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SUMMARY WITH CRITICAL APPRAISAL

Thrombolytics for Acute Myocardial Infarction in a Prehospital Setting: A Review of Comparative Safety, and Guidelines

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Abbreviations

ACC	American College of Cardiology
ACS	acute coronary syndrome
AE	adverse events
AGREE II	Appraisal of Guidelines for Research Evaluation 2
AHA	American Heart Association
AMI	acute myocardial infarction
AMSTAR 2	A Measurement Tool to Assess Systematic Reviews 2
CABG	coronary artery bypass graft
CAIC	Canadian Association of Interventional Cardiology
CCS	Canadian Cardiovascular Society
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CRD	University of York Centre for Reviews and Dissemination
CS	cardiogenic shock
ECG	Electrocardiograph
GPI	Glycoprotein IIb/IIIa inhibitor
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
ILCOR	International Liaison Committee on Resuscitation
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical subject headings
PCI	Percutaneous coronary intervention
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SIGN	Scottish Intercollegiate Guidelines Network
SR	systematic review
STEMI	ST-elevation myocardial infarction

Context and Policy Issues

Myocardial infarction is an acute coronary syndrome in which the heart muscle undergoes injury due to ischemia (lack of blood supply).[1] About 63,200 adult Canadians had a first myocardial infarction in the 2012-2013 fiscal year.[2] Older Canadians are disproportionately affected, causing major morbidity and mortality, with an estimated 630,203 years of life lost[3] and 30,894 years lived with disability[4] attributable to ischemic heart disease in 2017. Furthermore, males are disproportionately affected, with an estimated 2.7-fold incidence rate that of females.[5] In addition, based on 2002 Canadian data, most myocardial infarctions occur out-of-hospital, with nearly 79% occurring at home and nearly 15% in public places (e.g., shopping malls and stores, streets and highways, recreation facilities, office buildings, hotels).[6]

The clinical management of out-of-hospital myocardial infarctions requires the most rapid assessment and initiation of treatment possible to ensure optimal patient outcomes. Once a diagnosis is made, the goals of therapy are to decrease mortality and complications, limit the infarct size, and re-establish blood flow to the affected artery.[7] In the absence of contraindications, thrombolytics administered as soon as possible after symptom onset are part of the treatment arsenal frequently given to patients following a myocardial infarction.[7]

The purpose of thrombolytics (also known as fibrinolytics) is to break up the thrombus (blood clot) that obstructs the affected artery, in order to restore blood flow.[1] In Canada, the thrombolytics alteplase and tenecteplase are currently available for use.[7] These are a synthetic form of tissue plasminogen activator, which convert plasminogen, bound to fibrin clots, to plasmin resulting in the degradation of the clot.[1] However, a re-infarction is possible and underscores the need for prompt transfer of the patient to a hospital for an invasive assessment and possible percutaneous coronary intervention.[1,7] In addition, when the drug is administered in a prehospital setting, the ability to safely manage adverse events and the optimum protocol remains unclear.

The objective of this report is to evaluate the safety and evidence-based guidelines regarding thrombolytic administration for the treatment of acute myocardial infarction in prehospital settings.

Research Questions

1. What is the comparative safety of thrombolytic administration performed in a prehospital versus hospital setting for treatment of acute myocardial infarction?

2. What is the comparative safety of thrombolytic administration performed in a prehospital setting compared with no or significantly delayed thrombolytic administration for the treatment of acute myocardial infarction?

3. What are the evidence-based guidelines regarding thrombolytic administration for the treatment of acute myocardial infarction in prehospital settings?

Key Findings

One relevant systematic review was identified regarding the safety of thrombolytic administration performed in a prehospital setting versus hospital setting for the treatment acute myocardial infarction. The systematic review included one relevant primary study, which revealed uncertainty in the safety findings between prehospital and hospital administration of thrombolytics. No evidence was found regarding the comparative safety of thrombolytic administration performed in a prehospital setting compared with no or significantly delayed thrombolytic administration for the treatment of acute myocardial infarction.

Five evidence-based guidelines were identified regarding thrombolytic administration for the treatment of acute myocardial infarction in prehospital settings. Overall, the guidelines were of acceptable quality and recommendations were based on varying quality of evidence. Three guidelines provided optimal timing recommendations for the administration of thrombolytics. The recommendations also varied as a function of the proximity of the patient to a percutaneous coronary intervention capable hospital. Two other guidelines recommended prehospital administration of thrombolytics, under specific protocols and dependent on expected transportation time. One guideline did not recommend the use of thrombolytics in patients with non-ST-elevation acute coronary syndrome.

The limitations of the included study and guidelines, such as gender equity in the applicability of the evidence (i.e. unclear whether gender differences were considered), incomplete outcome reporting, or lack of studies from Canadian settings, should be considered when interpreting the results.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were prehospital settings, thrombolytic administration, and myocardial infarction. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and June 7, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Q1-3: Patients of all ages with acute myocardial infarction in a prehospital setting (e.g., community health centre, remote and isolated care facilities, medical outposts)
Intervention	Q1: Thrombolytics (i.e., alteplase, tenecteplase) administered in a prehospital setting Q2: Thrombolytics (i.e., alteplase, tenecteplase) Q3: Thrombolytics for the treatment of acute myocardial infarction in prehospital settings
Comparators	Q1: Thrombolytics (i.e., alteplase, tenecteplase) administered in a hospital setting. Q2: No thrombolytics, "usual non-thrombolytic care" in a prehospital setting (e.g. treatment with acetylsalicylic acid, management with pain medications, basic care while waiting for transport or while being transported), significantly delayed thrombolytics (greater than 12 hours)
Outcomes	Q1,2: Safety (e.g., side effects, adverse events, bleeding complications, stroke, pulmonary embolism, acute renal failure, death, need for tertiary management after thrombolytic administration, reperfusion arrhythmias, hemodynamic instability) Q3: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Systematic reviews that had broader inclusion criteria than the present review were examined in detail to ascertain whether data could be extracted from a relevant sub-set of included studies, rather than excluding the systematic review entirely. If it was not possible to identify relevant primary studies upon detailed investigation, the systematic review was excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Finally, guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised by one reviewer using A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2),[8] and guidelines were assessed with the Appraisal of Guidelines for Research Evaluation II (AGREE II) instrument.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 230 citations were identified in the literature search. Following screening of titles and abstracts, 202 citations were excluded and 28 potentially relevant reports from the electronic search were retrieved for full-text review. In addition, two potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 30 potentially relevant articles, 24 publications were excluded for various reasons, while six publications met the inclusion criteria and were included in this report. These comprised one systematic reviews (SR),[10] and five evidence-based guidelines.[11-15] Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[16] flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

One SR,[10] and five evidence-based guidelines[11-15] were identified and included in this review. Detailed characteristics are available in Appendix 2, Table 2, and Table 3.

Study Design

The included SR[10] had objectives and inclusion criteria that were broader than for the present report (i.e. wider in scope); only information from the subset of relevant studies is included here. Published in 2014, authors searched the literature for published and unpublished randomized controlled trials (RCTs) up to June 2014. This review included one relevant RCT primary study published in 1993 which collected data from November 1988 to December 1991.[17]

Five evidence-based guidelines were identified regarding thrombolytic administration for the treatment of acute myocardial infarction (AMI) in prehospital settings.[11-15]

The first guideline, published in 2019 from the Canadian Cardiovascular Society (CCS) and Canadian Association of Interventional Cardiology (CAIC),[11] is a SR of English language randomized or non-randomized studies from 1988 to 2018. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool was used to evaluate the quality of evidence and strength of recommendations.[11] Recommendations are based on a 75% majority vote by all authors.[11]

The second guideline, published in 2016 by the Scottish Intercollegiate Guidelines Network (SIGN), is an update to their SIGN 93 – Acute Coronary Syndromes released in 2007 (updated in 2013).[12] A SR was conducted for the years 2005 to 2014 and included filters for SRs, RCTs, observational studies, and economic evaluations.[12] Quality of evidence is reported using SIGN Levels Of Evidence, which a rates quality from 1^{++} (high-quality meta-analyses, SRs of RCTs, or RCTs with a very low risk of bias) to 4 (expert opinion).

Similarly, strength of recommendation is reported using SIGN Strength Of Recommendation methodology, which rates quality as “strong should”, “conditional”, or “strong should not”. Recommendations are made by a multidisciplinary guideline development group in consideration of evidence obtained from systematic reviews (details in Table 3).[12]

The next two guidelines are related yet distinct in scope, since one is national[14] (for the American setting) and the other international.[13] The third guideline, published in 2015, by the American Heart Association (AHA) is based on a previous document developed by the International Liaison Committee on Resuscitation (ILCOR): “2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations”. The team conducted a systematic review for each clinical question.[14] Recommendations are consensus-based and adjusted for regional considerations. AHA Level of Evidence and Class of Recommendation methodology was used to evaluate the quality of evidence and strength of recommendations, respectively (details in Table 3).[14]

The fourth is an international guideline published by ILCOR as an update, but not a complete revision of their 2010 guidelines.[13] Also published in 2015 the methodology is the same as for the AHA guideline except that the GRADE tool was used to evaluate the quality of evidence and strength of recommendations.[13] The task force of expert physicians and other health care professionals made consensus-based recommendations, at the international level, in consideration of evidence obtained from systematic reviews (details in Table 3).[13]

The fifth guideline, published in 2014, by the AHA and the American College of Cardiology (ACC), is the results of a systematic search of English SRs, RCTs, and non-randomized studies through to April 2014. The guideline writing committee reviewed the literature and made recommendations using group decision-making consensus development methods.[18] AHA Level of Evidence and Class of Recommendation methodology was used to evaluate the quality of evidence and strength of recommendations, respectively (details in Table 3).[19]

Country of Origin

The included SR was authored in South Africa.[20] The relevant primary study included in the SR was conducted in the United States of America.[20]

The guidelines were developed in Canada,[11] Scotland,[12] and the United States of America.[13-15]

Patient Population

The participants from the relevant study[17] in the SR[20] were individuals with suspected AMI, pain for six hours or less, aged 75 years or less, with no risk of bleeding. The final decision to randomize was done over the phone by a physician after reviewing a 12-lead electrocardiograph (ECG). There were 175 and 185 participants in the prehospital group and the hospital group, respectively.

The target population for the CCS/CAIC guidelines are patients with acute ST-elevation myocardial infarction (STEMI).[11] The intended users are Canadian specialists and allied health professionals.[11] The SIGN guidelines apply to patients with acute coronary syndromes (ACS) (e.g., unstable angina, transmural myocardial infarction), and the intended users are healthcare professionals, carers, voluntary organisations, and policy

makers.[12] The AHA guidelines apply to North American patients with suspected ACS (from first medical contact to disposition from the emergency department) and the intended users are practitioners (e.g., emergency medical service dispatchers, first responders, paramedics, nurses, physicians).[14] The ILCOR guidelines apply to patients with ACS or STEMI and the intended users are regional health care authorities involved in prehospital and hospital management of patients with ACS or STEMI.[13] The AHA/ACC guidelines apply to patients with non-ST-elevation acute coronary syndrome and are intended for clinicians in the United States.[15]

Interventions and Comparators

In the SR, eligible interventions included any thrombolytic agent used to treat STEMI in prehospital settings compared to any thrombolytic agent used to treat STEMI in hospital settings.[20] The study relevant to this review compared the administration of alteplase 100 mg and acetylsalicylic acid 325 mg in a prehospital setting, to the same drug combination in a hospital setting.[17]

The CCS/CAIC guidelines consider various reperfusion strategies in prehospital, non-percutaneous coronary intervention (PCI) capable hospital settings, and PCI capable hospital settings, including: pharmacological therapy, oxygen administration, and mechanical reperfusion.[11] The SIGN guidelines consider various interventions, including: early pharmacological intervention and reperfusion therapy.[12] The AHA and ILCOR guidelines both consider prehospital and hospital thrombolytics.[13,14] The AHA/ACC guidelines also consider various interventions, including intravenous thrombolytic therapy.[15]

Outcomes

The safety outcomes considered in the relevant study from the SR were mortality and AEs.[20]

The outcomes of interest in the guidelines are varied and include reperfusion rates,[11] reperfusion delay,[11] mortality,[12-15] stroke,[12] reinfarction,[12,15] ischemia,[12] need for coronary artery bypass graft (CABG),[12] intracranial hemorrhage,[13-15] and bleeding.[13]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 4, and Table 5.

Systematic Review

Strengths of the SR[20] included: clear objectives and inclusion criteria, report of key search terms and search strategies, detailed descriptions of the processes used for article selection, data extraction, and quality assessment, provision of a list of included studies and summary of their characteristics, as well as a list of excluded studies and reasons for exclusion. The authors published a detailed protocol containing their proposed methodologies prior to conducting the review. These strengths of reporting increase confidence in the findings and the reproducibility of the systematic review. Furthermore, multiple databases were used to identify relevant literature and various strategies to identify grey literature were performed by review authors, decreasing the risk of missing relevant, non-indexed studies.[20] There were no language restrictions in the search and articles were translated where necessary. The possibility of publication bias was not investigated and the impact on the results of the review were not discussed. The authors disclosed their

conflicts of interest and sources of funding, none of which were considered likely to have influenced the findings.[20]

Evidence-Based Guidelines

In all guidelines[11-15] the scope and purpose are described, along with the target users, criteria for evidence selection, methods for formulating recommendations, and include different options for management of myocardial infarction in a prehospital setting. Overall, the methodology used to develop the guidelines were rigorous and well described, including the methods used for formulating the recommendations.[11-15] The SIGN[12] and ILCOR[13] guidelines sought the views and preferences of the target population. Three guidelines[12,13,15] sought external review by experts, while two guidelines[12,15] provided an explicit procedure for future updates.

The SIGN[12] guidelines provided an explicit statement on funding as well as the competing interests of their guideline development group members, which did not appear to have influenced the content of the guidelines. Three other guidelines[13-15] also provided the later. The generalizability of the AHA/ACC,[15] ILCOR,[13] AHA,[14] and SIGN[12] guidelines is limited given that they are conducted outside of the Canadian healthcare system.

Summary of Findings

A detailed summary of findings and recommendations is provided in Appendix 4, Table 6 and Table 7.

Comparative Safety of Thrombolytic Administration Performed in a Prehospital Versus Hospital Setting for Treatment of Acute Myocardial Infarction

Adverse effects

Evidence regarding the comparative safety of thrombolytic administration in a prehospital or hospital setting was available from the SR.[20] It included one primary study from 1993[17] that compared prehospital versus hospital all cause mortality, bleeding complications, and stroke rate. For all three outcomes, there was insufficient evidence to conclude that the groups were statistically significantly different, indicating that there may be no difference between prehospital and hospital administration of thrombolytics.[20]

Comparative Safety of Thrombolytic Administration Performed in a Prehospital Setting Compared With no, or Significantly Delayed, Thrombolytic Administration for the Treatment of Acute Myocardial Infarction

No relevant evidence was identified; therefore, no summary can be provided.

Evidence-Based Guidelines Regarding Thrombolytic Administration for the Treatment of Acute Myocardial Infarction in Prehospital Settings

Five evidence-based guidelines[11-15] were identified regarding recommendations for the use of thrombolytics for treatment of AMI in prehospital settings.

The first guideline, from the CCS and CAIC,[11] recommends a goal of first medical contact to thrombolytic needle time of less than or equal to 30 minutes (strong recommendation, low-quality evidence).[11] In cases where cardiogenic shock (CS) complicates the STEMI, they suggest thrombolytic therapy prior to transfer to a PCI centre (weak recommendation, very low-quality evidence).[11] However, CCS and CAIC strongly recommend “against a strategy of pharmacologic facilitation with full-dose fibrinolysis or combination fibrinolysis and

glycoprotein IIb/IIIa inhibitor (GPI) or GPI when access to cardiac catheterization is available within 120 minutes of [first medical contact]" based on high-quality evidence [11]

The second guideline, from SIGN[12] recommends administering immediate thrombolytic therapy in cases where PCI cannot be performed within 120 minutes of ECG diagnosis ("strong should" recommendation; of varying quality from meta-analyses, systematic reviews, or RCTs with a high risk of bias to expert opinion).[12] They further recommend that a fibrin-specific agent is preferred, particularly in the prehospital setting ("strong should" recommendation; of varying quality from high-quality meta-analyses, SRs of RCTs, or RCTs with a "very low" risk of bias to those with a "low" risk of bias).[12]

The third guideline, by the AHA[14] indicates that "it may be reasonable for trained nonphysician ECG interpretation to be used as the basis for decision-making, including activation of the catheterization laboratory, administration of fibrinolysis, and selection of destination hospital" in cases where a prehospital ECG cannot be transmitted to the emergency department (class IIa [moderate], level of evidence B-nonrandomized).[14] They also recommend the administration of thrombolytics when transport time is expected to be more than 30 minutes (class IIa [moderate], level of evidence B-randomized) and that the patient be directly transferred to a PCI capable hospital to prevent drug-related AEs (class IIb [weak], level of evidence B-randomized).[14]

The fourth guideline by ILCOR[13] suggests administration of thrombolytics "by prehospital personnel using well-established protocols, comprehensive training programs, and quality assurance programs under medical oversight" (*p*S160)[13] if transfer is expected to be longer than 30 minutes (strong recommendation, moderate-quality evidence).[13] Interestingly, they recommend a prehospital triage to a PCI capable hospital, in regions where this is possible, versus prehospital thrombolytics to prevent drug-related AEs; however, if a PCI capable facility is not available, prehospital thrombolytics would be a reasonable alternative (weak recommendation, low-quality evidence.[13]

The fifth guideline, by the AHA and the ACC[19] focused on patients with non-ST-elevation acute coronary syndrome and recommend that intravenous thrombolytics should not be used (class III [harm], level of evidence A).[15]

Limitations

A number of limitations were identified in the critical appraisal (Appendix 3, Table 4, and Table 5); however, additional limitations exist. The main limitations of this review are related to risk of bias, limited study populations and generalizability of findings.

The relevant primary study included in the SR[20] was from 1993. Caution should be used when considering older data since the clinical landscape and therapeutic options are unlikely to mirror the contemporary alternatives.

A primary limitation that should be considered when interpreting these results is that in many of the guidelines, recommendations are based on RCTs where blinding of participants and personnel was not possible (performance bias affecting all outcomes) and thrombolytics were administered in an open-label manner. Given that several of the outcomes reported in these guidelines were based on objective measures (e.g., mortality, intracranial hemorrhage, bleeding), the implications of open-label findings are at a lower risk of bias; however, they may still have been influenced (in either direction) depending on the perceptions and expectations of participants and clinicians involved.

Furthermore, there is a lack of gender considerations in the included literature. There exists gender differences in presentation, treatment, and outcomes after acute myocardial infarction;[21-23] yet it is not clear from the included guidelines if recommendations apply equally for males and females.

In the SR,[20] the study relevant for this review[17] did not report whether participants withdrew or were lost to follow up, introducing the possibility of incomplete outcome reporting (attrition bias affecting all outcomes).

The applicability of the evidence to Canadian settings is unclear as all relevant literature,[12-15,20] except one,[11] were conducted outside of Canada.

Conclusions and Implications for Decision or Policy Making

This report identified safety studies and evidence-based guidelines regarding thrombolytic administration for the treatment of AMI in prehospital settings. One relevant SR,[20] and five evidence-based guidelines were identified.[11-15] No evidence was found regarding the comparative safety of thrombolytic administration performed in a prehospital setting compared with no or significantly delayed thrombolytic administration for the treatment of acute myocardial infarction.

The SR[20] included one relevant primary study,[17] which revealed uncertainty in the safety findings between prehospital and hospital administration of thrombolytics.[20]

Five evidence-based guidelines[11-15] were identified that provided recommendations regarding the use of thrombolytics for treatment of AMI in prehospital settings. One guideline provides a strong recommendation (low-quality evidence) for a goal of first medical contact to thrombolytic needle time of less than or equal to 30 minutes;[11] however, they strongly recommend (high-quality evidence) against pharmacologic facilitation when access to cardiac catheterization is available within 120 minutes.[11] Similarly, a second guideline recommends thrombolytics if PCI cannot be performed within 120 minutes.[12] The third and fourth guidelines recommend, with varying strength in recommendations, the prehospital administration of thrombolytics, under specific protocols, if transportation time will be greater than 30 minutes.[13,14] The fifth guideline does not recommend (class III [harm], level of evidence A) the use of thrombolytics in patients with non-ST-elevation acute coronary syndrome.[15]

The limitations of the included studies and of this report should be considered when interpreting the results. The findings highlighted in this review come with a high degree of uncertainty. Further research investigating the safety of thrombolytic administration performed in a prehospital setting, especially through the use of large, methodologically-sound RCTs or well-designed meta-analyses, would help reduce this uncertainty.

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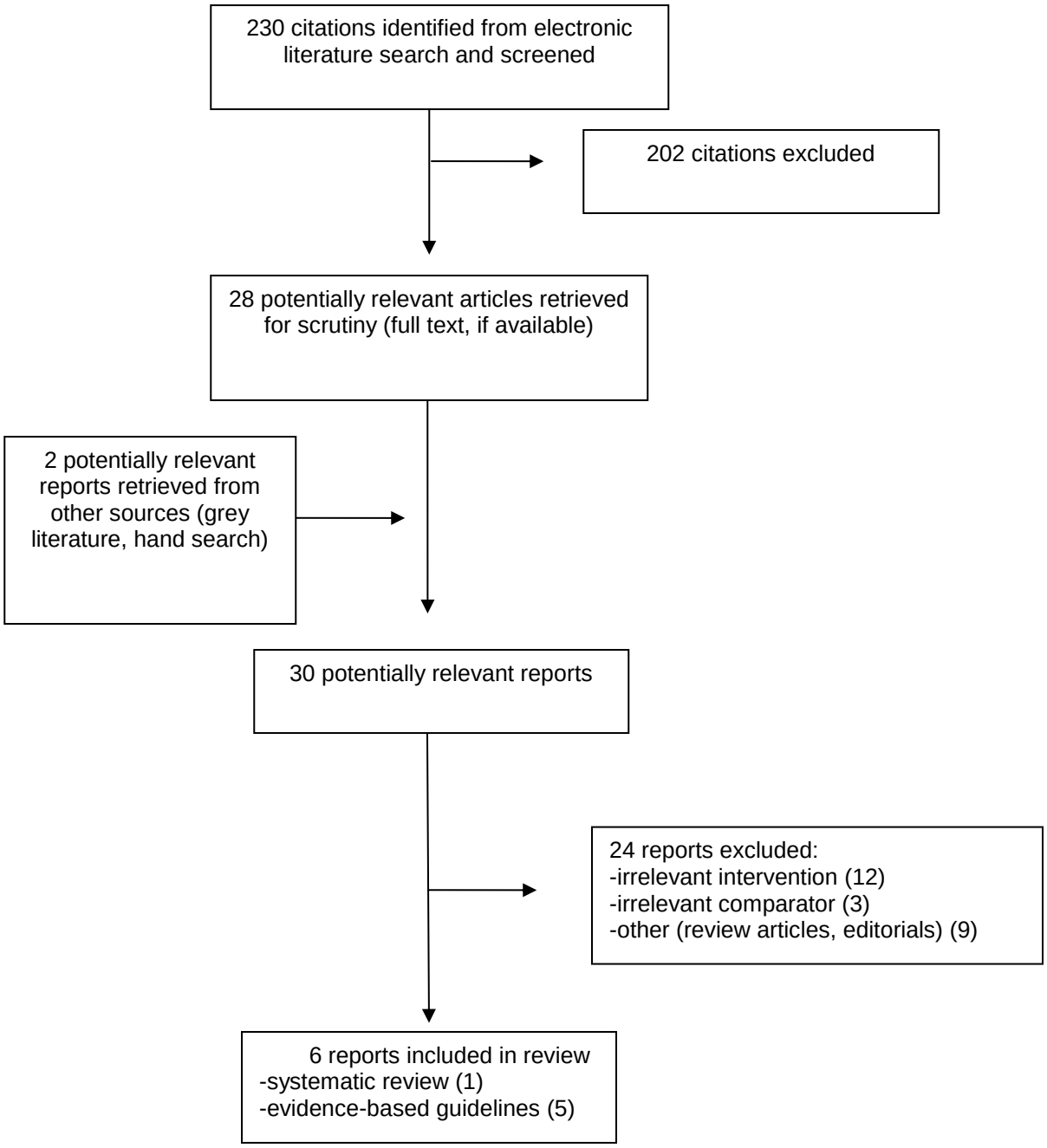
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
McCaul, 2014[10] South Africa	**Study design**: SR of relevant published and unpublished RCTs excluding cross-over trials up to June 2014 **Literature search strategy**: Authors searched the CENTRAL, MEDLINE (Ovid), EMBASE (Ovid), Web of Science, and CINAHL (EBSCO) up to June, 2014. Ongoing clinical trials were identified using Clinical Trials.gov, International Standard Randomised Controlled Trial Register, and the WHO International Clinical Trials Registry Platform. These searches were supplemented by a manual search of the reference lists of relevant trials and by contacting primary authors for identification of other potentially relevant studies. **Number of studies included**: In total, 3 studies were included, with 1 relevant for this review[17] **Quality assessment tool**: GRADE methodology was used to describe the quality of the evidence. **Objective**: "To assess the morbidity and mortality of pre-hospital versus in-hospital thrombolysis for STEMI."[10] (*p*5)	"Adults (16 years and older) with STEMI diagnosed by a medical healthcare provider in either the pre-hospital or in-hospital setting."[10] (*p*5) The participants in the study relevant to this review were individuals with suspected AMI, pain for six hours or less, aged 75 years or less, with no risk of bleeding, and a 12-lead ECG reviewed by a physician by phone.[17]	**Interventions**: any thrombolytic agent used to treat STEMI in prehospital settings. **Comparators**: any thrombolytic agent used to treat STEMI in hospital settings. The study relevant to this review compared alteplase 100 mg and acetylsalicylic acid 325 mg in a prehospital setting, to the same drug combination in a hospital setting.[17]	**Relevant Outcomes:** - All-cause hospital mortality at one month and one year. - AEs - Ejection fraction - Classification of heart failure - Time to discharge or days in hospital **Follow-up:** NR

AEs = adverse effects; AMI = acute myocardial infarction; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; EBSCO = Elton Bryson Stephens Company; ECG = electrocardiograph; EMBASE = Excerpta Medica database; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MEDLINE = Medical Literature Analysis and Retrieval System Online; NR = not reported; RCT = randomized controlled trial; SR = systematic review; STEMI = ST-elevation myocardial infarction

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Canadian Cardiovascular Society / Canadian Association of Interventional Cardiology (CCS/CAIC), 2019[11]						
Intended users: Specialists and allied health professionals involved in the care of STEMI patients **Target population:** Acute STEMI patients	Various reperfusion strategies in prehospital, non-PCI capable hospital, and PCI capable hospital settings, including: pharmacological therapy, oxygen administration, and mechanical reperfusion.	Various outcomes, including: reperfusion rates, reperfusion delay, time to fibrinolysis,	A systematic review was conducted for English literature from 1988 to 2018 in MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and CENTRAL (Ovid). Two reviewed independently screened the results and applied inclusion and exclusion criteria.	Quality of the evidence and presence of bias evaluated with GRADE and classified as:[24,25] • High • Moderate • Low • Very low	A panel convened by teleconference voted on the final recommendations. Adoption of recommendation required at least 75% of the votes. Strength of recommendation assigned using GRADE and classified as:[24,25] • Strong • Weak	NR
Scottish Intercollegiate Guidelines Network (SIGN), 2016[12]						
Intended users: Healthcare professionals involved in specialized and primary care of patients with acute coronary syndrome, carers, voluntary organisations,	Various interventions, including: early pharmacological intervention, reperfusion therapy	Various outcomes, including: mortality, stroke, reinfarction, recurrent ischemia, need for CABG	Systematic literature review was conducted in accordance with SIGN methodology for the years 2004 to 2014 in MEDLINE, CINAHL, PsycINFO; EMBASE,	Evidence quality was assessed against the SIGN levels of evidence:[12] (*p*2) • 1^{++} (high-quality meta-analyses, SR of RCTs, or RCTs with a very low risk of bias) • 1^{+} (Well-conducted meta-analyses, SRs, or RCTs with a low risk of bias) • 1^{-} (meta-analyses, SRs, or	Recommendations were made by a multidisciplinary guideline development group in consideration of evidence obtained from systematic reviews. Strength of recommendation assigned using SIGN	Draft guidelines were reviewed by independent expert referees and posted online for comment.

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
policy makers **Target population:** Patients with ACS (e.g., unstable angina, transmural myocardial infarction)			CENTRAL, Cochrane, NEED, HEED.	RCTs with a high risk of bias) • 2^{++} (high-quality SR of case-control or cohort studies, high-quality case-control or cohort studies with a very-low risk of confounding or bias and a high probability that the relationship is causal) • 2^{+} (Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal • 2^{-} (Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal • 3 (Non-analytic studies: e.g., case reports, case series) • 4 (expert opinion)	methodology:[12] (*p2*) • Strong "should" • Conditional • Strong "should not"	
American Heart Association (AHA) Guidelines Update for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC), 2015[14]						
Intended users: North American practitioners who provide care to the target population, including: emergency medical service	Various interventions, including prehospital fibrinolysis and hospital fibrinolysis	Various outcomes, including: mortality, intracranial hemorrhage	"The ACS Task Force ultimately completed 18 systematic reviews (14 based on meta-analyses) on more than 110 relevant studies	Quality of the evidence and presence of bias evaluated with GRADE and classified as:[24] • High • Moderate • Low • Very low	Consensus-based treatment recommendations were created by the Task Force and the writing group assessed the evidence and assigned a level of	NR

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
dispatchers, first responders, paramedics, nurses, physicians, etc. **Target population: North American** patients with suspected ACS, from first medical contact to disposition from the emergency department.			spanning 40 years."[26] (*p*S483) Systematic searches were conducted in PubMed, EMBASE, and the Cochrane Library.	Level (quality) of evidence was also assigned using AHA methodology:[19] • A • B-Randomized • B-Nonrandomized • C Limited data • D Expert Opinion	evidence by using AHA definitions. Strength of recommendation assigned using GRADE and classified as:[24] • Strong • Weak Class (strength) of recommendation was also assigned using AHA methodology:[19] • I (Strong) • IIa (Moderate) • IIb (Weak) • III No benefit (Moderate) • III Harm (Strong)	
International Liaison Committee on Resuscitation (ILCOR), 2015[13]						
Intended users: Regional health care authorities involved in prehospital and hospital management of patients with ACS or STEMI **Target population:** Patients with ACS or STEMI	Various interventions, including prehospital fibrinolysis and hospital fibrinolysis	Various outcomes, including: hospital mortality, intracranial hemorrhage, bleeding	"The ACS Task Force ultimately completed 18 systematic reviews (14 based on meta-analyses) on more than 110 relevant studies spanning 40 years."[13] (*p*S148) Systematic searches were	Quality of the evidence and presence of bias evaluated with GRADE and classified as:[24] • High • Moderate • Low • Very low	A task force of expert physicians and other health care professionals made consensus-based recommendations in consideration of evidence obtained from systematic reviews. Strength of recommendation assigned using GRADE	Systematic reviews and draft recommendations were posted for public comments and presented at a conference for commentary from experts.

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
			conducted in PubMed, EMBASE, and the Cochrane Library.		and classified as:[24] • Strong • Weak	
American Heart Association / American College of Cardiology (AHA/ACC), 2014[15]						
Intended users: United States clinicians involved in management of patients with non-ST-elevation acute coronary syndrome **Target population:** Patients with non-ST-elevation acute coronary syndrome	Various interventions, including intravenous fibrinolytic therapy	Various outcomes, including: mortality, myocardial infarction, intracranial hemorrhage	"An extensive evidence review was conducted through October 2012, and other selected references published through April 2014 were reviewed by the [guideline writing committee]."[15] (*p*E144) Systematic searches were conducted for literature in English in databases such as PubMed, EMBASE, the Cochrane Library, and AHRQ reports.	Evidence quality was judged using AHA level of evidence methodology:[19] (levels A [high] to C [low]).	The guideline writing committee was composed of clinicians, cardiologists and other health care professionals. They reviewed the literature and assessed the quality of evidence, and made recommendations using group decision-making consensus development methods.[18]	Guidelines were reviewed by two official reviewers nominated by the American College of Cardiology and AHA, as well as 37 individual content reviewers.

ACS = acute coronary syndrome; AHA = American Heart Association; AHRQ = Agency for Healthcare Research and Quality; CABG = coronary artery bypass graft; CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; EMBASE = Excerpta Medica database; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; HEED = Health Economic Evaluations Database; MEDLINE = Medical Literature Analysis and Retrieval System Online; NEED = National Health Service Economic Evaluation Database; NR = not reported; PCI = percutaneous coronary intervention; PsycINFO = psychological information database; PubMED = Public MEDLINE; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network; SR = systematic review; STEMI = ST-elevation myocardial infarction

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Review using AMSTAR 2[8]

Strengths	Limitations
McCaul, 2014[10]	
• The objectives and inclusion/exclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Greater than two databases were searched (CENTRAL, MEDLINE, EMBASE, Web of Science, CINAHL). In addition, a manual search of references from identified literature was performed • Search terms and dates were provided (June 2014) • Grey literature searching of unpublished thesis sources was conducted. • A detailed protocol of the methods was published in the Cochrane Database of Systematic Reviews • Study selection was completed in duplicate and described in detail • Data extraction was completed in duplicate and described in detail • A list of included studies was provided, and the characteristics of included studies were described in detail • A list of excluded studies was provided including the reason for exclusion • The quality of included studies was assessed based on the GRADE criteria • Review authors considered risk of bias in individual studies when interpreting and discussing the results. • Sources of funding were disclosed (no direct funding). • There was no language restriction on the search and articles were translated where necessary. • The review justified significant deviations from the protocol (e.g., changes to mortality data reporting)	• The choice of included study designs was not justified • Review authors did not report on source of funding for the included studies • The relevant primary study was conducted in the United States of America from 1988 to 1991; findings may not be generalizable to the current Canadian setting • Publication bias was not investigated and the impact on results of the review not discussed

CENTRAL = Cochrane Central Register of Controlled Trials; CINAHL = Cumulative Index to Nursing and Allied Health Literature; EMBASE = Excerpta Medica database; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; MEDLINE = Medical Literature Analysis and Retrieval System Online

Table 5: Strengths and Limitations of Guidelines using AGREE II[9]

Item	Guideline				
	Canadian Cardiovascular Society / Canadian Association of Interventional Cardiology (CCS/CAIC), 2019[11]	Scottish Intercollegiate Guidelines Network (SIGN), 2016[12]	American Heart Association (AHA) Guidelines Update for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC), 2015[14]	International Liaison Committee on Resuscitation (ILCOR), 2015[13]	American Heart Association / American College of Cardiology (AHA/ACC), 2014[15]
Domain 1: Scope and Purpose					
1. The overall objective(s) of the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes	Yes	Yes	Yes	Yes

Item	Guideline				
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes	Yes	Yes	Yes	Yes
Domain 2: Stakeholder Involvement					
4. The guideline development group includes individuals from all relevant professional groups.	Yes	Yes	Unclear	Yes	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No	Yes	No	Yes	No
6. The target users of the guideline are clearly defined.	Yes	Yes	Yes	Yes	Yes
Domain 3: Rigour of Development					
7. Systematic methods were used to search for evidence.	Yes	Yes	Yes	Yes	Yes
8. The criteria for selecting the evidence are clearly described.	Yes	Yes	Yes	Yes	Yes
9. The strengths and limitations of the body of evidence are clearly described.	Yes	Yes	Yes	Yes	Yes
10. The methods for formulating the recommendations are clearly described.	Yes	Yes	Yes	Yes	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes	Yes	Yes	Yes	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes	Yes	Yes	Yes	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	No	Yes	No	Yes	Yes
14. A procedure for updating the guideline is provided.	No	Yes	No	No	Yes
Domain 4: Clarity of Presentation					
15. The recommendations are specific and unambiguous.	Yes	Yes	Yes	Yes	Yes
16. The different options for management of the condition or health issue are clearly presented.	Yes	Yes	Yes	Yes	Yes
17. Key recommendations are easily identifiable.	Yes	Yes	Yes	Yes	Yes
Domain 5: Applicability					
18. The guideline describes facilitators and barriers to its application.	Yes	Yes	No	No	Yes

Item	Guideline				
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Yes	Yes	No	No	Yes
20. The potential resource implications of applying the recommendations have been considered.	Yes	Yes	No	Yes	Yes
21. The guideline presents monitoring and/or auditing criteria.	Yes	Yes	No	No	No
Domain 6: Editorial Independence					
22. The views of the funding body have not influenced the content of the guideline.	No	Yes	No	No	No
23. Competing interests of guideline development group members have been recorded and addressed.	No	Yes	Yes	Yes	Yes

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Review

Main Study Findings	Authors' Conclusion
McCaul, 2014[10]	
Relevant individual studies: The systematic review included one relevant primary study on the comparative safety of thrombolytic administration performed in a prehospital versus hospital setting for treatment of acute myocardial infarction. **Primary study citation**: Weaver, 1993[17] **All cause hospital mortality**: • Prehospital thrombolysis: n = 10/175 • Hospital thrombolysis: n = 15/185 • Risk ratio favours prehospital (95% CI): 0.70 (0.33, 1.53) **Adverse effects – Bleeding complications**: • Prehospital thrombolysis: n = 10/175 • Hospital thrombolysis: n = 11/185 • Risk ratio favours prehospital (95% CI): 0.96 (0.42, 2.21) **Adverse effects – Stroke**: • Prehospital thrombolysis: n = 4/175 • Hospital thrombolysis: n = 2/185 • Risk ratio favours hospital (95% CI): 2.21 (0.39, 11.40)	"In settings where it can be safely and correctly administered by trained staff, pre-hospital thrombolysis may therefore be an appropriate intervention. We were unable to determine whether pre-hospital thrombolysis is superior to in-hospital thrombolysis with regard to mortality, ejection fraction or adverse effects. Pre-hospital thrombolysis for STEMI has the potential to reduce the burden of disease in [lower- and middle-income countries], especially in individuals who have limited access to in-hospital thrombolysis or PCI (e.g. those living in rural areas)."[10] (*p*16) "In Weaver 1993, pre-hospital thrombolysis was performed by paramedics (emergency care professionals) with physician guidance, highlighting the advantage of a paramedic lead with physician teamwork as an alternative to a physician-led thrombolysis team, especially when considering physician availability in [lower- and middle-income countries]."[10] (*p*16)

AMI = acute myocardial infarction; CI = confidence interval; PCI = percutaneous coronary intervention; SD = standard deviation;

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Canadian Cardiovascular Society / Canadian Association of Interventional Cardiology (CCS/CAIC), 2019[11]	
1. "If fibrinolysis is used as a default reperfusion strategy, we recommend that STEMI networks target a total [first medical contact] time of ≤ 30 minutes."[11] (*p*116) 2. "We suggest that fibrinolysis before transfer to a PCI centre be considered in patients with STEMI complicated by CS when excessive delays to cardiac catheterization are anticipated."[11] (*p*116) a. "The writing group recognizes that Canada's unique geography and climate might contribute to very long transport times to PCI-capable hospitals for patients who present to nonurban hospitals or remote nursing stations. We valued the potential benefits of fibrinolysis reperfusion in such a setting for the treatment of this time-sensitive condition that is associated with a high mortality rate."[11] (*p*116) 3. "We recommend routine rapid transfer to PCI centres after fibrinolysis, immediate PCI for patients with failed reperfusion, and routine angiography with or without PCI within 24 hours after successful fibrinolysis."[11] (*p*117) a. "This recommendation is on the basis of the established benefits such as	Quality of the evidence was judged using GRADE. 1. Strong Recommendation, Low-Quality Evidence 2. Weak Recommendation, Very Low-Quality Evidence 3. Strong Recommendation, Moderate-Quality Evidence

Recommendations	Strength of Evidence and Recommendations
reduced short-term reinfarction, recurrent ischemia, and heart failure and the absence of any increase in major bleeding. However, some regions might not have the resources required to transfer all STEMI patients early after fibrinolysis and might need to transfer only high-risk patients."[11] (*p*117) 4. **"**We recommend against a strategy of pharmacologic facilitation with full-dose fibrinolysis or combination fibrinolysis and GPI or GPI when access to cardiac catheterization is available within 120 minutes of [first medical contact]."[11] (*p*117)	4. Strong Recommendation, High-Quality Evidence
Scottish Intercollegiate Guidelines Network (SIGN), 2016[12]	
1. "When primary percutaneous coronary intervention cannot be provided within 120 minutes of ECG diagnosis, patients with an ST-segment-elevation acute coronary syndrome should receive immediate (prehospital or admission) thrombolytic therapy."[12] (*p*18) 2. "Thrombolysis should be conducted with a fibrin-specific agent."[12] (pg. 19) a. "A bolus fibrin-specific agent is preferred on practical grounds, particularly in the prehospital setting.."[12] (*p*19)	Quality of the evidence was judged using SIGN methodology (levels 1^{++} [high] to 4 [low]) 1. "Strong should" recommendation; Quality of Evidence rated as 2^{+}, 4, 1^{-}, 2^{+}, and 4 2. "Strong should" recommendation; Quality of Evidence rated as 1^{+} and 1^{++}
American Heart Association (AHA) Guidelines Update for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC), 2015[14]	
1. "While transmission of the prehospital ECG to the [emergency department] physician may improve positive predictive value (PPV) and therapeutic decision-making regarding adult patients with suspected STEMI, if transmission is not performed, it may be reasonable for trained nonphysician ECG interpretation to be used as the basis for decision-making, including activation of the catheterization laboratory, administration of fibrinolysis, and selection of destination hospital"[14] (*p*S485) 2. "Where prehospital fibrinolysis is available as part of a STEMI system of care, and in-hospital fibrinolysis is the alternative treatment strategy, it is reasonable to administer prehospital fibrinolysis when transport times are more than 30 minutes"[14] (*p*S487) 3. **"**Where prehospital fibrinolysis is available as part of the STEMI system of care and direct transport to a PCI center is available, prehospital triage and transport directly to a PCI center may be preferred because of the small relative decrease in the incidence of intracranial hemorrhage without evidence of mortality benefit to either therapy". "[14] (*p*S488)	Quality of the evidence was judged using AHA recommendation system,[19] 1. Class IIa (moderate), level of evidence B-nonrandomized 2. Class IIa (moderate), level of evidence B-randomized 3. Class IIb (weak), level of evidence B-randomized
International Liaison Committee on Resuscitation (ILCOR), 2015[13]	
1. "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."[13] (*p*S160)	Quality of the evidence was judged using GRADE. 1. Strong recommendation, Moderate-Quality Evidence

Recommendations	Strength of Evidence and Recommendations
2. "We suggest that where PCI facilities are available in a geographic region, that direct triage and transport for PCI is preferred."[13] (*p*S161) a. "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."[13] (*p*S161)	2. Weak recommendation, Low-Quality Evidence
American Heart Association / American College of Cardiology (AHA/ACC), 2014[15]	
1. "In patients with [non-ST-elevation acute coronary syndrome] (i.e., without ST-elevation, true posterior [myocardial infarction], or left bundle-branch block not known to be old), intravenous fibrinolytic therapy should not be used."[15] (*p*E166)	Quality of the evidence was judged using AHA recommendation system,[19] 1. Class III (Harm) recommendation, Quality of Evidence rated as Level A

ECG = electrocardiograph; GPI = glycoprotein IIb/IIIa inhibitor; GRADE = Grading of Recommendations, Assessment, Development, and Evaluation; PCI = percutaneous coronary intervention

Appendix 5: Additional References of Potential Interest

Systematic Review

Alternative Comparator – in hospital percutaneous coronary intervention

Roule V, Ardouin P, Blanchart K, et al. Prehospital fibrinolysis versus primary percutaneous coronary intervention in ST-elevation myocardial infarction: a systematic review and meta-analysis of randomized controlled trials. *Crit Care*. 2016;20(1):359.
PubMed: PM27814743

Randomized Controlled Trial

Alternative Comparator – in hospital percutaneous coronary intervention

Welsh RC, Goldstein P, Sinnaeve P, et al. Relationship between community hospital versus pre-hospital location of randomisation and clinical outcomes in ST-elevation myocardial infarction patients: insights from the Stream study. *Europ Heart J Acute Cardiovasc Care*. 2018;7(6):504-513.
PubMed: PM28627230

Non-Randomized Studies

Alternative Intervention – Reteplase

Luiz T, Wilhelms A, Madler C, et al. Outcome of out-of-hospital cardiac arrest after fibrinolysis with reteplase in comparison to the return of spontaneous circulation after cardiac arrest score in a geographic region without emergency coronary intervention. *Exp Ther Med*. 2017;13(4):1598-1603.
PubMed: PM28413515

Solhpour A, Chang KW, Arain SA, et al. Comparison of 30-day mortality and myocardial scar indices for patients treated with prehospital reduced dose fibrinolytic followed by percutaneous coronary intervention versus percutaneous coronary intervention alone for treatment of ST-elevation myocardial infarction. *Catheter Cardiovasc Interv*. 2016;88(5):709-715.
PubMed: PM27028120

Solhpour A, Chang K-W, Balan P, et al. Comparison of outcomes for patients >=75 years of age treated with pre-hospital reduced-dose fibrinolysis followed by percutaneous coronary intervention versus percutaneous coronary intervention alone for treatment of ST-elevation myocardial infarction. *Am J Cardiol*. 2014;113(1):60-63.
PubMed: PM103997584.

Alternative Intervention – Type of thrombolytic not specified

Beauloye C, Vrolix M, Claeys MJ, van de Borne P, Vandendriessche E, Van De Werf F. Pre-hospital management of acute coronary syndrome patients in Belgium and Luxembourg and other Western European countries. *Acta Cardiol*. 2016;71(1):15-24.
PubMed: PM26853249

No Comparator

Mannsverk J, Steigen T, Wang H, et al. Trends in clinical outcomes and survival following prehospital thrombolytic therapy given by ambulance clinicians for ST-elevation myocardial infarction in rural sub-arctic Norway. Europ Heart J Acute Cardiovasc Care. 2019;8(1):8-14. PubMed: PM29256635