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NITROGLYCERIN SAFETY IN INFERIOR ST ELEVATION MYOCARDIAL
INFARCTION (STEMI) PATIENTS: A RETROSPECTIVE REVIEW

By

Olivia Montgomery

DNP PROJECT

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SIGNATURE APPROVAL FORM

NITROGLYCERIN SAFETY IN INFERIOR ST ELEVATION MYOCARDIAL
INFARCTION (STEMI) PATIENTS: A RETROSPECTIVE REVIEW

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ABSTRACT

NITROGLYCERIN SAFETY IN INFERIOR ST ELEVATION MYOCARDIAL INFARCTION (STEMI) PATIENTS: A RETROSPECTIVE REVIEW

By

Olivia Montgomery

Nitroglycerin (NTG) is medication used to reduce chest pain (Boden et al., 2015) and is the suggested analgesic for angina associated with ST elevation myocardial infarction (STEMI) (de Alencar Neto, 2018). Due to the potential for right ventricular (RV) infarct and hemodynamic collapse in inferior STEMI patients (Nagam, Vinson, & Levis, 2017), the American Heart Association (AHA) recommends avoidance of NTG in patients with suspected RV infarct (Antman et al., 2004). The purpose of this DNP project was to explore the safety of NTG use in the treatment of patients diagnosed with STEMI by evaluating the effects of NTG on hemodynamic measures and angina. Data were collected via a retrospective chart review at a rural Midwestern hospital and analyzed via Fisher's Exact and multiple linear regression analyses. There were no significant differences between STEMI groups for occurrence of hypotension ($p=0.521$), bradycardia ($p=0.064$), medical need for hemodynamic support ($p=0.530$), or cardiac arrhythmia ($p=0.465$). For this sample of patients, the results show no difference in adverse occurrences between patients who received NTG with a diagnoses of inferior STEMI versus patients who received NTG with a diagnoses of non-inferior STEMI. A recommendation is that patients with identified inferior STEMI receive a right-sided ECG to evaluate for RV infarct (Bischof et al., 2018), in order to guide individualized

patient care including the use of NTG, which was shown to significantly reduce chest pain in this sample of patients ($p < 0.001$).

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OLIVIA MONTGOMERY
May 11, 2021

DEDICATION

This DNP project is dedicated to my husband, Adam, and to my family and friends for their continued support throughout my education and career.

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Chapter One

Introduction

Nitroglycerin (NTG) is the most commonly prescribed short-acting nitrate to reduce the intensity of chest pain in those experiencing angina (Boden, Padala, Cabral, Buschmann, & Sidhu, 2015). NTG is a front-line medication used to relieve chest pain in individuals experiencing acute coronary syndrome (ACS) (Boden et al., 2015) and is also the most frequently delivered treatment to individuals having a myocardial infarction (MI) (Ferreira & Mochly-Rosen, 2012). Although there is no study identifying reduction of mortality, NTG remains a suggested analgesic medication for angina associated with ST elevation myocardial infarction (STEMI) as well as for the treatment of hypertension (de Alencar Neto, 2018).

ACS represents the signs and symptoms a person experiences relating to myocardial ischemia or infarction, with or without electrocardiogram (ECG) ST segment changes (Camm & Camm, 2016) and includes unstable angina, non-ST elevation myocardial infarction (NSTEMI) and STEMI. The most damaging and life-threatening diagnosis associated with ACS is STEMI. The diagnosis of STEMI occurs when there is complete occlusion of a coronary artery causing cardiac tissue death, which is the cause of angina, and is identified by ST segment elevation on an ECG (Camm & Camm, 2016). The purpose of this DNP project was to explore the safety of NTG use in the treatment of patients diagnosed with STEMI by evaluating the effects of NTG on hemodynamic measures and angina.

Significance and Background

The American Heart Association (AHA) continues to designate cardiovascular disease as the leading cause of mortality for both men and women in the United States (Benjamin et al., 2018). Between the years 2011 and 2014, there were 8.7 million individuals diagnosed with angina, and in 2014 alone, there were 957,000 individuals diagnosed with MIs (Benjamin et al., 2018). The total number of individuals with angina and MIs suggests a significant number of individuals who may have received NTG or been provided with a NTG prescription. The rapid onset of NTG effects results in venous and arterial dilation, ultimately increasing blood flow to the heart and reducing myocardial stress, which are desired during a STEMI (Ferreira & Mochly-Rosen, 2012).

Currently, the AHA advises extreme caution with the use of NTG, or against the use of NTG entirely, with inferior STEMIs with potential right ventricular (RV) infarction and failure (Antman et al., 2004, O'Connor et al., 2010). RV infarction most commonly occurs with the occlusion of the marginal branch of the right coronary artery (RCA), resulting in dyskinetic RV wall motion, decreased compliance of the ventricle, and subsequent reduced stroke volume (Namana et al., 2018). Clinical indications that are more specific to RV infarction and pending RV failure include elevated jugular distention, clear lung sounds with auscultation, hypotension, pulsus paradoxus, and a tricuspid murmur (Namana et al., 2018).

The reasoning behind avoiding NTG use in patients with potential RV involvement is that the medication could potentiate hypotension and cardiac arrhythmias (Antman et al., 2004, O'Connor et al., 2010). An inferior STEMI, which is identified on a standard 12-lead ECG as ST segment elevation in leads II, III and aVF (Taglieri et al.,

2014), often indicates occlusion of the RCA (Namana et al., 2018). Because occlusion of this coronary artery is also the most common to cause RV infarct, concern for RV involvement may influence clinical interventions.

Inferior wall MIs represent 40% to 55% of all MIs (Jaton, 2017; Warner & Tivakaran, 2020), while the occurrence of right ventricle (RV) infarct has been reported to occur in approximately 20% to 50% of inferior STEMIs (Bischof, Worrall, & Smith, 2018; Nagam, Vinson, & Levis, 2017). A standard 12-lead ECG provides limited data on RV infarct (Nagam et al., 2017), and therefore, it is recommended that a right-sided ECG be obtained when there is inferior STEMI identification on a standard 12-lead ECG (Antman et al., 2004).

Nagam et al. (2017) discuss how a conventional 12-lead ECG largely shows involvement of the left ventricle, while minimally showing RV wall involvement. A right-sided ECG analyzes leads V1R-V6R, allowing for improved evaluation of the RV (Somers, Brady, Bateman, Mattu, & Perron, 2003). With the right-sided ECG, precordial leads mirror the locations of the standard 12-lead but on the right side of the patient's chest (Somers et al., 2003). Because lead V4R has high sensitivity and specificity for identifying RV involvement, when obtained via a right-sided ECG, this lead may provide pertinent information on the status of the RV and help guide treatment of patients diagnosed with inferior STEMI (Nagam et al., 2017; Somers et al., 2003).

NTG has systemic venous dilating properties, which reduces cardiac preload (Ferreira & Mochly-Rosen, 2012) and may contribute to hypotension and decreased cardiac output, especially in those with RV infarct (Antman et al., 2004). The effects of NTG generally last less than 30 minutes, with a standard sublingual dose of 0.4 mg

resulting in temporary coronary artery dilation. Higher doses of intravenous infusions between 160 and 600 micrograms per minute result in sustained systemic arterial and venous dilation (Jaton, 2017). The effects of NTG are transient and the benefits of NTG for angina reduction in patients with inferior STEMIs requires evaluation on a patient-specific basis.

The use of opioid medications, such as morphine (de Alencar Neto, 2018), as an analgesic for angina should be avoided unless angina is unresponsive to NTG (Frampton, Devries, Welch, & Gersh, 2020). Evaluation of morphine, which was traditionally used to reduce angina during ACS and STEMIs, has been shown to reduce the therapeutic effects of commonly used medications, such as ticagrelor, prasugrel, and clopidogrel, all of which are used for platelet inhibition before and after percutaneous coronary intervention (PCI) (Frampton et al., 2020; Ibanez et al., 2018). Although morphine is still listed as a potential analgesic for angina resulting from STEMI (Antman et al., 2008), it should be noted that newer research implies the risks of reducing therapeutic effects of antiplatelet medications outweigh the benefits of morphine and potentially other opioids for analgesia (Duarte et al., 2019; Frampton et al., 2020; Koh, Fernando, Peter, & Stub, 2019).

Treating angina associated with STEMI becomes challenging when risks could impact patient morbidity and mortality. An individualized approach to patient care requires ongoing analysis of the safety and efficacy of medications currently used in the treatment of STEMI.

Purpose of DNP Project

The purpose of this DNP project was to explore the safety of NTG use in the treatment of patients diagnosed with STEMI by evaluating the effects of NTG on

hemodynamic measures and angina. Comparisons occurred between patients who received NTG with the diagnosis of inferior STEMI to those diagnosed with non-inferior STEMI, all of whom presented to a rural Midwestern hospital for treatment. The hospital used in this project serves as the only PCI center in a large geographical region spanning approximately 16,000 square miles, providing services to individuals that reside in the town in which the hospital is located, as well as to individuals in the many surrounding rural communities. NTG administration was tracked retrospectively via healthcare professionals' documentation, in order to assess the safety implications of using NTG for angina reduction in this rural area. As the development of hemodynamic instability is a major concern resulting from administration of NTG to patients with inferior STEMIs due to RV infarct (Antman et al., 2004), the following research questions were explored:

- 1) Does the administration of NTG result in hypotension more often in inferior STEMI patients than non-inferior STEMI patients?
- 2) Do patients with inferior STEMIs require additional interventions more frequently to correct hypotension or bradycardia than non-inferior STEMI patients following NTG administration?
- 3) Do inferior STEMI patients experience more bradycardia and cardiac arrhythmias compared to non-inferior STEMI patients?
- 4) Does NTG significantly reduce chest pain levels reported by STEMI patients?

Methods

A retrospective chart review examined charts of previously hospitalized patients who were diagnosed with inferior or non-inferior STEMI who presented to the rural Midwestern hospital between January 1, 2019 and December 31, 2019. Systolic blood

pressure (SBP), heart rate, cardiac arrhythmias, need for hemodynamic interventions, and patient reported chest pain were compared between patients diagnosed with inferior STEMI to patients diagnosed with non-inferior STEMI. All patients in both groups also had received NTG, which was identified while examining each individual's chart.

The sample consisted of patients who had received NTG in conjunction with the diagnosis of STEMI. The listed discharge diagnosis of STEMI, which was determined by a cardiology physician, was how the presence of STEMI was determined in this project. Data were grouped according to patient diagnoses of inferior versus non-inferior STEMI, and the outcome measurements of SBP, heart rate, and occurrence of cardiac arrhythmias were compared between the two groups. Reduction in reported angina experienced by patients following NTG administration was also examined for both groups, as well as the use of fluid resuscitation or vasopressors in response to hypotension or bradycardia following NTG administration.

Theoretical Framework

The theoretical framework used for this project was the Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) model (© The Johns Hopkins Hospital/ The Johns Hopkins University, permissions viewable in Appendix A). The JHNEBP model is an evidence-based practice model that allows for nurses and other interdisciplinary team members to identify and make changes to practice in order to provide evidence-based individualized care to patients (McEwen & Wills, 2018). For the purposes of this project, results will be reported to the hospital STEMI coordinator in order to add to discussions on the care of patients presenting with ACS at this hospital. Based on the JHNEBP model, the problem identified is that inferior STEMI patients may receive generalized

treatment based on current AHA guidelines for RV infarct (Antman et al., 2004), which may not account for individualized potentially beneficial interventions, especially in the absence of diagnostic measures to identify RV infarct. Specifically, this project seeks to add to the evidence regarding the impact of NTG on the hemodynamic outcome variables of SBP, heart rate, cardiac arrhythmias and chest pain experienced by patients diagnosed with STEMI. Ultimately, the goal of this project is to contribute data to the conversation of how to safely improve the quality and individualization of care to patients diagnosed with STEMI.

Chapter Two

RV infarct has been reported to occur in as low as 20% of patients (Bischof et al., 2018) and as high as 50% of patients (Nagam, Vinson, & Levis, 2017) with inferior STEMI identification on ECG. The most common culprit lesion causing RV infarct is the acute marginal branch of the RCA with ST elevation on ECG in lead V1, II, III, and aVF (Namana et al., 2018). Although RV infarct may occur with other culprit lesions, such as the left circumflex artery (Namana et al., 2018), the RCA is often suspected in individuals with inferior STEMI identification on ECG.

As inferior STEMIs represent approximately 40% to 55% of all STEMI cases (Jaton, 2017; Warner & Tivakaran, 2020), and with current recommendations to withhold NTG from patients with RV infarct (Antman et al., 2004), it is pertinent to include methods to identify RV infarct in patient care (Ibanez et al., 2018). Without proper identification of RV infarct in inferior STEMI patients, hesitancy in the provision of NTG may exist due to the associated occurrence of RCA and RV involvement observed in patients with inferior STEMIs (Namana et al., 2018). NTG may provide necessary analgesia for angina experienced by patients throughout their MI, as angina has been identified as a common symptom experienced by both men and women during a STEMI (Sederholm Lawesson et al., 2018). Recent literature has warned that angina treated with morphine may result in lengthened hospital admission, increased infarct size and subsequent higher mortality rates (McCarthy, Bhambhani, Pomerantsev, & Wasfy, 2018). A reason cited for these adverse effects is that morphine decreases the therapeutic action of certain antiplatelet medications (Duarte et al., 2019; Frampton et al., 2020; Koh et al., 2019).

Nurses have an ethical standard that applies to providing evidence-supported analgesia to individuals experiencing pain, in addition to providing patients with individualized care (Stokes, 2018). With interdisciplinary involvement, healthcare providers should evaluate various modalities for pain reduction in patients. For acute pain in patients experiencing STEMI, reduction of angina needs to consider an individualized approach to guide the provision or withholding of medications. Re-establishment of blood flow to the occluded coronary artery with PCI will ultimately relieve angina experienced by patients, however, angina should be treated to reduce myocardial stress in the interim (Ibanez et al., 2018). Because of the current recommendations for NTG use in STEMIs (Antman et al., 2004), inferior STEMI patients are potentially blanketed into a group that may not receive NTG with subsequent angina reduction, especially in the absence of interventions to specifically identify RV infarct. Although caution for adverse events and unwanted side effects needs to be considered in all patients with all medications, it is necessary to address each patient case individually and to uphold the ethical implications of managing pain. To provide evidence-driven and individualized care, it is important to evaluate the safety of NTG use between inferior STEMI and non-inferior STEMI patients, and to question whether current practices are best for patients.

Literature Review

A review of literature was conducted using Northern Michigan University's online Lydia Olson Library, CINAHL, PubMed, and Google Scholar. Online searches focused on finding information relating to NTG, ECG, inferior STEMI, RV infarct, and opioid medications.

The Use of NTG

In a retrospective chart review of patients with suspected STEMI in a prehospital setting, Bosson et al. (2019) evaluated blood pressure changes, pain scores and heart rates after the administration of NTG. The study reviewed records from July, 2015 to December, 2016, from three PCI centers to which patients were transported in Los Angeles County, California. A 12-lead ECG was performed on patients with suspected cardiac-related chest pain. Suspected STEMI was determined by software analysis in combination with paramedic interpretation, with additional assistance provided by online medical control (Bosson et al., 2019). Bosson et al. (2019) describe the primary treatment of persistent angina was 0.4 mg sublingual NTG, which was repeated twice if pain persisted. Patients with initial SBP < 100 mmHg were not included in the study, as they were ineligible for NTG or opioid medications.

Bosson et al. (2019) identified change in blood pressure as a key safety issue that was evaluated in the study in patients that received NTG compared to those who did not. Triage SBP < 100 mmHg, bradycardia or heart rate < 60 beats per minute, drop in systolic blood pressure > 30 mmHg and cardiac arrest occurring out of the hospital were secondary safety outcomes evaluated by the researchers. Pain was evaluated on a 0 to 10 scale to assess for efficacy of NTG in angina reduction, which was compared to pain reported by individuals who did not receive NTG (Bosson et al., 2019). Subgroups, including individuals who received PCI to the right coronary artery (RCA), were evaluated for the same outcome criteria and compared to individuals who had PCI to other coronary arteries.

STEMI was confirmed in 193 patients, with 155 individuals receiving NTG

(Bosson et al., 2019). The average chest pain score was reduced by 2.4 on a 0 to 10 point scale in STEMI patients treated with NTG (n=145), while all individuals who did not receive NTG had an average reduction in chest pain score of 1.4. Bosson et al. (2019) identified that a pain reduction of 1.39 was the minimum for reduction that represented clinical significance. When comparing chest pain reduction to the clinically significant value of 1.39, both groups had reduced angina, but the individuals treated with NTG had what was considered to be a significant reduction in angina ($p < 0.001$), compared to those who did not receive NTG ($p=0.5$). Bosson et al. (2019) report that of the 75 patients with RCA occlusions, 80% received NTG. Comparable occurrence of hypotension and bradycardia resulted in the patients receiving PCI for non-RCA occlusions RR 0.64 (95% CI, 0.21, 1.95) versus those with RCA occlusion RR 1.30 (95% CI, 0.57, 2.94).

Bosson et al. (2019) discuss the significant reduction in pain following administration of NTG. There also was no increased risk of hypotension or bradycardia with pre-hospital administration of NTG at arrival to the emergency department (ED). The researchers concluded that the protocols directing withholding NTG from patients diagnosed with inferior STEMI may need to be revisited. Limitations of the study included that only 193 patients of the 780 suspected actually had STEMIs, which limited the assessment of hemodynamics in this group. Although the number of patients with actual STEMI was significantly smaller than the suspected number, the researchers provide information on all patients as well as subgroups, which is suggested as evidence for the safety of NTG use in pre-hospital settings.

In a similar study, Robichaud et al. (2016) conducted a retrospective chart review between February, 2010 and July, 2012 in Quebec, Canada, to analyze the impact of

NTG on blood pressure in patients experiencing inferior STEMI as compared to those diagnosed with non-inferior STEMI. Hypotension was defined as systolic blood pressure (SBP) < 90 mmHg and was compared between inferior and non-inferior STEMI groups. Additionally, researchers evaluated any reductions in SBP > 30 mmHg between inferior and non-inferior patient groups. The chart review included 805 STEMI patients, all of whom received NTG prior to hospital arrival (Robichaud et al., 2016).

Robichaud et al. (2016) discovered that patients with inferior STEMIs did have more frequent initial hypotension than non-inferior STEMI patients, with 9.9% of inferior STEMI patients presenting with hypotension, compared to 4.9% of patients with non-inferior STEMIs. Patients that presented with hypotension would not meet criteria to receive NTG based on blood pressure regardless of infarct location, and therefore were not included in the study (Robichaud et al., 2016). With regard to bradycardia, 1.1% of inferior STEMI patients (n=5/474) experienced heart rates < 50 beats per minute, while no patients with non-inferior STEMIs had heart rates documented at < 50 beats per minute (n=0/347).

Following statistical analyses, Robichaud et al. (2016) reported that based on computer-interpreted ECGs, there was no statistically significant difference in incidence of hypotension between inferior STEMI patients (n= 38/466, 8.2%) and non-inferior STEMI patients (n= 30/339, 8.9%) following NTG administration (p= 0.73). There was also no significant difference between the two groups for decrease in SBP > 30 mmHg, which occurred in 23.4% of inferior STEMI patients and in 23.9% of non-inferior STEMI patients (p = 0.87). Robichaud et al. (2016) described that based on the results of their research, ST segment elevation in lead III that measured greater than ST segment

elevation in lead II, which would suggest RV involvement, was not a good predictor for patients who would be at risk for developing hypotension. However, Robichaud et al. (2016) observed lower rates of hypotension than their expected rate of 15%, even given their large sample size. This was identified as a limitation to the study as, Robichaud et al. (2016) estimated a need to have a much larger sample size of approximately 38,000 individuals in order to show the same occurrence of hypotension among inferior and non-inferior STEMI groups using a power of 80%.

Another retrospective chart review evaluating the effectiveness of sublingual NTG in reducing chest pain and adverse events associated with NTG administration was completed by Engleberg et al. (2000). The researchers reviewed all advanced life support (ALS) cases in the Emergency Medical Services' (EMS) System of Suffolk County, New York, for which IRB approval had been granted. Patients included in this study had received NTG from an emergency medical technician (EMT) or paramedic prior to hospital arrival between January, 1993, and June, 1994. A single dose of 0.4 mg sublingual NTG was provided to 1,662 patients. NTG was administered to individuals reporting chest pain (n=901), respiratory distress likely caused from congestive heart failure (n=251), or a combination of both (n=510). The researchers analyzed chest pain rating reported by patients, hemodynamic measurements, including systolic and diastolic blood pressure, as well as the occurrence of adverse events.

Of the 1,662 patients who received NTG in this study, there were a total of 779 records with complete data on chest pain ratings. Chest pain was rated by patients using a verbal numeric scale ranging from 0 to 10, with 0 representing no pain and the most severe pain rated at 10. Chest pain scores were reported before and after receiving NTG,

with a mean decrease in chest pain reported by patients after receiving NTG of 2.6 (95% CI [2.4, 2.8]). After receiving NTG, the mean SBP in all patients decreased by 11.8 mmHg (95% CI [10.7, 13.0]), while heart rate had a mean increase by 2.7 beats per minute (95% CI [0.6, 4.9]).

Engleberg et al. (2000) reported 12 adverse events within the study, which included patients that experienced a drop in SBP of > 100 mmHg that responded to fluid or elevation of the patients' legs (n=6), hypotension following receiving NTG with a documented SBP of < 90 mmHg (n=4), syncope (n=1) and profound bradycardia and hypotension (n=1). Zero deaths were reported. Of these patients, individuals with a > 100 mmHg decrease in SBP had initial SBP > 210 mmHg prior to receiving NTG, and no adverse events were associated with individuals who self-administered NTG prior to EMS arrival. In total, the estimated adverse events for the study were reported as 0.7% (95% CI [0.4, 1.3]).

The researchers (Engleberg et al., 2000) reported that the average reduction in chest pain ratings was 2.6 on the 10-point scale which equated to an approximate 40% reduction of pain, although pain was completely relieved in only 10% of patients. In discussion of limitations, Engleberg et al. (2000), point out that final diagnoses were not included, meaning generalizations should not be made in relation to patients experiencing cardiac ischemia or MI, but suggest future investigation of the effects of NTG in this patient population. This study documents the importance of NTG's role in chest pain reduction in patients and a low occurrence of adverse events associated with administration of NTG, regardless of diagnosis.

Bosson et al. (2019), Engleberg et al. (2000), and Robichaud et al. (2016) all cite a retrospective study conducted by Ferguson, Diver, Boldt, and Pasternak (1989) whom identified a significant occurrence of hypotension in inferior STEMI patients with suspected RV infarct. In discussion of their research, Ferguson et al. (1989) report concomitant administration of calcium channel blockers in several of the patients included in their study, noting that this may have potentiated the occurrence of observed hypotension. A prospective study to identify patients with RV infarct via multiple diagnostic modalities, as well as their response to NTG, was recommended by the researchers (Ferguson et al., 1989).

Robichaud et al. (2016) discuss how the study conducted by Ferguson et al. (1989) was a singular study supporting the recommendations that currently stand about NTG use in inferior STEMI patients. As the occurrence of RV infarct in patients with inferior STEMIs is considered highly variable (Ferguson et al., 1989), the risk of using this medication in inferior STEMI patients with the potential of RV infarct was higher than the benefits. With more current retrospective reviews that refute avoidance of NTG in inferior STEMI patients (Bosson et al, 2019; Robichaud et al., 2016), and the apparent time gap in related research, it is suggested that further investigation into this topic is warranted.

The Use of ECG Findings

Another component in evaluating the safety of NTG for patients experiencing inferior STEMI is the use of ECG to determine RV infarct. Bischof et al. (2018) conducted a retrospective review of patients with inferior STEMIs to evaluate ECG sensitivity and specificity for identification of RV infarct and the roles of ST segment

depression or elevation in standard 12-lead ECGs. Patients included in their study were those that presented to Hennepin County Medical Center, Minnesota, who had ST elevation > 1 mm identified in inferior leads (II, III, aVF), between January, 2002 and March, 2008. IRB approval was granted for this project.

Manual measurement of ST segments in leads I, II, III, aVF, aVL, V1 and V2 was completed by researchers (Bischof et al., 2018) and compared between patients who were categorized into two groups, right ventricular myocardial infarction (RVMI) and non-RVMI. Culprit lesions were previously identified in the cardiac catheterization laboratory, which was the basis for categorizing patients into the respective groups. RVMI patients had culprit lesions identified in the RCA proximal to the RV marginal branch, which is the artery that supplies the RV myocardium. Non-RVMI patients had occlusions in the middle or distal RCA or circumflex artery. Subsequently, ST elevation or depression measured by researchers was compared to evaluate the sensitivity and specificity of ST segment changes on ECG in identifying RVMI and non-RVMI infarcts.

Bischof et al. (2018) reported a sample size of 43 patients in the RVMI group and 106 patients in the non-RVMI group. In ECG analysis, there was no difference in ST segment depression in lead I between RVMI patients ($n=37$, 86%) and non-RVMI patients ($n=85$, 80%) ($p=0.54$), with sensitivity and specificity of lead I in determining RVMI reported as 86% and 20%, respectively. A lower frequency of non-RVMI patients had ST elevation in V1 ($n=17$, 16%, 95% CI [10, 24]) compared to patients with RVMI ($n=15$, 35%, 95% CI [22, 50]), which was a significant finding ($p=0.015$). Specificity and sensitivity for RVMI was thus calculated to be 84% (95%, CI [76, 90]) and 35%, respectively, for ST elevation in lead V1.

In the absence of ST segment depression in lead V2, sensitivity for RVMI was found to be higher (69%, 95% CI [44, 86]) when compared to the presence of ST segment depression in lead V2 (15%, 95% CI [6, 32]), which was a significant finding ($p < 0.001$). In lead V1 in RVMI patients, ST segment depression was present in V2 in 85% of patients who did not have concurrent ST segment elevation in lead V1. Bischof et al. (2018) thus concluded that ST segment depression in lead I was not dependable in differentiating patients with or without RV infarct. However, ST segment elevation in V1 was found to be specific for RVMI, with higher sensitivity identified in the absence of ST segment depression in lead V2.

Bischof et al. (2018) did identify limitations within their study, including wide confidence intervals and a small sample size of patients identified with RVMI. A prospective study was suggested, in addition to further investigation of ECG analysis in patients with RV dysfunction in relation to culprit lesions, which may alter sensitivity and specificity of leads I and V1 in identification of RV dysfunction. Due to lack of consistent sensitivity and specificity of leads in a standard 12-lead ECG, the researchers made an important recommendation, which was to obtain a right-sided ECG, specifically lead V4R, to accurately diagnose RV infarct (Bischof et al., 2018).

The importance of ECG analysis for patients presenting with STEMI is magnified in the presence of inferior infarct identification, as treatments such as the administration of NTG hinge on the potential for RV infarct. The European Society of Cardiology (ESC), American College of Cardiology (ACC), and the AHA (Ibanez et al., 2018; O’Gara et al., 2013) recommend obtaining right precordial views of the heart, specifically V4R, to evaluate for ST elevation that would signify RV infarct in patients with inferior

STEMI identification. As completion of a right-sided ECG involves inversion of leads and few additional supplies, it could easily be completed in a prehospital or emergency room setting and provide identification of RV infarct using leads with the highest sensitivity for diagnosis (O’Gara et al., 2013).

The Use of Opioid Medications

The ESC report reduction in patients’ pain as essential during STEMI, as vasoconstriction occurs as a sympathetic nervous system response to pain, ultimately increasing the workload of the heart (Ibanez et al., 2018). The ESC states the use of intravenous opioids for pain should be considered but with a low level of evidence to support opioid use. Recommendations also warn of the effects of morphine and the reduction of therapeutic effects of ticagrelor, prasugrel, and clopidogrel antiplatelet medications (Ibanez et al., 2018) when provided to patients concomitantly. The ESC also recommends the administration of one of the previously mentioned antiplatelet medications in a prehospital setting or prior to PCI due to improved patient outcomes, with a high level of evidence to support the recommendation (Ibanez et al., 2018). With a higher level of evidence and recommendation to provide these important antiplatelet medications, treating pain with opioid medications, such as morphine, may be counterintuitive due to the reduction in antiplatelet efficacy.

The AHA and ACC continue to list morphine as the analgesic of choice for pain management in patients experiencing STEMI (O’Gara et al., 2013). This is despite the growing research showing reduced efficacy of recommended antiplatelet medications for patients experiencing STEMI that receive morphine and other opioid medications (Frampton et al., 2020). In the same AHA/ACC guidelines, it is recommended to provide

ticagrelor, prasugrel, or clopidogrel, as soon as possible to patients prior to or at the time of PCI. Again, this recommendation is provided with a higher level of evidence to support the therapeutic effects of antiplatelet medications and improved patient outcomes when compared to the use of opioid medications to treat chest pain associated with STEMI.

Clinical trials conducted by researchers Hobl et al. (2014) and Kubica et al. (2016) evaluated the effects of morphine on clopidogrel and ticagrelor, respectively. The results of the study conducted by Hobl et al. (2014) showed significant reduction in the active metabolite of clopidogrel and decreased gastric absorption of the medication in individuals who received morphine. Similarly, Kubica et al. (2016) reported significant reduced blood plasma concentrations and bioavailability of ticagrelor in individuals who received morphine for pain. Both clinical trials show that morphine reduces the efficacy of the antiplatelet medications, warranting exploration into alternative pain relief measures.

The Platelet Aggregation with tiCagrelor Inhibition and FentanYl (PACIFY) trial was conducted by Ibrahim et al. (2018) to evaluate effects of intravenous fentanyl on ticagrelor. Fentanyl, which is a potent opioid medication that is frequently provided to patients during PCI (Ibrahim et al., 2018), was evaluated due to the previously identified adverse effects of morphine on antiplatelet medications. The results from this clinical trial showed reduction in the efficacy of ticagrelor in individuals who received fentanyl when compared to those who did not receive the opioid medication, indicating that morphine is not the sole opioid with this type of interaction.

It is suggested that opioid medications are reserved for chest pain that is unresponsive to NTG (Frampton et al., 2020), as commonly used opioid medications reduce the efficacy of important antiplatelet medications that are currently recommended to be provided as early as possible during a STEMI. Chest pain associated with STEMI is important for providers to manage (Ibanez et al., 2018; Ibrahim et al., 2018), indicating the need to explore medication options and their potential impact on patient outcomes. With the knowledge that opioid medications may reduce the efficacy of antiplatelet medications, the use of NTG remains a viable option in treating chest pain in patients experiencing STEMI.

In summary, several studies have been conducted to evaluate the safety of NTG use in patients with the diagnosis of STEMI, including inferior STEMI, in relation to hemodynamic outcome variables, as well as to analyze NTG's ability to reduce chest pain in patients (Bosson et al., 2019; Engleberg et al., 2000; Robichaud et al., 2016). Bischof et al. (2018) recommend other measures to identify RV infarct, due to the lack of sensitivity and specificity in identifying RV infarct with a standard 12-lead ECG within their study. Based on this literature review, further investigation into NTG use in STEMI patients, and specifically inferior STEMI patients, is warranted. Furthermore, patient care should be individualized to optimize patient outcomes, including provision of analgesic medication for chest pain and identification of RV infarct in patients with inferior STEMI identified on an ECG. The purpose of this DNP project was to explore the safety of NTG use in the treatment of patients diagnosed with STEMI by evaluating the effects of NTG on hemodynamic measures and angina. From this, this DNP project may potentially add

to evidence for future recommendations designed to individualize care for patients, as well as the safe use of NTG in patients presenting with the diagnosis of STEMI.

Theoretical Framework

The theoretical framework that is the basis of this project is that patients should receive evidence-based individualized care. Nurses and interdisciplinary team members have the capability of identifying areas in practice that propose a certain question or problem, and may use the Johns Hopkins Nursing Evidence-Based Practice (JHNEBP) model as an evidenced-based practice model to make changes to practice (McEwen & Wills, 2018; Dang & Dearholt, 2018). For the purposes of this project, providing additional data with evidence to a hospital allows for discussions on current practice and contributes to debate on changes if warranted.

The JHNEBP model consists of a question pertaining to practice, evidence relating to the question, and subsequent translation to practice (McEwen & Wills, 2018). The initial step of this theoretical model is to question certain problems or concerns that are identified in practice (Dang & Dearholt, 2018). For this project, it is not clear if inferior STEMI patients receive individualized care based on the AHA guidelines to withhold NTG without additional interventions, such as the recommended right-sided ECG.

Following the JHNEBP model, the identification of an evidence-based practice (EBP) question for this project was strictly based on using a standard 12-lead ECG and whether exclusive standard views of the heart are enough to provide appropriate and patient-specific interventions to inferior STEMI patients. From this, the questions for this project are as follows:

1) Does the administration of NTG result in hypotension more often in inferior STEMI patients than non-inferior STEMI patients?

2) Do patients with inferior STEMIs require additional interventions more frequently to correct hypotension or bradycardia than non-inferior STEMI patients following NTG administration?

3) Do inferior STEMI patients experience more bradycardia and cardiac arrhythmias compared to non-inferior STEMI patients?

4) Does NTG significantly reduce chest pain levels reported by STEMI patients? As NTG is used to reduce angina, patient report of angina rating will be compared among inferior and non-inferior STEMI groups for analysis of therapeutic reduction in angina intensity.

The initial practice question in the JHNEBP model requires recruitment of an interdisciplinary team. The Northern Michigan University Graduate Nursing Committee approval for graduate research relating to this project in conjunction with the author's DNP Chair approval were the initial steps towards developing a team. Cardiologists, Emergency Department physicians, Emergency Medical Service (EMS) personnel, quality improvement and the STEMI coordinator are all key stakeholders in this project, as STEMI patients are cared for by several different teams prior to and at the time of PCI. The acronym Patient population, Intervention, Comparison, Outcome and Time table (PICOT) format is used in the JHNEBP model to refine the evidence-based practice question (McEwen & Wills, 2018). As applied to this DNP project PICOT was formulated as:

- The Patient population consisted of patients with inferior and non-inferior STEMIs presenting to the rural Midwestern hospital for PCI intervention.
- The Intervention is the administration of NTG to patients in inferior and non-inferior STEMI groups, which was reviewed in a retrospective manner due to the controversy and ethics of a prospective study evaluating the same topic.
- Comparison and Outcomes consisted of a comparison of data between the inferior and non-inferior STEMI groups in terms of hemodynamic measurements, additional interventions required in each group, and angina experienced between the two groups.
- Time was defined as patients presenting to the rural Midwestern hospital between January 1, 2019 and December 31, 2019, with inclusion of patients experiencing STEMI and meeting other inclusion criteria presenting to the facility.

The next section of the JHNEBP model relates to evidence. Based on the JHNEBP model, the problem identified is that patients are categorized into an inferior STEMI group and may not receive patient-specific interventions but more general treatment based on inferior infarct identification on a standard 12-lead ECG due to the potential of RV involvement. Medication, such as NTG, may be withheld based on guidelines for RV infarct (Antman et al., 2004), as the occurrence of RV infarct is largely associated with inferior STEMI. To improve quality of care and individualized care to patients with STEMI identification, research addressing blood pressure and patient hemodynamic stability between inferior and non-inferior STEMI groups should be utilized (Jaton, 2017; Robichaud et al., 2016). Research utilization should help in guiding

the use of NTG for patients experiencing angina during a STEMI, whether an inferior or non-inferior infarct is identified. A review of patient charts at a rural Midwestern hospital was conducted to analyze the previously identified research questions. A review of literature with appraisal of information relating to the problem signifies the external search for evidence. From this, both internal and external evidence will be used to facilitate discussions on current policy.

Translation of evidence to practice will depend on the fit and feasibility of additional interventions at the rural Midwestern hospital. Findings of internal and external evidence appraisal, and guidance gained from the literature on how to implement any changes to practice will be disseminated to the hospital through the STEMI coordinator.

Chapter Three

RV infarct in inferior STEMI patients has led to the recommendation by the AHA to use extreme caution with the use of NTG or exclude NTG entirely as a medication to treat chest pain in this patient population due to the possibility of hypotension and cardiac arrhythmias (Antman et al., 2004). Several studies (Bosson et al., 2019; Engleberg et al., 2000; Robichaud et al., 2016) have evaluated the safety of prehospital NTG in suspected STEMI and actual STEMI patients, as well as the significance of NTG in chest pain reduction. Similar to previous studies, this DNP project explored the safety of NTG by evaluation of hemodynamic measures and angina in patients experiencing STEMI in a rural Midwestern setting.

Sample and Setting

Data collection for this DNP project was conducted at a rural Midwestern hospital through a retrospective chart review. The designated hospital serves as the only PCI center for STEMI patients in the region, providing much needed services to the community in which it is located, as well as to numerous outlying communities. The sample consisted of STEMI patients presenting to the designated hospital, either directly or by transfer to the hospital from an outlying area.

This project focused on a convenience sample of patients, all of whom presented to the designated hospital with STEMI between January 1, 2019 and December 31, 2019. As the purpose of this DNP project was to evaluate the safety of NTG, only STEMI patients (confirmed on 12-lead ECG by a cardiologist) who received NTG were included in this project and subsequent data analysis. Additional inclusion criteria were the requirements that individuals were 18 years of age or older with chest pain of suspected cardiac origin. Chest pain of cardiac origin must not have resulted from trauma and

patients must have been eligible to receive NTG upon first medical contact. As alternate diagnoses may mimic a STEMI on an ECG (Gu, Svilaas, van der Horst, & Zijlstra, 2008), final discharge diagnosis of STEMI was used in conjunction with preliminary STEMI identification on ECG analysis.

The universal definition of STEMI on ECG is new ST-elevation at the J-point \geq 0.1 mV in two contiguous leads, other than V2 and V3 (Thygesen et al., 2012). Inferior STEMI is identified by ST elevation \geq 0.1 mV in leads II, III and aVF (Robichaud et al., 2016; Thygesen et al., 2012). Non-inferior STEMI patients are identified by having ST elevation \geq 0.1 to 0.2 mV in other contiguous leads (Thygesen et al., 2012). For the purposes of this project, STEMI location was determined by a member of the interventional cardiology group, and was noted in the patient chart along with the culprit vessel causing the STEMI noted in the catheterization note. Four cardiologists, all having between 10 and 30 years of experience, were active in treating STEMI patients during the study timeframe. If patients had infarction in the inferior region as well as another region, they were included in the inferior STEMI group.

Exclusion criteria for this study included anyone who did not receive NTG based on initial hemodynamics, pregnant women, anyone with thoracic trauma, and those who did not receive NTG based on allergy or recent ingestion of medications for which NTG would be contraindicated. Due to variance in protocols among medical providers and regional services, patients with initial SBP $<$ 100 mmHg and heart rate $<$ 60 beats per minute were still included in this study if they received NTG. Prisoners and individuals with cognitive disabilities were excluded as vulnerable populations. To reduce bias in

interpretation while communicating level of chest pain, those individuals who listed their primary language as something other than English, were excluded from the study.

Necessary sample size was calculated using Creative Research Systems (2012) sample size calculator, and was based on the population of STEMI patients who received NTG. The necessary sample size was determined using a 95% confidence level ($\alpha=0.05$) and margin of error of 5%. The necessary sample size based on 76 STEMI patients who received NTG was 64 individuals. Due to incomplete data recorded on two patients, data were collected on 74 STEMI patients that received NTG in 2019.

IRB Approval Process

This project was presented to and approved by the university IRB and hospital IRB in May of 2020. During data collection, patient information was de-identified, relinquishing the necessity for consent from patients included in the study. Stored data were stripped of any patient name, address or birth date to guard anonymity. University IRB approval documents may be viewed in Appendix B. To preserve hospital anonymity, IRB approval documents are not included from the facility and identifying information found on the university IRB was removed. The university IRB acknowledges the receipt of the hospital IRB.

Design and Procedures

The retrospective chart review and data collection occurred May through June of 2020, and included STEMI patients presenting to the rural Midwestern hospital from January 1, 2019 through December 31, 2019. Patients were identified using the STEMI tracking system used by the hospital and STEMI coordinator. Charts were reviewed for final diagnosis of STEMI, ECG identification of STEMI, chest pain analysis,

hemodynamic trends, as well as administration of NTG. Chart review methodology is located in Appendix C. Patients that did not meet inclusion criteria were marked as ineligible, with no further data collection.

Measures and Instruments

Outcome measures were recorded for each patient upon initial contact with medical personnel, and included SBP, heart rate, and chest pain intensity. For patients that self-administered NTG, initial patient hemodynamics were used from first medical contact, with note of self-administration doses. Repeat hemodynamic measurements following NTG administration were recorded from the patient chart based on the pharmacokinetic onset of NTG. For sublingual and intravenous NTG, post-NTG hemodynamics were recorded within a three and fifteen minute period following the administration of the medication. Both sublingual and intravenous NTG have an average onset between one and three minutes, with average maximum effects occurring between five and seven minutes after administration (Food and Drug Administration, 2011; U.S. National Library of Medicine, 2020a, 2020b). Patients who received transdermal NTG had repeat vital signs recorded between 30 and 60 minutes, due to the delayed onset of therapeutic effects and absorption (U.S. National Library of Medicine, 2020c).

Chest pain intensity was rated by patients on a 0-10 Likert scale, with 0 representing no chest pain, and 10 representing the maximum rating for chest pain intensity. Initial and repeat analysis of chest pain levels were recorded at the same interval as repeat hemodynamics to allow for analysis of maximal therapeutic effects on chest pain. Initial and repeat SBP were measured on each patient with a manual

sphygmomanometer or automatic external blood pressure monitor, while heart rate was obtained from an external cardiac monitoring device or via palpation.

As in other studies that have evaluated the safety of NTG use in STEMI patients (Bosson et al., 2019; Engleberg et al., 2000; Robichaud et al., 2016), hypotension was defined as SBP < 90 mmHg and bradycardia as a heart rate < 60 beats per minute. Interventions to correct hypotension, including a fluid bolus or vasoactive medication, were recorded for each patient if they were required. Chest pain was recorded based on the verbal-numeric scale previously mentioned.

Multiple brands of 12-lead ECG machines were used to collect preliminary ECGs on each patient. Due to monitor variation in sensitivity and specificity in the identification of STEMI (Garvey, Zegre-Hemsey, Gregg & Studnek, 2016) and low positive predictive value of computer interpretation of STEMI (Wilson et al., 2013), automated ECG interpretations were not used to determine eligibility. A discharge diagnosis of STEMI, which was made by an interventional cardiologist, was essential for identifying eligible individuals for this study. Patients' medical histories were also obtained from chart data, which allowed for evaluation of relationships between comorbidities and impact on outcome variables.

Data Analysis

Data were categorized during extraction from the patients' charts. The presence of STEMI was grouped into either inferior or non-inferior categories. Descriptive statistics (mean + standard deviation, percentage) were computed for clinical characteristics of the study population (age, gender, and need for intervention following NTG administration).

Inferential statistical analyses were computed by statistician J. Rich (personal communication, August 16, 2020) using various software programs (Appendix D).

Fisher's Exact tests were used to analyze differences in occurrence of hypotension, the occurrence of bradycardia, the need for a fluid bolus or vasoactive medication, as well as the occurrence of cardiac arrhythmias or cardiac arrest, between inferior STEMI patients compared to non-inferior STEMI patients. Multiple linear regressions were used to analyze for a difference in the effect of NTG on SBP between inferior and non-inferior STEMI patients as well as to compare differences in heart rate among STEMI groups, while controlling for comorbidities and interventions.

To evaluate chest pain, a mixed effects model was used to initially evaluate for interactions between time and STEMI location, as well as for morphine administration, and their effects on chest pain. This allowed for evaluation of potential differences between inferior and non-inferior STEMI groups and to determine if NTG reduced chest pain in one group significantly more than in the other. A multivariable linear regression was then used to evaluate for a significant reduction in chest pain levels in all STEMI patients when comparing pre-NTG administration and post-NTG administration chest pain ratings. This model controls for comorbidities, age and other medications that were administered to the patients in the study, while analyzing for a significant difference in chest pain rating following NTG administration.

For all regression models, an initial best subsets regression was completed and included all of the following variables: age, hypertension, previous MI, gender, diabetes mellitus, chronic obstructive pulmonary disease (COPD), cardiac arrhythmias, coronary artery disease (CAD), STEMI location, obesity, analgesic medications, bradycardia,

hypotension, vasopressor or fluid bolus, smoking history, morphine, and the use of an antihypertensive. Following the best subsets regression, Akaike information criterion (AIC) was used as an automated model selection. This allowed for the inclusion of variables that had a stronger association to the response variable of interest within each separate regression. Following statistical analyses, results and discussion of the research questions within this DNP project were compiled, which are presented in the subsequent chapter. Additionally, recommendations for future practice and research were identified from analyses within this project.

Chapter Four

The purpose of this DNP project was to explore the safety of NTG use in the treatment of patients diagnosed with STEMI by evaluating the effects of NTG on hemodynamic measures and angina. The intent of statistical analyses was to compare differences in SBP, heart rate, cardiac arrhythmias, and chest pain ratings, between inferior and non-inferior STEMI patients that presented at one rural Midwestern hospital between January 1, 2019 and December 31, 2019. The research questions for this project were:

1) Does the administration of NTG result in hypotension more often in inferior STEMI patients than non-inferior STEMI patients?

2) Do patients with inferior STEMIs require additional interventions more frequently to correct hypotension or bradycardia than non-inferior STEMI patients following NTG administration?

3) Do inferior STEMI patients experience more bradycardia and cardiac arrhythmias compared to non-inferior STEMI patients?

4) Does NTG significantly reduce chest pain levels reported by STEMI patients? Similar to previous studies (Bosson et al., 2019; Engleberg et al., 2000; Robichaud et al., 2016), this project seeks to provide further information on the use of NTG in STEMI patients, as well as to provide recommendations for individualized patient care.

Demographics and Descriptive Statistics

Seventy-four patients who presented to the Midwestern hospital with the diagnosis of STEMI in 2019 received NTG and were eligible for inclusion in this project. Initial routes of administration of NTG included sublingual (n= 47), intravenous (n= 22),

and transdermal (n=5). Doses of 0.4 mg sublingual varied between one (n= 17), two (n=13), three (n=15), or four (n=1) tablets. Patients whom were started initially on intravenous NTG also had variable doses, which may be viewed below in Table 1. The maximum reported dose of intravenous NTG was 180 micrograms per minute, while the lowest infusion dosage was reported as 1 microgram per minute. Titrations of intravenous NTG were documented on 18 different patients, with noted increases to reduce SBP and chest pain, or decreases to maintain hemodynamic stability. Of the 74 total patients, seven individuals self-administered 0.4 mg sublingual NTG prior to initial contact with a healthcare provider. Self-administrations doses ranged from one to four tablets taken by the patients. One patient who self-administered NTG had initial hypotension but was subsequently placed on a NTG infusion.

Table 1

Initial Route and Dosage of Nitroglycerin

Nitroglycerin Route/Dose	Number of Patients
Sublingual	
0.4 mg	46
0.3 mg	1
Intravenous	
1 mcg/min	1
3 mcg/min	1
5 mcg/min	11
10 mcg/min	5
20 mcg/min	1
40 mcg/min	1
60 mcg/min	1
Undocumented dose	1
Transdermal 2%	
½ inch	3
1 inch	2

Note. Initial NTG routes were sublingual, intravenous (IV) or transdermal. Twenty two patients were initially started on a NTG IV infusion, with doses reported in micrograms per minute (mcg/min). Higher doses of IV NTG between 20 and 60 mcg/min were

documented on patients with initial SBP > 150 mmHg. IV NTG infusions were started on additional patients (n=23), totaling 45 documented NTG infusions. Transdermal dosage of ½ inch equates to 7.5 mg of NTG and 1 inch equates to 15 mg, which is gradually absorbed with therapeutic onset between 30 and 60 minutes (U.S. National Library of Medicine, 2020c). Transdermal 2% NTG paste of ½ inch equates to approximately 5 mcg/min of IV NTG, while 1 inch equates to a range of 10 to 39 mcg/min of IV NTG (Esposito, Dunham, Granger, Tudor, & Granger, 1998).

Male patients (n= 53) represented a larger proportion of the sample than female patients (n=21), representing approximate male and female patient percentages of 72 and 28, respectively. The average age (\pm SD) of all individuals included in this project was 62.8 years (\pm 11.8 years). Female age was higher with an average of 63.7 (\pm 12.3) years, while males had an average age of 62.5 (\pm 11.7) years. The most common cardiovascular risk factors that were recorded in patients' health histories included hypertension (n= 41), hyperlipidemia (n=34), and any history of smoking (n=32). Additional comorbidities and cardiovascular risk factors are provided below in Table 2.

Table 2

Health History Diagnoses of 2019 STEMI Patients

Comorbidity	Occurrence
Hypertension	41
Hyperlipidemia	34
Smoking	32
Coronary Artery Disease	19
Diabetes Mellitus	17
Obesity	11
Previous MI	11
Chronic Obstructive Pulmonary Disease	6

Note. Diagnoses in patient health histories as listed within the patient chart. Patient occurrence represents total number of patients with the specific diagnosis, with 74 total patients. Additional diagnostic histories by number of occurrence included cerebral vascular accident (n=3), chronic kidney disease (n=4), obstructive sleep apnea (n=3), previous coronary artery bypass grafting (n=3), and atrial fibrillation (n=3). Although several additional diagnoses were present in the study population, they were not included for the purposes of this study.

Inferior STEMI was the diagnosis in a larger number of patients (n=44) than non-inferior STEMI patients (n=30). Of the patients in the inferior STEMI group, the majority of patients had the culprit vessel identified as the right coronary artery (RCA) (n=21), while non-inferior STEMI patients had the left anterior descending (LAD) coronary artery (n=21) identified as the most common culprit vessel. Seven patients in the inferior STEMI group had multiple vessels occluded, while three patients in the non-inferior STEMI group had multiple vessels occluded. Takotsubo cardiomyopathy was identified in one patient within the non-inferior STEMI group (data located in Table 3).

Table 3

STEMI Location and Culprit Vessels

Vessel	Number of Patients	
	Inferior	Non-inferior
RCA	21	-
LAD	4	21
DIAG	-	3
OM1/OM2	2	-
CIRC	7	-
PDA	1	-
Multiple	7	3
Takotsubo	-	1
Unknown	2	2
Total	44	30

Note. Vessel location as identified in cardiac catheterization laboratory. Unknown is due to no catheterization or no specification noted. Coronary arteries by name and abbreviation: Right coronary artery (RCA). Left anterior descending (LAD). Diagonal (DIAG). Obtuse marginal (OM1/OM2). Circumflex (CIRC). Posterior descending artery (PDA). Takotsubo cardiomyopathy is an acute condition that often results in elevated cardiac markers and ECG changes (Boyd & Solh, 2020) and can result from a strong emotional or physical event that causes left ventricular dilation and acute heart failure. With Takotsubo cardiomyopathy, ST- segment elevation can occur, with diagnosis made following an absence of plaque rupture or obstructed coronary artery (Boyd & Solh, 2020).

Bradycardia was observed in approximately 31% of patients (n=23) and was the most common cardiac aberration. Hypotension occurred in 8% of patients (n=6), while cardiac arrhythmias occurred in 12% of patients (n=9). Cardiac arrhythmias included ventricular fibrillation (n=3), ventricular tachycardia (n=3) and symptomatic bradycardia (n=3). Additional medications that were provided to patients included vasopressors, fluid boluses, antihypertensive medications, and analgesics (illustrated below in Table 4).

Table 4

Medications Administered to 2019 STEMI Patients

Medications	Number of Patients
Fluid Bolus/Vasopressor	
Normal Saline	25
Dopamine	1
Atropine	3
Norepinephrine	1
Epinephrine	1
Analgesics/Anxiolytics/Sedatives	
Morphine	28
Fentanyl	8
Hydromorphone	1
Lorazepam	2
Diazepam	1
Midazolam	1
Diprivan	1
Antihypertensive	
Metoprolol	19
Diltiazem	1
Hydralazine	1

Note. The above table includes alternate medications that patients received in addition to NTG. The number of patients who received a medication does not account for potentially receiving medications within the same class or a different class. Patients that received a fluid bolus or vasopressor (n=28), analgesia/anxiolytic/sedative (n=38), or an antihypertensive(s) (n=19) represents the total number of individual patients that received medications within the specific grouping.

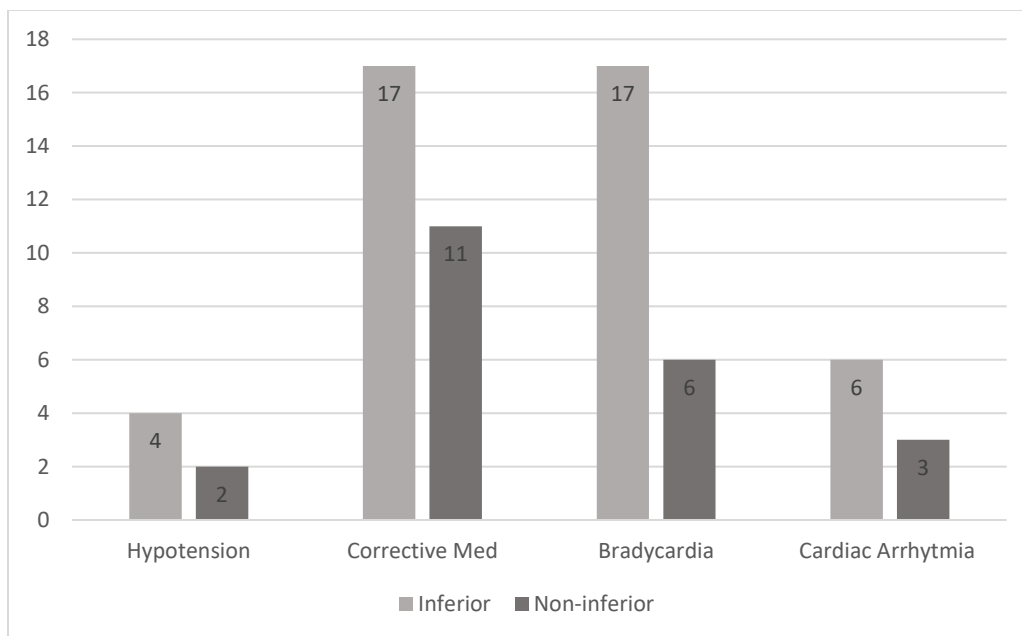
Inferential Statistics to Answer Research Questions

Research Question 1: Does the administration of NTG result in hypotension more often in inferior STEMI patients than non-inferior STEMI patients?

Inferior STEMI patients had 1.429 times the risk of developing hypotension than non-inferior STEMI patients after receiving NTG (OR 1.429, 95% CI [0.248, ∞]). The results were not significant ($p=0.521$), with four inferior STEMI patients and two non-inferior STEMI patients experiencing hypotension after receiving NTG (comparisons illustrated in Figure 1).

Figure 1

STEMI Patient Events by Occurrence



Note. Total number of patients ($n=73$) compared for hypotension and bradycardia. Total number of patients ($n=74$) for occurrence of administration of corrective medication, as a fluid bolus or vasoactive medication to correct hypotension or bradycardia, and occurrence of cardiac arrhythmias. There were no significant differences in occurrence of hypotension ($p=0.521$), administration of corrective medications ($p=0.530$), bradycardia ($p=0.064$), and cardiac arrhythmias ($p=0.465$).

There was a significant difference in SBP noted between inferior STEMI patients and non-inferior STEMI patients after receiving NTG ($p=0.012$), with inferior STEMI patients' mean SBP reduced by 15.23 mmHg more than non-inferior STEMI patients after receiving NTG. After receiving NTG, inferior STEMI patients had a mean difference in SBP of -19 mmHg (95% CI [-27.4, -10.74]), compared to non-inferior STEMI patients, who had a mean difference in SBP of -10.9 mmHg (95% CI [-20.6, -1.1]). Table 5 below indicates the control variables with significant impacts on mean SBP which included antihypertensive medications ($p=0.025$) and diabetes mellitus ($p=0.023$), with a mean SBP decrease of 15.47 mmHg and mean SBP increase of 16.03 mmHg for each variable, respectively.

Table 5

Effects Estimates of Variables on Systolic Blood Pressure

Variable	Estimate	Std. Error	t	p
Inferior STEMI	-15.23	5.90	-2.58	0.012*
Hypertension	9.98	5.82	1.72	0.091
Diabetes Mellitus	16.03	6.86	2.34	0.023*
Obesity	13.14	8.38	1.57	0.122
Morphine	6.35	5.76	1.10	0.274
Antihypertensive	-15.47	6.74	-2.29	0.025*
Vasopressor/Bolus	5.34	5.91	0.90	0.370
(Intercept)	-18.59	6.43	-2.89	0.005

Note. P-values are of absolute t-values for each variable. Intercept is included for a point of reference, although no inferences will be made based on intercept data. Variables included above were decided with AIC, an automated model selection, to allow for inclusion of variables that had a stronger association to the response variable (SBP).

* $p < 0.05$

Research Question 2: Do patients with inferior STEMIs require additional interventions more frequently to correct hypotension or bradycardia than non-inferior STEMI patients following NTG administration?

When analyzing the need for a fluid bolus or corrective medication for hypotension or bradycardia, the odds of requiring one of these interventions was 1.086 times the risk for inferior STEMI patients compared to non-inferior STEMI patients (OR 1.086, 95% CI [0.439, ∞]). A total of 17 inferior STEMI patients and 11 non-inferior STEMI patients received a fluid bolus or corrective medication in this study, equating to 38.6% of inferior STEMI patients and 36.6% of non-inferior STEMI patients (illustrated in to Figure 1). The results were not significant ($p=0.530$).

Research Question 3: Do inferior STEMI patients experience more bradycardia and cardiac arrhythmias compared to non-inferior STEMI patients?

The occurrence of bradycardia was not significantly different between inferior and non-inferior STEMI groups ($p=0.064$), with inferior STEMI patients having 2.582 times the risk of bradycardia than non-inferior STEMI patients (OR 2.582, 95% CI [0.940, ∞]). Approximately 40% of inferior STEMI patients ($n=17$) had at least one documented occurrence of bradycardia, while approximately 20% of non-inferior STEMI patients ($n=6$) had at least one documented occurrence of bradycardia. There also was no significant difference in heart rate between inferior STEMI and non-inferior STEMI groups after NTG ($p=0.239$), with a lower mean difference in heart rate of 2.84 beats per minute observed in inferior STEMI patients following NTG.

The administration of an antihypertensive and the occurrence of a cardiac arrhythmia each significantly reduced mean heart rate ($p<0.001$, $p=0.015$), with a

reduction in mean heart rate of 14 beats per minute associated with antihypertensive medications while cardiac arrhythmias were associated with a mean reduction in heart rate of approximately nine beats per minute. Other variables evaluated with heart rate may be viewed below in Table 6. The risk for developing a cardiac arrhythmia was 1.415 times higher for inferior STEMI patients (n=6) than non-inferior STEMI patients (n=3) (OR 1.415, 95% CI [0.340, ∞]), however, this was not significant (p=0.465).

Table 6

Effects Estimates of Variables on Heart Rate

Variable	Estimate	Std. Error	t	p
Inferior STEMI	-2.84	2.39	-1.19	0.239
Diabetes Mellitus	-3.59	2.84	-1.26	0.211
Smoking	-4.03	2.37	-1.70	0.094
Morphine	3.34	2.39	1.40	0.167
Antihypertensive	-14.02	2.76	-5.09	<0.001**
Cardiac Arrhythmia	-8.65	3.47	-2.50	0.015*
(Intercept)	6.09	2.44	2.49	0.015

Note. P-values are of absolute t-values for each variable. Intercept is included for a point of reference, although no inferences will be made based on intercept data. Significant effects were found for antihypertensive medications and cardiac arrhythmias.

*p < 0.05; **p < 0.001

Research Question 4: Does NTG significantly reduce chest pain levels reported by STEMI patients?

Chest pain rating following the administration of NTG did not differ significantly between inferior and non-inferior STEMI groups (p=0.391). When rating chest pain on the numerical 0 to 10 Likert scale after receiving NTG, inferior STEMI patients reported less of a mean chest pain score reduction, with mean chest pain scores 0.61 higher than chest pain scores reported by non-inferior STEMI patients. For all STEMI patients in this

project, NTG administration did significantly reduce the mean chest pain score reported by the patients by 1.87 on the 0 to 10 Likert scale ($p < 0.001$). The administration of morphine also was associated with significantly increased chest pain levels ($p = 0.008$), with a mean chest pain score increase of 1.96 (Refer to Table 7 below).

Table 7

Effects Estimates of Variables on Chest Pain Rating

Variable	Estimate	Std. Error	t	p
Post-NTG CP	-1.87	0.35	-5.31	<0.001**
Inferior STEMI	-0.99	0.76	-1.30	0.200
Age	-0.05	0.03	-1.47	0.148
CAD	1.24	1.30	-0.96	0.342
Previous MI	-1.46	1.47	-0.99	0.326
Obesity	-1.90	1.17	-1.62	0.114
Morphine	1.96	0.71	2.77	0.008*
Analgesics	1.25	1.12	1.11	0.274
(Intercept)	9.32	2.11	4.42	<0.001

Note. Post-NTG CP represents chest pain (CP) ratings following the administration of NTG, with significant reductions for all STEMI patients ($p < 0.001$). Morphine was associated with significantly higher CP ratings ($p = 0.008$), while all other variables did not have a significant effect on CP changes before and after receiving NTG. Initial comparison to evaluate differences in CP reported by inferior and non-inferior STEMI patients after receiving NTG was not significant ($p = 0.391$), but due to model selection, STEMI location was included and again not significant ($p = 0.200$).

* $p < 0.05$; ** $p < 0.001$

Discussion

The route and dosage of NTG administered to STEMI patients varied greatly within this project. Bosson et al. (2019) and Engelberg et al. (2000) reported the use of only 0.4 mg sublingual NTG in patients within their studies. Robichaud et al. (2016) also reported 0.4 mg sublingual NTG, but included 0.4 mg intranasal NTG spray as a treatment modality for patients as well. Although this project did not seek to evaluate the variability of different routes of administration of NTG, with the account of

pharmacokinetics and therapeutic onset for each route. The variation was attempted to be accounted for by documenting medication doses, times, and routes for all medications during data extraction to allow for a more complete evaluation.

The four patients diagnosed with inferior STEMI that experienced hypotension had variable initial NTG doses and routes. One patient developed hypotension with a documented SBP of 89 mmHg following three doses of 0.4 mg sublingual NTG. Another patient developed hypotension and subsequent ventricular fibrillation following two doses of 0.4 mg sublingual NTG approximately three minutes following NTG administration. Successful management of the patient's condition occurred, and the patient was then placed on five micrograms per minute of intravenous NTG. The third patient with inferior STEMI had hypotension following a single dose of 0.4 mg sublingual NTG, but was eventually placed on a NTG intravenous infusion at five micrograms per minute without further incident. The fourth patient with inferior STEMI had "hypotension" documented by an EMS transport crew for a patient who was on a titrated dose of NTG, which was at 20 micrograms per minute at the time of discontinuation. SBP documented prior to discontinuation was consistently > 90 mmHg, with ability to down-titrate the NTG infusion. This patient was restarted on the NTG infusion per the cardiologist upon arriving to the cardiac catheterization laboratory.

The two patients diagnosed with non-inferior STEMI who developed hypotension both had received intravenous NTG. One patient had an undocumented amount of NTG, but also received diltiazem, metoprolol, and lorazepam before becoming hypotensive. The second patient was on five micrograms per minute of intravenous NTG when they

developed symptomatic bradycardia and hypotension. The patient responded to interventions and remained on the intravenous NTG without further adverse events.

The occurrence of hypotension observed in this project following administration of NTG does not appear to occur in a predictable fashion, with hypotension occurring after variable doses and routes of NTG. Interestingly, three of the six patients who developed hypotension remained on intravenous NTG, which supports continued use and titration of NTG in an individualized manner in response to each patient. Although it is unclear within this project, it is possible that healthcare provider preference or medical training played a role in the variability observed between NTG dosages and routes. However, regardless of the doses and routes of NTG that were provided to patients in this project, there was no significant difference in occurrence of hypotension between patients diagnosed with inferior STEMI compared to those with non-inferior STEMI.

The doses reported in previous studies ranged from a single dose (Engelberg et al., 2000), to three doses (Bosson et al., 2019), while Robichaud et al. (2016) accounted for unlimited doses. As in this project, Bosson et al. (2019) and Robichaud et al. (2016) did not specifically investigate the effects of multiple doses of NTG, but rather for the occurrence of hypotension, bradycardia, and adverse events. In this project, the observed initiation of intravenous NTG infusions after alternative sublingual or transdermal routes, in conjunction with intravenous dose titrations, provides information about how management and care of patients diagnosed with STEMI varies within the patient encounter. This observation likely relates to adapting to the patients' needs rather than adhering to an undeviating plan of care, ultimately supporting individualized patient care.

Robichaud et al. (2016) reported several of the same comorbidities and cardiovascular risk factors that were controlled for in this project, including previously diagnosed CAD, diabetes mellitus, hypertension, and hyperlipidemia. Demographic variables were controlled for in statistical analyses within this project to allow for identification of potential influences on outcome variables, although the aims of this project were not focused on detailed demographic analyses. Demographics were included to allow for simple comparisons between patients within this project to demographic information of patients with STEMIs in other studies.

In the analysis of gender frequency, females represented approximately 28% of the total patients included in this project. The approximate occurrence of female patients with STEMIs reported by Bosson et al. (2019), Engelberg et al. (2000), and Robichaud et al. (2016) was 39%, 48%, and 30%, respectively. O’Gara et al. (2013) reported female patients representing 30% of all STEMI patients in their study as well. Robichaud et al. (2016) and O’Gara et al. (2013) have the most comparable female frequencies reported when compared to the frequency of female patients found with this project.

The average age of all patients in this project (62.8 ± 11.8 years) is similar to that noted in a study that evaluated demographics of STEMI patients, with researchers reporting an average age of 62 (± 13.9) years for all patients (Boyer et al., 2012). The study conducted by Bosson et al. (2019), which had similar research questions to those analyzed in this project, reported a median age of 63 (IQR 54-75) for patients that received NTG. With this information, it does not appear that patients in this project were considerably different in demographics, with gender and age occurrences that are comparable to those reported in other studies.

In evaluating STEMI location, inferior STEMI patients represented approximately 59% of the patients included in this study, compared to the approximate 47% of patients in the study by Robichaud et al. (2016). A higher percentage of patients experienced an inferior STEMI in this project than the predicted range of 40% to 50% of patients with STEMIs (Warner & Tivakaran, 2020). The RCA was the most commonly occluded vessel in the inferior STEMI group, which is most often suspected with inferior STEMI identification on a standard 12-lead ECG (Namana et al., 2018). The left circumflex artery was the second most commonly occluded coronary artery in this project for patients with inferior STEMI, which may indicate left dominant circulation in these patients (Namana et al., 2018). For the non-inferior STEMI group, the LAD was the most commonly occluded vessel, which is consistent with anterior STEMI and left ventricular involvement (Taglieri et al., 2014). The observations of occurrence in this project support the most likely culprit vessels associated with each STEMI location (Namana et al., 2018; Taglieri et al., 2014), but also that inferior STEMI is not always associated with RCA occlusion.

It is important to note that the inferior STEMI patients in this project represent a subgroup of all STEMI patients that presented to the rural Midwestern hospital in 2019. It is not clear how this translates to the entire STEMI population that is treated at this facility, but does suggest the prevalence of patients that receive NTG with the diagnosis of inferior STEMI. Although RV infarct was not evaluated for specifically within this project, there were no documented additional diagnostic interventions in patients presenting with inferior STEMI. As RV infarct is a contraindication to administration of

nitrates to patients (Antman et al., 2004; Ibanez, 2018), specific identification of RV involvement would be beneficial.

The patient with Takotsubo cardiomyopathy was included in this study due to their clinical presentation, treatment, and diagnosis of STEMI within their medical record. Boyd and Solh (2020) discuss how closely ACS and Takotsubo may present, including ST segment elevation on a 12-lead ECG tracing. The potential for hemodynamic instability in patients with Takotsubo is related to left ventricular dysfunction and acute heart failure (Templin et al., 2015) and may be similar to that of STEMI patients. The inclusion criteria were met for this patient, even though the patient did not have a culprit vessel identified as causing ST-segment elevation due to lack of thrombotic or plaque occlusion. Had the patient not had STEMI included in the discharge diagnosis made by a cardiologist, the patient would have been excluded from this study.

Discussion of Research Question 1: Does the administration of NTG result in hypotension more often in inferior STEMI patients than non-inferior STEMI patients?

With regard to blood pressure, there is very weak evidence in this project to support any significant difference in occurrence of hypotension, defined as SBP < 90 mmHg, between inferior STEMI patients and non-inferior STEMI patients. The results in this project were similar to those reported by Robichaud et al. (2016), with no significant difference in occurrence of hypotension between inferior and non-inferior STEMI groups ($p=0.80$). Inferior STEMI patients in this project did, however, have a significantly greater reduction in mean SBP compared to non-inferior STEMI patients following receipt of NTG. Although the mean reduction in SBP between inferior and non-inferior

STEMI groups was significant ($p=0.012$) after receiving NTG, the lower observed SBP in the inferior STEMI group did not equate to a significantly higher occurrence of hypotension, as previously reported. This shows that patients with inferior STEMIs experienced increased effects from NTG compared to those with non-inferior STEMIs within this group of patients, without hemodynamic instability.

For all patients that received NTG in the study conducted by Bosson et al. (2019) there was a median change in SBP of -11 mmHg (IQR -26, 0), while in the study by Engleberg et al. (2000), the mean decrease in SBP in patients after receiving NTG was -11.8 mmHg (95% CI [-10.7, -13]). In this project, non-inferior STEMI patients had similar reduction in mean SBP compared to those in the previously listed studies, with mean SBP decrease of -10.9 mmHg, while inferior STEMI patients had a mean SBP decrease of -19 mmHg. The previously listed studies did not compare differences in SBP between inferior and non-inferior STEMI patients, whereas this project did, showing a significant difference in mean SBP reduction between the two groups. The difference in mean SBP may suggest increased effects of NTG on patients with inferior STEMIs, although Robichaud et al. (2016) found no significant difference in occurrence of drop in $SBP \geq 30$ mmHg following NTG between inferior and non-inferior STEMI groups ($p=0.87$). The decrease in $SBP \geq 30$ mmHg as investigated in previous studies (Bosson et al. 2019; Robichaud et al. 2016) was a threshold used to evaluate the sensitivity of patients to nitrates and how those with RV infarct would have a higher incidence in larger SBP decreases. Neither study found significant results, indicating the need to reconsider a blanket avoidance of nitrates in inferior STEMI patients. Although this project did not evaluate for a specific level of decrease in SBP, the lack of significance in comparing

occurrence of hypotension adds to the evidence supplied by previous studies, as patients diagnosed with inferior STEMI in this project did not experience hemodynamic instability after receiving NTG.

Antihypertensive medications were found to be a significant factor in reducing the mean SBP while all other variables were controlled for in this project. This suggests that the medications were effective in decreasing blood pressure, but also that antihypertensive medications may have contributed to the observed difference in decreased mean SBP between each inferior and non-inferior STEMI groups. This observation warrants further investigation, as the effects of antihypertensive medications were not compared with statistical analyses between patients with inferior and non-inferior STEMIs in this project. Although morphine and hemodynamic supportive measures did not have significant effects on SBP in this project, the regression model identified these variables as affecting the outcome variable of SBP more than other demographic variables or comorbidities.

Although it is not clear why NTG was associated with a significantly increased mean SBP in patients with diabetes, there are some potential explanations. Muntner, Whelton, Woodward, and Carey (2018) note that 66.3% of patients with diabetes have concurrent hypertension by American Diabetes Association (ADA) guidelines, while 77.1 % of patients with diabetes have hypertension by the ACC and AHA guidelines. The high prevalence in general, regardless of which guideline is used for defining hypertension, illustrates the close relationship between diabetes and hypertension. This may represent an overall higher SBP in patients presenting with STEMI with concurrent diabetes mellitus, however, this was not analyzed within this project. Additionally,

patients with diabetes may not respond to NTG with arterial dilation as well due to impaired nitric oxide pathways, which can occur with damaged endothelium (Tessari et al., 2010; Vavuranakis et al., 1999). As nitroglycerin converts to nitric oxide within the body (Kim, Kerndt, & Schaller, 2020), reduced efficacy may result given impaired metabolic pathways in diabetes. Although this is not a definite explanation for the observed significant increase in this project, it may indicate a need to investigate other factors relating to STEMI patients with diabetes mellitus and how standard medications may impact that specific population.

Discussion of Research Question 2: Do patients with inferior STEMIs require additional interventions more frequently to correct hypotension or bradycardia than non-inferior STEMI patients following NTG administration?

In comparing inferior and non-inferior STEMI groups and the number of patients requiring a medication to correct hypotension or bradycardia, there is a lack of evidence to support any true difference in need between the groups based on the occurrences observed in this project. Individuals who received these pharmacological interventions may not have needed the specific intervention based on hemodynamic data reviewed within the charts. Multiple individuals in both inferior and non-inferior STEMI groups received fluid boluses without concomitant hypotension, with no clear basis for administration identified during the chart review. The fluid boluses may have been administered as a prophylactic measure or fluid challenge to the patients, but were not documented as such. A total of 28 patients received a fluid bolus or vasoactive medication, while only six patients experienced true hypotension and three experienced symptomatic bradycardia. The patients with hypotension and bradycardia all responded

to fluid or medication administration and remained stable within the timeframe of interest for this project. Fluid bolus and vasoactive medication were included in the multivariable linear regression in the analysis of SBP following administration of NTG, however, these variables were not associated with a significant increase in SBP (refer to Table 5). Six patients experienced a ventricular arrhythmia, but none died within the timeframe of interest in this project.

Discussion of Research Question 3: Do inferior STEMI patients experience more bradycardia and cardiac arrhythmias compared to non-inferior STEMI patients?

Inferior STEMI patients in this project had lower mean heart rates than non-inferior STEMI patients, which ultimately was not a significant finding. In the entire observed population, there were 23 patients who had bradycardia, with a higher occurrence in inferior STEMI patients. Three patients in this project had symptomatic bradycardia, all of whom had inferior STEMIs, but all of whom also responded to medical interventions. Many patients with bradycardia were either noted to have stable bradycardia upon initial contact or have one documented heart rate below 60. This is similar to the observations made in Bosson et al. (2019), with 75% of bradycardic patients having a heart rate between 50 and 59 beats per minute, with a comparable occurrence of bradycardia noted in patients with RCA and non-RCA occlusions.

Antihypertensive medications were observed to have a significant effect on heart rate in this project. Of these medications, metoprolol was administered to 100% (n=19) of patients who received an antihypertensive medication. Diltiazem (n=1) and hydralazine (n=1) were also administered to separate patients in addition to at least one dose of metoprolol. Metoprolol, which is a cardiac-selective medication categorized as a beta-

blocker, has the ability to cause a decrease in heart rate, cardiac output, and blood pressure (Morris & Dunham, 2020). Similarly, Roolvink et al. (2016) identified a significant heart rate reduction in STEMI patients who received metoprolol. As the predominant antihypertensive medication provided to patients in this project, metoprolol and its effects on outcome variables of heart rate and SBP had strong hemodynamic influences identified in patients within this project.

When controlling for other variables, cardiac arrhythmias also affected mean heart rate in patients, with a mean reduction of approximately eight beats per minute. This observation points to the potential for adverse events following NTG administration, with lower heart rates observed in patients who experienced a cardiac arrhythmia. However, there is no evidence in this project that the occurrence of a cardiac arrhythmia differed significantly between inferior and non-inferior patients. STEMI location in this project was not a strong predictor of an adverse event occurring, while other variables with strong effects on SBP and heart rate may have been more likely to contribute to the occurrence.

Discussion of Research Question 4: Does NTG significantly reduce chest pain levels reported by STEMI patients?

There was no significant difference in chest pain reduction between inferior and non-inferior STEMI patients, meaning no single group experienced a greater benefit from NTG in this project. Interestingly, morphine was associated with increased mean chest pain, which might be attributed to higher initial and subsequent chest pain scores reported by individuals who received this medication. This may be because morphine was truly reserved for patients with higher pain ratings that were not responsive to NTG, as

recommended by Frampton et al. (2020), since the use of morphine inhibits the therapeutic effects of commonly used antiplatelet medications.

Kendrick and Strout (2005) identified a change in pain rated on the numeric pain scale of 1.39 ± 1.05 (95% CI, 1.27-1.51) to be significant, which is how chest pain was evaluated in this project. As the verbal analog scale (VAS) for pain can be correlated with the numeric pain scale (Holdgate, Asha, Craig, & Thompson, 2003), pain reduction around 1.3 was also considered significant in an alternative study using VAS to assess pain (Todd, Funk, Funk, & Bonacci, 1996). The mean reduction in chest pain scores in this project was 1.9 for all STEMI patients, representing a significant reduction in pain and demonstrating the benefit of NTG and its ability to reduce chest pain in STEMI patients in this project. Mean chest pain reduction reported by both Bosson et al. (2019) and Engleberg et al. (2000), was 2.6, again providing support for the role of NTG in chest pain reduction, including chest pain experienced by STEMI patients. The results from this project, as well as the results in previous studies, indicate that patients experiencing STEMI benefit from the effects of NTG by significant reductions in chest pain.

Clinical Implications for Practice

This DNP project contributes to clinical practice by identifying variables that influence hemodynamic variables as well as differences that occur in inferior and non-inferior STEMI patients who received NTG. NTG, which was provided to a large number of patients with the diagnosis of inferior STEMI, did not result in a significant difference in occurrence of hypotension when compared to non-inferior STEMI patients. Although there should not be generalizations transferred directly to practice, there are implications for provision of care to patients on an individual basis.

The concern relating to NTG administration to patients with inferior STEMI identified on a 12-lead ECG is RV infarct and the potential for hemodynamic collapse. In this project, RV infarct was not evaluated for specifically. Even though patients with inferior STEMI received NTG with few adverse events, it is unclear if these patients did have RV involvement that precipitated adverse events. Further investigation in the effects of NTG on patients with inferior STEMI and concomitant RV infarct would be beneficial, as well as diagnostic tools to identify RV involvement.

One intervention that could assist healthcare providers in identifying RV infarct would be to perform a right-sided ECG. Increasing views of the heart by adding additional leads to a standard 12-lead ECG can increase sensitivity to diagnosing STEMI, improve infarct location identification, and identify infarctions that may not be visible on a standard 12-lead ECG (Tragardh, Claesson, Wagner, Zhou, & Pahlm, 2007; Vogiatzis et al., 2019). Bischof et al. (2018) recommend evaluation of lead V4R to identify RV involvement during an acute MI, because of low sensitivity and specificity of standard 12-lead ECG analysis. Similarly, Kanovsky et al. (2016) discuss the value of the right-sided ECG in identifying RV infarct, as patients with occlusions to the RCA, circumflex artery and LAD may have RV involvement that may not be recognized using standard 12-lead ECG analysis. No patients in this study had a right-sided ECG analysis, which would be one recommendation for future patients presenting to the rural Midwestern hospital. The right precordial leads would assist healthcare providers in identifying RV involvement, which would help to guide individualized treatment.

This project identified that NTG was associated with a significant reduction in chest pain experienced by patients with the diagnosis of STEMI. Ethically, healthcare

providers should be providing analgesia to patients, and doing so with evidence to support such interventions. As newer research shows that opioids reduce the efficacy of antiplatelet medications used in STEMI patients (Frampton et al., 2020), it is important to use medications that provide the most overall benefit. As adverse events were not significantly different between inferior and non-inferior STEMI patients in this project, the safety of NTG by these standards supports the viability of this medication as a possible analgesic choice for both inferior and non-inferior STEMI patients.

As patients with RV infarct have higher immediate mortality rates (Noguchi et al., 2019), implementing a right-sided ECG would help to more easily identify RV infarct, guiding treatment of the patient. Providers would have additional information from which to base decisions, including making informed decisions on whether or not to withhold NTG from patients. Additionally, with the identification of RV infarct, providers would be able to anticipate the need for fluid resuscitation, vasoactive medications and potential external pacing (Inohara, Kohsaka, Fukuda, & Menon, 2013; Noguchi et al., 2019), and respond to the patients' needs in the event of hemodynamic collapse.

Recommendations for Future Research

Several recommendations for future research can be made based on results in this DNP project. The first recommendation would be for a prospective study to evaluate the effects of NTG on hemodynamic variables and chest pain on inferior and non-inferior STEMI patients. This project, as a retrospective review, has limitations in generalizability to STEMI patients and cannot explain direct causality, for which a prospective study would be necessary.

In a prospective study or similar future retrospective studies, more strict criteria may be warranted when evaluating the occurrence of bradycardia, with modifications to what identifies a patient as bradycardic. Recommendations may be to include patients that experience symptomatic bradycardia or consistently documented bradycardia with heart rates < 60 beats per minute. This way, a transient or asymptomatic decrease in heart rate would not be considered as an adverse event in patients. In this project, one occurrence of a documented heart rate below 60 beats per minute was counted toward an occurrence of bradycardia, even though only 3 patients had hemodynamic instability and several others had one heart rate below 60 beats per minute, providing an occurrence rate but not necessarily a clear picture of patient condition.

As NTG doses and routes of administration varied among patients within this project, a future prospective study or similar retrospective study would control for this variable. Although it is possible to evaluate patient hemodynamics based on therapeutic onset and pharmacokinetic properties of NTG, a controlled dose and route would help remove potential limitations with the results. With the removal of variation, the effects of NTG on hemodynamic variables may be more clearly identified in STEMI patients.

The effects of metoprolol on STEMI patients should also be evaluated, as this medication served as a variable that had significant effects on both SBP and heart rate within this project. Research has been conducted to evaluate potential benefits of metoprolol prior to PCI and its impact on infarct size (García-Ruiz et al., 2016; Roolvink et al., 2016), however, the data does not have consistent results with regard to the medication's ability to reduce infarct size and mortality during the acute phase in STEMI

patients. As 19 patients in this study received this medication, further investigation on its effects on this patient population would be beneficial.

Another recommendation for future research would be to include the identification of RV infarct within the study sample. This could be done in comparative analyses between STEMI patients with and without RV infarct, but also as a simple observation of occurrence. Because RV infarction occurs at a variable frequency within inferior STEMI patient populations (Bischof et al., 2018; Nagam et al., 2017), further analysis into the specific topic would be a beneficial contribution to the knowledge regarding STEMI patients. Although this project did not seek to identify patients with RV infarct within the sample, the results of the effects of NTG on inferior STEMI patients contribute to the research suggesting the elimination of avoidance of NTG in individuals with inferior STEMI identification. Additional diagnostic tools, such as the right-sided ECG, may be utilized to identify RV involvement with the goal of removing hesitancy in the provision of NTG to patients with inferior STEMI identified on ECG analysis.

Strengths

To mitigate potential errors that may occur with retrospective chart reviews, this DNP project aimed to follow recommendations on how to conduct such a project (Kaji, Schriger, & Green, 2014; Vassar & Holzmann, 2013). The sample size exceeded the minimum number of individuals that was determined by the sample size calculator, reducing probability of type II error. Although several patients were excluded from the multiple variable regressions evaluating blood pressure and heart rate due to incomplete data for these specific analyses models, there were 66 and 67 patients, which exceeded the minimum of 64 individuals that was determined by the sample size calculator. IRB

approval was obtained from both the hospital and through Northern Michigan University prior to data collection, and a data template was used to organize extracted data to allow for organization and to maintain patient confidentiality. These measures as recommended by Vassar and Holzmann (2013), increase the strength of studies by adhering to systematic data extraction and upholding patient confidentiality. Additionally, exclusion criteria for this project addressed vulnerable populations, which addresses ethical considerations that may arise when conducting a retrospective chart review (Vassar & Holzmann, 2013).

Limitations

One of the main limitations identified in this project is the retrospective design and subsequent sampling technique. Because the sampling of patients was a convenience sample, bias is not accounted for due to the non-random sampling techniques used. Because of this, generalizations cannot be made about entire STEMI populations (Vassar & Holzmann, 2013), as analyses describe only the observations within the specific sample of patients within this project. Although effects estimates were provided for variables within this project, their influence on outcome measures should be viewed as associations and only applied to patients within this project due to lack of randomization. Additionally, selection bias is introduced to the project with the exclusion of patients from statistical analyses due to missing data (Kaji et al., 2014). Although the minimum number of required individuals as determined by the sample size calculator was surpassed with each analysis, it is important to address potential selection bias resulting from the exclusion of patients. Other limitations in this project include conducting the project at a single facility and including patients that presented to the facility within a one-year time-

frame. Including data on patients from additional locations and extending the time frame from which patients could be included may have been beneficial in reducing bias as well as when drawing observational inferences. Additionally, the doses and routes of NTG administration were not controlled for within this project, and may be considered a limitation due to the high variability among patients.

Conclusion

As NTG remains a frontline medication used in STEMI patients, both to reduce angina and as an antihypertensive (de Alencar Neto, 2018), this DNP project sought to contribute further to what is known about the effects and safety of NTG in STEMI patients. The purpose of this DNP project was to explore the safety of NTG use in the treatment of patients diagnosed with STEMI by evaluating the effects of NTG on hemodynamic measures and angina. Outcome variables of SBP, heart rate, occurrence of cardiac arrhythmias, and need for medical interventions to correct hemodynamic instability thus were compared between inferior and non-inferior STEMI patients who received NTG. As the AHA discourages the use of NTG in patients with RV infarct (Antman et al., 2004), further investigation into the provision of NTG to patients with inferior STEMI and RV infarct is warranted. Although identification of the occurrence of RV infarct was not conducted within this project, diagnostic measures to improve identification of RV infarct could provide valuable information to healthcare providers, and subsequently used to guide individualized patient care.

In this project, there was no significant difference in occurrence of hypotension in inferior STEMI patients and non-inferior STEMI patients who received NTG. Mean SBP was lower in inferior STEMI patients, however, not to the extent of instability or

significant increased need for medical intervention. There was also no significant difference in occurrence of cardiac arrhythmias or bradycardia between the two groups, but inferior STEMI patients did have lower mean heart rates. Additionally, NTG provided patients with significant reductions in chest pain in both inferior and non-inferior STEMI groups, supporting its therapeutic use in this patient population. Overall, these results suggest the general safety of NTG in patients eligible to receive it, even without specific diagnostic measures to identify RV involvement.

For advanced practice nurses, the information in this project may be a valuable component to their role in providing individualized patient care. As a member of the interdisciplinary team, it is necessary to consider individualized treatment options for patients. This includes medications, associated safety concerns prior to administration, and potential adverse events that may occur in patient populations. Advanced practice nurses may use clinical judgement and incorporate additional diagnostic tools in the treatment of STEMI patients, including the use of right-sided ECG analysis in inferior STEMI patients. This may help guide the provision of medications such as NTG, which may relieve angina associated with STEMI, and ultimately improve the level of individualized patient care.

In this project, NTG use in inferior STEMI patients did not result in significantly more adverse events than in non-inferior STEMI patients, even without the identification of RV infarct. This suggests reevaluating the avoidance of NTG based on concerns of hemodynamic adverse events due to potential RV infarct. Inferior STEMI patients should receive a right-sided ECG to detect RV infarct, with lead V4R serving as the most sensitive marker (O’Gara et al., 2013). Additional views of the heart and higher

sensitivity in detecting the presence of RV infarct with a right-sided ECG can help guide healthcare providers in providing highly-individualized care. As in similar studies (Bosson et al., 2019; Engleberg et al., 2000; Robichaud et al., 2016), a prospective study to evaluate the safety and effects of NTG in STEMI patients is recommended.

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Appendix A

JHNEBP MODEL AND TOOLS- PERMISSION



Johns Hopkins Nursing Center for Evidence-Based Practice

Thank you for your submission. We are happy to give you permission to use the JHNEBP model and tools in adherence of our legal terms noted below:

-
- You may not modify the model or the tools without written approval from Johns Hopkins.
 - All reference to source forms should include “©The Johns Hopkins Hospital/The Johns Hopkins University.”
 - The tools may not be used for commercial purposes without special permission.

If interested in commercial use or discussing changes to the tool, please email ijhn@jhmi.edu.

Downloads:

[**JHNEBP Tools-Printable Version**](#)

[**JHNEBP Tools-Electronic Version**](#)

Do you prefer hands-on learning?

We are offering a 5-day intensive Boot Camp where you will learn and master the entire EBP process from beginning to end. Take advantage of our retreat-type setting to focus on your project, collaborate with peers, and get the expertise and assistance from our faculty. Click [**HERE**](#) to learn more about EBP Boot Camp. Group rates available, [email ijhn@jhmi.edu](mailto:ijhn@jhmi.edu) to inquire.

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Appendix B



Graduate Studies and Research
 Marquette, MI 49855-5301
 906-227-2300
www.nmu.edu/graduatestudies/

Memorandum

TO: Olivia Montgomery
 School of Nursing

CC: Kristi Robinia
 School of Nursing

FROM: Lisa Schade Eckert
 Dean of Graduate Education and Research

DATE: May 15, 2020

SUBJECT: IRB Reciprocal Approval
 NMU Approval Number: HS20-1131
 “A retrospective review to evaluate and compare the use of nitroglycerin in patients diagnosed with inferior ST elevated myocardial infarction and patients diagnosed with non-inferior ST elevated myocardial infarction”
IRB Approval Date: 5/15/2020
 Proposed Project Dates: 5/20/2020 – 6/27/2020

This IRB proposal, “A retrospective review to evaluate and compare the use of nitroglycerin in patients diagnosed with inferior ST elevated myocardial infarction and patients diagnosed with non- inferior ST elevated myocardial infarction,” has been approved under the reciprocal review process.

The study is approved by [REDACTED] “hospital” IRB.

Include the NMU proposal number (HS20-1131) and the contact information of the NMU researcher and the NMU IRB Administrator on all research materials and on any correspondence regarding this project at Northern Michigan University.

Any changes or revisions to your approved research plan must be approved by the Institutional Review Board (IRB) prior to implementation.

If you do not complete your project within 12 months from the date of your approval notification, you must submit a Project Renewal Form for Research Involving Human Subjects. You may apply for a one-year project renewal up to four times.

All forms can be found at the NMU Grants and Research website: <http://www.nmu.edu/grantsandresearch/node/102>

Appendix C

Chart Review Methodology

1. Obtain Institutional Review Board (IRB) approval
2. Construct template for data extraction
3. Obtain list of patient's with STEMI
 - a. Contingent on STEMI tracking system
 - b. May include individuals that activated a STEMI alert – requiring further inquiry
4. Access patient information
 - a. Begin with searching for discharge diagnosis of STEMI
 - b. Not all patients that activate a STEMI response are true STEMIs
 - c. If patient has discharge diagnosis of STEMI, continue with chart review for that patient
 - d. If discharge diagnosis does not include STEMI, patient excluded from project
5. Review chart for patient inclusion and exclusion criteria
 - a. Inclusion criteria
 - i. Received NTG
 - ii. Chest pain of suspected cardiac origin
 - iii. 18 years of age or older
 - iv. Diagnosis of STEMI (ECG/expert cardiologist diagnosis)
 - b. Exclusion criteria
 - i. Did not receive NTG
 - ii. Pregnant women
 - iii. Thoracic trauma
 - iv. Vulnerable populations
 - v. English as secondary language
6. Begin extraction of data into template
 - a. Patient demographics: Age, gender, past medical history relating to cardiac risk factor (ie: Previous MI, Diabetes mellitus, smoking)
 - b. Identify through documentation on patient location and region of STEMI
 - i. Culprit vessel causing STEMI (coronary artery)
 - ii. Inferior/Anterior/Posterior/Lateral
 - iii. Obtained from cardiology documentation
 - c. Extract all heart rates, blood pressures, oxygen saturations, respirations with associated time (oxygen saturation and respirations not evaluated in this project)
 - d. Extract patient rated chest pain and times
 - e. Extract all medications with associated administration time, route, and dose
 - f. Extract arrhythmias noted in chart and time of occurrence

7. Sort data
 - a. Hemodynamics prior to administration of NTG and first documented after NTG based on medication onset and half-life to be used for ratio level analyses on effects of NTG
 - b. Review all hemodynamics for each patient
 - i. Note if patient was hypotensive or bradycardic based on parameters
 - ii. Note if patient experienced a cardiac arrhythmia or adverse event
 - iii. Note corrective medications, either as vasopressor or fluid bolus and if patient was responsive medically to interventions
8. Analyze data based on specific research question

Appendix D

Software Citations

Name	Citation
R	R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/ .
cAIC4	Saefken, B., Ruegamer, D., Kneib, T., and Greven, S. (2018), Conditional Model Selection in Mixed-Effects Models with cAIC4, ArXiv e-prints 1803.05664.
lme4	Douglas Bates, Martin Maechler, Ben Bolker, Steve Walker (2015). Fitting Linear Mixed-Effects Models Using lme4. <i>Journal of Statistical Software</i> , 67(1), 1-48. doi:10.18637/jss.v067.i01.
lmerTest	Kuznetsova A, Brockhoff PB, Christensen RHB (2017). “lmerTest Package: Tests in Linear Mixed Effects Models.” <i>Journal of Statistical Software</i> , 82(13), 1-26. doi: 10.18637/jss.v082.i13 (URL: https://doi.org/10.18637/jss.v082.i13).
lmSubsets	Hofmann M, Gatu C, Kontoghiorghes E, Colubi A, Zeileis A (2020). <i>lmSubsets: Exact Variable-Subset Selection in Linear Regression</i> . R package version 0.5-1, (URL: https://CRAN.R-project.org/package=lmSubsets).
psych	Revelle, W. (2020) psych: Procedures for Personality and Psychological Research, Northwestern University, Evanston, Illinois, USA, https://CRAN.R-project.org/package=psych Version = 2.0.7,.
tidyverse	Wickham et al., (2019). Welcome to the tidyverse. <i>Journal of Open Source Software</i> , 4(43), 1686, https://doi.org/10.21105/joss.01686
xtable	David B. Dahl, David Scott, Charles Roosen, Arni Magnusson and Jonathan Swinton (2019). xtable: Export Tables to LaTeX or HTML. R package version 1.8-4. https://CRAN.R-project.org/package=xtable
yarr	Nathaniel Phillips (2017). yarr: A Companion to the e-Book “YaRrr!: The Pirate’s Guide to R”. R package version 0.1.5. https://CRAN.R-project.org/package=yarr