperfusion is critical to saving myocardium at risk. Multiple studies have been conducted that demonstrate that improved care processes are linked to improved survival in patients having an acute myocardial infarction. This clinical policy from the American College of Emergency Physicians addresses key issues in reperfusion for patients with acute ST-segment elevation myocardial infarction. A writing subcommittee conducted a systematic review of the literature to derive evidence-based recommendations to answer the following clinical questions: (1) In adult patients having an ST-segment elevation myocardial infarction, are there patients for whom treatment with fibrinolytic therapy decreases the incidence of major adverse cardiac events when percutaneous coronary intervention is delayed? (2) In adult patients having an ST-segment elevation myocardial infarction, does transfer to a percutaneous coronary intervention center decrease the incidence of major adverse cardiac events? (3) In adult patients undergoing reperfusion therapy, should opioids be avoided to prevent adverse outcomes? Evidence was graded and recommendations were made based on the strength of the available data.

INTRODUCTION

Although timely percutaneous coronary intervention (PCI) has become the standard treatment for ST-segment elevation myocardial infarction (STEMI), the fact remains that only a minority of hospitals in the United States are capable of performing this intervention on site, and even fewer can provide 24-hour access to the intervention. When a patient presents with STEMI, national guidelines recommend a first medical-contact-to-device time of less than 90 minutes for individuals presenting to a PCI-capable site and less than 120 minutes from first medical-contact-to-device time for those who need to be transferred to a PCI-capable hospital.[2] Although very few patients are treated solely with fibrinolytic therapy without an angiographic assessment of their coronary arteries, the time-dependent nature of getting the patient to a PCI center requires knowledge of how delays affect clinical outcomes.

Systems have been developed for rapid out-of-hospital triage to PCI-capable centers and for rapid interhospital transfer from a noncapable PCI facility to one that can perform the intervention. What are the sources of these delays? What are the indications for fibrinolytic therapy in the age of PCI? These questions are critical for emergency physicians who practice in rural and remote locations without immediate access to PCI centers. Aside from the immediate outcomes for reperfusion and death, data on long-term functional outcomes are critical to determine the impact these interventions ultimately have on patient lives. Finally, the role of pain relief—in particular, opioid use—is discussed in light of newer research that raises some concern over long-term outcomes in chest pain patients treated with opioids.

This clinical policy addresses 3 issues that are relevant to practicing emergency physicians. The first 2 questions address whether there is a benefit to giving fibrinolytic therapy to STEMI patients when PCI will be delayed and whether transfer to a PCI-capable facility for the STEMI patient decreases the incidence of major adverse cardiac events (MACE). The clinical heterogeneity among the research studies investigating these topics make interpretation of the results challenging. For example, there is no standard definition of MACE. MACE may include such endpoints as death, revascularization, stroke, and congestive heart failure, but not all studies use the same endpoints. Definitions for MACE will be identified in the policy as appropriate for clarity. In addition, there is no uniformity on timing metrics. The final critical question examines the safety of opioid use in this population.

This is a revision of the 2006 American College of Emergency Physicians (ACEP) clinical policy on reperfusion therapy in emergency department (ED) patients with suspected acute myocardial infarction (MI).[3]

METHODOLOGY

This clinical policy is based on a systematic review with critical analysis of the medical literature meeting the inclusion criteria. Searches of MEDLINE, MEDLINE InProcess, Cochrane, EMBASE, and Scopus databases were performed. All searches were limited to human studies published in English. Specific key words/phrases, years used in the searches, dates of searches, and study selection are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the ACEP clinical policy development process, including internal and external review, and is based on the existing literature; when literature was not available, consensus of Clinical Policies Committee members was used and noted as such in the

recommendation (ie, consensus recommendation). Review comments were received from emergency physicians, cardiologists, individual members of the American College of Cardiology Foundation/American Heart Association, a patient representative, and members of ACEP's Medical-Legal Committee. Comments were received during a 60-day open-comment period, with notices of the comment period sent in an e-mail to ACEP members, published in *EM Today*, and posted on the ACEP Web site. The responses were used to further refine and enhance this clinical policy; however, responses do not imply endorsement. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology, methodology, or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

Assessment of Classes of Evidence

Two methodologists independently graded and assigned a preliminary Class of Evidence for all articles used in the formulation of this clinical policy. Class of Evidence is delineated whereby an article with design 1 represents the strongest study design and subsequent design classes (ie, design 2 and design 3) represent respectively weaker study designs for therapeutic, diagnostic, or prognostic studies, or meta-analyses (Appendix A). Articles are then graded on dimensions related to the study's methodological features, such as randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, generalizability, data management, analyses, congruence of results and conclusions, and conflicts of interest. Using a predetermined process combining the study's design, methodological quality, and applicability to the critical question, articles received a Class of Evidence grade. An adjudication process involving discussion with the original methodologist graders and at least one additional methodologist was then used to address any discordance in original grading, resulting in a final Class of Evidence assignment (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or ultimately determined to not be applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. However, content in these articles may have been used to formulate the background and to inform expert consensus in the absence of robust evidence. Grading was done with respect to the specific critical questions; thus, the Class of Evidence for any one study may vary according to the question for which it is being considered. As such, it was possible for a single article to receive a different Class of Evidence rating when addressing a different critical question. Question-specific Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Based on the strength of evidence grading for each critical question (ie, Evidentiary Table), the subcommittee drafted the recommendations and the supporting text synthesizing the evidence using the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (eg, based on evidence from one or more Class of Evidence I or multiple Class of Evidence II studies).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (eg, based on evidence from one or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of any adequate published literature, based on expert consensus. In instances in which consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

The recommendations and evidence synthesis were then reviewed and revised by the Clinical Policies Committee, which was informed by additional evidence or context gained from reviewers.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude, and publication bias, among others, might lead to a downgrading of recommendations.

When possible, clinically oriented statistics (eg, likelihood ratios, number needed to treat) are presented to help the reader better understand how the results may be applied to the individual patient (Appendix C).

This policy is not intended to be a complete manual on the evaluation and management of patients with STEMI but rather a focused examination of critical issues that have particular relevance to the current practice of emergency

medicine. Potential benefits and harms of implementing recommendations are briefly summarized within each critical question.

It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a critical question. When the medical literature does not contain adequate empirical data to answer a critical question, the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

This clinical policy is not intended to represent a legal standard of care for emergency physicians. Recommendations offered in this policy are not intended to represent the only diagnostic or management options available to the emergency physician. ACEP recognizes the importance of the individual physician's judgment and patient preferences. This guideline provides clinical strategies for which medical literature exists to answer the critical questions addressed in this policy.

Scope of Application. This guideline is intended for health care providers working in EDs.

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with suspected acute STEMI.

Exclusion Criteria. This guideline is not intended for pediatric patients, pregnant patients, or patients with contraindications to fibrinolytic treatment.

CRITICAL QUESTIONS

1. **In adult patients having a STEMI, are there patients for whom treatment with fibrinolytic therapy decreases the incidence of MACE when PCI is delayed?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. Fibrinolytics may be administered to patients when door-to-balloon (D2B) time is anticipated to exceed 120 minutes.

Level C recommendations. A dose reduction should be considered when administering fibrinolytics to patients aged 75 years or older.

Potential Benefit of Implementing the Recommendations: The use of fibrinolytics when D2B time is delayed may result in better long-term outcomes with a decrease in MACE.

Potential Harm of Implementing the Recommendations: Time estimates are challenging to obtain in the context of an emergency, therefore patients may not receive the recommended therapy within the appropriate time frame necessary to achieve optimal outcomes.

Key words/phrases for literature searches: STEMI, myocardial infarction, angioplasty, balloon, coronary, percutaneous coronary intervention, adverse effects, mortality, fibrinolytic agents, thrombolytic therapy, recombinant proteins, antithrombins, platelet aggregation inhibitors, risk assessment, risk factors, time factors, survival rate, survival analysis, treatment outcome, adverse cardiac, delay, transportation of patients, patient transfer, health services accessibility, emergency medical services, myocardial reperfusion, time-to-treatment, pharmaco-invasive therapy, facilitated PCI, and variations and combinations of the key words/phrases. Searches included January 1, 2006 to search dates of January 12, 2016, January 29, 2016, February 9, 2016, February 24, 2016, and January 10, 2017.

Study Selection: Two hundred thirty-four articles were identified in the search. Forty-three articles were selected from the search results for further review, with 6 Class III studies included for this critical question.

Many hospitals in the United States with inpatient beds do not have a cardiac catheterization laboratory with direct access to PCI. Although PCI as a revascularization procedure is desirable within 90 minutes of first medical contact, this time frame is impossible to achieve in such facilities. Quality initiatives have demonstrated time benefit to coordination of out-of-hospital performance and transmission of ECG data with emergency care and with response of catheterization laboratory personnel and interventional cardiology. There are barriers to efficient transfer, including the availability of on-call specialists and impediments to transportation, such as inclement weather; therefore, time to PCI will vary between health systems and individual situations.

With the rise of freestanding emergency centers from which any patient sustaining an MI must be transferred for care, and with the closure of rural hospitals, it is expected that the number of patients with chest pain and STEMI presenting to non-PCI-capable facilities will increase. Given the availability of fibrinolytic therapy to any practitioner of emergency care, it is important to define a time frame during which these patients will derive benefit from fibrinolysis as initial therapy for STEMI.

Rather than using fibrinolytics, multiple studies favor PCI with a D2B time of less than 120 minutes, including transfer time.[4-11] It is not always feasible to achieve PCI in less than 120 minutes even at PCI-capable hospitals; therefore, fibrinolytics followed by PCI may be considered in select circumstances. There is variation in the dosing of

fibrinolytics before transfer for PCI, namely full-dose versus reduced dose.

A Class III study by Vora et al[12] consisting of a registry of 22,481 patients (Acute Coronary Treatment and Intervention Outcomes Network Registry) indicated that when estimated interhospital drive time exceeded 30 minutes, only 42.6% of transferred patients achieved the first D2B time of less than 120 minutes. Among 15,437 patients eligible for full-dose fibrinolysis or PCI with estimated transfer drive times of 30 to 120 minutes, 34.3% received fibrinolysis (median door-to-needle time of 34 minutes). Median transfer time was 49 minutes. Patients treated with fibrinolysis versus PCI had no significant mortality difference (3.7% versus 3.9%; odds ratio 1.1; 95% confidence interval [CI] 0.9 to 1.4), but had higher bleeding risk, which included a decrease in hemoglobin level ($\geq$4 g/dL), or intracranial hemorrhage, or RBC transfusion (10.7% versus 9.5%; odds ratio 1.2; 95% CI 1.0 to 1.3). The mortality rates took into consideration multiple confounders such as transfer times, presence of heart failure, shock, and within-hospital clustering. A Class III study[13] from Canada measured the primary endpoint, which was the composite of death, cardiogenic shock within 30 days, new or worsening heart failure, reinfarction, recurrent ischemia, or new or worsening congestive heart failure within 30 days in all patients who received full-dose fibrinolysis. Five hundred thirty-seven patients were randomly assigned to be immediately transferred for PCI within 6 hours after fibrinolytics. Five hundred twenty-two patients were randomized to standard fibrinolytic therapy without PCI, but 182 patients (39.9%) received urgent catheterization (rescue PCI), with stents implanted in 98.3%. The immediate transfer for PCI group had better primary endpoints (11% versus 17.2%). However, no patients received PCI within 90 minutes.[13]

A 2008 Class III report[14] of 2,869 STEMI patients treated at 5 high-volume centers demonstrated significantly lower mortality with reduced dose fibrinolysis followed by urgent PCI compared with primary PCI. Mean time to PCI was 253 minutes, whereas mean time to fibrinolysis was 54 minutes. A Class III randomized study[15] of a total of 2,452 patients suggested a mortality benefit to reduced-dose reteplase plus abciximab as opposed to abciximab alone, or placebo, followed by expedited primary PCI when PCI delays of greater than 1 hour were anticipated. Data in a Class III study[16] from Minnesota attempted to address reperfusion options in STEMI patients with expected delays to a PCI-capable hospital. More than 2,600 consecutive STEMI patients from 31 referral hospitals were entered into a registry, as well as 600 who presented to the PCI center. Patients who presented to the PCI hospital or who were transferred from a zone 1 hospital (<60 miles away) underwent primary PCI as the reperfusion method. Patients transferred from zone 2 hospitals ($\geq$60 miles away) received aspirin, clopidogrel, unfractionated heparin, a β-blocker, and reduced-dose fibrinolytic, most frequently tenecteplase with comparable outcomes in stroke, major bleeding, 30-day mortality, and reinfarction. The authors' conclusions were that an argument should be made for fibrinolytic therapy if there is inclement weather or for a 60-mile transport cutoff if there is no inclement weather.[16]

Finally, in a Class III study,[17] STEMI patients who presented within 3 hours of symptom onset and could not receive PCI within 1 hour were randomized in the out-of-hospital setting to either transport for primary PCI or treatment with full-dose tenecteplase plus clopidogrel and enoxaparin before transfer to a PCI-capable hospital. The primary endpoints were a composite of death, shock, congestive heart failure, or reinfarction within 30 days. Emergency angiography was required in 36% of the tenecteplase group and the remainder underwent angiography at a median 17 hours after randomization. In this study, the composite endpoint was similar regardless of whether the patient received fibrinolytic therapy or primary PCI (12.4% versus 14.3%, respectively). There was a higher incidence of intracranial hemorrhage in patients who received fibrinolytic therapy. This increase was mitigated by the use of half-dose tenecteplase in patients older than 75 years.[17]

In summary, use of fibrinolytics is recommended when, by physician judgment, the D2B time will exceed 120 minutes for any reason. When fibrinolytics are used in patients older than 75 years, consideration should be given to using half-dose to mitigate the potential for bleeding complications.

Future Research

There may be a subset of patients who benefit from fibrinolysis before PCI depending on, for example, age or anatomic location of the infarction, as well as time to PCI. It is unknown whether a given time limit for, say, a 45-year-old man with an inferior MI applies to a 77-year-old woman with an anterior MI. It may be that the benefit of PCI over fibrinolysis is most pronounced in high-risk patients: those with anterior MI or with hemodynamic compromise.

Transport time to a PCI-capable institution is frequently not known with any precision and may be underestimated by receiving PCI centers. If timing is really important, ways to accurately estimate transfer times must be identified. How accurate is any assessment of time given weather and

transport conditions? This question should be answered before any hard and fast guidelines are developed on PCI versus fibrinolysis. Emergency physicians should know the framework within which they are working. Any recommendations must be predicated on a realistic estimate of time to transport and time to intervention.

Many studies, especially those from overseas, have disparate endpoints, such as stroke, recurrent ischemia, reinfarction, death, cardiogenic shock, congestive heart failure, and readmissions. Although this policy looked at MACE, future research should explore functional status (functional capacity or ejection fraction) and survival.

2. **In adult patients having a STEMI, does transfer to a PCI center decrease the incidence of MACE?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. To decrease the incidence of MACE, patients with STEMI should be transferred to a PCI-capable hospital as soon as possible.

Level C recommendations. None specified.

Potential Benefit of Implementing the Recommendations: Patients who receive timely PCI may experience better outcomes with a decrease in MACE.

Potential Harm of Implementing the Recommendations: Patients may decompensate en route to the PCI facility resulting in poor outcomes.

Key words/phrases for literature searches: ST-elevation myocardial infarction, myocardial infarction, percutaneous coronary intervention, thrombolytic therapy, PCI center, time factors, time-to-treatment, treatment outcomes, patient transfer, survival rate, survival rates, risk, timing, complications, adverse effects, delayed intervention, emergency medical services, hospital, and variations and combinations of the key words/phrases; Searches included January 1, 2006, to search dates of January 12, 2016, January 29, 2016, and February 24, 2016.

Study Selection: Two hundred two articles were identified in the search. Forty-five articles were selected from the search results for further review, with 1 Class II and 1 Class III study included for this critical question.

There are many articles and guidelines published on this topic. Given the rigorous methodological process to answer this specific critical question, 2 studies were used to inform the final recommendation. Many articles were eliminated because they were indirectly or not applicable. There has been a significant paradigm shift in the treatment of acute coronary syndrome (ACS) worldwide during the past few decades. Previously, treatment choices included PCI and fibrinolytic therapy. The literature has shifted away from choosing between these 2 therapies and is now centered on the expedited treatment of patients with PCI and the construction of systems and networks to facilitate this, including interhospital transfer. The introduction of STEMI care programs has reduced mortality.[18] This raises the question of which patients benefit the most from rushing to the PCI-capable institution and what those benefits are. The American Heart Association guidelines recommend transfer of patients with STEMI to a PCI center even if they have received fibrinolytic therapy.[19]

There is literature in regard to the out-of-hospital activation of catheterization laboratories and the timing effects of emergency medical services' selection of the receiving facility. However, the question was framed from the perspective of a community emergency physician who needs to make critical decisions about transferring a STEMI patient who presents to a non-PCI-capable hospital.

According to a Class II study by Widimsky et al,[20] the treatment of STEMI with PCI has a mortality and MACE advantage over fibrinolytic administration alone and that treatment is time dependent. This study was a randomized controlled trial in the Czech Republic that compared fibrinolysis at a community hospital not capable of PCI (421 patients) versus interhospital transfer (429 patients) for PCI. Pain onset to randomization was similar in both groups. Transfer time was 48 minutes (SD 20), and D2B once arrived at a PCI capable center was 26 minutes (SD 11). Inclusion criteria for this study were that patient transport to a PCI facility was feasible within 30 minutes of enrollment and the distance to the PCI center was less than 120 km (approximately 75 miles). Clinical outcomes measured were 30-day and 5-year death, MI, stroke, and revascularization. The incidence of MACE was lower in the transfer for PCI group for both 30-day (24% in the fibrinolytic group versus 14% in the PCI group; difference 10% [95% CI 4% to 15%]; number needed to treat 10) and 5-year MACE (53% in the fibrinolytic group versus 40% in the PCI group; difference 13% [95% CI 6% to 20%]; number needed to treat 8), respectively.[20]

A Class III study by Wöhrle et al[21] compared the outcomes of STEMI patients who presented to a PCI center versus patients who presented to a non-PCI center and were transferred to a PCI-capable hospital and found no significant difference in MACE at 30 days and 1 year. There was a total delay (symptom-to-balloon inflation) of 67 minutes because of transfer to a PCI facility in this study. The actual time from symptom onset to a PCI-capable facility for transferred patients was 195 versus 116 minutes for patients who presented directly to a PCI hospital.

Transfer to PCI-capable hospitals can result in delays to D2B time. How long can a patient wait before PCI loses its advantage over fibrinolytics? Patients show favorable outcomes when they receive PCI for STEMI. The goal is to begin transfer from a non-PCI-capable hospital once a STEMI is identified with a goal of total time from first medical contact to intervention of less than 120 minutes.[19]

In summary, best outcomes will likely be met by developing systems in which STEMI is identified early in the out-of-hospital process and the patient is transported directly to a PCI-capable facility. For patients who develop STEMI after ED presentation in the non-PCI-capable hospital, systems can be constructed to expedite transfer to a PCI-capable facility. Therefore, the recommendation is to transfer patients with STEMI to a PCI-capable facility to decrease the incidence of MACE.

Future Research

No studies exist to determine the exact interval after symptom onset when the benefits of emergent transfer dissipate. Current literature cited as support for transfers as best practice are based on observational studies with little uniformity with respect to measured outcomes or the patient populations. The development of standardized metrics, definitions, and outcomes would allow comparison of studies and robust meta-analyses. For example, what does first medical contact mean? Does it mean the time when a patient is cared for by out-of-hospital providers or by the first hospital contact point? Standardized prospective trials using well-designed integrated network protocols in the United States or abroad may be the best setting for future prospective trials needed to provide a high degree of clinical certainty while avoiding ethical concerns in randomizing patients to different treatment arms. Better delineation of the expected delay that would lead to fibrinolytic administration, as well as the optimal dose of fibrinolytics, would be useful to the referring emergency physician.

3. **In adult patients undergoing reperfusion therapy, should opioids be avoided to prevent adverse outcomes?**

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Because safety has not been established, clinical judgment should be used in deciding whether to provide or withhold morphine in patients undergoing reperfusion therapy.

Potential Benefit of Implementing the Recommendations: Opioids offer relief to chest pain patients by reducing discomfort and helping them relax during a highly stressful medical event.

Potential Harm of Implementing the Recommendations: Opioids can potentially result in less salvageable myocardium if administered to patients having an MI.

Key words/phrases for literature searches: opioids, opiates, analgesics, fentanyl, morphine, hydromorphone, drug interactions, age factors, adenosine, piperazines, platelet aggregation, thiophenes, acute coronary syndrome, suspected acute coronary syndrome, myocardial infarction, reperfusion therapy, percutaneous coronary intervention, angioplasty, thrombolytics, fibrinolytics, harm, risk, adverse, treatment outcome, patient risk, and variations and combinations of the key words/phrases; Searches included January 1, 2006, to search dates of January 12, 2016, January 29, 2016, and February 24, 2016.

Study Selection: Twenty-five articles were identified in the search. Nine articles were selected from the search results for further review, with 1 Class III study included for this critical question.

In the absence of a history of hypersensitivity, judicious use of opioids has generally been considered safe in hemodynamically stable patients with suspected ACS. Largely based on expert opinion, current guidelines from the American College of Cardiology/American Heart Association[2] and European Society of Cardiology[22] recommend intravenous morphine as the drug of choice to relieve pain and anxiety and warn against the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclo-oxygenase (COX)-2 inhibitors due to increased risk for MACE associated with their use in patients with STEMI and non–ST-segment elevation ACS. The American College of Cardiology/American Heart Association recently reduced the level of recommendation for morphine administration in non-STEMI chest pain and unstable angina patients to a Class IIb recommendation.[23]

As background, a retrospective cardiac magnetic resonance study of STEMI patients reperfused by PCI showed that patients who received intravenous morphine displayed larger infarct size, larger extent of microvascular obstruction and less salvageable myocardium compared with those who did not.[24] Evidence arguing against the routine use of opioids for patients with ACS who are undergoing reperfusion therapy comes from studies aimed at evaluating the pharmacokinetic and pharmacodynamics of $P2Y_{12}$ receptor inhibitors (such as prasugrel and ticagrelor).[25] A recent retrospective study[26] and a 2016 prospectively designed study[27] demonstrate delayed

absorption and activity of $P2Y_{12}$ receptor inhibitors and their metabolites in patients receiving morphine compared with those who did not. Impaired gastrointestinal absorption is the suspected cause of the underlying mechanism of morphine's effect. Although provocative, the last 4 studies[24-27] cited received Class of Evidence grade "X" because they lacked the methodological design to definitively address the clinical question.

The traditional support for use of opioids in patients with ACS undergoing reperfusion therapy has been challenged in recent years, with studies suggesting that morphine may actually be harmful in this population; given that clinicians often cannot predict which chest pain patients will be undergoing reperfusion therapy, the routine use of morphine to treat chest pain has been called into question. Initial concerns for potential harmful effects of morphine were raised as a result of registry data revealing higher rates of adverse clinical outcomes in non-STEMI ACS patients treated with clopidogrel who received intravenous morphine compared with those who did not. Using a propensity-score-matching method, the use of morphine was associated with increased inhospital mortality (odds ratio 1.5; 95% CI 1.3 to 1.6), and the increased risk of death in patients persisted across all risk groups in a study by Meine et al[28] (Class III).

Taken together, these data show that a therapeutic dilemma exists between the traditional beliefs in morphine's beneficial effects for non-STEMI ACS patients versus the recently identified potential harmful effects when morphine is used in the context of reperfusion therapy. Therefore, physicians should be aware of this theoretical treatment dilemma and understand the lack of evidence to recommend for or against the use of opiates in STEMI patients. Physicians are left with making case-by-case decisions until further data helps delineate a stronger recommendation.

Future Research

Adequately powered prospective trials are needed to support or refute and quantify a potential negative clinical effect of opioids on patient outcomes for patients undergoing revascularization. If the causal effect is real, the detailed underlying mechanism of the interaction requires further study because it may apply only to morphine and not to other opioids, such as those that are ultrashort-lasting. If the effect is mostly related to gastrointestinal absorption, then intravenous preparations of $P2Y_{12}$ inhibitors may provide alternatives to oral routes for patients who benefit most from opioids such as those with severe pain or those with ongoing pain and anticipated long travel times from non-PCI to PCI centers.

Relevant industry relationships: There were no relevant industry relationships disclosed by the subcommittee members for this topic.

Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical question.

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Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series	Case series	Case series

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

	Design/Class		
Downgrading	**1**	**2**	**3**
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X

Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (–)	
1.0	1.0	Does not change pretest probability
1–5	0.5–1	Minimally changes pretest probability
10	0.1	May be diagnostic if the result is concordant with pretest probability
20	0.05	Usually diagnostic
100	0.01	Almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reduction×100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Evidentiary Table.

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Vora et al[12] (2015)	III	Secondary analysis of ACTION registry, the largest ongoing quality improvement registry of AMI in the U.S.; objective to assess the association of estimated interhospital drive times with reperfusion strategy selection (fibrinolysis vs primary PCI)	1,771 STEMI referring centers to 366 STEMI receiving centers; outcomes: inhospital mortality and major bleeding	22,481 patients with STEMI eligible for fibrinolysis or PCI; no significant mortality benefit between fibrinolysis vs PCI (3.7% vs 3.9%; OR=1.1; 95% CI 0.9 to 1.4), but had a higher bleeding risk (10.7% vs 9.5%; OR=1.2; 95% CI 1.0 to 1.3)	Generalizable; MACE not specifically evaluated
Cantor et al[13] (2009)	III	Randomized clinical trial (TRANSFER-AMI Trial); 52 sites in Canada	Random allocation of fibrinolytic therapy+rescue or delayed PCI vs fibrinolytic therapy+immediate transfer to another hospital for PCI within 6 h of fibrinolysis; all patients received aspirin, heparin or enoxaparin, and fibrinolysis (tenecteplase); outcome: MACE at 30 days (death, reinfarction, cardiogenic shock, or new or worsening heart failure)	N=1,059; 522 to fibrinolytic group, 537 to fibrinolytic+transfer group; 89% of fibrinolytic+rescue or delayed PCI underwent PCI, median 33 h after randomization; 99% of fibrinolytic+immediate transfer for PCI underwent PCI, median 3 h after randomization;17.2% of those with fibrinolysis+rescue or delayed PCI met outcome vs 11% of those with fibrinolysis+immediate transfer and PCI met outcome (RR=0.6; 95% CI 0.5 to 0.9, *P*=.004)	Unblinded; concern that patients in intervention group were ultimately cared for more aggressively; early PCI was not early: no attempts made within 90 min

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Denktas et al[14] (2008)	III	Secondary analysis of registry data from multiple centers in the US; objective to evaluate reduced-dose out-of-hospital fibrinolysis for STEMI patients followed by PCI vs PCI alone	Local protocols dictated use of aspirin, heparin, clopidogrel, and low-molecular-weight heparin; multivariable analyses used to adjust for differences between groups; primary outcome: mortality at 30 days; secondary outcomes: death, reinfarction, stroke, PCI, and shock	N=2,869; 1,200 fibrinolysis+PCI, 1,669 PCI; significant differences in baseline characteristics between study groups; mean time to PCI was 253 min; mean time to fibrinolysis was 54 min; mortality significantly lower with fibrinolysis+PCI vs PCI alone; however, fibrinolysis+PCI was not a significant predictor of any outcome after adjusting for age, creatinine level, hyperlipidemia, and diabetes mellitus	Use of stepwise logistic regression; no blinding; protocols were locally dependent
Ellis et al[15] (2009)	III	Randomized clinical trial (FINESSE Trial); objective to evaluate 12-mo outcomes of facilitated PCI	Random allocation to reduced-dose reteplase+abciximab, abciximab alone, or placebo, followed by expedited PCI; outcome: 1-y mortality (prespecified secondary endpoint of principal study)	N=2,452; no significant differences in mortality among the 3 groups (6.3%, 7.4%, and 7.0%; *P*=NS)	Outstanding follow-up rates (≈98%) in all groups; excluded patients <60 y with inferior MI because they were considered low risk; blinded, placebo controlled; MACE not considered; primary endpoint underpowered because principal study stopped early

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Larson et al[16] (2012)	III	Prospective data collection for STEMI registry; 31 centers in Minnesota; objective to evaluate safety and efficacy of half-dose fibrinolysis+transfer for immediate PCI vs primary PCI	Standardized protocol across all hospitals; all patients received aspirin, clopidogrel, unfractionated heparin, and β-blocker; multivariable statistical methods, including use of propensity score matching to compare groups	N=2,634; 600 received primary PCI; excellent balance between propensity-score-matched groups; no significant difference between groups in regard to stroke, major bleeding, 30-day mortality or reinfarction	Although methodologically limited by use of a data registry, this may also incur strength in terms of pragmatic evaluation; no new data about optimal anticipated transfer time, but presents argument for fibrinolysis first if inclement weather, transfer using 60-mile cutoff if no inclement weather (distance and weather considerations)

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Armstrong et al[17] (2013)	III	Open-label, prospective, multicenter, randomized trial from 99 sites in 15 countries	Patients were randomized if they presented within 3 h of symptom onset and an ST-segment elevation on ECG but could not receive PCI within 1 h after first medical contact; the treatment group received fibrinolytic therapy and the PCI within 24 h, and the control group received PCI alone; in the event that there was not ST-segment resolution of at least 50% in the fibrinolytic group, they received PCI; primary endpoint was a 30-day composite of death from any cause, shock, congestive heart failure, or reinfarction; after enrollment of 21% of the anticipated final study population, the fibrinolytic dose was reduced by half for patients >75 y secondary to increased intracranial hemorrhage rate	N=1,915 patients, 1,892 of whom underwent randomization; after loss to follow-up and withdrawal of consent there were 944 patients in the fibrinolysis group and 948 in the PCI group; 36% of the patients randomized to the fibrinolysis group required rescue PCI; the composite endpoint occurred in 12.4% of the fibrinolysis group and 14.3% of the primary PCI group; RR=0.86 (95% CI 0.68 to 1.09); the total number of strokes was small but statistically greater in the fibrinolysis group at 1.6% vs 0.5% mainly driven by the rate of hemorrhagic stroke at 1.0% compared with 0.3%; there was no difference in nonintracranial major bleeding	Open label; study sponsored by Boehringer Ingelheim; baseline imbalance in the number who had previous PCI with 6.4% in the fibrinolytic group and 8.8% in the primary PCI group; 36% of patients in the fibrinolysis group underwent rescue PCI

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Widimsky et al[20] (2007)	II	PRAGUE-2 trial with 5-y follow-up; prospective randomized trial; Czech Republic	Fibrinolysis at a community hospital not capable of PCI vs interhospital transfer for primary PCI; outcome: death, reinfarction, stroke, and revascularization at 30 days and 5 y	421 in fibrinolytic group and 429 in PCI group transported to nearest hospital; 30 day: death/reinfarction/stroke/revascularization 24% in fibrinolytic group vs 14% in PCI group, difference 10%; NNT 10 (P<.001); 5 y: death any cause/re-MI/stroke/revascularization 53% in fibrinolytic group vs 40% in PCI group, difference 13%; NNT 8 (P<.001)	Open label; outcome defined but not masked to intervention; high proportion (≈99%) follow-up
Wöhrle et al[21] (2010)	III	Secondary analysis of the HORIZONS-AMI trial, which included 1:1 randomization of patients to bivalirudin vs unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor	Comparison of patients who required transfer for primary PCI vs direct admission for PCI; outcome: MACE (death, reinfarction, revascularization, or stroke) or major bleeding	988 (24.7%) patients were transferred for primary PCI and 2,614 were directly admitted for PCI; at 30 days and 1 y, there were no significant differences between study groups (5.8% vs 5.4%); use of multivariable modeling to adjust for differences between groups resulted in similar nonsignificant differences in outcomes	Secondary analysis of a randomized trial; groups different from the allocation scheme, thus not balanced or comparable at baseline; outcome blinded to study group

Evidentiary Table (continued).

Study & Year Published	Class of Evidence	Setting & Study Design	Methods & Outcome Measures	Results	Limitations & Comments
Meine et al[28] (2005)	III	Retrospective cohort from 443 hospitals in the US	Compared patients who received IV morphine with those who did not with respect to outcomes (eg, postadmission infarction, cardiogenic shock, congestive heart failure, death, and the composite outcome of postadmission infarction or death); propensity score matching used to account for potential imbalance between those who received morphine and those who did not, in an effort to isolate the effect of morphine on outcomes; also compared patients who received IV morphine vs IV nitroglycerin only, and both IV morphine and IV nitroglycerin, where the comparator was patients who received IV nitroglycerin	N=57,039; 17,003 (30%) patients received morphine; rates of adverse clinical outcomes were higher in patients who received IV morphine compared with those who did not; MI increased from 3.0% to 3.8% (OR 1.3; 95% CI 1.2 to 1.5), death increased from 4.7% to 5.5% (OR 1.5; 95% CI 1.3 to 1.6), and the composite end point of death or MI increased from 7.1% to 8.5% (OR 1.4; 95% CI 1.3 to 1.6); these findings persisted even when controlled for the concomitant use of IV nitroglycerin	Doses and timing of medications not collected; outcomes not adjudicated; adverse clinical outcomes even though these patients were more likely to be treated with evidence-based medications and to undergo invasive cardiac procedures

ACTION, Acute Coronary Treatment and Intervention Outcomes Network; *AMI*, acute myocardial infarction; *CI*, confidence interval; *ECG*, electrocardiogram; *FINESSE*, Facilitated Intervention With Enhanced Reperfusion Speed to Stop Events; *h*, hour; *HORIZONS-AMI*, Harmonizing Outcomes With Revascularization and Stents-Acute Myocardial Infarction; *IV*, intravenous; *MACE*, major adverse cardiac event; *MI*, myocardial infarction; *min*, minute; *mo*, month; *NNT*, number needed to treat; *NS*, not significant; *OR*, odds ratio; *PCI*, percutaneous coronary intervention; *PRAGUE-2*, Primary Angioplasty in Patients Transferred From General Community Hospitals to Specialized Percutaneous Coronary Intervention Units With or Without Emergency Thrombolysis-2; *RR*, relative risk; *STEMI*, ST-segment elevation myocardial infarction; *TRANSFER-AMI*, Trial of Routine Angioplasty and Stenting After Fibrinolysis to Enhance Reperfusion-Acute Myocardial Infarction; *US*, United States; *vs*, versus; *y*, year.