Society Guidelines

2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines on the Acute Management of ST-Elevation Myocardial Infarction: Focused Update on Regionalization and Reperfusion

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ABSTRACT

Rapid reperfusion of the infarct-related artery is the cornerstone of therapy for the management of acute ST-elevation myocardial infarction (STEMI). Canada's geography presents unique challenges for timely delivery of reperfusion therapy for STEMI patients. The Canadian

RÉSUMÉ

La reperfusion rapide de l'artère responsable de l'infarctus est la pierre angulaire thérapeutique de la prise en charge de l'infarctus aigu du myocarde avec élévation du segment ST (STEMI). Les caractéristiques géographiques du Canada posent des défis particuliers pour prodiguer aux

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

Cardiovascular Society/Canadian Association of Interventional Cardiology STEMI guideline was developed to provide advice regarding the optimal acute management of STEMI patients irrespective of where they are initially identified: in the field, at a non-percutaneous coronary intervention-capable centre or at a percutaneous coronary intervention-capable centre. We had also planned to evaluate and incorporate sex and gender considerations in the development of our recommendations. Unfortunately, inadequate enrollment of women in randomized trials, lack of publication of main outcomes stratified according to sex, and lack of inclusion of gender as a study variable in the available literature limited the feasibility of such an approach. The Grading Recommendations, Assessment, Development, and Evaluation system was used to develop specific evidence-based recommendations for the early identification of STEMI patients, practical aspects of patient transport, regional reperfusion decision-making, adjunctive prehospital interventions (oxygen, opioids, antiplatelet therapy), and procedural aspects of mechanical reperfusion (access site, thrombectomy, antithrombotic therapy, extent of revascularization). Emphasis is placed on integrating these recommendations as part of an organized regional network of STEMI care and the development of appropriate reperfusion and transportation pathways for any given region. It is anticipated that these guidelines will serve as a practical template to develop systems of care capable of providing optimal treatment for a wide range of STEMI patients.

patients victimes d'un STEMI une reperfusion dans les délais requis. Les lignes directrices sur l'STEMI de la Société canadienne de cardiologie et de l'Association canadienne de cardiologie d'intervention ont été élaborées pour formuler des recommandations sur la prise en charge aiguë optimale des patients victimes d'un STEMI sans égard à l'endroit où l'infarctus a été initialement constaté, que ce soit à l'extérieur ou dans un établissement en mesure ou incapable de pratiquer une intervention coronarienne percutanée. Nous avions prévu d'évaluer également et d'intégrer la prise en compte du sexe et du genre dans l'élaboration de nos recommandations. Malheureusement, le nombre insuffisant de femmes recrutées dans les essais avec répartition aléatoire, le manque de publications sur les critères d'évaluation principaux stratifiés en fonction du sexe et l'omission fréquente du sexe à titre de variable de l'étude dans la littérature limitaient la faisabilité d'une telle approche. Le système GRADE (« Grading Recommendations, Assessment, Development, and Evaluation ») a été utilisé pour formuler des recommandations précises, fondées sur des données probantes, pour le repérage précoce des patients victimes d'un STEMI, les aspects pratiques concernant le transport des patients, la prise de décision au sujet de la reperfusion au niveau régional, les interventions d'appoint préhospitalières (oxygène, opioïdes, traitement antiplaquettaire), ainsi que les aspects procéduraux de la reperfusion mécanique (voie d'accès, thrombectomie, traitement antithrombotique, étendue de la revascularisation). Une importance particulière est accordée à l'intégration de ces recommandations à un réseau régional structuré de prise en charge du STEMI et à l'élaboration de parcours appropriés de reperfusion et de transport dans chaque région. On s'attend à ce que ces lignes directrices servent de modèle pratique pour l'élaboration de systèmes de soins permettant d'offrir un traitement optimal à un large éventail de patients victimes d'un STEMI.

Prompt, complete, and sustained reperfusion of the infarct-related artery (IRA) with fibrinolysis, primary percutaneous coronary intervention (PPCI), or the combination within 12 hours of symptom onset remains the cornerstone of ST-elevation myocardial infarction (STEMI) care.[1] The choice among these strategies is on the basis of individual patient characteristics, timely access to PPCI, and variation between regionalized systems of care.[2-4] Optimizing prehospital as well as in-hospital STEMI care processes, including improving prehospital STEMI identification, streamlining the flow of patients from the prehospital to the hospital setting, and reducing overall reperfusion times might all improve clinical outcomes by reducing the thrombotic, mechanical, and electrical complications of the index event.[5]

The Canadian Cardiovascular Society (CCS) has previously provided clinical perspectives on the American Heart Association/American College of Cardiology STEMI guidelines.[6,7] The present document provides guidance regarding the optimal choice and delivery of STEMI reperfusion strategies for patients in the prehospital setting as well as for those who present to hospitals with and without percutaneous coronary intervention (PCI) capability. This document also provides recommendations regarding other components of STEMI care that are applicable to patients who are identified in these 3 clinical settings, including the use of adjunctive medications, oxygen administration, and other management considerations specific to the delivery of pharmacological and mechanical reperfusion therapy. This guideline has been reviewed and endorsed by the Canadian Association of Emergency Physicians.

Methods

This document was developed in accordance with CCS best practices and in accordance with the Framework for Application of Grading of Recommendations, Assessment, Development, and Evaluation (see https://www.ccs.ca/images/Development_Process/CCS_GRADE_Framework_June2015.pdf for details). The Methods are provided in the Supplementary Material. In addition, we systematically appraised the included literature for modifying effects of sex and gender on outcomes, and determined whether the quality of evidence and strength of recommendations should differ on the basis of sex or gender. Although the systematic appraisal of sex and gender considerations of included literature as part of clinical practice guideline development was feasible, inadequate enrollment of women in randomized trials, lack of publication of main outcomes stratified according to sex, and lack of inclusion of gender as a study variable prevented us from providing sex- and gender-specific strengths of recommendations for the clinical questions evaluated. Although we make the agnostic assumption that the recommendations in this guideline hold equally for men and for women, we acknowledge that the published literature are inadequate to clearly and objectively confirm this.

Table 1. Elements of a regional STEMI network

A preplanned default initial reperfusion strategy (PPCI or fibrinolysis) for each hospital within the network on the basis of geographic and transport considerations.

The ability to deliver appropriate adjunctive PCI after fibrinolysis.

The capability of EMS and emergency department teams to rapidly diagnose and treat STEMI.

For PPCI, the ability for EMS and emergency departments to activate the STEMI team for reperfusion therapy through a "single call" mechanism immediately from the point of first medical contact with the patient.

The implementation of a "no-refusal" policy at PCI centres for STEMI patients who are deemed appropriate for PPCI.

The ability for EMS teams that diagnose STEMI patients in the field to bypass non-PCI centres and transport patients directly to a PCI centre.

The ability for appropriately selected patients to bypass the emergency department of a PCI centre and proceed directly to the cardiac catheterization laboratory.

EMS, emergency medical service; PCI, percutaneous coronary intervention; PPCI, primary PCI; STEMI, ST-elevation myocardial infarction.

Regionalization of STEMI Care

Development of regional STEMI centres (hub and spoke) and regional reperfusion strategies

Reperfusion therapy within 12 hours of symptom onset reduces mortality in STEMI patients.[1] Although PPCI is the preferred reperfusion strategy when it can be rapidly performed, there are patient, hospital, and geographic factors that can affect the ability for it to be delivered within recommended timelines. Fibrinolysis remains a suitable alternative for appropriately selected patients who cannot undergo timely PPCI. These considerations should be accounted for when selecting a reperfusion strategy for a STEMI patient.

Although logistical considerations vary across Canada, each regional care system can work to streamline the diagnosis and management of patients with STEMI. Evidence suggests that STEMI care is best performed within the setting of an organized STEMI network with a PPCI centre (the "hub") receiving referrals from surrounding hospitals (the "spokes") and a defined catchment area from the field via emergency medical services (EMS).[8-14] Table 1 shows a list of important fundamental elements of such a program.

Reperfusion decision-making within a regional STEMI network

STEMI patients can potentially be identified either in the prehospital setting by EMS or in a hospital (with or without PCI capability) within a given regional network of STEMI care. Geographical proximity to centres that perform 24/7 PPCI, along with the presence of appropriate EMS transport systems, can help determine the optimal default reperfusion strategy for these STEMI patients (Fig. 1).[15] Regional
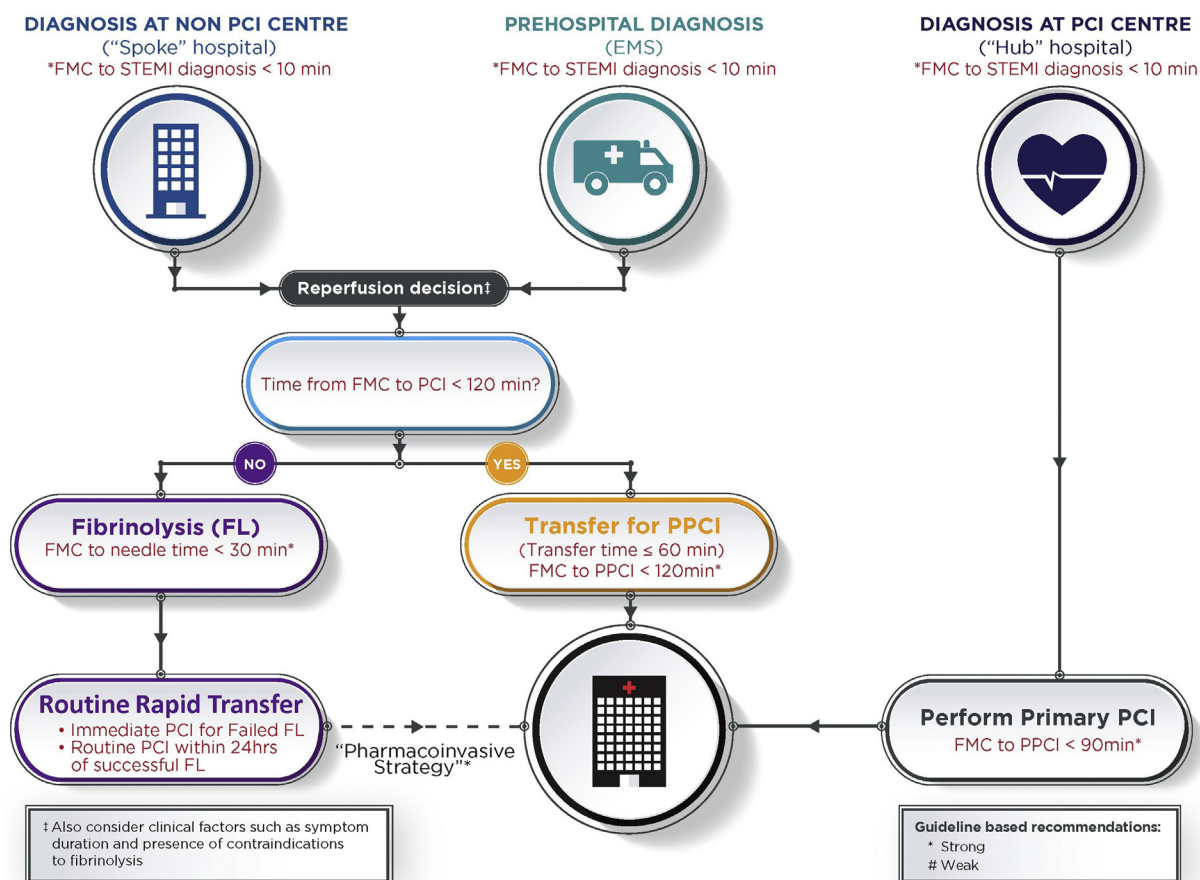

Figure 1. ST-elevation myocardial infarction (STEMI) reperfusion strategies. EMS, emergency medical services; FL, fibrinolysis; FMC, first medical contact; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention.

strategies have been developed to increase the proportion of patients from non–PCI-capable hospitals or in the prehospital setting who can receive appropriate PPCI.[16-18] On-site or prehospital fibrinolysis can also be considered as a preferred reperfusion strategy for non–PCI-capable hospitals within a regional STEMI network if timely transfer for PPCI cannot be consistently achieved.[19-21] Every non–PCI-capable hospital should have a formal agreement with a designated PCI centre within the network ("hub-and-spoke" model) that includes processes to allow for adjunctive PCI after initial fibrinolysis.

Many regions and STEMI care networks in Canada have shown improvements in reperfusion times and clinical outcomes in STEMI patients who have been treated through the development of organized regional STEMI programs that emphasize prehospital electrocardiogram (ECG) diagnosis, EMS bypass of non–PCI-capable hospitals, and geographic and resource-based decision-making regarding the choice of an upfront reperfusion strategy.[22-26] The Ottawa program showed that EMS diagnosis of STEMI in the field with direct transfer to a PPCI centre was associated with a reduction in in-hospital mortality compared with treatment at the nearest hospital.[17] It has been suggested that prehospital STEMI diagnosis in conjunction with prehospital fibrinolysis could also be similarly driven by EMS.[27] Finally, the rapid regionalization across multiple STEMI networks as part of the American Heart Association STEMI Accelerator Programs in the United States was associated with significant reductions in in-hospital mortality.[28-30] These findings support the development of an intensive and organized regional approach to emergency care for these patients.

Successful STEMI networks regularly track time intervals and provide timely feedback to network stakeholders for continuous quality improvement. Important time components that affect overall program efficiency are defined in Table 2 and listed in Table 3. Routine audit practices can serve to identify treatment delays in EMS and hospital-based processes, which can be fed back to team members involved in STEMI care. Important reperfusion treatment goals that should be tracked by regional STEMI networks are listed in Table 3.

RECOMMENDATION

1. We recommend the development and implementation of regional STEMI networks using a hub-and-spoke model to define optimal reperfusion strategies, reduce reperfusion delay, improve reperfusion rates, and apply protocols for comprehensive ongoing STEMI care (Strong Recommendation, Moderate-Quality Evidence).

2. We recommend a first medical contact (FMC) to STEMI diagnosis (ECG acquisition and interpretation) time of ≤ 10 minutes (Strong Recommendation, Low-Quality Evidence).

3. We recommend development of a STEMI network of care that incorporates the use of prehospital catheterization laboratory activation, single-call patient transfer protocols, and in-field bypass of non-PCI centres to minimize FMC-to-device times for patients who are

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treated with PPCI (Strong Recommendation, Moderate-Quality Evidence).

4. We recommend the use of protocols to minimize time to fibrinolysis, and the development of a formal relationship with a PCI centre to enable adjunctive PCI for patients who are treated with fibrinolysis within a STEMI network (as outlined in the section entitled "Reperfusion strategies for suspected STEMI patients managed in a non–PCI-capable hospital") (Strong Recommendation, Moderate-Quality Evidence).

5. We recommend that hospitals and EMS services within STEMI networks maintain written, updated STEMI management protocols, and audit treatment delays, reperfusion rates, and false activation rates to monitor quality metrics (Strong Recommendation, Low-Quality Evidence).

Practical tip. All hospitals within a STEMI network should define their default STEMI reperfusion strategy on the basis of local geography and resource availability.

Prehospital and interfacility EMS transportation within regional networks

There are 4 national designations for the health care providers in ambulances in Canada: Emergency Medical Responders, similar to Basic Emergency Medical Technicians, Primary Care Paramedics (PCPs), Advanced Care Paramedics (ACPs), similar to Emergency Medical Technician Paramedics, and Critical Care Paramedics. The transportation of suspected STEMI patients by EMS might be accomplished by any of these providers.

In Canada, many regions rely on PCPs to transport STEMI patients.[31-33] PCPs have the capability to recognize STEMI on 12-lead ECGs, to administer aspirin and nitroglycerin, and to defibrillate if needed.[24,25] ACPs can provide more advanced life support such as synchronized cardioversion, transcutaneous pacing, and advanced airway management, and they can administer advanced cardiac life support medications such as vasopressors, antiarrhythmics, and fibrinolytic therapy. A number of observational studies have shown that complications requiring ACP intervention during prehospital transport of selected STEMI patients are infrequent (< 5%).[31,32,34-36] The most commonly observed complications during STEMI patient transport included chest pain, hypotension, tachycardia, and bradycardia.[34,37] Other serious complications requiring advanced or critical care interventions such as cardiac arrest, acute pulmonary edema, and cardiogenic shock (CS) were rare, especially among patients in whom complications were not anticipated before transport.[18,34,36]

Transportation of uncomplicated STEMI patients with PCPs appears to be safe but some caveats remain. The studies outlined generally considered transport times of < 60 minutes and excluded patients who were hemodynamically unstable at the scene.[18,31,32,34,36] Evidence showing the safety of PCP transportation of STEMI patients with transport times > 60 minutes or for patients who are unstable at the scene is presently lacking. Therefore, on the basis of resources,

geography, and other system factors, STEMI regional networks should develop EMS transport protocols that define which patient scenarios mandate a more advanced scope of practice for patient transfer and which reperfusion strategies are appropriate for a given anticipated transfer time. Patients who are too unstable for PCP transport to a PPCI centre should be considered for ACP transportation if available, or taken to the nearest emergency department (ED) for further reassessment regarding the most appropriate reperfusion options taking into consideration the safety of interfacility transfer.

RECOMMENDATION

6. We suggest that PCPs may transport clinically stable STEMI patients from the field to a PPCI centre when an ACP crew is not readily available. If patients under the care of a PCP crew clinically deteriorate en route to a PPCI centre, the ambulance should redirect to the closest ED and/or rendezvous with an ACP crew depending on resource availability in the particular region (Weak Recommendation, Low-Quality Evidence).

7. We suggest that PCPs may transport clinically stable STEMI patients from a non-PCI centre to a PCI centre when an ACP crew is not readily available. For patients who have hemodynamic instability, early CS, respiratory failure, life-threatening arrhythmias, or are comatose post arrest, transport should be facilitated by a critical care crew and/or medical personnel from the sending facility (Weak Recommendation, Low-Quality Evidence).

Values and Preferences. Most paramedics in ground ambulances in Canada are PCPs. Because of the low rates of clinically important events that require ACP training, our recommendation enables regions that have few or no ACPs to transport stable STEMI patients with no anticipated complications for PPCI without compromising patient safety. Additional medical personnel or ACPs might be required for transfer if the patient requires intravenous (I.V.) medications that are beyond the scope of PCP care.

Management of the STEMI Patient Diagnosed in the Prehospital Setting

The recommendations for STEMI management in the prehospital setting are summarized in Figure 2.

Prehospital diagnosis of suspected STEMI with use of prehospital ECGs

Prehospital ECG (PHECG) enables early identification and prehospital management of STEMI patients and influences clinical decision-making and the choice of destination hospital. Advance notification to the receiving hospital shortens the time to reperfusion therapy.[38] A meta-analysis of 8 observational studies (N = 6339 patients) concluded that PHECG with advance hospital notification was associated

Table 2. Definitions

Term	Definition
Time point definitions	
First medical contact	Time of EMS arrival at scene (prehospital) or hospital registration ("walk in")
Time of STEMI diagnosis	Time of performance and interpretation of first electrocardiogram diagnostic of STEMI
First device deployment	Deployment of first PCI device (balloon or direct stent)
DIDO	Time between registration of patient at non—PCI-capable hospital and patient leaving non—PCI-capable hospital via EMS
Interfacility transport time	Time on the road between leaving non—PCI-capable hospital and arrival at PCI-capable hospital
Reperfusion strategy definitions	
PPCI	Mechanical reperfusion techniques aimed at restoring flow to the culprit vessel in acute STEMI. May include balloon angioplasty, coronary stenting, or thrombectomy
Pharmacoinvasive strategy	A reperfusion strategy using adjunctive PCI after initial pharmacological reperfusion with fibrinolysis. Consists of: (1) routine rapid transfer to PCI centres after fibrinolysis; (2) immediate PCI for patients with failed fibrinolysis; and (3) routine angiography with or without PCI within 24 hours after successful fibrinolysis
Facilitated PCI	A reperfusion strategy in which adjuvant therapies such as fibrinolysis or glycoprotein IIb/IIIa inhibitors are administered while in transit to immediate diagnostic angiography with the intent to perform immediate PPCI

Clinical end points are considered as: MI, STEMI, MACE, and NACE.
DIDO, door-in door-out; EMS, emergency medical services; MACE, major adverse cardiovascular events; MI, myocardial infarction; NACE, net adverse clinical events; PCI, percutaneous coronary intervention; PPCI, primary PCI; STEMI, ST-elevation myocardial infarction.

with a significant reduction in short-term mortality among patients treated with PPCI (risk ratio, 0.61; 95% confidence interval [CI], 0.42-0.89; $P = 0.01$).[39] A similarly significant 29% mortality reduction with PHECG was also seen among > 17,000 STEMI patients who were treated with fibrinolysis.[39] The consistent benefit in reduced reperfusion time and reduced mortality confirms the value of utilizing PHECG in a STEMI system of care.[38,40]

PHECG STEMI identification can be accomplished either by paramedic interpretation in the field, ECG transmission for interpretation by another health care provider, or by automated computer algorithm interpretation. Small studies have shown that non-physician interpretation had a moderate to high sensitivity and specificity in STEMI identification compared with physicians.[17,40] Computer-assisted interpretation has modest sensitivity and high specificity for STEMI diagnosis.[22,38] Although ECG transmission for physician confirmation is feasible, implementation of PHECG transmission within a STEMI system of care might incur additional cost,

Table 3. Reperfusion treatment goals

Metric	Goal[*]
FMC to diagnosis (ECG acquisition and interpretation)	≤ 10 minutes
Diagnosis to catheterization lab activation	≤ 10 minutes
Door-in to door-out time for emergency departments	≤ 30 minutes
Transport times for interfacility transfers or STEMI patients diagnosed in the field	≤ 60 minutes
Time from arrival at catheterization lab to first device activation	≤ 30 minutes
Total time from FMC to first device activation (for primary PCI); for non-PCI centres or patients diagnosed in the field	≤ 120 minutes
Total time from FMC to first device activation (for primary PCI); for patients presenting to PCI centres	≤ 90 minutes
Time from FMC to fibrinolysis	≤ 30 minutes
Time from fibrinolysis to coronary angiography	< 24 hours

ECG, electrocardiogram; FMC, first medical contact; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

[*] Regional goal: ≥ 75% of cases to achieve each target metric.

time delays, present technical difficulties, and might not be necessary if appropriately trained personnel are available.[17,41] However, prehospital transmission might reduce the rate of false positive activations.[41]

ECG interpretation for STEMI recognition is a core competency for Canadian ACPs and many PCPs also receive STEMI recognition training. The most appropriate option (paramedic interpretation, transmission, and/or computer interpretation) for prehospital STEMI recognition and advance notification will depend upon the regional resources and expertise. Therefore, decisions related to how best to interpret the PHECG and who provides prearrival STEMI notification should be made at the regional level. Regardless of the method used to identify STEMI in the prehospital setting, networks of care should strive to optimize the diagnostic accuracy of PHECG STEMI recognition through education programs, standardized guidelines, and quality improvement programs.

RECOMMENDATION

8. We recommend that EMS personnel acquire an ECG in the field to identify STEMI and alert STEMI care teams of an imminent patient arrival (Strong Recommendation, Low-Quality Evidence).

Reperfusion therapy for suspected STEMI patients identified in the prehospital setting

When performed rapidly, PPCI is associated with lower rates of mortality compared with fibrinolytic therapy.[42] Although the mortality benefit of PPCI diminishes with PCI-related delays, the maximum FMC-to-device time beyond which PPCI is inferior to fibrinolytic therapy remains uncertain and controversial. Recent American and European guidelines recommend

PPCI over fibrinolytic therapy if the FMC-to-device (or diagnosis to wire-crossing time) is anticipated to be ≤ 120 minutes.[43,44] Data supporting the efficacy and safety of a target FMC-to-device time ≤ 120 minutes among patients with STEMI identified in a prehospital setting is derived from observational studies and secondary analyses of clinical trials. In a propensity-matched analysis of > 18,000 patients from the National Registry of Myocardial Infarction, the mortality advantage of PPCI over fibrinolysis was consistent until the PCI-related delay exceeded 2 hours.[45] A pooled analysis of randomized clinical trials (RCTs) showed that patients with delays in the > 79- to 120-minute range achieved a similar benefit of PPCI compared with patients with delays in the 35- to 79-minute range.[46] In an evaluation of interfacility transfer for PPCI vs on-site lysis, 96% of patients in the **Dan**ish Trial in **A**cute **M**yocardial **I**nfarction-2 (DANAMI-2) trial achieved a FMC-to-device time of < 120 minutes (median, 114 minutes), which was associated with improved outcomes, including a mortality benefit among those at greatest risk.[4,47] It should be noted that these studies are older, did not include routine early PCI after fibrinolysis (see *Pharmacoinvasive PCI* section and definition in Table 2), and that these findings are on the basis of post hoc analyses. In the **St**rategic **R**eperfusion **E**arly **A**fter **M**yocardial Infarction (STREAM) trial, patients randomized to the PPCI group achieved a median FMC-to-device time of 117 minutes, with no difference in major adverse cardiac events (MACE) compared with the pharmacoinvasive group that included prehospital fibrinolysis.[48] These findings suggest that PPCI with an FMC-to-device time within 120 minutes for patients directly diagnosed in the field is as beneficial as early or prehospital fibrinolysis followed by a pharmacoinvasive strategy. Although these studies support a maximum FMC-to-device time of 120 minutes for choosing PPCI over fibrinolytic therapy, there are compelling data that mortality rates can be reduced with shorter treatment times. In one study, every 10-minute treatment delay led to an additional 3.3 deaths among 100 PPCI-treated patients for FMC-to-balloon times ranging from 60 to 180 minutes; treatment delay-related mortality was even higher among patients with CS.[49] Therefore whenever possible, particularly in urban settings, the goal should be to achieve a FMC-to-device time ≤ 90 minutes. Shorter maximum transport times should be considered when only PCPs are available.

RECOMMENDATION

9. If primary PCI is used as a default reperfusion strategy for suspected STEMI patients in the field, we recommend that patients should bypass non−PCI-capable centres and instead be transported to the nearest PPCI centre with the goal of achieving a maximum FMC-to-device time of ≤ 120 minutes (ideal FMC-to-device time ≤ 90 minutes in urban settings). Fibrinolytic therapy should be considered if this timeline cannot be achieved (Strong Recommendation, Low-Quality Evidence).

Values and Preferences. The goal of ≤ 120 minutes was selected to maintain consistency with treatment of STEMI identified at non−PCI-capable centres, and to maximize access to PPCI in rural and remote regions.

Practical tip. Despite the goal of $\leq$ 120 minutes, PPCI should be performed as rapidly as possible, ideally $\leq$ 90 minutes in urban settings.

PCI centre ED bypass for primary PCI

Studies have shown that prolonged ED times contribute to a substantial proportion of overall delays among patients with prehospital STEMI identification and activation.[30] Protocols to bypass the PCI centre ED and bring patients with suspected STEMI directly to the catheterization laboratory have been associated with improved outcomes.[50-53] The use of ED bypass protocols in STEMI centres that implemented regionalized STEMI care resulted in significantly shorter reperfusion times compared with hospitals that did not.[28] These results support bypassing the ED in PCI-capable hospitals, where feasible, to reduce potential reperfusion delays.

RECOMMENDATION

10. We suggest it is reasonable to routinely transport STEMI patients identified in the prehospital setting by EMS directly to the catheterization laboratory by bypassing the PCI centre ED (Weak Recommendation, Very Low-Quality Evidence).

Values and Preferences. This recommendation is on the basis of the importance of minimizing reperfusion delays, but this strategy might not be feasible at all centres.

Practical tip. This recommendation should only be considered in centres where a receiving team is available to safely attend to the patient upon arrival to the catheterization centre, regardless of time of day. Contingency plans should be in place to respond to emergencies that might occur before initiation of PPCI, and for patients who become unstable before arrival at the hospital or shortly after arrival. Such plans include transferring the patient to the cardiac intensive care unit or ED.

Practical tip. Protocols should be developed to manage suspected STEMI patients who are subsequently shown to have an alternate diagnosis.

Adjunctive interventions administered in the prehospital setting

Prehospital use of oxygen. Limited evidence from the pre-reperfusion era suggested potential harm with the routine use of oxygen supplementation when oxygen saturation (SaO2) monitoring was not routinely used.[54] Subsequent studies in the reperfusion era (2 of which included only STEMI patients) have shown no reduction in mortality, recurrent myocardial infarction (MI), or MACE with oxygen supplementation in normoxic acute MI patients, with normoxia being defined as an SaO2 > 90%-94% depending on individual trials.[55-61] Small trials have shown inconsistent signals with respect to the effect of supplemental oxygen on infarct size, although different definitions of infarct size make interstudy comparisons difficult. A recent randomized study showed that supplemental oxygen use among normoxic STEMI patients was associated with higher CK-MB levels as well as an increase in infarct size at 6 months assessed using cardiac magnetic resonance imaging.[57]

RECOMMENDATION

11. We suggest avoiding routine prehospital administration of supplemental oxygen to STEMI patients with SaO2 $\geq$ 90% (Weak Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation is on the basis of the concern of potential harm from hyperoxemia. Furthermore, supplemental oxygen might cause anxiety or impair communication and does not appear to have any benefit in the absence of hypoxia.

Practical tip. If SaO2 monitoring is not available or not reliable (poor waveform), prehospital providers may provide oxygen supplementation during initial care to patients who exhibit signs of respiratory distress.

Prehospital use of opioids. Despite the longstanding use of opioids to alleviate discomfort and anxiety among STEMI patients, no RCTs of opioids have comprehensively examined hard clinical end points.[62] Opioids inhibit gastric emptying and increase rates of nausea and vomiting thereby potentially delaying or impairing absorption of orally administered antiplatelet drugs.[63-65] In addition, it has been suggested that there is an important drug-drug interaction between opioids and oral P2Y12 inhibitors that might lead to reduced absorption of P2Y12 inhibitors, which might theoretically increase the risk of additional thrombotic coronary events.[66,67] Kubica et al. randomized 70 STEMI patients to receive I.V. morphine (or placebo) to evaluate its effect on the pharmacokinetic and pharmacodynamic profile of a loading dose of ticagrelor.[63] Morphine-treated patients had significantly less total exposure to ticagrelor and its active metabolite and had a 2-hour delay in maximum plasma concentration of ticagrelor, leading to higher platelet reactivity in the morphine group during the first 12 hours.[63] Similarly, a small randomized study showed impairment of active metabolites and increased platelet reactivity among clopidogrel-treated patients who received morphine.[67] Several observational studies have subsequently confirmed this putative association between opioid administration and delayed onset of action of P2Y12 inhibitors.[64,65,68]

Bellandi et al. reported worse baseline **T**hrombolysis **I**n **M**yocardial **I**nfarction (TIMI) flow, lower ST-segment resolution rates, and higher peak cardiac enzyme elevations among STEMI patients who were treated with PPCI and also received morphine.[65] Patients in the **A**dministration of **T**icagrelor in the Cath **L**ab or in the **A**mbulance for **N**ew ST Eleva**t**ion Myocardial **I**nfarction to Open the **C**oronary Artery (ATLANTIC) trial who were randomized to prehospital ticagrelor and who did not receive concomitant morphine showed more frequent pre-PPCI ST-segment resolution compared with those who received morphine.[69] However, there was no association between morphine use and IRA patency at the time of angiography. There are no studies suggesting that one particular opiate is safer than another.[70]

There are conflicting signals for mortality associated with opioid use in the setting of acute MI. Although not a STEMI cohort, the **Can R**apid Risk Stratification of **U**nstable Angina Patients **S**uppress **Ad**verse Outcomes With **Ea**rly Implementation of the ACC/AHA Guidelines (CRUSADE) registry of 57,039 non-STEMI patients nevertheless showed a higher adjusted risk of death among clopidogrel-treated patients who were given morphine compared with those without morphine treatment.[71] In contrast, observational data suggest that use of morphine was not associated with increased mortality or MACE and had a variable effect on infarct size.[63,65,72-75]

RECOMMENDATION

12. We suggest avoidance of routine I.V. opioid analgesic (eg, morphine or fentanyl) administration for STEMI-related discomfort. However, selective use of opioid analgesic medications may be considered for severe pain with the goal of relieving pain and reducing anxiety (Weak Recommendation, Low-Quality Evidence).

   Values and preferences. The writing group recognizes the importance of managing the significant discomfort that can be associated with STEMI. Although there might be a potential for harm, measured according to surrogate outcomes, this recommendation permits for selective use of opioid analgesics by providers in patients experiencing severe STEMI-related pain.

Prehospital use of P2Y12 inhibitors. Dual antiplatelet therapy for acute STEMI is recommended with acetylsalicylic acid and a P2Y12 receptor antagonist.[43,44,76,77] However, it is unclear whether the prehospital administration of these medications confers additional benefits compared with in-hospital administration. Several trials have failed to show a benefit in mortality, MACE, or TIMI flow grade 3 in the IRA with the prehospital administration of P2Y12 receptor antagonists compared with the in-hospital setting,[78-81] although the ATLANTIC trial did show a reduction in stent thrombosis with the prehospital administration of ticagrelor.[79] Other studies have shown a potential reduction in ischemic complications and improvement in preprocedural TIMI flow with prehospital P2Y12 administration when the transfer time for PPCI was > 60 minutes.[82,83] Because of the relatively short time difference (30-60 minutes) between the prehospital and in-hospital administration of P2Y12 inhibitors in published studies,[79,81] the potential effect of prehospital dual antiplatelet therapy administration might not have been properly evaluated in patients who required more prolonged prehospital transport times and its use potentially could be of benefit for such patients.

RECOMMENDATION

13. We suggest that prehospital (in-ambulance) P2Y12 receptor antagonist medications not routinely be used in addition to acetylsalicylic acid in patients with STEMI transported for PPCI. The P2Y12 receptor antagonist should be administered in the ED or cardiac catheterization laboratory as early as possible before coronary angiography (Weak Recommendation, Low-Quality Evidence).

   Values and preferences. Administration of any medication to a critically ill patient might add complexity in the prehospital environment. On the basis of the currently available evidence, the writing group concluded that routine prehospital administration of a P2Y12 receptor antagonist could not be recommended for transport times < 60 minutes.

   Practical tip. Prehospital administration of P2Y12 receptor antagonist medications may be considered in systems or subsets of patients that have prolonged transport times (those > 60 minutes) for PPCI. Similarly, administration may be considered for systems that administer prehospital fibrinolysis.

Management of the STEMI Patient Diagnosed in a Non−PCI-Capable Centre

Reperfusion strategies for suspected STEMI patients managed in a non−PCI-capable hospital

Primary PCI. Although a population-based analysis has shown that almost 80% of Canadians reside within 120 minutes of a PCI-capable facility,[84] STEMI patients often present to a non−PCI-capable facility.[85] Patients who then undergo interhospital transfer for PPCI often have treatment times that exceed acceptable reperfusion goals.[86-89] This might be partially because of local geography, weather constraints, delays in diagnosis, and prolonged time spent in the non-PCI centre ED or the ED at the PPCI hospital.[14] Although multiple studies have shown improved outcomes with PPCI vs fibrinolysis, the mortality benefit of this strategy might be lost if PPCI is performed > 120 minutes from FMC.[3,19,45,47,90-97] To achieve the ≤ 120-minute target for PPCI transfers, observational studies have shown that referral hospital door-in-door-out times should routinely be ≤ 30 minutes, with interhospital transport times ≤ 60 minutes.[98,99] Finally, in addition to striving for individual FMC-to-device times of 120 minutes, a regional system goal of ≤ 120 minutes from referring hospital door to receiving hospital device time for at least 75% of patients appears to be a reasonable treatment target.[30]
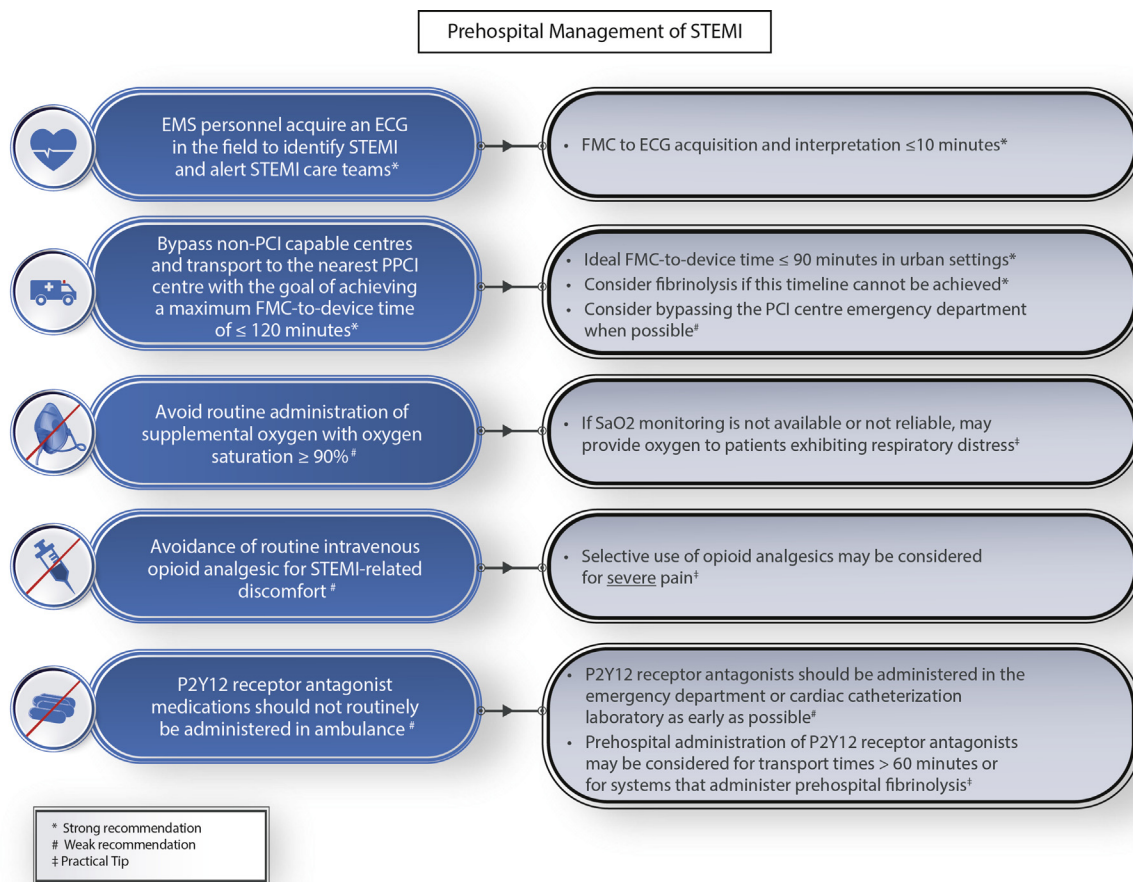
Prehospital Management of STEMI

EMS personnel acquire an ECG in the field to identify STEMI and alert STEMI care teams*

- FMC to ECG acquisition and interpretation ≤10 minutes*

Bypass non-PCI capable centres and transport to the nearest PPCI centre with the goal of achieving a maximum FMC-to-device time of ≤ 120 minutes*

- Ideal FMC-to-device time ≤ 90 minutes in urban settings*
- Consider fibrinolysis if this timeline cannot be achieved*
- Consider bypassing the PCI centre emergency department when possible#

Avoid routine administration of supplemental oxygen with oxygen saturation ≥ 90%#

- If SaO2 monitoring is not available or not reliable, may provide oxygen to patients exhibiting respiratory distress‡

Avoidance of routine intravenous opioid analgesic for STEMI-related discomfort #

- Selective use of opioid analgesics may be considered for severe pain‡

P2Y12 receptor antagonist medications should not routinely be administered in ambulance #

- P2Y12 receptor antagonists should be administered in the emergency department or cardiac catheterization laboratory as early as possible#
- Prehospital administration of P2Y12 receptor antagonists may be considered for transport times > 60 minutes or for systems that administer prehospital fibrinolysis‡

* Strong recommendation
# Weak recommendation
‡ Practical Tip

Figure 2. Prehospital management of ST-elevation myocardial infarction (STEMI). EMS, emergency medical services; ECG, electrocardiogram; FMC, first medical contact; PCI, percutaneous coronary intervention; PPCI, primary PCI; SaO2, oxygen saturation.

RECOMMENDATION

14. For patients with STEMI identified at a non–PCI-capable centre, if primary PCI is used as the default reperfusion strategy, we recommend that STEMI networks target a total FMC-to-device time (including interfacility transfer) of ≤ 120 minutes. Fibrinolytic therapy should be considered if this timeline cannot be achieved (Strong Recommendation, Low-Quality Evidence).

15. If primary PCI is used as a default reperfusion strategy, we recommend a target door-in-door-out time at the transferring hospital of ≤ 30 minutes (Strong Recommendation, Low-Quality Evidence).

Fibrinolysis. Fibrinolytic agents that have been used as reperfusion therapy for STEMI include streptokinase, tenecteplase, reteplase, and alteplase. A recent network meta-analysis showed lower mortality rates with fibrin-specific agents (tenecteplase, reteplase, and accelerated infusion alteplase).[100] Fibrinolysis given within 12 hours of symptom onset significantly reduces mortality for STEMI. However, it has been estimated that 1.6 lives per 1000 patients treated are lost for every 1 hour of delay in administering fibrinolytic

therapy.[101] On the basis of this time-dependent mortality benefit, previous guidelines have recommended a goal of FMC to needle time of ≤ 30 minutes.[6] This goal is achievable for most STEMI patients in Canadian centres.[102,103] Although European guidelines recommend fibrinolytic therapy within 10 minutes, this is on the basis of 10 minutes from STEMI diagnosis, not from FMC.[43] Strategies to minimize treatment delays in sites that use fibrinolysis as their default initial reperfusion strategy include prehospital diagnosis and advance notification, use of triage algorithms to expedite ECG acquisition and interpretation, and prehospital fibrinolysis if feasible.

Fibrinolytic therapy might be particularly suitable for STEMI patients who present early in the course of their infarct, with the greatest benefit seen within the first 2-3 hours after symptom onset.[48,104,105] Administration of fibrinolysis provides an opportunity to deliver reperfusion therapy early in the course of an evolving infarct.[106] Indeed, fibrinolysis administered within the first hour of symptom onset successfully aborted the MI in approximately 30% of STEMI patients.[107] The feasibility of paramedic-based administration of prehospital fibrinolysis was established within the **As**sessment of the **S**afety and **E**fficacy of a **N**ew **T**hrombolytic Agent (ASSENT) 3+ trial.[108] Prehospital fibrinolysis administered within 2 hours of chest pain in the **C**omparison of **A**ngioplasty and **P**rehospital **T**hrombolysis in Acute **M**yocardial

Infarction (CAPTIM) trial was associated with a strong trend toward reduced 30-day mortality compared with PPCI; this signal was reversed when the ischemic time exceeded 2 hours.[109] The STREAM trial enrolled STEMI patients who were within 3 hours of the onset of chest pain and who also had an anticipated PCI delay of > 60 minutes.[48] Patients were randomized to receive either PPCI or fibrinolysis with a pharmacoinvasive strategy (see *Pharmacoinvasive PCI* section and Table 2). The composite end point of death, shock, heart failure, or reinfarction at 30 days was similar between the 2 groups.[48] Although an interim analysis did show an increase in intracranial hemorrhage among elderly patients randomized to pharmacoinvasive strategy, this difference was negated after a protocol change implementing a half dose of tenecteplase among patients older than 75 years of age.[110]

RECOMMENDATION

16. If fibrinolysis is used as a default reperfusion strategy, we recommend that STEMI networks target a total FMC-to-needle time of ≤ 30 minutes (Strong Recommendation, Low-Quality Evidence).
17. We suggest that a pharmacoinvasive strategy could be considered as an alternative to primary PCI for patients who are early presenters (symptom onset < 3 hours), who are at low risk of bleeding, and who cannot undergo rapid primary PCI (Weak recommendation, Moderate-Quality Evidence).

Practical tip. For patients with a contraindication to fibrinolysis, transfer for PPCI should be initiated even if the FMC-to-device time is expected to be > 120 minutes.

Practical tip. Prehospital fibrinolysis may be applied within STEMI systems of care with appropriate EMS training and physician oversight in appropriate patients.

Practical tip. A half dose of fibrinolytic therapy may be considered for patients undergoing a pharmacoinvasive strategy who are older than 75 years of age.

Fibrinolysis for CS. There are limited data regarding the efficacy and safety of fibrinolysis in STEMI patients complicated by CS because very few of the randomized trials included patients with CS.[111] The 1994 Fibrinolytic Therapy Trialists' Collaborative Group meta-analysis included 9 randomized trials that enrolled at least 1000 patients with acute MI treated with streptokinase, anistreplase, urokinase, or tissue plasminogen activator (tPA).[101,112] In the subgroup of 2466 patients with hypotension, defined as a systolic blood pressure < 100 mm Hg, fibrinolytic therapy was associated with a significantly lower risk of 35-day mortality (28.9%) compared with placebo or open-label control (35.1%). Importantly, the interpretation of this result should be tempered by the recognition that hypotension is not synonymous with CS, and mortality rates in the era of medical therapy only for CS exceeded 50%.[113,114] In addition, the applicability of these studies is limited by a lack of contemporary adjunctive antiplatelet and antithrombotic therapy, and/or routine immediate PCI after fibrinolysis.[112]

Patients who received fibrinolysis in the **Sh**ould We Emergently Revascularize **O**ccluded **C**oronaries for Cardiogenic Sho**ck** (SHOCK) registry had lower rates of TIMI 0/1 flow (60% vs 91%; $P = 0.051$) at angiography. In addition, those treated with fibrinolysis and an intra-aortic balloon pump had lower mortality rates compared with fibrinolysis alone,[115,116] thus suggesting that coronary perfusion pressure might be an important determinant of fibrinolytic efficacy. However, important methodological issues such as limited multivariable adjustment and the lack of randomization raise the potential for bias in this analysis.[117]

RECOMMENDATION

18. 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 (Weak Recommendation, Very Low-Quality Evidence).

   Values and preferences. 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.

Practical tip. The decision to administer fibrinolysis should be individualized on the basis of the perceived likelihood of reperfusion as a function of symptom duration, risk of bleeding, and estimated time to angiography.

Practical tip. Adequate coronary perfusion pressure might be necessary for effective fibrinolysis. It is reasonable to aim to keep mean arterial pressure > 60-65 mm Hg with vasopressors after fibrinolysis.

Pharmacoinvasive PCI. Fibrinolytic therapy remains the reperfusion therapy of choice for patients with STEMI who cannot undergo PPCI within 120 minutes of FMC and who have no contraindications to fibrinolysis. The pharmacoinvasive strategy involves 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. No randomized data have defined the optimal criteria and timing for the identification of failed fibrinolysis. Clinical trials have defined failed fibrinolysis as a failure to achieve > 50% ST-segment resolution in the ECG lead with maximal ST elevation, and/or persistent chest pain or hemodynamic or electrical instability 60-90 minutes after the initiation of fibrinolysis.[48,118-120]

The pharmacoinvasive strategy was evaluated in 3195 patients enrolled in 8 RCTs.[121-129] Compared with usual care, this strategy was associated with reductions in the composite end points of 30-day all-cause mortality, reinfarction, or recurrent ischemia in most of these RCTs, although none of these trials was sufficiently powered to detect a significant

reduction in mortality. D'Souza et al. and Borgia et al. completed 2 meta-analyses that evaluated individual end points.[130,131] Overall, early PCI after fibrinolysis was associated with a marked reduction in 30-day reinfarction (odds ratio [OR], 0.62; 95% CI, 0.42-0.90; $P = 0.01$).[130] However, there was no significant reduction in 30-day mortality (OR, 0.87; 95% CI, 0.59-1.30; $P = 0.51$) and no increase in stroke (OR, 0.63; 95% CI, 0.31-1.26; $P = 0.21$) or major bleeding (OR, 0.93; 95% CI, 0.67-1.34; $P = 0.70$).[130] The pharmacoinvasive strategy was associated with a significant reduction in heart failure in some studies[124] but not in others.[48,127] Myocardial salvage was also inconsistently observed with the **S**outhwest German **I**ntervention Study in **A**cute **M**yocardial Infarction (SIAM) III investigators, who reported higher left ventricular ejection fraction (LVEF)[128] whereas no effect was observed on LVEF, peak troponin, or natriuretic peptide in the **Nor**wegian Study on **Di**strict Treatment of **ST-E**levation **M**yocardial **I**nfarction (NORDISTEMI)[123] and **C**ombined **A**ngioplasty and **P**harmacological **I**ntervention vs **T**hrombolysis **Al**one in **A**cute **M**yocardial **I**nfarction CAPITAL-AMI[127] trials. Combining data from these trials, no difference was observed in long-term mortality (OR, 0.74; 95% CI, 0.45-1.22; $P = 0.23$) or reinfarction (OR, 0.73; 95% CI, 0.46-1.16; $P = 0.18$).[132] Several observational studies and 1 RCT have also suggested that clinical outcomes are similar with a pharmacoinvasive strategy compared with PPCI.[133-135] Although the pharmacoinvasive trials show improved outcomes when PCI was performed within 24 hours of fibrinolysis, the optimal timing of PCI within the first 24 hours remains uncertain. In some pharmacoinvasive studies, PCI was delayed at least 6 hours after successful fibrinolysis,[48] whereas in other studies PCI was routinely performed 2-3 hours after fibrinolysis.[124,136] However, recent data suggest that even very early angiography with or without PCI performed < 2 hours after successful fibrinolysis appears to be safe.[136] Conversely, favourable outcomes were still seen among patients in the STREAM trial who underwent scheduled PCI approximately 18 hours after successful fibrinolysis compared with patients randomized to PPCI.[137]

RECOMMENDATION

19. 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 (Strong Recommendation, Moderate-Quality Evidence).

    Values and preferences. This recommendation is on the basis of the established benefits such as 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.

Facilitated PCI. Facilitated PCI is a reperfusion strategy in which adjuvant therapies such as fibrinolytic agents or glycoprotein (GP) IIb/IIIa inhibitors are administered while in transit for immediate diagnostic angiography with the intent to perform PPCI. Regimens that have been tested include full-dose I.V. fibrinolytic agents, combination of I.V. fibrinolytics and I.V. GP IIb/IIIa inhibitors (GPIs), and I.V. GPIs alone. In a meta-analysis of 17 studies of facilitated PCI vs PPCI performed by Keeley et al., the facilitated PCI approach was associated with increased rates of death, nonfatal reinfarction, urgent target vessel revascularization, major bleeding, total stroke, and hemorrhagic stroke even though initial TIMI grade 3 flow at the time of angiography was higher.[138] However, most of these studies were small and performed in an era before routine use of coronary stents and upfront oral antiplatelet agents including clopidogrel, ticagrelor, and prasugrel. The 2 largest trials most reflective of contemporary STEMI practice are ASSENT 4 PCI and **F**acilitated **In**tervention With **E**nhanced Reperfusion **S**peed to **S**top **E**vents (FINESSE).[139,140] ASSENT 4 PCI compared pharmacologic facilitation with full-dose tenecteplase vs PPCI, whereas FINESSE was a 3-arm trial that compared half-dose reteplase with abciximab, abciximab alone, and placebo. ASSENT 4 PCI was terminated prematurely because of excess in-hospital mortality (6% vs 3%; $P = 0.0105$) in the facilitated arm. The primary outcome of death, congestive heart failure, or shock at 90 days (19% vs 13%; OR, 1.39; 95% CI, 1.11-1.74; $P = 0.0045$), and in-hospital stroke (1.8% vs 0%; $P < 0.001$) were significantly higher with full-dose tenecteplase.[139] FINESSE was terminated early because of protracted recruitment, with no difference in the 90-day primary composite end point among the 3 arms (9.8% vs 10.5% vs 10.7%; hazard ratio for the combination arm vs primary arm = 0.91 (95% CI, 0.67-1.23; $P = 0.55$), but increased nonintracranial TIMI major and minor bleeding (14.5% vs 10.1% vs 6.1%; $P < 0.0001$) in both facilitated PCI arms.[140]

RECOMMENDATION

20. 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 FMC (Strong Recommendation, High-Quality Evidence).

It is important to acknowledge the differences between the reperfusion strategies of facilitated PCI (not recommended [strong recommendation, high-quality evidence]) and pharmacoinvasive reperfusion (recommended [strong recommendation, moderate-quality evidence]). With facilitated PCI all patients receive a facilitating agent en route to immediate PCI, which failed to improve patient outcomes compared with immediate PCI alone. With the pharmacoinvasive strategy fibrinolysis is administered followed by immediate PCI for those who fail to reperfuse or have scheduled PCI within the first 24 hours for those with successful fibrinolysis. The pharmacoinvasive strategy was associated with improved outcomes compared with fibrinolysis with standard of care[124] and similar outcomes compared with PPCI among patients who presented early.[48]
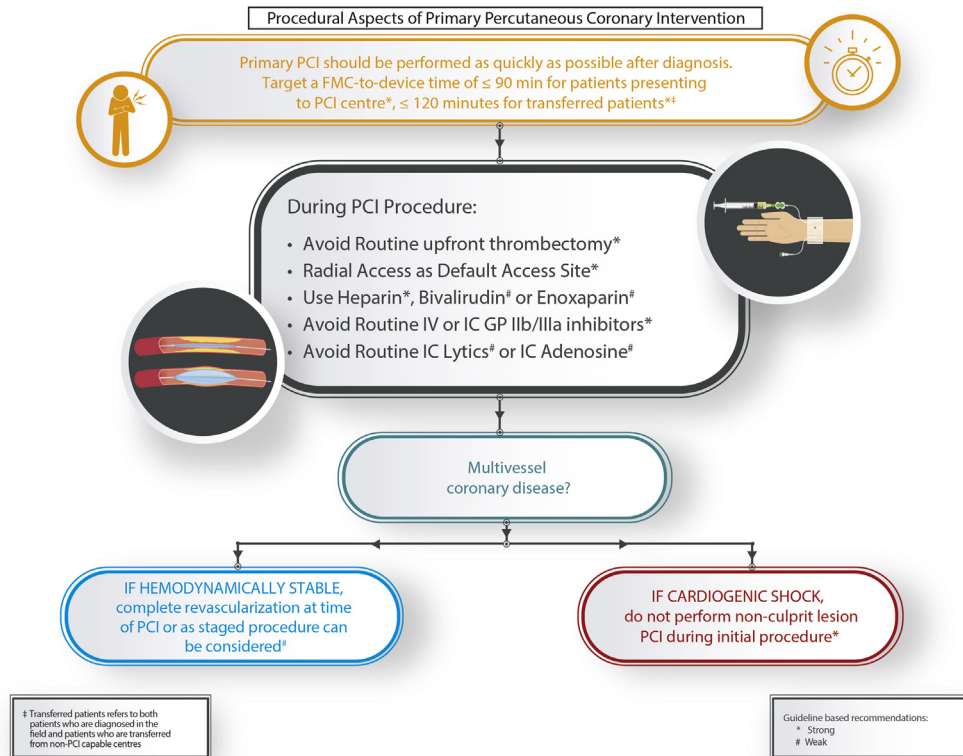
Figure 3. Procedural aspects of primary percutaneous coronary intervention (PPCI). FMC, first medical contact; GP IIb/IIIa, glycoprotein IIb/IIIa; I.C., intracoronary; I.V., intravenous; PCI, percutaneous coronary intervention.

Management of the STEMI Patient at a PCI-Capable Centre

The recommendations regarding the procedural aspects of PPCI are summarized in Figure 3.

Performance of primary PCI

Many large, retrospective observational studies have shown improved, risk-adjusted outcomes among patients who present directly to a PCI-centre with the shortest reperfusion times, including door-to-balloon times of $\leq$ 90 minutes compared with patients with longer delays.[20,141,142] Although some studies have shown a neutral mortality benefit of reduced reperfusion times at the population level,[143,144] it has more recently been shown among patients who received PPCI that shorter patient-specific reperfusion is consistently associated with lower mortality rates.[142]

Contemporary cohort studies have shown that prospectively targeting an FMC-to-device time of $\leq$ 90 minutes is feasible and is associated with improved outcomes. Implementation of STEMI regionalization in the American Heart Association Accelerator 1 and 2 programs resulted in an increase in the proportion of patients with an FMC $\leq$ 90 minutes from 67% to 74%, with an associated 50% reduction in in-hospital mortality.[29,30] Multiple regional STEMI programs in Canada have also been able to achieve this metric for most STEMI patients who present to PCI centres.[14,23,24,145]

RECOMMENDATION

21. For patients with STEMI identified at a primary PCI centre, we recommend that STEMI networks target a FMC-to-device time of $\leq$ 90 minutes (Strong Recommendation, Low-Quality Evidence).

Practical tip. Fibrinolytic therapy should be considered as a viable reperfusion strategy at a PPCI centre if it is anticipated that PCI will be significantly delayed because of extenuating circumstances (eg, multiple STEMI patients arriving concurrently).

Multivessel vs culprit-only PCI in STEMI patients with and without CS

Approximately one-third to one-half of patients who present with STEMI have multivessel disease, defined as a significant stenosis in at least 1 nonculprit vessel (NCV).[146] Whether patients should receive routine revascularization of angiographic or hemodynamically significant nonculprit lesions, or culprit lesion-only revascularization in addition to optimal medical therapy remains a common dilemma.[147] Furthermore, the optimal timing of intervention remains uncertain if revascularization of the NCV(s) is considered.

A total of 9 randomized trials have compared routine nonculprit lesion PCI with optimal medical therapy alone in

Table 4. Selected ongoing clinical trials on reperfusion of STEMI patients

Trial	NCT number	Population	Comparator/control	Primary end point
Radial vs femoral PCI				
SAFARI-STEMI	NCT01398254	STEMI patients undergoing PPCI	Transradial vs transfemoral access for PPCI	30-day all-cause mortality
Multivessel vs culprit only PCI				
COMPLETE	NCT01740479	STEMI patients with multivessel disease undergoing PPCI	Staged PCI of nonculprit lesion and OMT vs OMT alone	3-year CV death or MI and CV death/MI/ischemia-driven revascularization*
ASSIST MI	NCT03263468	STEMI patients with multivessel disease undergoing PPCI	Complete revascularization during index PPCI vs staged complete revascularization > 48 hours from index PPCI	90-day all-cause mortality, MI, heart failure, and unplanned revascularization
FULL REVASC	NCT02862119	STEMI/high-risk NSTEMI patients with multivessel disease undergoing PCI	Fractional flow reserve guided PCI of nonculprit lesions during index admission vs conservative management	1-year all-cause mortality and MI
Intracoronary fibrinolysis				
STRIVE	NCT03335839	STEMI patients undergoing PPCI with angiographically large thrombus burden (TIMI thrombus grade ≥ 3)	Low-dose intracoronary recombinant tissue plasminogen activator (10- or 20-mg) vs placebo	180-day CV death, reinfarction, or new-onset heart failure
Pharmacoinvasive strategy vs primary PCI				
STREAM 2	NCT02777580	STEMI patients older than 70 years who are within 3 hours of symptom onset	Half-dose tenecteplase followed by pharmacoinvasive PCI vs PPCI	30-day > 50% ST resolution pre-/post-PCI, TIMI flow grade, reinfarction, aborted MI, stroke, and MACE

ASSIST MI, Revascularization Strategies for ST Elevation Myocardial Infarction Trial; COMPLETE, Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI; CV, cardiovascular; FULL REVASC, FFR-Guidance for Complete Non-Culprit Revascularization; MACE, major adverse cardiovascular events; MI, myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; PPCI, primary percutaneous coronary intervention; SAFARI-STEMI, Safety and Efficacy of Femoral Access vs Radial for Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction; STEMI, ST-elevation myocardial infarction; STREAM, Strategic Reperfusion Early After Myocardial Infarction; STRIVE, Adjunctive, Low-dose Intracoronary Recombinant Tissue Plasminogen Activator (tPA) Versus Placebo for Primary PCI in Patients With ST-segment Elevation Myocardial Infarction; TIMI, Thrombolysis In Myocardial Infarction.

* Co-primary endpoint.

patients with multivessel disease who underwent PPCI for STEMI, none of which were powered for the hard end points of death or MI.[148-156] The 4 largest trials showed a lower rate of future revascularization with a strategy of initial nonculprit PCI, regardless of whether revascularization was performed during the same procedure as the index STEMI, as a staged procedure, or whether fractional flow reserve was used to identify target lesions for PCI.[149,150,155-157] Consistent with the results of the randomized studies, several meta-analyses have also noted safety, and some have suggested clinical benefit with PCI of the NCV to achieve complete revascularization compared with culprit-only PCI with medical treatment of the NCV.[158-160] Importantly, pooled analyses suggest that PCI of the NCV was not associated with increases in all-cause mortality, bleeding, contrast-induced nephropathy, or stroke, as was suggested by earlier observational data.[161,162]

A pooled analysis of 7 trials showed a nominally significant benefit of routine nonculprit lesion PCI compared with culprit-only PCI for the combined end point of death or MI (OR, 0.71; 95% CI, 0.52-0.96). The benefit of complete revascularization was observed among patients with nonculprit revascularization performed during the index PPCI procedure, but not as a staged procedure. However, this indirect comparison has significant limitations and there remains a marked paucity in randomized data directly comparing the timing of complete revascularization.[159] Ongoing studies will provide additional data with greater statistical power to further inform the role of nonculprit revascularization and its timing in the management of these patients (Table 4).

RECOMMENDATION

22. In hemodynamically stable patients with STEMI and multivessel disease, we suggest that complete revascularization can be considered (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. This recommendation places a greater emphasis on safety than efficacy because currently only small studies with composite end points have been published.

Practical tip. Until further randomized evidence is available, the decision whether to treat or not to treat obstructive nonculprit lesions and the optimal timing of such a procedure should be thoughtfully considered and individualized. In hemodynamically stable patients, several factors should be considered in decision-making including success of the culprit vessel PCI, patient comorbidities (eg, renal dysfunction), left ventricular function, nonculprit lesion severity, and complexity as well as the logistics of care delivery.

Practical tip. PCI of nonculprit lesions that are chronic total occlusions is not recommended during the initial PPCI procedure.

Practical tip. Staged multivessel revascularization can be accomplished with either percutaneous or surgical revascularization depending on anatomical and clinical characteristics. Until further randomized evidence is available, either invasive fractional flow reserve-guided revascularization or noninvasive

testing may be used to determine the appropriateness of NCV revascularization.

STEMI with multivessel disease and CS

In patients with STEMI with multivessel disease and CS, the Culprit Lesion Only PCI Versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial randomized 706 patients to either PCI of the culprit lesion only, with the option of staged revascularization of nonculprit lesions, or immediate multivessel PCI.[163] At 30 days, the end points of death or renal replacement therapy (45.9% vs 55.4%; relative risk [RR], 0.83; $P = 0.01$) and death alone (RR, 0.84; $P = 0.03$) were lower in the culprit lesion-only group.[163] These benefits were maintained at 1 year, although a culprit-only PCI strategy was associated with increased rates of repeat revascularization (RR, 3.44; 95% CI, 2.39-4.95) and rehospitalization for heart failure (RR, 4.46; 95% CI, 1.53-13.04) at 1 year.[164] A large-scale observational study from the British Columbia Cardiac Registry showed that culprit lesion-only PCI vs multivessel PCI was associated with a lower mortality rate at 30 days (23.7% vs 34.5%; $P = 0.004$) and at 1 year (32.6% vs 44.3%; $P = 0.003$).[165] Taken together, the CULPRIT SHOCK trial and the British Columbia Cardiac Registry data suggest that culprit lesion-only PCI is superior to multivessel PCI in STEMI patients with multivessel disease and CS.

RECOMMENDATION

23. In STEMI patients with CS and multivessel disease, we recommend against nonculprit lesion PCI during the initial primary PCI procedure (Strong Recommendation, Moderate-Quality Evidence).

Thrombectomy

Initial studies of routine thrombectomy among STEMI patients who undergo PPCI showed improvements in epicardial coronary flow measured according to TIMI flow grade in addition to a reduction of distal embolization and improvements in myocardial tissue perfusion assessed using myocardial blush grade and ST-segment elevation resolution.[166-171] Despite these benefits, recent large RCTs have not shown any reduction in mortality[172-176] nor infarct size[168] with routine thrombectomy when used in conjunction with PPCI.[169,175,177,178] However, it is important to note that bailout thrombectomy was allowed in the PCI-alone group in the randomized Trial of Routine Aspiration **Th**rombectomy With PCI vs PCI **Al**one in Patients With STEMI Undergoing Primary PCI (TOTAL) trial for large thrombus burden and TIMI 0/1 flow after balloon dilatation or large thrombus irrespective of TIMI flow after stenting.[173] In the TOTAL trial, an increase in risk of stroke was observed with upfront thrombectomy used in conjunction with PPCI.[173,179] However, this signal was not seen in the **Th**rombus **A**spiration in **ST**-**E**levation Myocardial Infarction in Scandinavia (TASTE) trial[172] and the **Th**rombus **A**spiration During **P**ercutaneous Coronary Intervention in **A**cute Myocardial Infarction **S**tudy (TAPAS) trial did not collect stroke data.[171] A recent individual patient meta-analysis of RCTs showed no difference in stroke overall but a significant increase in stroke with thrombectomy

was seen among patients with a high thrombus burden.[180] Randomized trials to date have failed to identify high-risk subgroups who might benefit from thrombectomy.[181]

RECOMMENDATION

24. We recommend that upfront thrombectomy not be performed routinely in patients with STEMI who undergo primary PCI (Strong Recommendation, High-Quality Evidence).

Values and preferences. This recommendation is on the basis of the absence of any clear benefit in clinical end points in the 2 largest randomized trials, and the possibility of increased stroke with thrombectomy observed in the largest trial.

Practical tip. Bailout thrombectomy might still be useful when there is a high residual thrombus burden after balloon angioplasty and/or stenting.

Radial vs femoral access

Several randomized trials have shown a consistent reduction in access site bleeding along with a signal toward reduced mortality using transradial access (TRA) compared with transfemoral access (TFA) in the setting of PPCI.[182-186] The **ST** **E**levation **M**yocardial **I**nfarction Treated by **Radi**al or Femoral Approach (STEMI-RADIAL) trial showed a significant reduction in bleeding and access site complications with TRA compared with TFA among 707 STEMI patients who underwent PPCI, although no reduction in mortality was seen.[182] In contrast, the **Ra**dial vs **Fe**moral Randomized Investigation in **ST**-**E**levation **A**cute **C**oronary **S**yndrome (RIFLE-STEACS) trial reported significantly lower rates of cardiac death and bleeding with TRA compared with TFA among 1001 STEMI patients who underwent primary or rescue PCI.[185] However, this trial used GPIs in more than two-thirds of patients, which might have accounted for the increased bleeding.[187,188] The **Ra**dial vs Femoral Access for Coronary Angiography or Intervention (RIVAL) trial randomly assigned 7021 acute coronary syndrome patients to either TRA or TFA.[183] TRA significantly reduced the composite of death, MI, or stroke ($P = 0.031$; $p^{interaction} = 0.011$), and death ($P = 0.006$; $p^{interaction} = 0.001$) among the 1958 patients in the STEMI cohort.[184] Although the 30-day primary composite outcome of death, MI, stroke, or major bleeding was not different between the 2 groups in the main trial, there was a significant interaction for the primary outcome with greater benefits of TRA seen in the highest tertile volume radial centres. Although there was no difference between groups using the trial-specific definition of non-coronary artery bypass graft major bleeding, TIMI bleeding, or the need for blood transfusions in the main RIVAL trial, there was a significant reduction in bleeding with TRA using the **A**cute **C**atheterization and **U**rgent **I**ntervention **T**riage Strategy (ACUITY) definition.[183]

The **M**inimizing **A**dverse Haemorrhagic Events by **T**rans-radial Access Site and Systemic **I**mplementation of Angio**X** (MATRIX) trial showed a reduction in net adverse clinical events with TRA compared with TFA through a reduction in major

bleeding and all-cause mortality.[186] However, the benefit was confined to centres that used TRA for > 80% of cases. No differences in MACE (death, MI, or stroke) or net adverse clinical events (death, MI, stroke, or bleeding) were seen among the subset of patients with STEMI randomized to TRA compared with TFA (6.0% vs 6.3%; $P = 0.77$; p^{interaction} = 0.19, and 7.1% vs 8.2%; $P = 0.19$; p^{interaction} = 0.44, respectively).[189] Finally, a systematic review that included all RCTs that compared TRA with TFA among STEMI patients treated with PPCI showed significant reductions in all-cause mortality, major and access site bleeding, and MACE with TRA compared with TFA.[190] Ongoing trials will provide additional evidence on the safety and efficacy of TRA vs TFA among STEMI patients who undergo PPCI (Table 4).

RECOMMENDATION

25. We recommend TRA over TFA as the preferred access site in STEMI patients undergoing PCI when it can be performed by an experienced radial operator (Strong Recommendation, Moderate-Quality Evidence).

   Values and preferences. Procedural volume and expertise are important in considering the access mode. High-volume radial centres and high-volume radial operators are needed to achieve the best clinical results. This recommendation places emphasis on the observed reduction of bleeding complications and possible reduction in mortality.

Practical tip. High-volume operators and centres should maintain expertise in both access sites to avoid any paradoxical increase in vascular complications when femoral access is needed.

Adjunctive medications used with primary PCI

Antithrombotic agents. Procedural anticoagulation reduces ischemic and thrombotic complications for STEMI patients undergoing PPCI. Anticoagulation choices for PPCI include unfractionated heparin (UFH), enoxaparin, and bivalirudin.[191] Studies support the use of I.V. UFH at a dose of 70-100 units per kilogram body weight for periprocedural anticoagulation targeting an activated clotting time of 200-300 seconds with GP IIb IIIa inhibitor or ≥ 300 seconds without GP IIb IIIa inhibitors.[192,193]

I.V. enoxaparin can be used as an alternate to UFH for PPCI. A meta-analysis of 10 studies that compared enoxaparin and UFH in the setting of PPCI for STEMI showed a reduction in mortality (RR,0.51; 95% CI, 0.41-0.61) and major bleeding (RR, 0.68; 95% CI, 0.49-0.94) with enoxaparin; this benefit was more pronounced in STEMI patients with higher risk.[194] The Acute Myocardial Infarction Treated with Primary Angioplasty and Intravenous Enoxaparin or Unfractionated Heparin to Lower Ischemic and Bleeding Events at Short- and Long-Term Follow-up (ATOLL) trial randomized STEMI patients to a 0.5 mg/kg I.V. dose of enoxaparin or UFH in the setting of primary PCI.[195,196]

Although the study failed to meet its combined primary end point (death, MI, procedural failure, and major bleeding at 30 days; 28% with enoxaparin vs 34% with UFH $P = 0.06$), enoxaparin was superior to UFH in reducing the main secondary end point of death, MI, or major bleeding (7% vs 11%; $P = 0.015$ and other clinically significant ischemic end points).[195,196] The use of enoxaparin (1 mg/kg subcutaneously twice per day) was found to be safe among patients initially treated with fibrinolysis and who subsequently required adjunctive PCI in the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment Thrombolysis in Myocardial Infarction 25 (ExTRACT-TIMI 25) trial study. Enoxaparin was associated with a reduction in the combined end point of death and MI in this cohort (10.7% vs 13.8%; $P < 0.001$).[197]

Bivalirudin has been compared extensively with UFH with or without GPIs in patients with STEMI who underwent PPCI. The Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial randomized 3602 STEMI patients undergoing PPCI to either UFH with GPI or bivalirudin monotherapy. Bivalirudin therapy was associated with a significant reduction in net adverse clinical events at 30 days, defined as a composite of major bleeding and major adverse cardiovascular events (death, reinfarction, target vessel revascularization for ischemia and stroke) compared with the combination of UFH and GPI (9.2% vs 12.1%; $P = 0.005$).[188] The reduction in events was driven primarily by a decrease in major bleeding (4.9% vs 8.3%; $P < 0.001$). Bivalirudin was also associated with a significantly lower 30-day mortality rate. Although stent thrombosis within the first 24 hours was higher with bivalirudin therapy, this signal was not present at 30 days. These results were sustained at 3 years.[187] The European Ambulance Acute Coronary Syndrome AngioX (EURO-MAX) study randomized 2218 STEMI patients being transported for PPCI to receive either bivalirudin or UFH or low molecular-weight heparin (LMWH) with or without GPI. Although bivalirudin reduced the primary composite end point of death or major non-coronary artery bypass graft-related bleeding compared with UFH/LMWH with or without GPI (5.1% vs 8.5%; $P = 0.001$) and the risk of major bleeding (2.6% vs 6.0%; $P < 0.001$), the use of bivalirudin was associated with an increased risk of stent thrombosis (1.1% vs 0.2%; $P = 0.007$). However there were no differences in rates of death (2.9% vs 3.1%) nor reinfarction (1.7% vs 0.9%).[198] In contrast, the How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI) trial showed a lower MACE rate with heparin compared with bivalirudin (5.7% UFH vs. 8.7%; RR, 1.52; 95% CI, 1.09-2.13; $P = 0.01$) with no difference in major bleeding.[199] Finally, the Bivalirudin Versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web-System for Enhancement and Development of Evidence-based Care in Heart disease Evaluated According to Recommended Therapies (VALIDATE-SWEDEHEART) trial showed no difference in the primary end point of stent thrombosis, nor the secondary end points of death, MI, stroke, or major bleeding with bivalirudin compared with UFH; results were consistent in the STEMI and non-STEMI subgroups.[200]

Several subsequent randomized studies and meta-analyses have shown variable clinical results with bivalirudin with most showing no difference in mortality with the use of bivalirudin compared with UFH alone or in combination with GPI.[189,198,199,201-206] Although bivalirudin use has been associated with a reduced risk of major bleeding this benefit might be attenuated with the use of radial access.[207]

The cost of bivalirudin over UFH might be an important consideration regarding its routine use in PPCI. Amin et al. calculated that routine use of bivalirudin instead of UFH for PCI would add $571 USD per patient, but it was seen to be cost effective when its use was limited to patients at high risk of bleeding.[208] Bivalirudin is recommended for patients with higher bleeding risk or with history of heparin-induced thrombocytopenia. When bivalirudin is used for procedural anticoagulation preprocedural UFH and/or a postprocedural bivalirudin infusion might reduce the risk of acute stent thrombosis.[209]

Fondaparinux had no clinical benefit over UFH when used in PPCI and was associated with a higher risk of catheter thrombosis in the **O**rganization to **A**ssess **S**trategies in **I**schemic **S**yndromes (OASIS)-6 trial; as such its use is not recommended for procedural anticoagulation during PPCI.[210] Additional adjunctive UFH might be considered for patients who require PCI and who have already received fondaparinux.[1,210,211]

UFH.

RECOMMENDATION

26. We recommend the use of UFH for procedural anticoagulation in patients with STEMI undergoing primary PCI (Strong Recommendation, Low-Quality Evidence).

Bivalirudin.

RECOMMENDATION

27. We suggest bivalirudin can be used as an alternative option to UFH for procedural anticoagulation in patients with STEMI undergoing primary PCI (Weak Recommendation, Moderate-Quality Evidence).

28. We recommend the preferential use of bivalirudin over UFH or LMWH for procedural anticoagulation in patients with STEMI undergoing primary PCI who have a history of heparin-induced thrombocytopenia or a very high risk of bleeding (Strong Recommendation, Low-Quality Evidence).

Values and preferences. The higher cost of bivalirudin compared with UFH was a key consideration for determining the strength of the recommendation for routine bivalirudin use.

Practical tip. If bivalirudin is used for procedural anticoagulation, preprocedural UFH and/or a postprocedural bivalirudin infusion might reduce the risk of acute stent thrombosis.

Enoxaparin.

RECOMMENDATION

29. We suggest enoxaparin can be used as an alternative option to UFH for procedural anticoagulation in patients with STEMI undergoing primary PCI (Weak Recommendation, Moderate-Quality Evidence).

Fondaparinux.

RECOMMENDATION

30. We recommend against using fondaparinux for procedural anticoagulation in patients with STEMI undergoing primary PCI (Strong Recommendation, Moderate-Quality Evidence).

GPIs. Although several trials have shown a benefit of I.V. GPI in the setting of PCI, these trials were conducted before the routine use of oral dual antiplatelet therapy.[212] The **C**ontrolled **A**bciximab and **D**evice **I**nvestigation to **L**ower **L**ate **A**ngioplasty **C**omplications (CADILLAC) trial showed that the use of I.V. abciximab did not reduce the incidence of death, reinfarction, or stroke in STEMI patients who underwent PPCI assigned to stenting.[213] Compared with bivalirudin monotherapy, the use of GPI in combination with UFH was associated with higher rates of bleeding in the HORIZONS-AMI trial with no reduction in the primary composite end point of major bleeding death, reinfarction, target vessel revascularization for ischemia, and stroke compared with the combination of UFH and GPI (9.2% vs 12.1%; $P = 0.005$).[188]

Because intracoronary (IC) administration of a GPI during PPCI provides higher local drug concentration than I.V. administration, it was postulated that this mode of administration might lead to better outcomes. A meta-analysis of 10 randomized trials comparing IC vs I.V. GPI in 1590 acute coronary syndrome patients showed that IC compared with I.V. administration of GPI was associated with improved short-term clinical and angiographic outcomes and was associated with similar rates of bleeding. However, it was noted that larger randomized trials were required to show the long-term efficacy and safety of IC GPI use.[214] The **A**bciximab **I**ntracoronary Versus Intravenously **D**rug **A**pplication in **STEMI** (AIDA STEMI) trial then randomly assigned 2065 patients to IC vs I.V. abciximab bolus during PCI and found no difference in the composite 90-day primary end point of all-cause mortality, recurrent infarction, or new congestive heart failure.[215] In addition, there was no difference in final TIMI grade flow, early ST-segment resolution, or enzymatic infarct size between the IC or I.V. groups. An updated meta-analysis, which included 8 randomized STEMI trials (3259 patients), concluded that IC abciximab, compared with I.V. administration, was not associated with any benefits in mortality, reinfarction, or major bleeding.[216]

RECOMMENDATION

31. We recommend against the routine use of I.V. GPI for primary PCI (Strong Recommendation, High-Quality Evidence).
32. We recommend against the routine use of IC GPI for primary PCI (Strong Recommendation, High-Quality Evidence).

Practical tip. GPI might be useful for patients who have not received oral antiplatelet therapy or experience vomiting before PPCI.

Practical tip. GPI use may be considered when there are residual thrombotic complications post PPCI such as large residual thrombus burden, residual dissection, or no reflow.

IC fibrinolysis. Residual coronary thrombus post PPCI is associated with worse outcomes, and might be associated with abnormal microvascular perfusion after PPCI, which in turn is associated with larger infarct sizes and worse long-term outcomes. Accordingly, IC fibrinolysis has been suggested as an adjunctive agent to improve microvascular reperfusion with PPCI.

IC infusion of low-dose (250 kU) streptokinase immediately after PPCI was studied in 2 small randomized trials.[217,218] An initial study randomized 41 patients to receive IC streptokinase immediately after PPCI or no additional therapy after PPCI and showed improvements in short-term measurements of microvascular function in the streptokinase group compared with the control group, but no significant long-term improvement in either left ventricular size nor LVEF.[218] In contrast, a second larger analysis showed improved left ventricular end systolic volumes, end diastolic volumes, and LVEF in favour of the IC streptokinase group along with a 31% reduction in infarct size measured using single-photon emission computed tomography.[217] However, these studies were not powered to detect any difference in mortality.

Significant reductions in thrombus burden and improvements in TIMI flow were seen in 2 small case series with low-dose (up to one-third of systemic dose) IC alteplase and tenecteplase, although were both were underpowered to detect an improvement in clinical outcomes.[219,220] The use of IC fibrinolysis was not associated with increased rates of major bleeding.

RECOMMENDATION

33. We suggest that IC fibrinolysis should not be routinely administered during primary PCI (Weak Recommendation; Low-Quality Evidence).

Values and preferences. Although available studies suggest a potential benefit on angiographic outcomes, routine treatment with IC fibrinolysis at this time is not indicated until larger studies that address clinical outcomes have been performed (Table 4).

Practical tip. Low-dose IC fibrinolysis might be considered in selected cases to treat large-burden residual thrombus during PPCI.

IC adenosine. Up to one-third of STEMI patients with successful epicardial reperfusion fail to achieve microvascular reperfusion. Several small RCTs have investigated the use of IC adenosine with PPCI to improve microvascular reperfusion. Adenosine is an endogenous nucleoside that binds to specific receptors in the endothelium and myocardium and might improve microvascular perfusion via multiple mechanisms including vasodilation, inflammation, and platelet inhibition.[221] Fokkema et al. randomized 448 patients to receive 2 boluses of either adenosine (120 μg) or placebo after thrombus aspiration and stenting; there was no significant difference in the primary end point of residual ST-segment elevation < 2mV 30-60 minutes post PCI between groups.[222] There were also no significant differences in ST-segment resolution, myocardial blush grade, TIMI flow, enzymatic infarct size, or clinical outcomes in the 2 arms. However, transient side effects (hypotension, first- and second-degree atrioventricular block) were more frequent in the adenosine group.

Niccoli and colleagues conducted an open-label, randomized, placebo-controlled trial and compared IC adenosine and nitroprusside with placebo after thrombus aspiration in 240 patients (**R**andomized **E**valuation of Intracoronary Nitroprusside Versus Adenosine After Thr**o**mbus Aspiration During **P**rimary Percutaneous Coronary Intervention for the **P**revention of **N**o-Reflow in **A**cute **M**yocardial **I**nfarction [REOPEN AMI] study).[223] The primary end point of ST-segment resolution > 70% at 90 minutes was seen more frequently in the adenosine group (71%) compared with 54% and 51% in the nitroprusside and placebo groups, respectively ($P = 0.0009$). Microvascular obstruction (defined as TIMI flow grade 2 or 3 with TIMI blush grade < 2) was seen in 18% of the adenosine group vs 24% and 30% in the nitroprusside and placebo groups, respectively ($P = 0.06$). The MACE rate at 30 days was not significantly different between the 3 groups.

Three randomized trials assessed the effect of IC adenosine on infarct size, myocardial salvage, and microvascular obstruction assessed using cardiac magnetic resonance imaging.[224-226] No significant differences were found in the primary cardiac magnetic resonance-measured end points in any of the 3 trials, but 30-day and 6-month MACE rates were increased with IC adenosine. Furthermore, 1 trial showed lower LVEF with IC adenosine.[226]

Several meta-analyses have reported inconsistent effects of adenosine on angiographic and clinical end points, with no signal toward improved mortality or MACE rates among STEMI patients treated with adjunctive adenosine before reperfusion therapy.[227-230]

RECOMMENDATION

34. We suggest that IC adenosine should not be routinely administered during primary PCI (Weak Recommendation, Low-Quality Evidence).

Values and preferences. This recommendation is on the basis of the absence of any improvement in clinical outcomes with IC adenosine, despite the improvement in ST resolution and myocardial perfusion seen in some studies.

Practical tip. IC adenosine may be considered for the selective treatment of no reflow during PPCI.

Overall Perspective and Future Directions

These guidelines were developed to help guide the appropriate diagnosis, triage, prehospital transportation, and reperfusion decision-making for the STEMI patient. We addressed clinical issues relevant and applicable to each of the 3 clinical settings where a STEMI patient could potentially be identified and provided guidance regarding the optimal delivery of STEMI reperfusion: non−PCI-capable centres, PCI-capable centres, and in the field (Fig. 1). We strongly recommend the development of regional networks of care and protocols to optimize safe, timely, and appropriate reperfusion decisions. We provide guidance regarding the optimal prehospital management of the suspected STEMI patient (Fig. 2). Finally, we specifically encourage the adoption of a pharmacoinvasive strategy to optimize use of adjunctive PCI after fibrinolysis, and provide guidance on important procedural aspects of PPCI (Fig. 3).

Other important aspects of STEMI care, including the use of adjunctive mechanical devices to support PPCI, and the postreperfusion care, postdischarge risk stratification, and pharmacological management of STEMI patients were not addressed in this document but remain important topics for future guideline development. Adjunctive oral antiplatelet therapy was not discussed in this document because this is covered in the 2018 CCS antiplatelet guidelines.[76] Similarly, STEMI reperfusion after an out-of-hospital cardiac arrest was addressed in the 2017 CCS position statement on the optimal care of the post arrest patient.[231]

Although ongoing clinical trials will provide additional insight on several aspects of STEMI reperfusion (Table 4), other aspects of STEMI reperfusion merit future study[232]: identifying additional electrocardiographic and/or clinical factors to identify patients best suited for either PPCI vs fibrinolysis,[233,234] defining the optimal antiplatelet and antithrombotic adjunctive regimen for patients receiving fibrinolysis,[235] and defining the optimal timing of PCI after successful or failed fibrinolysis.[236]

Conclusions

The delivery of timely and appropriate reperfusion therapy remains the cornerstone of STEMI care, and requires the integration of patient, health care professional, geographical, and regional resource issues. The Writing Panel believes that reperfusion therapy is best delivered within an organized network of STEMI care that incorporates differences in local and regional resources, physician and allied health care expertise, and geographical considerations. We believe that these recommendations can serve as a practical template to help guide the recognition, transportation, and reperfusion of STEMI patients in a variety of health care environments.

Acknowledgements

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2018.11.031.

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