AN EVIDENCE BASED APPROACH TO THE INITAL MANAGEMENT OF ST-ELEVATED MYOCARDIAL INFARCTION: WHY "MONA" IS NO LONGER A RELEVANT LEARNING TOOL FOR PHYSICIAN ASSISTANTS

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ABSTRACT

Introduction: Morphine, oxygen, nitrates and aspirin (MONA) have been used in the management of ST-elevated myocardial infarctions (STEMI) for over 40 years, despite the advancements in treatment. This literature review explores evidence-based research regarding the benefits and pitfalls of 'MONA' treatments in acute STEMI patients.

Methods: A qualitative literature review was performed looking at the recommendations and evidence surrounding the medical management of STEMI patients in the first two hours of diagnosis and within adequate travel times for percutaneous intervention.

Results: Morphine should not be used routinely in acute STEMI, but rather solely considered in the event of severe ischemic pain not relieved by other therapies. Due to the risks of hyperoxygenation on hemodynamics, supplemental oxygen is only beneficial in hypoxemic patients with an SpO2<90%. The limited evidence surrounding the use of nitroglycerin in acute STEMI is inconclusive to its benefit on mortality. Routine use of aspirin is recommended as soon as possible after the ischemic event.

Conclusion: The mnemonic MONA is not sufficient for understanding the proper acute management of STEMI patients. Care must be made to individualize treatments to each patient's condition while also considering contraindications to therapy.

INTRODUCTION

Coronary artery disease (CAD) is an extremely common medical condition in the Western world. Despite improved treatments over the last 40 years it is still the leading cause of mortality in the Western world (1). Acute Coronary Syndromes (ACS) define an acute exacerbation of CAD that presents with a range of myocardial ischemic states. These include unstable angina (UA), non-ST elevated myocardial infarction (NSTEMI) and ST elevated myocardial infarction (STEMI)(2).

There are around 70,000 acute myocardial infarctions (AMI) that occur every year in Canada and

about 30% of those will die from the condition (3). The highest rates of mortality usually occur before arriving at a hospital and most deaths occur one hour after symptom onset. Of those that make it to the hospital, around 12% will not survive to discharge (3). STEMI's account for approximately one third of ACS in Canada (4) and in-hospital mortality rates are double that of patients admitted with NSTEMI (3). "Time is muscle" is a common phrase that represents the direct link between delay of appropriate treatment and loss of cardiac muscle tissue. Reducing the time from symptom onset to diagnosis of ACSis vital to promptly initiate treatment algorithms for the mortality benefit of patients.

Patients presenting with any combination of ischemic symptoms should be worked up for potential ACS. Ischemic symptoms typically include chest and upper extremity pain, epigastric or mandibular pain, dyspnea, diaphoresis, nausea, fatigue or even syncope; with atypical presentations more common in women, elderly, diabetic and post-op patients(3). Other similar presenting conditions considered on the differential diagnosis include pericarditis, mitral valve prolapse, aortic dissection, pulmonary embolism, pneumothorax, pneumonia, gastroesophageal reflux, esophageal rupture, pancreatitis, cholecystitis, peptic ulcer, musculoskeletal pain and anxiety.(2,3)

The ability to diagnose ACS quickly is critical to ensure proper and timely management with the goal of reducing cardiovascular damage. To differentiate between ischemic states, one must consider the patients clinical presentation, electrocardiogram (ECG) findings and levels of myocardial ischemia biochemical markers. The ECG however, is the first investigation to be done and is critical in determining the next steps in management. Signs of myocardial ischemia on ECG include changes to the PR-segment, the QRS complex and, the most common consideration, the ST-segment (2). STEMI is by definition, characterized by the presence of persistent ST-segment elevations seen on an ECG. It is specifically defined as an ST segment increase of at least 1mm in two contiguous leads. In leads V1-V3 the elevation must be at least 2mm to qualify as a true

STEMI (4). An NSTEMI is defined as any one or more of the following: ST depression > 0.5-1 mm, transient ST elevation, deep (> 2 mm) symmetrical T inversion (3). Smith *et al*. define UA as "the presence of ischemic symptoms without elevations in biomarkers and transient, if any, ECG changes (2)." To properly interpret cardiac biomarkers, they must be interpreted within the clinical context and be trended over time with comparison to baseline levels. Troponin is the preferred cardiac biomarker due to its clinical sensitivity and specificity toward cardiac muscle tissue. STEMI and NSTEMI differ in their early treatment strategies due to a difference in pathophysiology and early outcomes.

MONA

In the 1970's mortalityfrom ACS reachedits peak and is still a significant burden on the health care system today with hundreds of thousands of people having new onset or recurrent ACS (5). The mnemonic MONA (morphine, oxygen, nitro-glycerine and aspirin) was also developed in the 1970s as the "go to" treatment for managing ACS. Since then it has been used as a common mnemonic for teaching about ACS treatment in Medical and PA schools, articles and medical blogs (5). This simple mnemonic no longer represents the current evidence-based medicine regarding acute STEMI management, and therefore presents a patient safety concern.

Opioids have been used as a mainstay of ACS management since the 1930's when it was first documented and they are still commonly used to treat pain caused by STEMIs (6). Typically, IV morphine is offered for pain control and symptom relief after failure of nitroglycerin therapy or if the latter is contraindicated (5,7). Severe pain can stimulate the sympathetic nervous system, increasing one's heart rate, blood pressure, cardiac workload, and myocardial oxygen demand. The goal of pain management is not only for analgesic and anxiolytic effects but can also theoretically reduce the infarct size (7,8). Morphine's hemodynamic properties give potential benefits including, decreased venous return, heart rate and blood pressure, therefore helping to decrease oxygen

demand on the myocardium (5–7). Although morphine may seem to be simply beneficial in helping ischemic chest pain, it is not without its drawbacks and the evidence surrounding its efficacy is varied.

The research concerning oxygen administration in ACS patients is quite vast and despite being a mainstay treatment of ACS, the consensus on its safety has varied quite a bit since its first use around 80 years ago(5,9). Oxygen is thought to increase the oxygen delivery to the myocardium, therefore decreasing the myocardial ischemic injury (5,6,9). Therefore its use is believed to be beneficial to patients who are hypoxic with oxygen saturations (SpO2) <90%, even though there is little evidence to back it up (6). There has been small studies that show anterior STEMI patients had decreased ST-segment elevation when given high volumes of oxygen (6). Several early studies in the 1930's and 1940's suggested that administration of 100% oxygenation could be used as a form of analgesia for chest pain,however studies as early as ten years later have evidence to suggest otherwise. The concerns with supplemental oxygen use in normoxemic (SpO2 >90%) STEMI patients is the potential for hyperoxygenation, which can lead to vasoconstriction (5), changes to hemodynamics, coronary blood flow, infarct size and mortality. Some observational studies have shown that normoxemic ACS patients receiving oxygen therapy resulted in lowered cardiac output as well as increased coronary vascular resistance, resulting in decreased coronary blood flow (6).

Nitroglycerin ('nitrates' or 'nitro') was first seen in the treatment regimen of ACS in the 1970's and is still used commonly for its capacity to help relieve symptoms associated with ischemia and has coronary and peripheral vasculature effects (5,6). One of the main benefits of nitrates is their ability to dilate coronary vasculature therefore decreasing resistance and allowing for increased coronary artery blood flow and oxygen delivery. A concern with using nitroglycerin is its capacity to cause peripheral venodilation, resulting in decreased cardiac preload, afterload and output leading to hypotension. If nitrates are given to STEMI patients who present with or have increased risk of

hypotension (bradycardia, tachycardia, or 5`phosphodiesterase inhibitor use within the previous 24–48 h) it can exacerbate hypotension to a dangerous level (6). Nitrates also result in peripheral venodilation which can decrease left ventricular (LV) wall tension, blood pressure and myocardial oxygen demand. This can be dangerous if paired with right ventricular (RV) myocardial wall infarction due to a decreased capacity of the RV to fill and pump blood effectively. This with a decreased preload can result in severe hypotension or cardiogenic shock (5).

Acetylsalicylic acid (ASA or aspirin) is an irreversible inhibitor of the cyclooxygense-1 receptor, reducing thromboxane A2 and inhibiting platelet aggregation (5). The antiplatelet effects of aspirin can help to disaggregate microscopic thrombi which help to re-open the coronary vasculature and allow for oxygenation of the myocardial tissue. Of the four common therapies given to patients with STEMI, aspirin is the only one with high quality evidence for its benefit (6,10).

Guidelines

The Canadian Cardiovascular Society (CCS) was created in 1947 as a way for cardiac specialists to collaborate with and learn from each other. The CCS has a Guidelines Committee that is formed of heart health specialists that have experience and knowledge in guideline development, reviewing articles and various practice assessment tools. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system is a helpful tool to help grade the quality of the evidence and the strength of the guideline recommendation (Appendix 2). The CCSs current guidelines regarding the acute management of STEMIs, question the efficacy of MONA therapies. This guideline discusses the current evidence surrounding these therapies and from that make recommendations regarding the proper use in the acute setting (8).

This literature review is limited to medical management in the first two hours post STEMI diagnosis with the assumption that reperfusion via percutaneous intervention (PCI) is the main goal of therapy when attainable within the necessary time window. The use of MONA therapies is

limited to the acute onset of symptoms and does not have a role in management outside of this acute window; therefore only the initial two hours after an event will be reviewed. The guidelines surrounding early diagnosis with ECG, patient transfer, reperfusion therapy and long-term management have been well researched elsewhere and are outside the scope of this literature review.

PROBLEM STATEMENT

The goal of this literature review is to understand the benefits and pitfalls of the application and use of MONA in the treatment of acute STEMI and to clarify its use within the first two hours of a STEMI diagnosis.

RESEARCH DESIGN AND METHODS

Overview

A literature review utilizing a systematic search strategy was performed on November 2, 2020 in order to examine previously reported evidence for the most efficacious management of ACS in the pre-hospital and acute care setting. The database Ovid MEDLINE was searched using the search terms “myocardial infarction”, “aspirin”, “nitroglycerin”, “morphine”, and “oxygen inhalation therapy” which yielded 45 results (see Appendix 1). The search was then narrowed to articles that were peer-reviewed publications after 2010, and had a full text available online. Applying these filters resulted in 19 applicable articles. Inclusion criteria for these 19 articles was any type of study that described a management strategy for pre-hospital STEMI and presentations to the ED. Exclusion criteria was any paper published before 2010, and management given outside the post-discharge setting. No language or geographic restrictions were applied. A few exceptions on the

2010 date cut off were allowed as the studies were foundational for our current practices of these pharmacotherapies and no more recent studies could be found.

In addition to the Ovid MEDINE database, The Canadian Cardiovascular Society Guidelines (CCSG) and Position Statement Library database was searched for articles related to the terms ACS, CAD, STEMI, NSTEMI or Cardiac Arrest. The most recent editions and publications were considered.

No ethical approval was sought for this article as this is purely a literature review and there were no interviews or chart reviews undertaken.

Data Analysis Strategies

This research paper is a qualitative literature review where the recommendations of the selected articles are reviewed and summarized. Primary research articles that assessed the efficacy of the MONA treatments were reviewed as applicable and relevant to the aim of this paper. Many of these articles gave a summary of the management options and efficacy surrounding acute STEMI's. This literature review is a compilation of the collective recommendations surrounding the adjuvant therapies, PCI and management algorithms for STEMI management. The CCSG use specific terminology to describe the quality of their recommendations for STEMI management (definitions outlined in Appendix 2). This paper does not include a quantitative analysis of raw data, which made it possible to use non-quantitative research articles.

RESULTS/REVIEW

Morphine

The concurrent administration of morphine and P2Y12 inhibitors, such as clopidogrel and ticagrelor, has been shown by many studies to be associated with a delayed onset of action of these

oral antiplatelet agents. In a 2016 study by Bellandi *et al.* patients who received morphine had an increased occurrence of emesis (11% vs. 6%; p =0.034) compared to control (11); demonstrating another feature impairing absorption of P2Y12 inhibitors. Evidence also supports a deleterious drug-drug interaction between morphine and P2Y12 inhibitors that results in a decreased plasma concentration of P2Y12 inhibitors, and an impairment of their active metabolite, resulting in increased platelet reactivity (1,6–8). One study showed that at the two hour mark, STEMI patients who received morphine with either prasugrel or ticagrelor had higher levels of residual platelet reactivity compared to patients without morphine (risk ratio=1.55 (95% CI, 1.28–1.87), p<0.001) (12).

A delay in antiplatelet agents runs the risk of increasing myocardial infarction size, however there is variable evidence regarding morphines effect on infarct size due to antiplatelet inhibition. In the Bellandi *et al.* study, patients treated with morphine had higher biomarker peaks [1821U/L vs. 1483 U/L, p=0.034), larger ST-segment elevation (mm) at 30 minutes (1.4 ± 1.2 vs. 0.8 ± 0.9, p=0.009), and were slower to resolve after reperfusion (76% vs. 87%, p=0.047) (11). A retrospective, non-randomized trial by de Waha *et al.* in 2015 also showed an increase in infarct size in STEMI patients who received morphine compared to those without morphine (19.1 % left ventricle vs. 14.1 % left ventricle, p=0.02) (7,13). This is in contrast to other studies that failed to show a significant increase in infarct size with the administration of morphine in STEMI patients undergoing PCI (46.1% versus 43.5%, p=0.11) (7,14).

Although there are a growing number of studies that show the deleterious effects of using morphine in STEMI patients the question of its impact on mortality is still unclear. The CRUSADE trial (Can Rapid Risk Stratification of Unstable Angina Patients Suppress ADverse Outcomes with Early Implementation of the ACC/AHA Guidelines) is a retrospective, nonrandomized, observational, multi-institutional study with 57,039 high-risk NSTEMI patients enrolled. This study shows higher

rates of MI (adjusted odds ratio [OR] 1.34, 95% CI 1.22-1.48) and death (adjusted OR 1.48, 95% CI 1.33-1.64) in patients who received IV morphine alongside clopidogrel (15). Other smaller studies, like that done in 2010 by Iakobishvili *et al.* showed no significant difference to the 30-day mortality rate with the administration of IV morphine (2.2% vs 6.3%, p=0.16) (16).

Oxygen

A sub-study of the SOCCER (Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion) trial set out to see if oxygen supplementation at 10L/min would relieve chest pain in STEMI patients. This randomized retrospective study of 111 patients with STEMI suggested that oxygen supplementation has no significant benefit on AMI associated chest pain (2.0 ± 2.2 vs. 1.0 ± 2.9; p=0.183) (9).

Many studies within the last ten years, including both the DETOX-AMI and the AVOID trial failed to show any significant increase in mortality rates at discharge (6) or at the one year mark (17). The DETO2X-AMI (DETermination of the role of OXygen in suspected Acute Myocardial Infarction) was a nationwide, multicentre, prospective, open-label, registry-based randomized clinical trial (RRCT) compared routine supplemental oxygen therapy (6L/min) to ambient air in normoxemic patients with suspected AMI (17,18). Hoffman *et al.* 2018 extended the results of the DETOX-AMI trial and showed there was no significant affect to all-cause death (hazard ratio [HR] 0.86, 95% CI 0.61-1.22, p=0.41), rehospitalization with MI (HR 0.92, 95% CI 0.57-1.48, p=0.73), cardiogenic shock (HR 1.05, 95% CI 0.21-5.22, p=0.95), or stent thrombosis (HR 1.27, 95% CI 0.46-3.51, p=0.64) at the 1 year mark for normoxemic patients that received supplemental oxygen (17).

The DETOX-AMI results were contrasted by a multicenter, prospective randomized control trial (RCT) done in 2015 studying the effect of 'Air Versus Oxygen in Myocardial Infarction' (AVOID) comparing effects of administering supplemental oxygen (8L/min) verses not in STEMI patients. This study yielded statistically significant data showing that patients with a STEMI and SpO2

>94% had increased: in-hospital MI recurrence rates (5.5% versus 0.9%; P=0.006), frequency of cardiac arrythmias (40.4% versus 31.4%; P=0.05), and infarct size at 6 months (12.6 % left ventricle vs. 9.0 % left ventricle, p=0.08 (19).

Nitroglycerin

The ISIS-4 (Fourth International Study of Infarct Survival) was a randomized 2×2 factorial placebo-controlled trial studied the effect of a slow-release isosorbide mononitrate in 58,050 MI patients compared to placebo. Administration of the mononitrate for 28 days failed to show a reduction in mortality at 5 weeks post-MI compared to placebo (7.34% vs. 7.54%, p=0.3) (20). The ISIS-4 trial also showed significantly higher rates of severe hypotension (resulting in termination of the treatment/study) in the mononitrate group compared to the placebo group (8.1% vs 6.7%, 2p<0.001) (20). Similar non-significant mortality results (6.5% vs. 6.9%, p=0.28) were seen in the GISSI-3 trial, which studied the effect of a 24-hour IV infusion of glyceryl trinitrate followed by the use of a glyceryl trinitrate patch for 6 weeks compared to placebo in 19,394 patients (21). Although the above results do not favour the use of nitrates, a meta-analysis combining the results of these trials (and many other smaller RCTs) suggested that nitrates give a small mortality reduction of about 5.5% (p=0.03) when used in ACS (6,22).

Aspirin

The 'Second International Study of Infarct Survival' (ISIS-2) in 1988 was a 2×2 factorial placebo-controlled trial with a study size of >17,000 that showed that early administration of aspirin reduced the five week mortality by 23% compared to the placebo (95% CI 15% to 30% 2p<0-0.0001). This study also showed that aspirin use was associated with a significant reduction in recurrent MI (1.0% vs 2.0%, 2p < 0.00001) and strokes (0.3 vs 0.6%, 2p<0.01) (23). A risk with giving any anti-platelet medication is bleeding. Aspirin is not excluded from that risk but its mortality benefit outweighs the bleeding risk (10). The ISIS-2 trial actually showed that aspirin and placebo rates of major bleeds requiring transfusion were similar (0.4% rates for both) (23).

Table 1: Benefits and adverse effects associated with the MONA pharmacotherapies in STEMI patients.

	Pharmacological Therapy			
	Morphine	Oxygen	Nitrates	Aspirin
Benefits	– Ischemic pain relief (5,7) – decreased cardiac workload (venous return, heart rate, blood pressure) (5–7)	– increased oxygenation in hypoxemic patients	– small mortality reduction (5,22) – ischemic pain relief (vasodilatory effects) (5,6)	– Decreased mortality (23) – Reduction in recurrent MI (23) – Reduction in strokes (23)
Adverse Effects	– Decreased absorption and onset of P2Y12 inhibitors (1,6–8,12) – Potential for increased infarct size (7,11,13) – Increased nausea and vomiting (11) – Potential increase in mortality and recurrent MI (15)	– increased in-hospital MI recurrence rates (19) – higher cardiac arrythmia frequency (19) – increased infarct size at 6 months (19) – potential hyperoxygenation leading to hemodynamic changes (4)	– increased risk of hypotension (20) especially with RV infarction (6)	– Small increase in minor-bleeds but no increase in major-bleeds (23)

DISCUSSION

Patients who are diagnosed with an acute STEMI need to have the proper management to ensure optimal mortality. The first two hours of management should be centered around symptom control and optimization for reperfusion. The largest mortality benefit is associated with myocardial reperfusion, therefore rapid diagnosis via EGC and timely reperfusion via PCI or fibrinolysis is critical.

Morphine

Morphine has been researched as a mainstay form of analgesia for those with pain in conjunction with ACS for many decades. Despite the quantity of research that has been done, there is limited convincing, quality evidence to support its use. Many trials conducted either have small sample sizes, are retrospective, nonrandomized or observational; and there has yet to be any RCTs with a large enough sample size to show significantly beneficial results with respect to improving STEMI outcomes (7,8).

Although morphine is effective at relieving pain, there are many drawbacks to its use: decreased gastric motility and absorption of medications, drug-drug interactions with P2Y12 inhibitors, (12) increased infarct size, (13) and a potential for increased mortality (15). A common adverse effect of opioid use is its effect on the gastrointestinal system including decreased gastric motility, nausea and vomiting (11). These side effects can complicate the management of a STEMI by decreasing the absorption of other critical medications, such as P2Y12 inhibitor agents (6–8).

The 2019 Canadian Cardiovascular Society (CCS) guidelines regarding the acute management of STEMI suggests “the avoidance of routine IV opioid analgesic administration for STEMI related discomfort.” (Weak Recommendation, Low-Quality Evidence). The CCS guidelines understand the need to manage severe pain and anxiety that is associated with a STEMI, but cautions practitioners

to use opioid analgesic medications selectively in order to balance the potential for harm with the need for severe pain control (8). Contraindications to the use of morphine including hypotension, bradycardia and respiratory depression; especially if the patient is hypovolemic, or using venodilators must always be considered prior to administration (5).

Oxygen

There has been no significant evidence to date that shows a benefit to supplemental oxygen in normoxemic patients; only patients with an SpO2<90% or in respiratory distress benefit from oxygen supplementation. Due to the risk of potential harm from hyperoxemia, anxiety and impaired communication, the CCS recommends selective use of supplemental oxygen for hypoxic patients or those in respiratory distress (8); while also providing continuous monitoring of normoxemic patients to ensure proper therapy if they do become hypoxic (17).

The Canadian Cardiovascular Society 2019 guidelines suggest “avoiding routine prehospital administration of supplemental oxygen to STEMI patients with an SpO2 >90%” (Weak Recommendation, Low-Quality Evidence) (8).

Nitroglycerin

There has been very little research done on the use of nitroglycerin in the last 20 years and the older data available are generally inconclusive surrounding its efficacy in reducing mortality rates in STEMI patients.(6,20–22). Nitroglycerin is beneficial for acute or recurrent ischemic pain, hypertension, and acute pulmonary edema, but it must not be administered to patients with RV infarction, hypotension, bradycardia, tachycardia, or recent 5`phosphodiesterase inhibitor use (1,5,6,10).

In the 2019 STEMI guidelines, the CCS did not make any specific recommendations regarding the administration of nitroglycerin in STEMI patients. (8). The American Heart Association/ American

College of Cardiology 2013 guidelines recommend the use of intravenous or sublingual nitroglycerin for management of angina, hypertension, acute pulmonary edema or recurrent ischemia (Class I indication) (1). Further caution must be used to not administer nitroglycerin to patients that have or are suspected of RV infarction, hypotension, bradycardia, tachycardia or recent 5`phosphodiesterase inhibitor use (6,10).

Aspirin

Of the four pharmacotherapies described in the 'MONA' mnemonic, chewing 162-325 mg of aspirin (1,2,5,10) as soon as possible after the infarct should be considered routine in acute STEMI patient as it is the treatment with the most evidence to support its mortality benefit (23). The CCS 2019 guidelines recommend aspirin as the first choice of antiplatelet therapy and should be started as soon as possible after the event (8).

Other Adjuvant Agents

The acute care of patients with a STEMI is not limited to the MONA therapies. Dual antiplatelet therapy (DAPT) with a P2Y12 inhibitors can play an important role in reperfusion (1), but is not discussed in this article. There are numerous other adjuvant pharmacotherapies that should be administered within 24 hours of STEMI diagnosis, such as beta blockers (1,2,5), renin-angiotensin system blockage agents (2). During PCI reperfusion there are other medications that should be considered, such as an anticoagulant or glycoprotein IIb/IIIa inhibitors (1,2,5,8). After hospitalization there are other agents that should be continued as long-term therapies, such as HMG-coenzyme A reductase inhibitors (statins) (2,5). These agents are well outlined in other guidelines and are outside the scope of this article.

For future and practicing PAs MONA is no longer an adequate teaching tool and should not be considered universal for all patients with ACS. Understanding the proper initial management of a

STEMI patient is critical for the PA as it is our responsibility to be able to identify the signs and symptoms, diagnose, and initiate management. PAs working on inpatient wards, those in urgent or emergency departments, or even those in the community and primary care could have patient that either presents with or is having a STEMI. PA's are skilled practitioners that can recognize the signs and symptoms of ACS and interpret ECG's, they can also order the proper treatments and protocols when a diagnosis of STEMI is suspected. The only barrier to this process is the current ambiguity regarding what the initial treatment for STEMI patients is and whether or not to practice local norms or follow EBM.

Further Research

Due to the importance of pain management in a STEMI patient, further research in the form of a RCT regarding the safety of opioid use or other methods of pain management would help clarify current guidelines. There is a lack of recent primary research regarding the use of glycerol trinitrate in STEMI patients, more current data could help to clarify the mortality benefits and its interaction with antiplatelet agents.

Further research in this area could be a study to see what areas of medicine PA's across Canada interact with STEMI patients the most, whether it be emergency/urgent care departments, primary practice clinics, inpatient wards or even with the PCI teams. Once we have a better understanding of where PA's interact with STEMI patients, we could then discern what types of training is most important to help them care for the patient most effectively. This could be focusing education on the treatments and guidelines for acute care, or what medications are necessary as adjuvants to reperfusion strategies or if a PA's expertise should be centred around primary and secondary prevention treatments.

Limitations

There has been a vast amount of research done on pharmacologic therapies for ACS, which has created limitations in this study. The sheer quantity of research papers on this topic made the process of gathering and analysing all the data avaliable challenging.

CONCLUSION

Even amongst the vast research and advancements in treatment regarding ACS, it is still one of the leading causes of death in Canada. The ability to recognize and diagnose a STEMI in a time sensitive manner is critical to the effective treatment of the condition. The practice of using MONA as a mnemonic for teaching how to deal with ACS is outdated and no longer a sufficient learning or reference tool. To provide patient-centered and comprehensive care it is critical that the education and resources provided for practitioners and students be evidence-based and up to date in all aspects of medicine and the acute STEMI management is no outlier. This article addressed the evidence-based recommendations for medical therapy within the first two hours of STEMI onset to hopefully provide some clarity to PA's during the acute care of a STEMI patient.

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20. ISIS-4: A randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. The Lancet. 1995 Mar 18;345(8951):669–85.

21. GISSI-3: effects of lisiriopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. The Lancet. 1994 May 7;343(8906):1115–22.

22. Yusuf S, Anand S, Avezum A Jr, Flather M, Coutinho M. Treatment for acute myocardial infarction: Overview of randomized clinical trials. European Heart Journal. 1996 Dec 1;17(suppl_F):16–29.

23. Randomised Trial Of Intravenous Streptokinase, Oral Aspirin, Both, Or Neither Among 17 187 Cases Of Suspected Acute Myocardial Infarction: ISIS-2. The Lancet. 1988 Aug 13;332(8607):349–60.

APPENDICES

Appendix 1: Search Strategy for Literature Review

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to October 30, 2020>
Search Strategy:
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1 MONA.ab,ti. (393)
2 morphine/ or oxygen/ or aspirin/ (247933)
3 morphine/ and oxygen/ and aspirin/ (6)
4 (oxygen adj1 aspirin).ab,ti. (11)
5 1 or 3 or 4 (408)
6 exp Myocardial Infarction/ (176628)
7 5 and 6 (6)
8 the demise of morphine oxygen nitroglycerin aspirin.ti. (1)
9 aspirin/ or aspirin.ab,ti. (67459)
10 oxygen/ or oxygen.ab,ti. (558244)
11 nitroglycerin/ or nitroglycerin.ab,ti. (15905)
12 morphine/ or morphine.ab,ti. (57919)
13 oxygen inhalation therapy/ (14597)
14 10 or 13 (563299)
15 9 and 11 and 12 and 14 (19)

Appendix 2: CCS GRADE system (Grading of Recommendations, Assessment, Development, and Evaluation)

Table adapted from PDF resource from 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. Canadian Journal of Cardiology (8) available at https://ars-els-cdn-com.uml.idm.oclc.org/content/image/1-s2.0-S0828282X18313217-mmc1.pdf

Quality of Evidence	High	further research very unlikely to change confidence in the estimate of effect
	Moderate	further research could have an important impact on confidence in the estimate of effect and may change the estimate
	Low	further research very likely to have an important impact on confidence in the estimate of effect and likely to change the estimate
	Very Low	estimate of the effect very uncertain
Grade of Recommendation	Strong	desirable effects clearly outweigh undesirable effects or clearly do not
	Weak	become mandatory when trade- offs are less certain, either because of low-quality evidence or because the evidence suggests that desirable and 3 undesirable effects are closely balanced.

I declare that the work I am submitting for assessment contains no section copied in whole or in part from any other source unless explicitly identified in quotation marks and with detailed, complete and accurate referencing.

 Signature