Unlocking the Mystery of Cardiogenic Shock in STEMI Patients: Why Concordance Matters and How PPCI Can Help

By

Mohammad Zahurul Islam

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Department of Physiology and Pathophysiology

University of Manitoba

Winnipeg

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Abstract

Background: ST Elevation Myocardial Infarction (STEMI) complicated by cardiogenic shock (CS) is associated with significant morbidity and mortality which remains unchanged over the last decade. One potential reason is lack of concordance among CS defining parameters: (1) systolic blood pressure (SBP) <90 mmHg for ≥30 min or requiring vasopressors and/or mechanical support, (2) cardiac index (CI) ≤1.8 L/min/m2 or ≤ 2.2 L/min/m^2 in the presence of inotropic agents/vasopressors, (3) lactate ≥ 2 mmol/L. Limited knowledge exists regarding the concordance among these three parameters in STEMI patients.

Objectives: We aim to evaluate (1) incidence and concordance among these CS defining parameters in STEMI patients; (2) impact of primary percutaneous coronary intervention (PPCI) on these parameters, and (3) identify their association with outcomes.

Material & methods: 204 STEMI patients were taken to cardiac catheter laboratory for primary PCI at the St. Boniface hospital were recruited by non-invasive cardiac system derived hemodynamic parameters, invasive blood pressure and lactate level on arterial blood gas analysis, pre-PPCI, post-PPCI, and POD-1.

Results: The incidence of CS defining parameters pre-PPCI [SBP: 17 (8.5%); CI: 31 (15.5%); lactate 58 (29%)], post-PPCI [SBP: 17 (8.5%); CI: 18 (9%); lactate 35 (17.5%)] demonstrated a low-degree of concordance of three CS defining parameters. PPCI improved CI and lactate parameters, but not SBP. Adverse outcomes (death at 30 days and in-hospital stay >4 days) were observed in 21.6% patients and these patients were marked by low stroke index, [pre-PPCI (28.9±9.5 vs 38.2±9.9) ml/m^2, p<0.001; post-PPCI (29.4±10.5 vs 39.5±9.5) ml/m^2, p<0.001 and POD-1 (28.7±9.5 vs 35.3±8.1) ml/m^2, p<0.001], low CI at rest, [(2.4±0.9 vs 2.9±0.9) L/min/m^2, p<0.05], low CPI at rest [(0.5±0.3 vs 0.6±0.2) Watt/m^2, p<0.05], low CPO at rest [(0.9±0.6 vs 1.2±0.5) Watt, p<0.05], and low Granov-Goor Index, [pre-PPCI (9.5±3.6) vs (12.4±3.6), p<0.001; post-PPCI (9.5±3.8) vs (12.8±3.8), p<0.001 and POD-1 (8.7±2.6) vs (10.7±2.8), p<0.001].

Conclusion: Incidence of a CS defining parameter is significantly different in STEMI patients compared to non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA), and cannot be used interchangeably. PPCI improves these parameters, with the exception of SBP. Low SI, GGI were observed in patients experiencing adverse outcomes.

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Dedication

This thesis is dedicated to my parents (Late. Mohammad Salim and Suraya Aktar), who have always believed in me and encouraged me to pursue my dreams. Your unwavering faith in me has been the driving force behind my success.

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Lastly, I extend my heartfelt appreciation to my friends and family for their love and support that have sustained me through the ups and downs of my journey. I am humbled and grateful to have had you all as a part of this incredible journey, and I dedicate this thesis to each one of you.

List of Abbreviations

A

ABG: Arterial Blood Gas
ABP: Arterial Blood Pressure
ACS: Acute Coronary Syndrome
ADH: Antidiuretic Hormone
AHA: American Heart Association
AMI: Acute Myocardial Infarction
ANCHOR study: Assessment of ECMO in Acute Myocardial Infarction with Non-reversible Cardiogenic Shock to Halt Organ Failure and Reduce mortality study
ASSENT-2 study: Assessment of the Safety and Efficacy of a New Thrombolytic-2 study

B

BMI: Body Mass Index

C

CABG: Coronary Artery Bypass Graft
CAD: Coronary Artery Disease
CCDSS: Canadian Chronic Disease Surveillance System
CI: Cardiac Index
CKD: Chronic Kidney Disease
cm: centimeter
CMR imaging: Cardiac Magnetic Resonance imaging
CO: Cardiac Output
CO2: Carbon dioxide
CPI: Cardiac Power Index
CPO: Cardiac Power Output
CRP: C- Reactive Protein
CS: Cardiogenic Shock
CULPRIT-SHOCK trial: Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock trial
CVP: Central Venous Pressure

D
DM: Diabetes Mellitus

E

ECMO: Extracorporeal Membrane Oxygenation
EHS-PCI study: Euro Heart Survey – Percutaneous Coronary Intervention study
EKG: Electrocardiogram
eNOS: endothelial Nitric Oxide Synthase
EPR: Electronic Patient Record
ESC: European Society of Cardiology
ESC-HF study: European Society of Cardiology – Heart Failure study
ESCAPE study: Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness study

F

FDA: Food and Drug Administration
fL: femtoliter

G

GBD: Global Burden of Disease
GGI: Granov-Goor Index
gm: Gram

I

IHD: Ischemic Heart Disease
IABP: Intra-aortic Balloon Pump
IABP-SOAP II trial: Intra-aortic Balloon Pump in Cardiogenic Shock II trial
IABP-SHOCK II trial: Intra-aortic Balloon Pump in Cardiogenic Shock II trial
IDBP: Invasive Diastolic Blood Pressure
iNOS: inducible Nitric Oxide Synthase
ISBP: Invasive Systolic Blood Pressure
IL-6: Interleukin-6

K

KAMIR-NIH study: Korean Acute Myocardial Infarction Registry – National Institutes of Health study
kg: Kilogram

L

L: Litre
LAD: Left Anterior Descending artery
LM: Left Main Artery
LV: Left Ventricle
LVAD: Left Ventricular Assist Device
LVEDP: Left Ventricular End Diastolic Pressure

M

MAP: Mean Arterial Pressure
m: Meter
meq: milliequivalent
min: minute
mm: millimeter
mmol: micromole
ml: milliliter

N

NE: Norepinephrine
ng: Nanogram
NIBP: Non-Invasive Blood Pressure
NICaS: Non-Invasive Cardiac System
NICOM device: Non-Invasive Cardiac Output Monitor device
NIDBP: Non-Invasive Diastolic Blood Pressure
NISBP: Non-Invasive Systolic Blood Pressure
NO: Nitric Oxide
NSTEMI: Non-ST Elevation Myocardial Infarction

P

PAC: Pulmonary Artery Catheterization
PCI: Percutaneous Coronary Intervention
PCWP: Pulmonary Capillary Wedge Pressure
PiCCO system: Pulse index Continuous Cardiac Output system
p-LVAD: percutaneous Left Ventricular Assist Device
p-MCS devices: percutaneous Mechanical Circulatory Support devices
POD-1: Post Operative Day-1
PPCI: Primary Percutaneous Coronary Intervention
PROCAM study: Prospective Cardiovascular Münster study

R

RAAS: Renin Angiotensin Aldosterone System
RCT: Randomized Control Trial
REB: Research Ethics Board
REDCap: Research Electronic Data Capture
RHC: Right Heart Catheterization

S

SBP: Systolic Blood Pressure
SCAI: Society for Cardiovascular Angiography and Interventions
SHOCK trial: Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock trial
SIRS: Systemic Inflammatory Response Syndrome
STEMI: ST Elevation Myocardial Infarction
SV: Stroke Volume
SVI: Stroke Volume Index
SVR: Systemic Vascular Resistance
SYNTAX score: Synergy Between PCI With Taxus and Cardiac Surgery score

T **TD:** Thermodilution **tPA:** tissue Plasminogen Activator **TPR:** Total Peripheral Resistance **TPRI:** Total Peripheral Resistance Index **TBW:** Total Body Water **TNF-α:** Tumor Necrosis Factor-α **U** **UA:** Unstable Angina **μmol:** micromole	**V** **VA-ECMO:** Veno-arterial Extracorporeal Membrane Oxygenation **VSR:** Ventricular Septal Rupture **VV-ECMO:** Veno-venous Extracorporeal Membrane Oxygenation **W** **WBEB:** Whole-Body Electrical Bioimpedance **WHO:** World Health Organization

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Chapter 01.

Introduction

1.1. What is Ischemic Heart Disease (IHD)?

Ischemic heart disease (IHD), also referred to as coronary artery disease (CAD), is a clinicopathological condition characterized by atherosclerotic plaque build-up beneath the inner endothelial layer of an epicardial coronary artery. The progressive nature of this pathological process leads to narrowing of the coronary arteries supplying oxygen-rich blood to the myocardium [1,2]. The onset and progression of plaque build-up occurs over a prolonged period of time and are primarily driven by modifiable risk factors such as unhealthy lifestyle choices, hypertension, diabetes mellitus, hypercholesterolemia, chronic kidney disease, and smoking. As a result of the arrowing of coronary arteries, myocardial blood supply is compromised, leading to myocardial ischemia or infarction in the event of an abrupt blockage due to plaque rupture and thrombus formation [1,3]. The myocardium is a highly metabolically active organ. Although, in an average sized person (~75-80 kg), heart weights between 233 to 383 grams (~0.45-0.5% of total body weight), however, it requires nearly 5% of the total cardiac output for its normal functioning at rest [4]. The myocardium extracts fairly high degree of oxygen from this coronary blood supply at rest; hence, exercise-induced augmented myocardial oxygen demand can be met only by increasing coronary blood supply [5].

1.2. Classification of IHD

Patients with atherosclerotic coronary artery disease present with a wide variety of symptoms. The classification of these presentations can be broadly divided into two categories: chronic (stable) coronary syndrome and acute (unstable or high-risk) coronary syndrome (ACS) **[Figure 1]** [1,6–8].

Chronic coronary syndrome is also known as stable IHD [7]. Such patients either remain asymptomatic at rest, and present with "exertional angina" that is predictably associated with a certain physical effort. Majority of the patients experience chest pain/pressure or discomfort at the time of physical activity (increase in myocardial blood supply demand due to activity) that is described as angina. However, it is important to note that some individuals may present with atypical symptoms, such as dyspnea, which is known as "angina equivalence". Despite significant individual variations, the characteristics of the pain experienced by a patient with chronic coronary syndrome tend to remain consistent over time [9].

In contrast, abrupt intra-coronary plaque rupture and subsequent thrombus formation resulting in either complete or partial occlusion of the coronary arteries with subsequent cardiac troponin elevation, with or without electrocardiogram (EKG) changes, leading to myocardial necrosis is known as heart attack or acute myocardial infarction (AMI) [1,10].It is a critical emergency and requires immediate medical attention, as any delay is associated with excess morbidity and mortality.

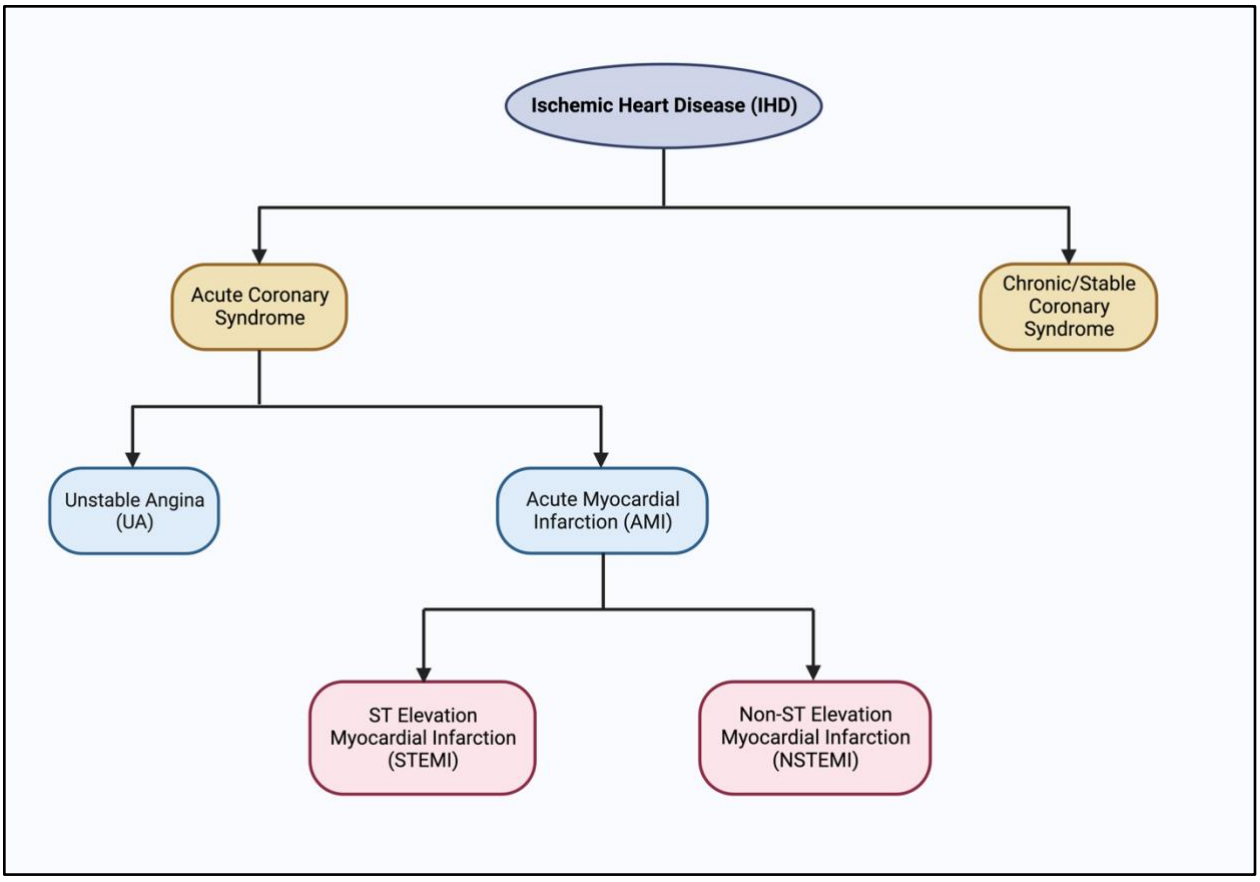

Figure 1: Classification of Ischemic Heart Disease

Clinical diagnosis of MI involves the use of diagnostic tools such as electrocardiogram (EKG) and measurement of plasma troponin levels. Troponin is a complex globular protein that is a component of tropomyosin, a contractile protein present in cardiomyocytes. In the event of myocardial infarction or injury, there is a release of troponin from cardiomyocytes into the bloodstream, with sequential rise in plasma troponin values indicative of myocardial necrosis. Thrombus can result in either complete or partial occlusion of coronary artery. Complete obstruction of the coronary artery results in ST segment elevation, known as ST Elevation Myocardial Infarction (STEMI), whereas partial obstruction leads to ST-T segment changes other than elevation, known as Non-ST Elevation Myocardial Infarction (NSTEMI) [11]. In cases where there is an abrupt change in clinical characteristics of chest pain (pain with lesser activity or at

rest) with or without EKG changes, but no troponin rises, the diagnosis of Unstable Angina (UA) is made. Such conditions are clustered under the diagnosis of "acute coronary syndrome (ACS)" encompassing unstable angina (UA) and acute myocardial infarction (AMI).

These ACS patients typically present with chest pain that may also be associated with dyspnea, nausea, or a combination of these symptoms. In a small number of patients, myocardial ischemia can lead to ventricular arrythmia, resulting in cardiac arrest.

1.3. Risk factors of IHD

IHD patients present with multiple risk factors, which can be broadly categorized non-modifiable and modifiable risk factors [12]. Non-modifiable risk factors include age, sex, race, and familial history of premature CAD [13–15]. Typically, IHD patients are predominantly male and older (>65 years) [12,9]. Mortality due to CAD is higher in black patients compared to their Caucasian counterparts [16]. Modifiable risk factors are mainly related to lifestyle [17], and include dietary habits (excess refined and processed food) [18], tobacco smoking, physical inactivity or sedentary lifestyle, obesity, hypertension, diabetes, hypercholesterolemia, and psychological stress [19–21]. Coexistence of multiple risk-factors, instead of an isolated one significantly increases the risk of CAD [22].

1.4. Incidence, prevalence and associated complications of IHD

IHD is prevalent globally, with an estimated 126.5 million individuals affected [23]. According to data from American Heart Association **(AHA)**, there are nearly 720,000 new coronary events diagnosed annually [24]. In Canada, the Canadian Chronic Disease Surveillance System **(CCDSS)** reports for 2017-18 that 8.5% (1 in 12 persons) of individuals over 20 years of age are affected by cardiovascular disease, primarily IHD, with 2.1% having a history of heart attack [25,26]. In Manitoba, the prevalence of IHD is reported 8.3% of individuals over 19 years affected [27]. NSTEMI is more prevalent than STEMI and contributes to approximately 75% of myocardial infarctions [28].

In contrast to typically observed presentations some patients may present with ischemia-induced complications, such as papillary muscle or chordal tear, ventricular septal or ventricular free wall rupture, life threatening ventricular arrhythmias or sudden cardiac death. Majority of these complications leads to significant hemodynamic instability that is associated with significantly higher mortality. Whereas in some patients, the myocardial damage from ischemia can abruptly impair the heart's ability to maintain adequate cardiac output, required for optimum tissue perfusion (in absence of any cardiac structural damage), a condition described as cardiogenic shock (CS). CS can complicate up to 5-10% of patients with AMI [29–31]. A prospective study evaluating 4647 consecutive AMI patients between 2010 and 2019 identified CS in (239/4647, 5.1%) all-comer patients (5.6% of STEMI patients, and 3.9% of NSTEMI patients) [32]. Other studies have also described higher incidence of CS among STEMI patients in comparison to those presenting with NSTEMI [29]. Additionally, CS is more frequently observed in older adults (aged

>75 years), females, previous history of myocardial infarction or heart failure, and individuals of Asian descent [29,31]. Patients with NSTEMI-CS were noted to have a higher prevalence of cardiovascular risk factors (smoking, hypertension, diabetes mellitus) and co-morbidities (previous MI, previous coronary revascularization) in comparison to those with STEMI-CS [32].

1.5. Pathophysiology of IHD

The epicardial coronary arteries are the primary location for atherosclerotic disease in IHD. The presence of multiple cardiovascular risk factors leads to endothelial dysfunction, resulting in lesion-prone areas of the arterial vasculature that allow for the focal permeation, trapping, and physiochemical modification of circulating lipoprotein particles in the sub-endothelial space [3,33]. These processes facilitate the recruitment of circulating monocytes, which transform into macrophages and eventually foam cells after engulfing cholesterol crystals, a hallmark of early atherosclerotic lesions [33]. Additionally, endothelial dysfunction promotes chemokines and growth factors that act on neighboring smooth muscle cells, causing their proliferation and generating a fibromuscular plaque within the intimal compartment [3].

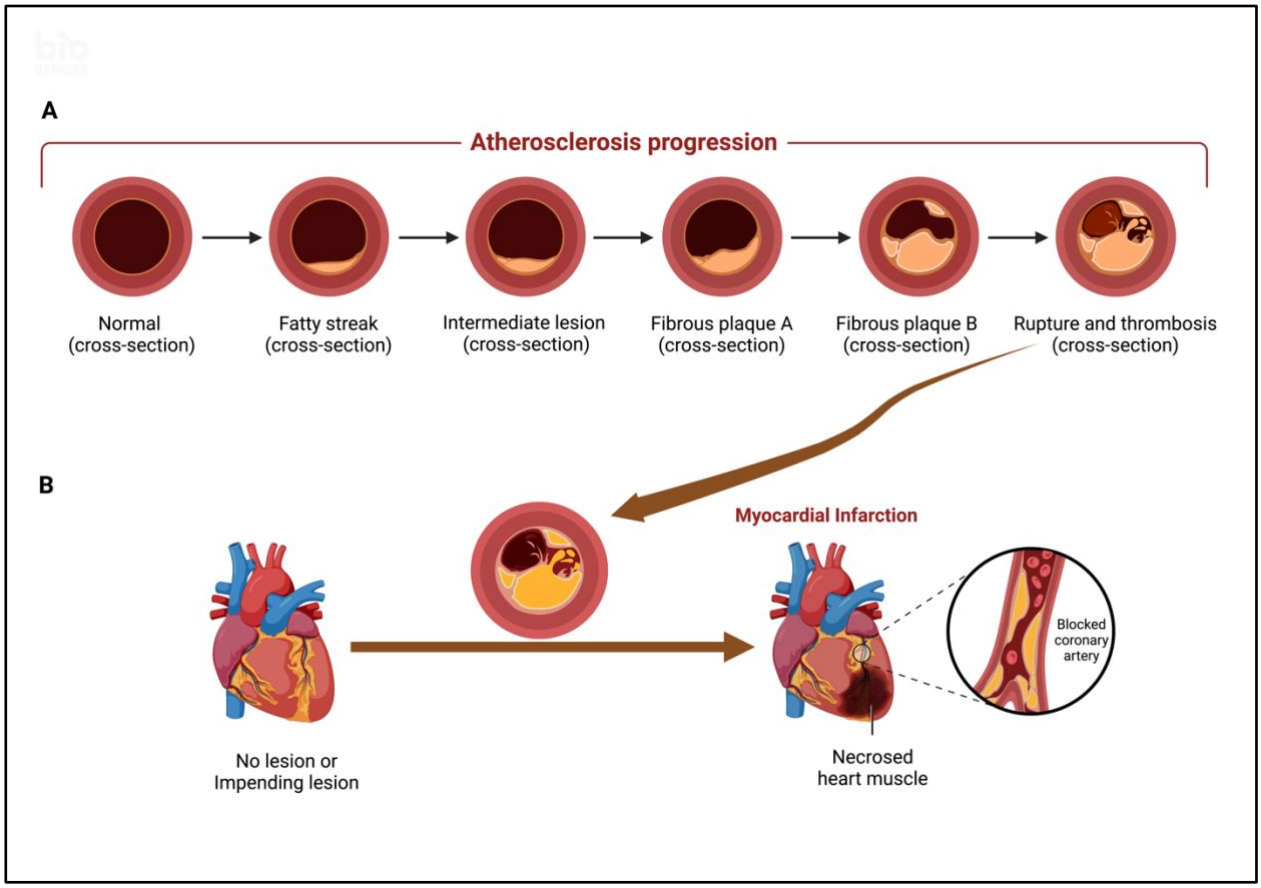

Figure 2: Pathophysiology of Ischemic Heart Disease

As lesions develop, they undergo a process of progressive structural remodeling that results in the formation of a fibrous cap over a lipid-rich, necrotic core consisting of oxidized lipoproteins, cholesterol crystals, and cellular debris. This process involves various degrees of matrix remodeling and calcification, ultimately leading to the formation of an atherosclerotic plaque [2,3] (as depicted in **Figure 2A**). Along the edges of these complex plaques are inflammatory cells, including activated macrophages, T-cells, natural killer T-cells, and dendritic cells. These cells contribute to the endothelial proinflammatory phenotype, further destabilizing the plaque's structure through proteolytic modification of its extracellular matrix components [3,33]. As the plaque

progressively builds up, it impairs vascular tone, leading to a reduction in myocardial blood supply, particularly during exercise or physical activity.

Acute coronary thrombosis frequently arises from the rupture or erosion of a vulnerable, lipid-laden, atherosclerotic coronary plaque, as shown in **Figure 2A**. This occurrence exposes the bloodstream to the thrombogenic components of the necrotic core, resulting in complete or partial occlusion of the coronary artery, as illustrated in **Figure 2B**. Consequently, patients may present with STEMI, NSTEMI, or UA, depending on the degree of arterial occlusion [3,34].

1.6. Management of IHD

Significant progress has been made in the management of IHD over the last two decades. The treatment approach for patients with stable coronary disease focuses on managing cardiovascular risk factors, including maintaining a healthy diet, regular exercise, smoking cessation, and stress management, as well as optimal management of cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes, as referenced in literature sources [17,19–21]. Patients with stable coronary disease may also be prescribed nitroglycerine to alleviate angina symptoms. In such patients, healthy endothelium releases nitric oxide in response to flow-mediated shear stress. However, for those who require it, an external source of nitric oxide can improve myocardial blood supply and alleviate symptoms.

Conversely, the management of patients with ACS primarily involves the use of antiplatelet and antithrombotic agents, as well as the evaluation of coronary anatomy through coronary

angiography, followed by the restoration of myocardial blood supply via percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) [28]. Multiple studies have demonstrated the ideal time for such revascularization. For instance, STEMI patients who can be brought to the catheter laboratory within 120 minutes of their first medical contact are typically better served by coronary angiography and PCI, while patients residing further away from catheter laboratories are treated with thrombolytic therapies and subsequently sent to the hospital with a catheter laboratory, where they can be further evaluated and treated appropriately. Stable NSTEMI patients without ongoing chest pain or hemodynamic instability should undergo cardiac catheterization within 72 hours from their presentation, while symptomatic NSTEMI patients should be investigated emergently by cardiac catheterization and revascularization.

1.6.1. Percutaneous coronary intervention (PCI)

According to the US and European guidelines, prompt reperfusion therapy is crucial for achieving a mortality benefit in patients with AMI [35,36]. The primary treatment of treatment for patients with IHD is PCI, which is performed to restore blood flow to the affected vessel(s) and prevent recurrent ischemia. PCI can be performed using either balloon angioplasty with or without stenting **(Figure 3).** Radial artery is considered the safest site for such an intervention due to its lower incidence of adverse clinical events compared to femoral artery access [37,38].The European Society of Cardiology **(ESC)** guidelines recommended the use of drug-eluting stents over balloon angioplasty for patients with AMI [36]. In cases of STEMI, the optimal timing for PCI is within 120 minutes of first medical contact, as this has been shown to correlate with improved mortality and morbidity [35,36,39]. At present, revascularization of only the infarct-related artery is the mainstay management of AMI

complicated by CS [40–43]. The use of PCI in non-culprit coronary arteries in the context of STEMI is a matter of ongoing debate, however, emerging evidences support intervention of non-culprit lesions as a staged PCI [44–48]. The Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic

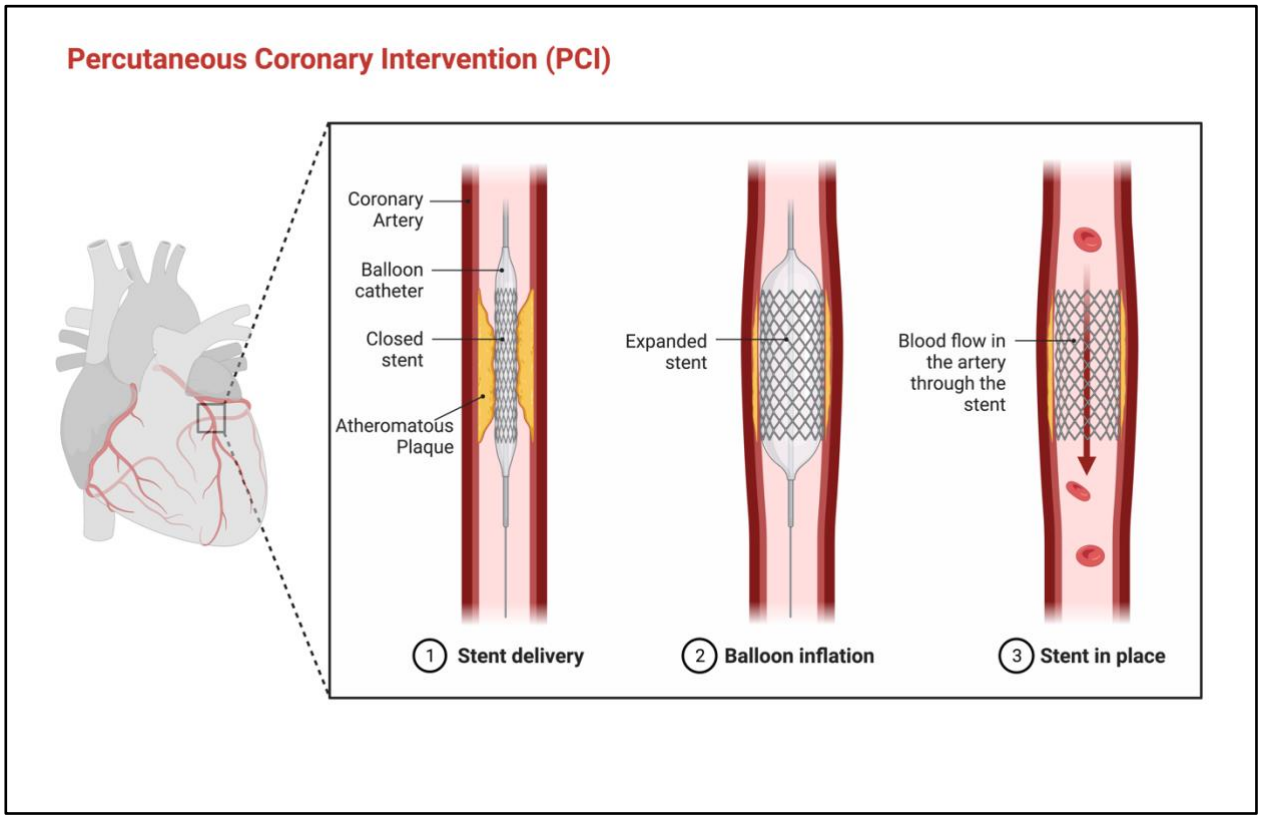

Figure 3: Percutaneous Coronary Intervention (PCI)

Shock **(CULPRIT-SHOCK)** trial reported that revascularization of the infarct-related artery reduced 30-day mortality from 51.6% to 43.3% [30]. The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (**SHOCK)** trial and registry, which included 302 patients with AMI-CS, outlined the importance of early coronary revascularization (within 12 hours of CS diagnosis) vs immediate medical stabilization, including fibrinolysis and intra-aortic balloon pump (IABP). The primary outcome of 30-day mortality was 46.7% (71 of 152 patients)

in the revascularization group and 56% (84 of 150 patients) in the pharmacotherapy group, which was not statistically significant [49]. The mortality reduction was notable for the early revascularization group at 6-months (50.3% vs 63.1%) and 1-year (53.3% vs 66.4%) follow up [49,50]. In the case of NSTEMI, PCI should be performed within 72 hours, although improved outcomes and shorter hospital stays have been reported when performed within 24 hours [51,52].

1.6.2. Fibrinolysis

Fibrinolysis is a widely accepted therapeutic approach for the management of STEMI in emergency situations where PCI is not immediately available, and patients cannot be transported to a catheterization laboratory within 120 minutes of symptom onset. The efficacy of fibrinolysis ranges between 33-60% [53,54]. The commonly utilized thrombolytic agents include streptokinase, tissue plasminogen activator (tPA) and its recombinant forms such as alteplase, reteplase, and tenecteplase. These agents convert the endogenous plasminogen to plasmin, which degrades fibrin and dissolves clots [54]. Both the American Heart Association **(AHA)** and European Society of Cardiology **(ESC)** guidelines recommend fibrinolysis only for STEMI patients presenting within 12 hours of symptom onset and in whom PCI will be delayed by a minimum of 120 minutes [35,36]. The therapy can be administered within 30 minutes of first medical contact if the patient does not have any contraindications [35,36]. The Assessment of the Safety and Efficacy of a New Thrombolytic-2 **(ASSENT-2)** study found that STEMI patients treated with alteplase or tenecteplase in combination with aspirin and heparin had similar 30-day mortality rates, with fewer complications such as non-cerebral bleeding and the need for blood transfusions observed in the tenecteplase group [55].

1.6.3. Coronary artery bypass grafting (CABG)

CABG is considered the most appropriate treatment option for patients with STEMI and NSTEMI who have not demonstrated adequate response to PCI or are deemed to be unsuitable candidates for PCI due to mechanical complications, multivessel disease, left main disease, or a high SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery: a grading system that evaluates the severity and extent of IHD) score of ≥34 [56,57].

1.6.4. Antithrombic agents

Antithrombic therapies include antiplatelet and anticoagulant agents. These patients are treated with dual antiplatelet therapies, including aspirin and an additional second antiplatelet agent such as clopidogrel, prasugrel, or ticagrelor. Among these agents, ticagrelor has been shown to be particularly efficacious in reducing the incidence of MI, with a lower incidence of adverse events compared to other antiplatelet therapies [58]. Similarly, prasugrel has also been demonstrated to be efficacious over clopidogrel, but this agent is usually administered after defining coronary anatomy by coronary angiography, whereas clopidogrel and ticagrelor are given pre-angiography. In Manitoba, we preferentially use aspirin and ticagrelor as the antiplatelet agents of choice.

In addition to antiplatelet therapies, anticoagulant agents, including unfractionated heparin, low molecular weight heparin (enoxaparin) and bivalirudin, are also utilized to prevent thrombus formation. Unfractionated heparin is commonly used in the context of CAD, while enoxaparin has

been shown to be particularly effective in the secondary prevention of AMI and may be used as an alternative to unfractionated heparin [59].

1.7. Outcomes of IHD

Despite recent advancements, which has markedly reduced IHD morbidity-mortality over the last four decades, IHD-associated mortality still remains higher and of a significant global public health concern, with an estimated 9 million deaths annually [23,60] and almost one-third of total deaths in individuals older than 35 years of age [16,61,62]. As estimated by the United Nations, the incidence rate of IHD is projected to increase in the elderly population (over 65 years) from 9% in 2019 to 16% by 2050 [12]. The Global Burden of Disease **(GBD)** has reported that 43% of all cardiovascular diseases are related to IHD [16]. However in comparison to developing countries, the mortality from IHD in western countries has decreased drastically over the past 15 years [60].

IHD is the second leading cause of death in Canada [25]. As per the Canadian Chronic Disease Surveillance System **(CCDSS)** report (2017-18), nearly 14 Canadians over 20 years of age die due to cardiovascular causes, mainly IHD [25]. The management of IHD is a significant financial burden and costs approximately 1-1.5% of the gross domestic product in the USA and up to 10% of total health expenses in developing countries [12].

Chapter 02. Literature review

Cardiogenic Shock (CS)

Cardiogenic shock (CS) complicating AMI is known to be associated with significantly high morbidity and mortality [63,64]. Despite multiple attempts using various pharmaco-mechanical circulatory support therapies, no such interventions have demonstrated mortality benefit [63,64].

2.1. What is Cardiogenic Shock (CS)?

CS is a hemodynamically diverse and highly morbid syndrome caused by primary cardiovascular disorders such as AMI, arrythmias and valvular disorders [29,30,65–67]. It is characterized by hypotension, critical end-organ hypoperfusion, and tissue hypoxia due to the heart's inability to maintain adequate cardiac output [29,30,65–67]. Pulmonary congestion or pulmonary edema may also be associated with CS. Cumulatively, low systemic perfusion and pulmonary congestion can result in systemic hypoxia [65,67]. Although a range of etiologies and mechanisms can lead to CS, this study focuses specifically on patients presenting with STEMI complicated by CS (STEMI-CS).

Current guidelines for defining CS include the identification of hemodynamic compromise, cardiac insufficiency, and/or tissue hypoperfusion. **1)** Hemodynamic compromise is defined as a systolic blood pressure (SBP) of <90 mmHg for a duration of ≥30 minutes, or the requirement of vasopressors and/or mechanical support to achieve an SBP ≥90 mmHg; **2)** Cardiac insufficiency is defined by a cardiac index (CI) of ≤1.8 L/min/m^2 or ≤ 2.2 L/min/ m^2 in the presence of inotropic/vasopressor therapy, with a pulmonary capillary wedge pressure (PCWP) of ≥15 mm Hg

(Left ventricular end diastolic pressure >15 mmHg characterizes absence of hypovolemia as the cause of shock); **3)** Tissue hypoperfusion is indicated by a lactate level of ≥ 2 mmol/L [29,30,65,66,68].

2.2. The CS definition used in various clinical trials

The **SHOCK** (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock) trial, conducted in 1999, established a widely recognized definition of CS as a triad of clinical features including hypotension, alteration of hemodynamic parameters and evidence of hypoperfusion or end-organ dysfunction. Specifically, the trial defined CS as a SBP <90 mm Hg for >30 minutes or vasopressor support to maintain SBP >90 mm Hg, in conjunction with a CI <2.2 L/min/m^2 and a PCWP >15 mm Hg, and low urine output <30 ml/hr or cool extremities [29,49]. Subsequent studies, such as the Intra-aortic Balloon Pump in Cardiogenic Shock II **(IABP-SOAP II** 2012**)**, Euro Heart Survey – Percutaneous Coronary Intervention **(EHS-PCI** 2012**)**, Korean Acute Myocardial Infarction Registry – National Institutes of Health **(KAMIR-NIH** 2018**),** and European Society of Cardiology – Heart Failure (**ESC-HF** 2016) have characterized CS in a similar fashion, with the **ESC-HF** 2016 study further identifying increased serum creatinine as a marker of CS [29,69–72].

2.3. Classification of CS

CS can also be sub-classified into three categories: non-hypotensive CS, classical CS and hypotension without hypoperfusion CS [73]. Non-hypotensive CS is characterized by a normal SBP (≥ 90 mmHg) without the need for vasopressor support and with the presence of clinical evidence of peripheral hypoperfusion. Classical CS present with low SBP (< 90 mmHg) and evidence of end-organ dysfunction [73]. Hypotension without hypoperfusion CS is identified by the presence of low SBP in the absence of hypoperfusion. A study found that patients diagnosed with classical CS had a higher mortality rate (66%) when compared to the other subtypes, specifically non-hypotensive CS (43%) and hypotension without hypoperfusion CS (26%) [73].

2.4. SCAI classification of CS

CS is an ongoing process that extends from pre-shock to an extreme phase [29]. End-organ damage is perhaps the most difficult parameter for physicians to define, leading to many discrepancies between studies. To overcome these limitations, the Society for Cardiovascular Angiography and Interventions (SCAI) has proposed a classification system for CS, which aims to standardize the characterization of this complex clinical syndrome. The SCAI-CS classification system categorizes CS into five stages **(Figure 4)**: A (at risk), B (beginning), C (classic), D (deteriorating), and E (extremis) [65,68,74,75]. Each stage is defined by a set of clinical criteria that are intended to reflect the evolving nature of the disease process and the degree of end-organ dysfunction. The system is intended to provide a more consistent and accurate characterization of CS and improve the ability to evaluate patient outcomes in clinical studies. However, the classification system is

largely based on subjective criteria and clinical judgement, which may limit its applicability in certain cases.

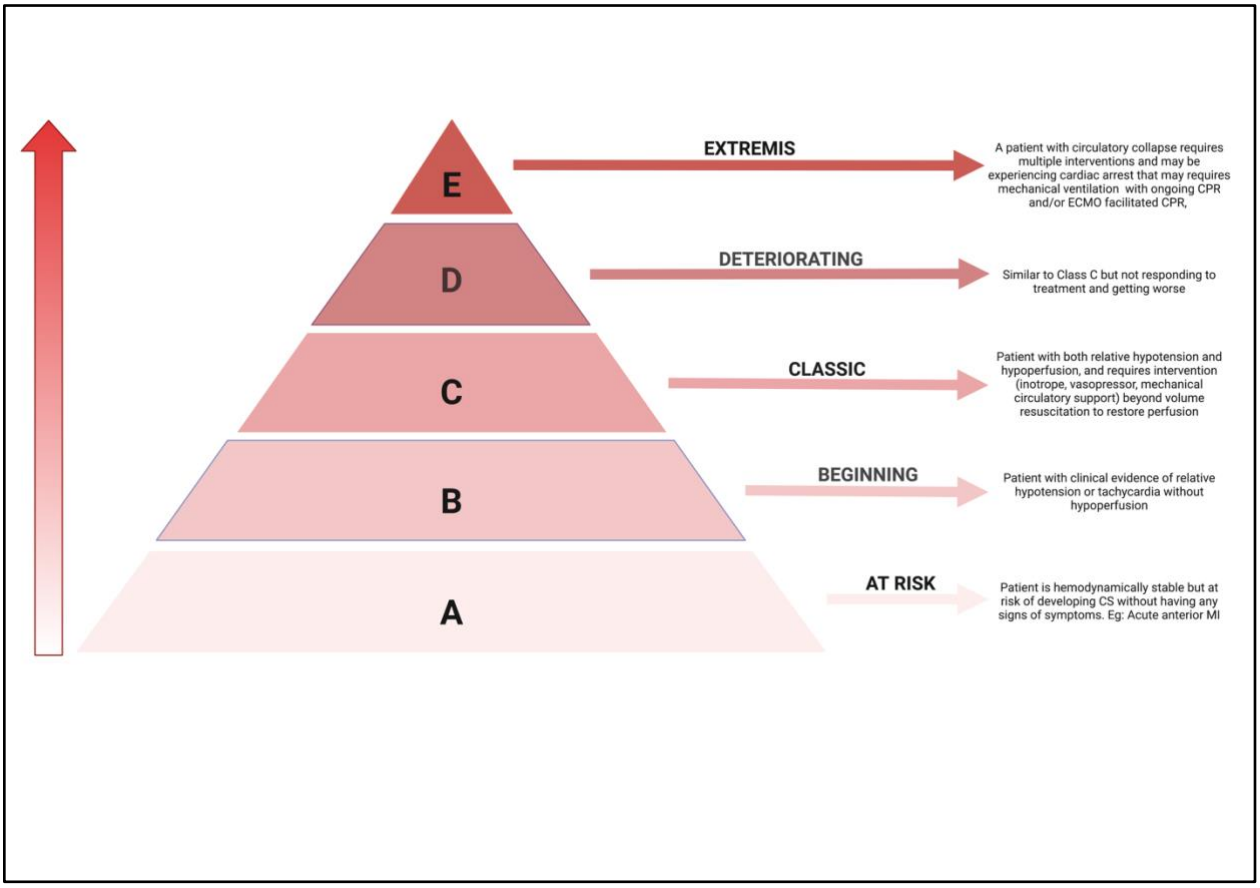

Figure 4: Society for Cardiovascular Angiography and Interventions (SCAI) classification of Cardiogenic Shock (CS). *MI, myocardial infarction; CPR, cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation. Adapted from Baran, D. A. et al. (2019)* [75]

2.5. Clinical features of CS

Based on clinical features of CS can be classified into three major groups: cold and wet, cold and dry, and warm and wet [29]. The "cold and wet" subtype is characterized by cool peripheries, and increased pulmonary congestion with a low CI, as well as elevated systemic vascular resistance (SVR) and pulmonary capillary wedge pressure (PCWP) [29]. The "cold and dry" subtype presents

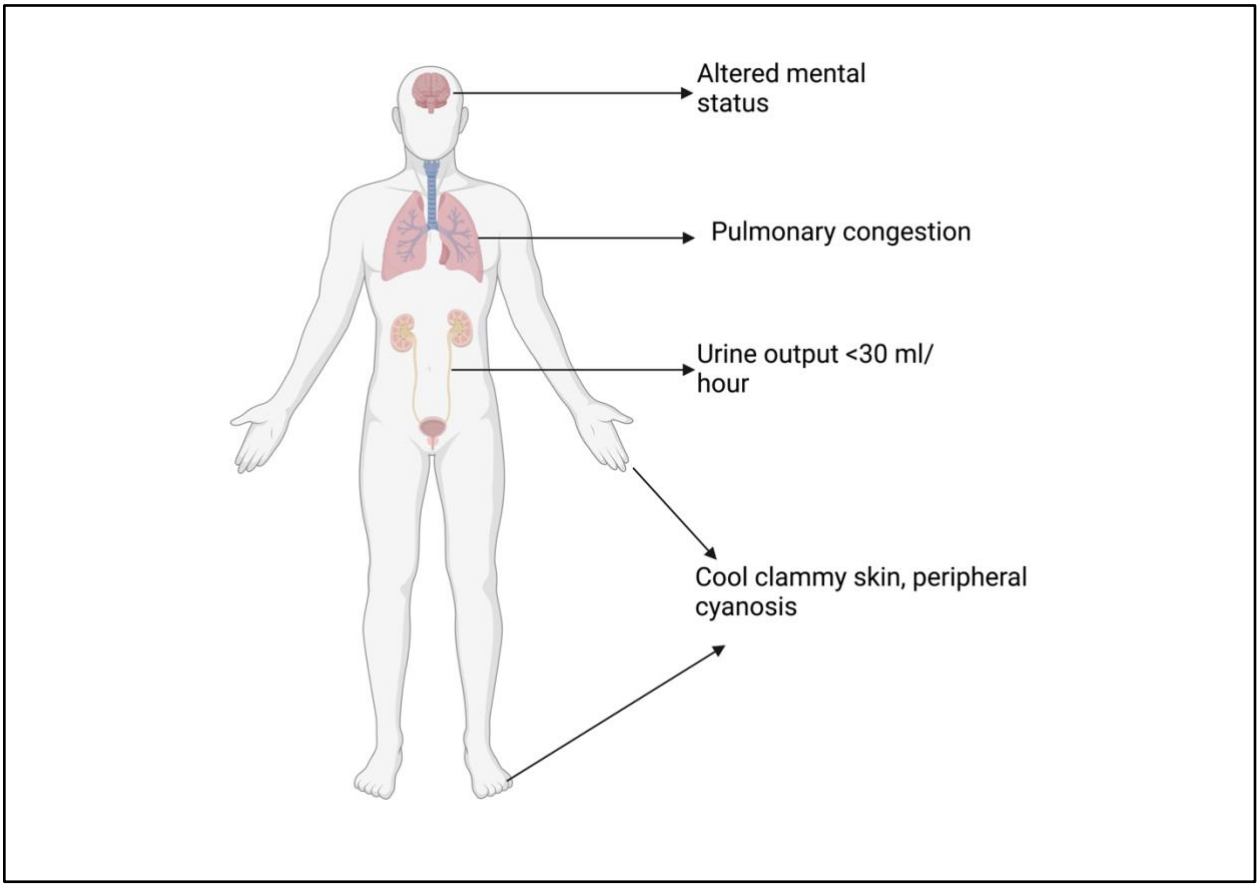

Figure 5: Clinical features of Cardiogenic Shock (CS)

with similar hemodynamic parameters but without signs and symptoms of pulmonary congestion, and may have a history of MI or chronic kidney disease (CKD) [29]. The "warm and wet" subtype is associated with systemic inflammatory response syndrome (SIRS) and AMI, and is associated

with a higher incidence of sepsis and mortality [29]. These patients may present with fever in addition to typical symptoms of CS [29].

According to the randomized **SHOCK**-trial, the median time from AMI symptom onset to CS is 5.5 hours [76]. The **SHOCK** registry classified CS according to the time of onset of symptoms, with three categories being: very early (onset within 6 hours of MI symptoms), early (onset within 24 hours) and late shock (onset ≥24 hours), and were identified in 46.6%, 74.1% and 25.9% of Registry patients respectively [76].

In combination with the typical symptoms of acute coronary syndrome (ACS), a CS patient may also present with dyspnea, pulmonary edema, elevated jugular venous pressure, cool extremities, feeble pulse, bradycardia, arrhythmia and/or low urine output (< 30 ml/hr) **[Figure 5]** [29,30,65,68]. Altered mental status is a severe manifestation of CS, resulting from cerebral hypoperfusion (given the brain being a vital organ, autonomic regulation attempts at maintains cerebral perfusion till very late) [65,77]. The most common etiology of CS is AMI, which leads to regional myocardial damage and ventricular dysfunction [78].

2.6. Pathophysiology of CS

Severe loss of ventricular (both systolic and diastolic) function following MI is the leading cause of CS, most commonly occurring after acute anterior MI along and its mechanical complications [30,77]. In the Culprit Lesion Only PCI versus Multivessel PCI in Cardiogenic Shock (**CULPRIT-SHOCK)** study, which included 686 patients, it was determined that the left anterior descending

artery (LAD) was most frequently identified culprit vessel in cases of severe ventricular dysfunction following a MI. Specifically, 42% of patients in the study had LAD disease and 7.7% of patients had left main (LM) disease [79]. These finding suggest that LAD disease is the most common cause of severe ventricular dysfunction following an MI.

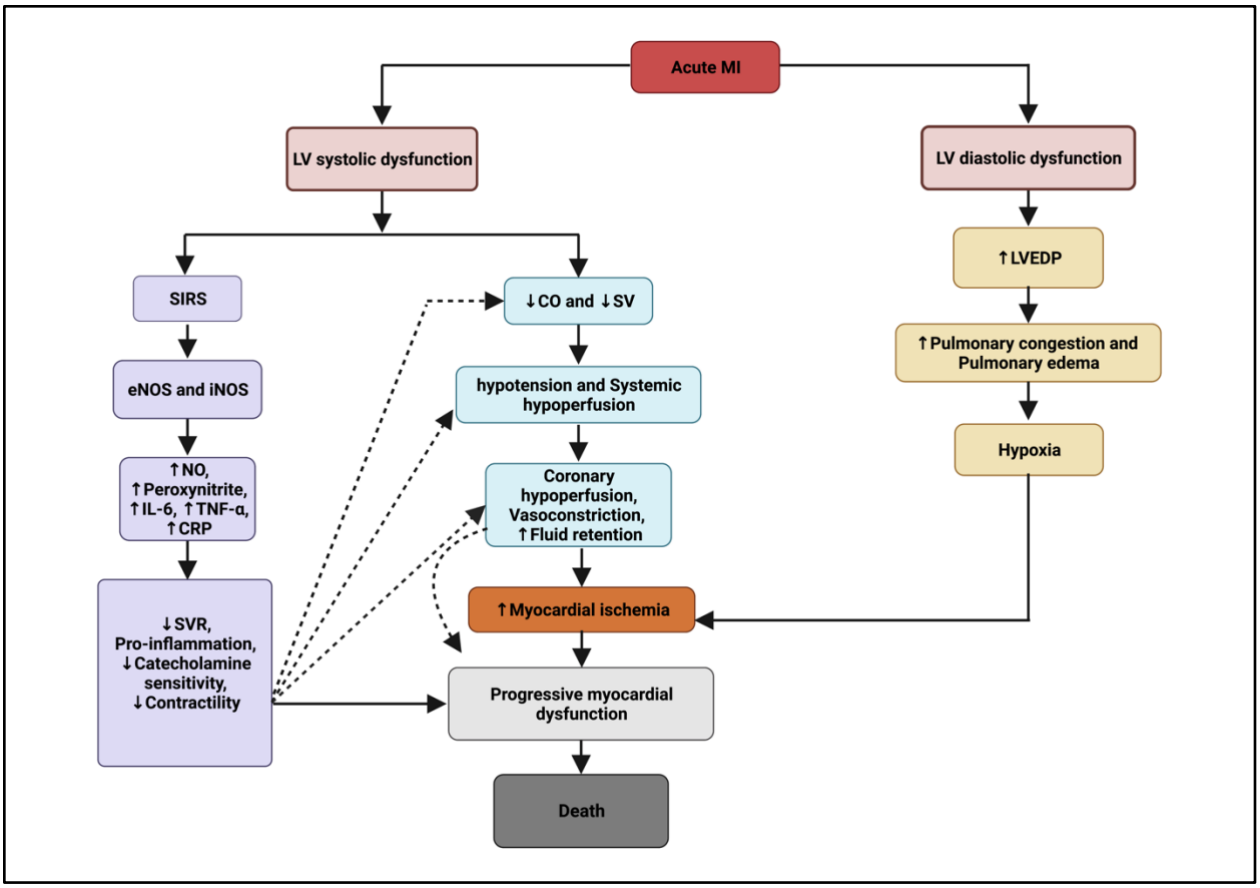

Figure 6: Pathophysiology of Cardiogenic Shock (CS). *MI, myocardial infarction; LV, left ventricle, SIRS, systemic inflammatory response syndrome; eNOS, endothelial NO synthase; iNOS, inducible NO synthase; NO, nitric oxide; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; CRP, c-reactive protein; SVR, systemic vascular resistance; CO, cardiac output; SV, stroke volume; LVEDP, left ventricular end diastolic pressure. Adapted from Van Diepen, S. et al. (2017)* [80]

AMI-CS is usually observed, once more than >40% ventricular myocardial function is compromised [81]. The **SHOCK-** trial also reported that mechanical complications, including

ventricular septal rupture (VSR), acute severe mitral regurgitation, and papillary muscle rupture, occurred in 12% of patients with AMI-CS [68,77,82]. VSR is a particularly critical complication, with a with a mortality rate of 87% [77]. Since introduction of primary PCI as the mainstay of therapy treating STEMI patients, there has been significant reduction in such ischemic mechanical complications.

After AMI, left ventricle (LV) dysfunction causes decrease cardiac output (CO), hypotension and insufficient tissue perfusion (both coronary and peripheral). Such acute hemodynamic compromise results in increased LV filling pressure, reflexive sympathetic activation, increased circulatory catecholamines and activation of the renin-angiotensin-aldosterone system (RAAS), pulmonary edema, compensatory peripheral vasoconstriction, circulatory collapse, and as a result progressive myocardial necrosis **[Figure 6]** [29,30,65,77]. Although at an early stage compensatory vasoconstriction improves coronary and vital organ perfusion, prolonged vasoconstriction leads to cardiac ischemia by increasing afterload [29,77]. While CS is associated with vasoconstriction state, in some patients AMI-CS can induce systemic inflammation, which can exacerbate cardiac damage through pathological vasodilation by releasing systemic inflammatory mediators (C-reactive protein, tumour necrosis factor-α and interleukin-6), nitric oxide (produced by NO synthases: eNOS and iNOS) and peroxynitrite (cytotoxic NO-derived species) [29,77,80]. Additionally, CS can also be caused by right ventricular systolic dysfunction (In majority of patients, its due to left ventricular dysfunction), which is seen in 5% of cases and more commonly in younger patients [82,83]. Impaired right ventricular dysfunction causes leftward bowing of the interventricular septum altering left ventricular geometry, and impaired contractility [83]. Therefore, patient right ventricular dysfunction is commonly present together with left ventricular dysfunction [82].

2.7. Assessment of CS

Due to the varied presentation of CS and associated dire consequences, clinicians should maintain a heightened level of suspicion for the early diagnosis of CS. An array of diagnostic work-up can be performed in conjunction with a comprehensive clinical examination. including but are not limited to, an electrocardiogram, arterial blood gas analysis, serum lactate level, liver and renal function tests, as well as various forms of hemodynamic monitoring, using invasive, minimally invasive and non-invasive modalities [30].

2.7.1. Invasive methods

Historically, invasive methods are considered the gold standard for measuring CO[84]. Invasive methods incorporate the principles of Fick and Thermodilution (TD) during cardiac catheterization. Despite their generalised acceptance in clinical practice, there remains various challenges with such methods; invasive nature and associated complications, need for specialized expertise, as well as various contraindications, such as significant tricuspid or pulmonary regurgitation and intracardiac shunt for using thermodilution method and multi-source blood supply or patient being on oxygen supplement for the Fick method.

Both Fick and TD methods require pulmonary arterial catheterization (PAC). However, the effectiveness of PAC as a clinical tool remains a subject of ongoing research and debate within the medical community. Studies such as the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness **(ESCAPE)** have included only stable heart

failure patients (excluded all CS patients) and failed to demonstrate significant improvements in clinical outcomes, using PAC [85]. Whereas recently published study has demonstrated mortality benefit in CS patients managed using PAC.

In addition to cardiac output and pressure measurement, PAC allows calculating cardiac power output (CPO=MAP x CO / 451); value <0.6 watts (normal value >1 watt) at the time of hospital presentation, is associated with an increased risk of mortality in AMI-CS patients [86]. Conversely, CPO >0.8 watts is thought to be linked to improved outcomes [86]. Both PCWP and CVP are essential for measuring the volume status of a patient, and can guide fluid administration, diuretic therapy or renal replacement therapy [87]. Complications associated with PAC include central venous access–related adverse events, arrhythmias, heart block, and pulmonary artery rupture [88].

Some treatment modalities stipulate peripheral arterial catheterization for continuous monitoring of SBP and mean arterial pressure (MAP) measurement, as well as for frequent titration of inotropes and/or vasopressors [89]. However, such monitoring is usually performed in intensive care setting that is associated with bleeding, infection and significantly higher cost. Moreover, non-invasively obtained blood pressure can also provide such information.

2.7.2. Echocardiography and magnetic resonance imaging (MRI)

Echocardiography and MRI examination of heart, both can provide stroke volume or blood volume ejected with each heart-beat. Hence one can calculate cardiac output multiplying it with the heart rate at the time of study. However, assuming left ventricular outflow tract to be circular for measuring such a calculation (whereas it is predominantly oval in shape) introduces stroke volume measurement and multiplying it with heart rate is likely to exaggerate such an error to a bigger scale.

Echocardiography is an entirely non-invasive procedure which helps to evaluate of cardiac output, systemic vascular resistance, pulmonary artery systolic pressure [90]. Additionally, this technique can also aid in the assessment of cardiac contractility, regional wall motion abnormalities, outflow obstruction and mechanical complications such as ventricular wall rupture and papillary muscle rupture [90]. Both echocardiography and CO2 rebreathing techniques more accurately measure CI compared to others. While these methods are considered to be more accurate than alternative techniques, it should be noted that they require trained expertise to performed and the necessary equipment can be expensive [91]. Additionally, it is worth nothing that these methods are not capable of continuously measuring CO [91–93].

2.7.3. Minimally invasive methods

Pulse index continuous cardiac output (PiCCO) system utilizes a thermodilution catheter, which is inserted into the peripheral blood vessel, to measure CO by injecting a small amount of cold saline and measuring the resulting change in temperature [94]. The PiCCO system is considered minimally invasive as it only requires the insertion of a small catheter, and it also offers the advantage of being a continuous monitoring method, making it useful for critically ill patients [94]. However, it is important to note that the use of PiCCO system, like any invasive procedure, carries a small inherent risk of complications.

2.7.4. Non-invasive methods

There has been emergence of a variety of non-invasive techniques that can be utilized to measure CO, including carbon dioxide (CO2) and inert gas rebreathing, thoracic bioimpedance cardiography, electrical velocimetry (modified bioimpedance), bioreactance and, whole-body electrical bioimpedance (WBEB) [91,95]. These techniques provide a means to assess CO without the need for invasive procedures and can be useful in a variety of clinical settings.

2.7.4.1. Bioreactance

Bioreactance is a novel, non-invasive method for continuous CO monitoring and has caught the attention of clinicians and researchers in the recent years [96]. This method estimates CO by analyzing the frequency of relative phase shift of electronic current across the thorax [96]. Despite

the increasing interest in this technology among clinicians and researchers, recent studies have raised concerns about the correlation of NICOM-derived CO measurements with traditional methods such as Fick and TD in CS patients [96].

2.7.4.2. Whole-body electrical bioimpedance (WBEB)

Whole-body electrical bioimpedance (WBEB) measures CO by transmitting a low-level electrical current throughout the body, with the current being measured at two electrodes placed on the patient's wrist-wrist or wrist-ankle configuration. This is called Non Invasive Cardiac Output (NICO) WBEB technology [91]. This technology allows for continuous monitoring of CO without the need for invasive procedures, making it a valuable tool in patient care.

2.7.4.3. Non-Invasive Cardiac System (NICaS)

Total-body bioimpedance is a non-invasive technique used to measure the electrical impedance of biological tissues and its principle is similar to WBEB technology. This method involves the application of low electrical current to the body, and the measurement of resulting voltage. The

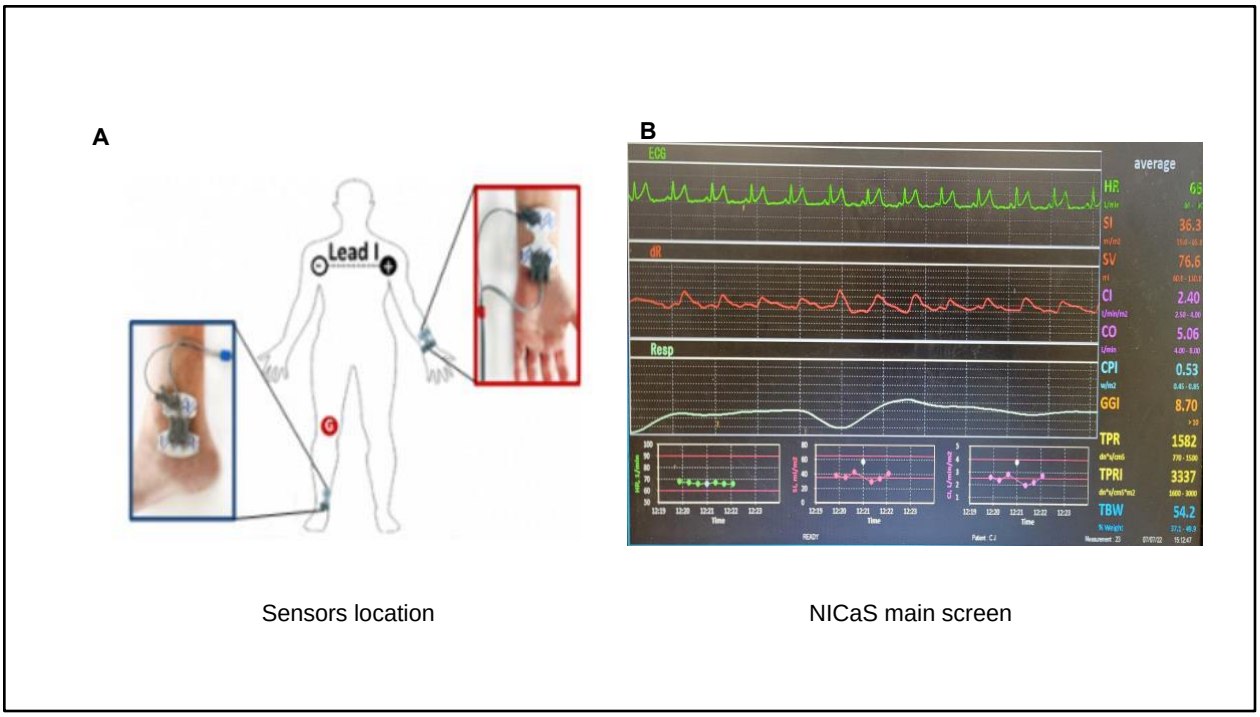

Figure 7: Non-Invasive Cardiac System (NICaS). *Figure 7A shows NICaS dual-polar impedance electrodes were applied to the patient's left wrist and right ankle pre-PPCI. Figure 7B shows NICaS main screen showing Intra-procedural bioimpedance-based hemodynamic parameters measured continuously pre-PPCI, during PPCI and post-PCI using NICaS. NICaS, non-invasive cardiac system; PPCI, primary percutaneous coronary intervention; PCI, percutaneous coronary intervention. Some parts of the figure adapted from Lavie, A. et al. (2018)* [97]

electrical conductance of blood, which is higher than that of surrounding tissues, results in lower resistance to electrical flow [91]. The technique is widely used for the assessment of body composition, including the determination of body fat percentage.

The NICaS system requires age, gender, height, weight, blood pressure, oxygen saturation, sodium level and hematocrit level to be incorporated prior to any measurement can be obtained. NICaS requires application of two skin sensors: patient's left wrist and right ankle (can also be wrist-wrist configuration) and it updates hemodynamic parameters every 20 seconds **(Figure 7)**. NICaS has immense clinical potential as 1) it has been validated against RHC, trans-thoracic

echocardiography, CMR [98–100], 2) previously we have validated this technology against CMR derived hemodynamic parameters [92,93], 3) it does not interfere with the life-saving primary PCI, 4) it is cost-effective, non-invasive and simple to use including in critically ill patients.

2.8. Current day management of CS

AMI-CS can be treated with various pharmaco-mechanical circulatory support therapies aim to enhance cardiac contractility and cardiac output, as well as augment central blood aortic pressure to improve tissue perfusion.

2.8.1. Pharmacotherapies

Pharmacotherapeutic agents, specifically inotropic agents such as dobutamine, milrinone, and levosimendan, and vasopressors including norepinephrine and vasopressin, are utilized in the management of AMI-CS patients[67,69]..

According to the European Society of Cardiology (ESC) guidelines, norepinephrine is the preferred vasopressor for the management of AMI-CS, as it has been demonstrated to be more effective in reducing mortality and improving cardiac function in comparison to dopamine [82]. Additionally, several studies have suggested that the combination of NE and dopamine may be superior to the use of single vasopressor in terms of reducing mortality and improving cardiac function, with a lower incidence of adverse events [101,102]. Despite these findings, a randomized control trial (RCT) involving 1,679 patients, have failed to demonstrate a significant difference in

28-day mortality rates between patients receiving dopamine (52.5%) versus norepinephrine (48.5%) [103]. Similarly, another study involving 57 patients found no significant variations in CI between patients treated with epinephrine(n=30) vs NE (n=27) [104].

Vasopressin, also known as antidiuretic hormone (ADH), is a non-catecholamine vasopressor secreted by the posterior lobe of the pituitary gland and the myocardium [105]. Its primary role is to regulate water balance in the body by reducing urine output and increasing water reabsorption in the kidneys. Additionally, vasopressin acts as a vasoconstrictor, increasing vascular tone and raising blood pressure [105]. Vasopressin use in treating AMI-CS patients have demonstrated increased MAP without adverse changes in PCWP and urine output [106]. However, it is recommended that vasopressin should be used with caution and at lower doses (<0.1 units/min), as higher doses (>0.15 units/min) may reduce cardiac output due to increased afterload [107].

Milrinone is a phosphodiesterase 3 inhibitor that has been shown to improve cardiac function by increasing cardiac inotropy and lusitropy, as well as peripheral vasodilation. Dobutamine, on the other hand, is a synthetic catecholamine that acts as a beta-1 and beta-2 receptor agonist, thereby increasing CO and improving blood pressure [40,108]. A recent study, comparing milrinone versus dobutamine in a total of 192 CS patients (n=96 per group) failed to demonstrate any statistically significant difference in primary and secondary outcomes between the two groups [108].

Levosimendan, a calcium-sensitizing second line inotropic agent. Although used in some countries, it is yet to receive approval from the Food and Drug Administration (FDA). Studies

have demonstrated that levosimendan has a short-term survival benefit when compared to dobutamine, with no notable difference in long-term outcomes [40]. .

2.8.2. Mechanical circulatory support (MCS) devices

Similar in principle to above-described pharmacotherapy, various mechanical circulatory support (MCS) therapies have been invented over the last 2 decades aiming at improving cardiac output in CS patients (as low cardiac output is thought to be the primary insult). These devices can be generally divided into (1) percutaneous mechanical circulatory support (p-MCS) devices [intra-aortic balloon pump, impella, tandem heart or extracorporeal membrane oxygenation (ECMO)], or centrally inserted MCS (c-MCS), such as ventricular assist device (VAD).

The IABP is a most commonly used MCS device treating AMI-CS patients. Although earlier studies demonstrated that IABP use augments cardiac output by 0.5 L/min, and also improves outcomes, recently published randomized study comparing IABP in a randomized fashion has failed to demonstrate any mortality benefit [109,110]. Hence, use of IABP has reduced since then, however, it is still used in patients with AMI-CS with or without mechanical complications, such as mitral regurgitation, ventricular septal defect.

ECMO is a portable and modified cardiopulmonary bypass system that has been utilized in clinical practice for over a half century [111,112]. Currently, there are two main types of ECMO available for use, namely veno-venous ECMO (VV-ECMO) and veno-arterial ECMO (VA-ECMO) [112]. VV-ECMO is exclusively used for respiratory failure, whereas VA-ECMO provides both respiratory

and cardiopulmonary hemodynamic support by increasing aortic blood flow and organ perfusion pressure [111,112]. An ongoing study trial, named Assessment of ECMO in Acute Myocardial Infarction with Non-reversible Cardiogenic Shock to Halt Organ Failure and Reduce mortality **(ANCHOR),** is currently investigating the use of ECMO in cases of CS during MI [111]. Use of ECMO is associated with certain inherent risks, such as lower limb ischemia, bleeding, device-related infections, acute kidney injury, and stroke [113].

As described above, other than coronary revascularization, no other interventions have consistently demonstrated mortality improvement in AMI-CS patients. Such challenges raises several fundamental questions.

1. What is the incidence of CS defining parameter in all-comer STEMI patients; both before and immediately after primary PCI?
2. How congruent are the current 3 CS-defining parameters in all-comer STEMI patients?
3. What is the correlation of CS hemodynamic parameters with clinical outcomes in patients presenting with STEMI?

To answer these questions, we formed our hypothesis and then conducted the present study.

2.9. Hypothesis and Objectives

Hypothesis

1. Parameters (cardiac index, arterial lactate, systolic blood pressure) defining CS are unlikely to be congruent.

2. PPCI may be improving hemodynamics and reducing incidence of CS defining parameters.

3. One individual CS defining parameter may not be associated with outcomes in STEMI patients.

Objectives

1. To determine the incidence and concordance of 3 known CS parameters currently used in identifying cardiogenic shock in STEMI patients;
2. To determine the clinical utility of NICaS in early detection of cardiogenic shock in patients presenting with STEMI;
3. To determine the impact of coronary reperfusion on NICaS derived hemodynamic parameters in patients presenting with STEMI;
4. To identify the outcome-associated hemodynamic parameters in STEMI patients.

Chapter 03.

Materials and Methods

3.1. Methods

3.1.1. Study populations & consent procedure

This is a single-centre, prospective cohort study that is being conducted at the cardiac catheterization laboratory of the Saint Boniface General Hospital in Winnipeg, Manitoba, Canada. St. Boniface Hospital is the only cardiac center in Manitoba, Canada. STEMI patients were recruited when they presented to cardiac catheterization laboratory for PPCI between October 2019 and November 2022 were recruited in the study. Prior to their inclusion in the study, all patients provided verbal consent. Given the PPCI is a lifesaving procedure and delay of even a few minutes can increase morbidity – mortality, verbal consent pre-PPCI was obtained. Within 24 hours post PPCI, full written informed consent was obtained from these patients, once they were pain free and hemodynamically stable. The REB (University of Manitoba) approved this protocol. Patients who did not provide full consent were removed from the study and collected data was discarded. In instances where a language barrier existed, consent was obtained through interpreter.

Inclusion criteria: Adult patients (18 years or older) with suspected STEMI, as determined through electrocardiogram and clinical findings, who were brought to the catheterization laboratory for primary PCI.

Exclusion criteria: Patients who did not provide consent or were unable to understand the consent document were excluded from the study.

3.1.2. Study time points

The study utilized NICaS system to obtain hemodynamic parameters along with systolic blood pressure and arterial blood gas lactate levels at three distinct time points: prior to the initiation of primary PCI (pre-PPCI), immediately following the completion of primary PCI (post-PPCI), and 24 hours post-PPCI (POD-1). Invasive systolic blood pressure (SBP) was obtained via an arterial sheath or a catheter, which was inserted to perform angiography, both pre-PPCI and post-PPCI. Non-invasive blood pressure was also recorded, utilizing a standard blood pressure cuff, both pre-PPCI and POD-1.

3.1.3. Study protocol

After obtaining verbal consent, demographic information, including patient's age, biological sex, height (cm), weight (kg), hematocrit (%), blood sodium level (mmol/L) and oxygen saturation (%), were incorporated into the NICaS software to ensure accurate calculation of hemodynamic parameters. Thereafter, two NICaS decapolar electrodes were applied, one on patient's left wrist [centered over the left radial artery], and another on the right ankle [centered over the posterior tibial artery] that is also described as a wrist-ankle configuration. The NICaS system electrodes can also be applied in a wrist-wrist configuration, however we consistently used wrist-ankle configuration for this study. Although, NICaS electrodes also acquire an electrocardiogram, an additional set of 3 ECG leads were also applied to improve the signal quality of the hemodynamic parameters. Non-invasive blood pressure (NIBP) was collected from paramedics/emergency room nurses at patient presentation and input into the NICaS software along with other required

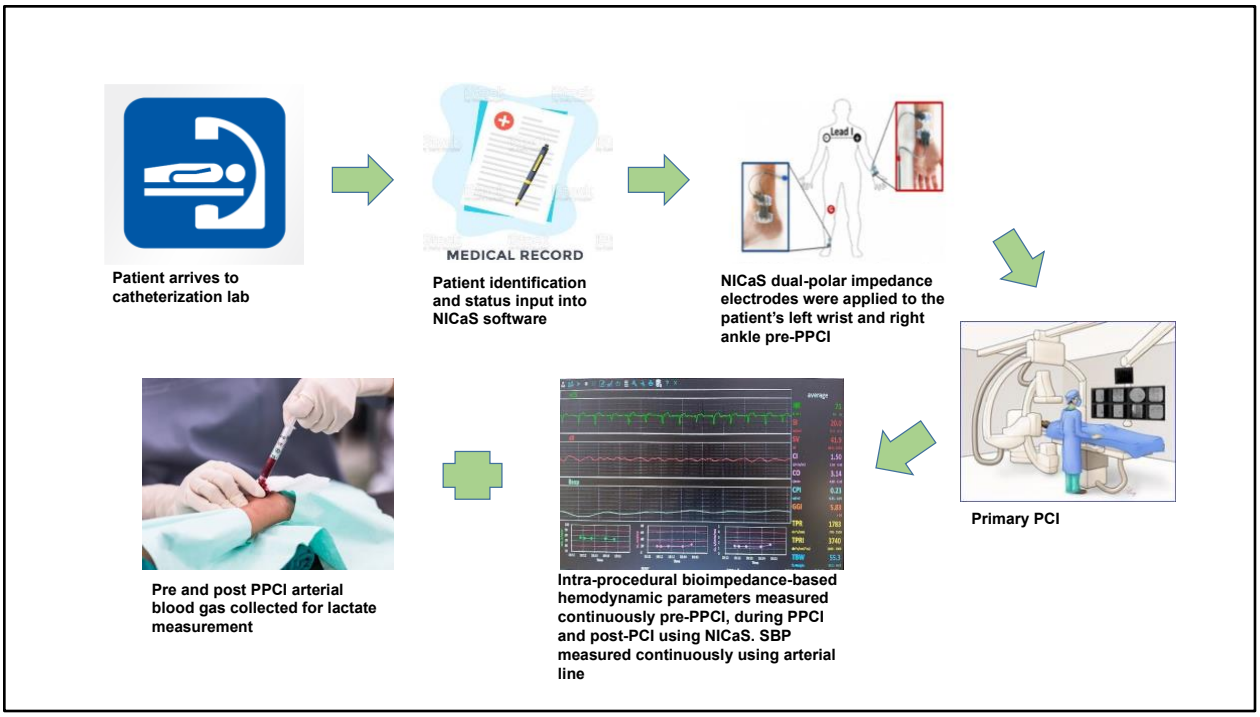

Figure 8: Flow diagram shows protocol of the ST Elevation Myocardial Infarction (STEMI) hemodynamic outcomes and role of NICaS. *NICaS, non-invasive cardiac system; PPCI, primary percutaneous coronary intervention; SBP, systolic blood pressure. Some parts of the figure adapted from Lavie, A. et al. (2018)* [97]

information which are mentioned above. Cables were then connected to the electrodes and hemodynamic measurements were obtained. Once NICaS obtains a good quality signal, hemodynamic measurements are recorded and updated each 20 second intervals **(Figure 8)**. After the insertion of the arterial sheath, opening invasive arterial blood pressure (ABP) was collected form the catheterization lab and input into NICaS system for another set of pre-PPCI hemodynamic measurements. Although hemodynamic parameters were recorded throughout the PPCI procedure, only an average of 5 consistent set of values were recorded for our study; both immediately pre- and post-PPCI [we used invasive blood pressure at the end of PPCI to measure NICaS derived post-PPCI hemodynamic parameters].

We also collected a 3 ml of arterial blood gas (ABG) samples for lactate measurements at the beginning of and immediately after the PPCI by the interventional cardiologist performing the PPCI.

Once PPCI is completed, these patients are transferred to the cardiology ward. After providing a detailed explanation of the study protocols, informed written consent was obtained on the following day. Furthermore, additional NICaS measurements were taken on the following day within 24 hours of post-PPCI (post operative day-1), in addition to non-invasive blood pressure (NIBP) using an OMRON blood pressure monitor (Model: BP742N).

3.1.4. Statistical analysis

Patient-level data were securely stored in the Research Electronic Data Capture (REDCap) program, which features double password protection and is hosted on servers located at the University of Manitoba. The data were extracted from REDCap for analysis. Statistical analysis was conducted using Microsoft Excel version 16.70, and the results were presented in the form of numerical values (n), percentages (%), mean and standard deviation (SD), median and interquartile range (IQR), as well as maximum and minimum values. In addition, we employed Student's t-test and one-way ANOVA to compare hemodynamic parameters between patients who experienced adverse outcomes (death and prolonged in-hospital stay) and those who did not. $p < 0.05$ considered statistically significant. Linear regression analysis (R^2) was used to identify association between different CS parameters, and Pearson correlation (R) was used to determine the strength and

direction of relationship between CS parameters. Figures were created using excel version 16.70 and GraphPad prism.

Chapter 4.

Results

4.1. Patients' characteristics

A total of 268 patients were initially approached to participate in the study. Of these, 204 patients met the eligibility criteria and were enrolled in this analysis. However, 64 patients were excluded as either they did not have STEMI, or did not stay in the hospital for long enough to collect complete data for all three time points (Pre-PPCI, Post-PPCI and POD-1). The mean age of the enrolled patients was 65.9±12.5 years (age range: 34-100 years), with majority being male 70.6%. The average height, weight, and BMI of the participants were 170.1±10.5 cm, 85.1±19.6 kg, and 29.3±5.7 kg/m^2, respectively. Patient demographics are described in **Table 1.**

Table 1. *Baseline characteristics of STEMI patients*

Variable (n=204)	**Mean ± SD Range Median (IQR)**
Age, years	65.9 ± 12.5 34-100 66 (57-75)
Sex (M/F), n (%)	Male: 144 (70.6) Female: 60 (29.4)
Height, cm	170.1 ± 10.5 144-195 172 (162-179)
Weight, kg	85.1 ± 19.6 40-148 81 (72-98.5)
Body mass index, kg/m^2	29.3 ± 5.7 16-56.3 28.3 (25.5-32.4)
Type of STEMI, n (%)	Inferior: 107 (52.5) Anterior: 77 (37.8) Lateral: 16 (7.9) Posterior: 4 (1.9)
Culprit artery, n (%)	Right coronary artery: 91 (44.6) Left anterior descending artery: 84 (41.2) Left circumflex artery: 18 (8.8) Obtuse marginal: 6 (2.9) Diagonal: 2 (0.98) Ramus: 2 (0.98) Left main: 1 (0.49)
SCAI classification, n (%)	A: 144 (70.6) B: 33 (16.2) C: 10 (4.9) D: 9 (4.4) E: 8 (3.9)
Thrombolysed patients, n (%)	26 (12.7)

Among the 204 enrolled patients, 52.5% presented with inferior ST-elevation myocardial infarction (STEMI), while 37.8% had anterior STEMI, 7.9% had lateral STEMI, and 1.9% had posterior STEMI. The most common culprit artery responsible for the myocardial infarction was the right coronary artery, accounting for 44.6% of cases. The left anterior descending artery was the second most commonly affected artery, identified in 41.2% of cases. Other arteries that were identified as culprit arteries included the left circumflex artery (8.8%), obtuse marginal artery (2.9%), diagonal artery (0.98%), ramus (0.98%), and left main artery (0.49%) **(Table 1).**

The enrolled patients were categorized based on the SCAI cardiogenic shock classification (A, B, C, D, E), which was determined by the treating interventional cardiologist upon the patients' arrival in the catheterization laboratory **(Table 1)**. Out of the 204 patients, 70.6% were categorized as SCAI-A, 16.2% as SCAI-B, 4.9% as SCAI-C, 4.4% as SCAI-D, and 3.9% as SCAI-E.

The mean hemoglobin and white blood cell (WBC) count for the study population were 139.4±18.8 gm/L and (10.8±3.5) $x10^9$/L, respectively **(Table 2).** The average creatinine and estimated glomerular filtration rate (eGFR) levels were within the normal range, with values of 93.9±60.8 μmol/L and 77.8±25.1 ml/min/1.73m^2, respectively. Additionally, the mean initial value of troponin-I was 1115.2±2367.1 ng/L (range: 6 - 10000), while the mean highest value was 3687.6±3378 ng/L (range: 8 – 10000).

Table 2. *Laboratory investigations*

Variable (n=204)	**Mean ± SD Range Median (IQR)**
Hemoglobin (gm/L) (n=203)	139.4 ± 18.8 81-183 140 (128-151)
WBC (x 10^9/L) (n=203)	10.8 ± 3.5 4.2-22.3 10.5 (8.1-12.8)
Neutrophils (%) (n=203)	70.8 ± 12.4 32.3-94.9 72.6 (63.1-80.9)
Platelets (x 10^9/L) (n=203)	256.2 ± 81.9 72-768 248 (206-298)
MPV (fL) (n=203)	10.4 ± 0.9 8.2-13.4 10.4 (9.7-10.9)
Creatinine (μmol/L)	93.9 ± 60.8 35-725 82 (67.0-99.8)
eGFR (ml/min/1.73m^2)	77.8 ± 25.1 7-136 80 (59.3-97.0)
First Troponin I value (ng/L) (n=201)	1115.2 ± 2367.1 6-10000 85 (28-780.5)
Peak Troponin I value (ng/L) (n=201)	3687.6 ± 3378.0 8-10000 2711 (783.5-5768.5)

4.2. Cardiovascular risk factors:

Hypertension (59.8%), dyslipidemia (44.1%), diabetes mellitus [type-1 – (0.49%) & type 2 - (27.5%)] were the commonly observed cardiovascular risk factors. A history of previous coronary revascularization either by PCI 12.8% or coronary artery bypass grafting (CABG) was observed in 94.4% of the patients. Other risk factors identified in the study population included chronic kidney disease (CKD), previous stroke and peripheral vascular disease in 10.8%, 6.4% and 2.5% of the patients, respectively (as shown in **Table 3)**.

Table 3. *CAD risk factors*

Risk factors	**No. of patients (%), (n=204)**
Hypertension	122 (59.8%)
Dyslipidemia	90 (44.1%)
Diabetes mellitus (DM)	Type-1: 1 (0.49%) Type-2: 56 (27.5%)
Previous PCI	26 (12.8%)
CKD	22 (10.8%)
Previous stroke	13 (6.4%)
Previous CABG	9 (4.4%)
Previous peripheral vascular disease	5 (2.5%)

4.3. Incidence of CS and concordance between CS defining parameters in STEMI patients and impact of primary PPCI

In the current study, the incidence of cardiogenic shock (CS) was evaluated using three accepted methods, which include lactate ≥2 mmol/L, cardiac index (CI) ≤1.8 L/min/m^2 [or ≤2.2 L/min/m^2, if the patient is on inotropic/vasopressor therapies], and systolic blood pressure (SBP) (<90 mm of Hg).

Pre-PPCI, the incidence rate of CS was found to be 29% based on lactate, 15.5% based on CI, and 8.5% based on SBP criteria **(Figure 9A).** The incidence of CS decreased post-PPCI; for lactate (17.5%) and CI (9%), but unchanged in SBP pre- and post-PPCI (8.5%) **(Figure 9A).** The incidence rates of CS were also evaluated by considering various combinations of CI, lactate, and SBP. For instance, the incidence of CI and lactate, CI and SBP, and SBP and lactate criteria were 7%, 3.5%, and 6%, respectively, in the pre-PPCI phase. These values decreased to 3.5%, 1%, and 2% post-PPCI, respectively. Finally, the incidence rate of CS based on all three criteria (lactate + CI + SBP) was found to be 3% pre-PPCI and 0.5% post-PPCI **(Figure 9A).**

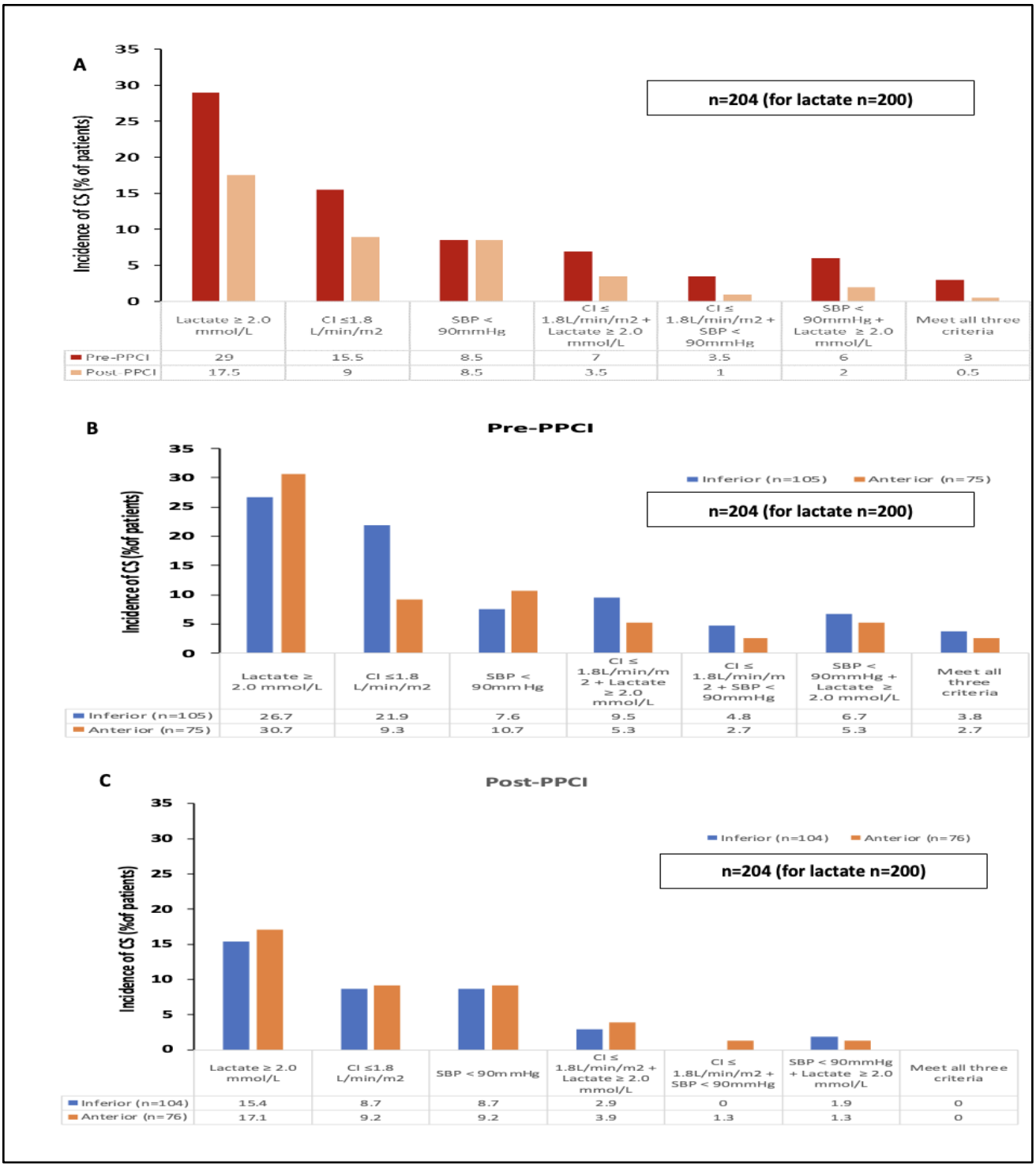

Figure 9: Incidence of CS in STEMI patients based on CS defining parameters (lactate, CI and SBP) pre-PPCI and post-PPCI. *A) Incidence of CS based on lactate, CI and SBP CS criteria in STEMI patients pre-PPCI and post-PPCI, B) Incidence of CS in inferior and anterior STEMI pre-PPCI, C) Incidence of CS in inferior and anterior STEMI post-PPCI. CI, cardiac index; SBP, systolic blood pressure; PPCI, primary percutaneous coronary intervention; STEMI, ST Elevation Myocardial Infarction*

The incidence of cardiogenic shock (CS) varied depending on the type of STEMI. In inferior STEMI, the pre-PPCI incidence of CS defining parameters of lactate, CI, SBP, were 26.7%, 21.9%, 7.6% respectively. Whereas using combination of parameters, such as CI + lactate, CI + SBP, SBP + lactate and CI + lactate + SBP, the incidence rate observed were 9.5%, 4.8%, 6.7% and 3.8%, respectively **(Figure 9B).** All parameters improved after PPCI except for SBP, which increased from 7.6% to 8.7% despite improvement in cardiac output **(Figure 9C).**

In anterior STEMI, the pre-PPCI incidence of CS parameters, lactate, CI and SBP were present in 30.7%, 9.3% and 10.7% of the patients, respectively, and all parameters decreased after PPCI to 17.1%, 9.2% and 9.2%, respectively **(Figure 9B, C).** Notably, the incidence of CS based on SBP alone increased post-PPCI in inferior STEMI, but decreased from 10.7% to 9.2% in anterior STEMI **(Figure 9B, C).** Combining these parameters such as CI + lactate, CI + SBP, SBP + lactate and lactate + CI + SBP, the incidence rates in anterior STEMI patients before PPCI were 5.3%, 2.7%, 5.3% and 2.7%, and post-PPCI the rates were 3.9%, 1.3%, 1.3% and 0%, respectively **(Figure 9B, C).**

The concordance between different parameters for defining CS in all-comer STEMI patients was found to be poor both before and after PPCI, as demonstrated by the low correlation coefficients and non-significant trendlines slopes **(Figure 10A-C)**. Specifically, SBP showed poor correlation with CI pre-PPCI and post-PPCI, with non-significant trendlines slopes (R^2=0.0165 and R^2=2x10^{-5}, respectively) **(Figure 10A)**. Similar trends were observed between lactate and CI both pre-PPCI and post-PPCI, with non-significant downward trendlines slopes (R^2=0.0544 and R^2=0.044, respectively) **(Figure 10B).** Moreover, the relationship between lactate and SBP was also found

to be poor with non-significant downward trendlines slopes (R^2=0.0542 and R^2=0.0082, respectively) **(Figure 10C).** All combinations showed significant p-values both pre- and post-PPCI, <0.001 **(Figure 10A-C).**

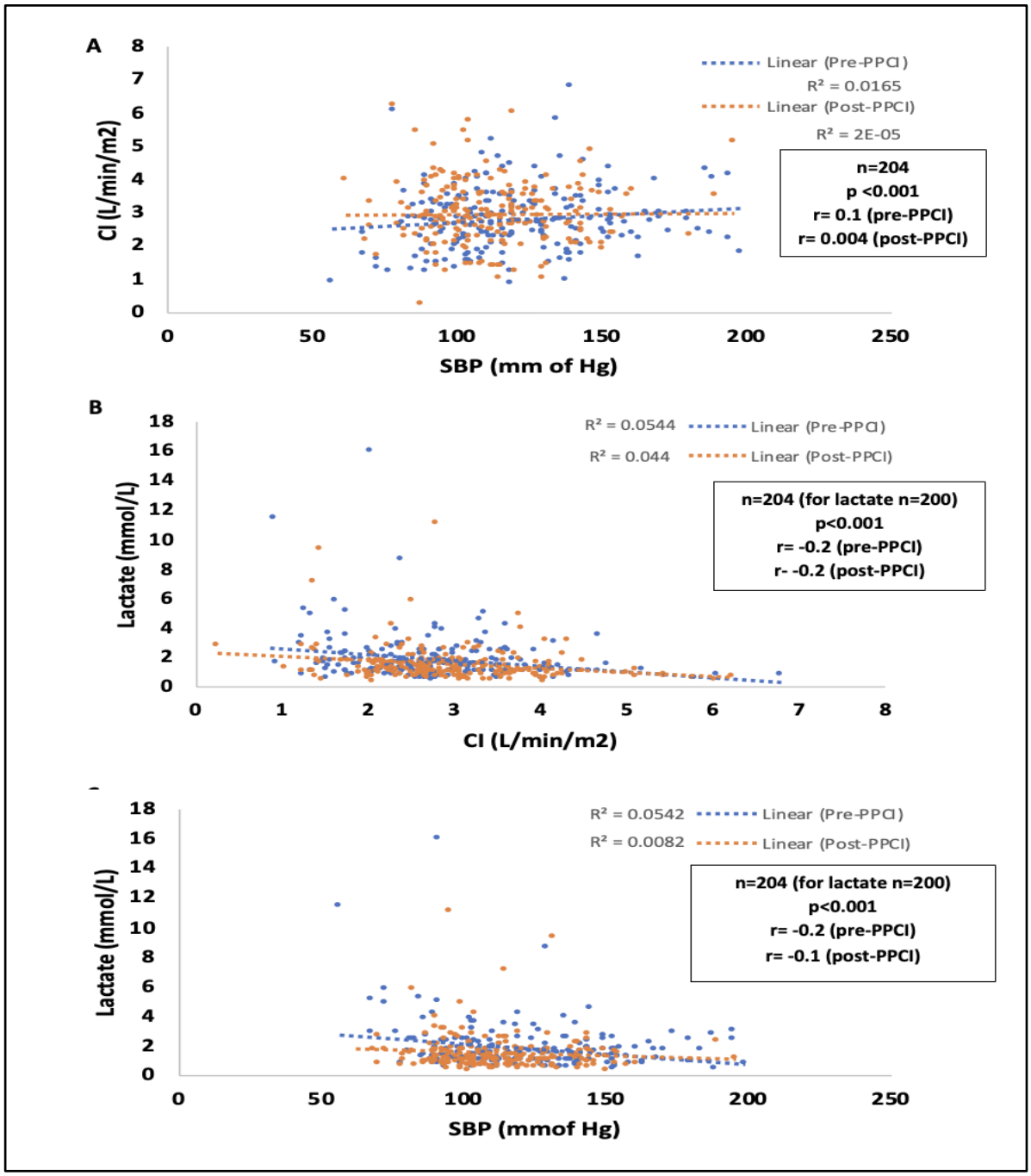

Figure 10: Scatterplots depicting the association between different CS in STEMI patients pre and post PPCI. *A) Association between CI and SBP pre-PPCI and post-PPCI, B) Association between Lactate and CI pre-PPCI and post-PPCI, C) Association between Lactate and SBP pre-PPCI and post-PPCI. Blue line represents trendline for pre-PPCI and orange line indicates trendline for post-PPCI. Here n=204, for lactate n=200 as ABG samples couldn't be collected from 4 patients. P-values were obtained by one-way anova using excel. R^2 indicates linear regression, r indicates Pearson correlation. CI, cardiac index; SBP, systolic blood pressure; STEMI, ST Elevation Myocardial Infarction; CS, cardiogenic shock; PPCI, primary percutaneous coronary intervention; ABG, arterial blood gas*

4.4. Hemodynamic changes in pre-PPCI, post-PPCI and POD-1 in STEMI patients

Table 4 and Figure 11A-J provides information on the general and hemodynamic profiles of 204 STEMI patients prior to, following, and one day after PPCI. The average SBP before PPCI was 121.6±27.1 mmHg **(Figure 11B)**, which decreased post-PPCI (113.3±21.9 mmHg, $p<0.001$) and on POD-1 (118.0±16.4 mmHg). SI slightly increased post-PPCI from (pre-PPCI: 36.2±10.6 to post-PPCI: 37.3±10.5 ml/m^2) **(Figure 11E)**, but subsequently decreased on POD-1 (33.8±8.8 ml/m^2, $p<0.05$). Similarly, CI values showed the same pattern, with an increase in post-PPCI (2.9±0.9 L/min/m^2) compared to pre-PPCI (2.8±0.9 L/min/m^2) **(Figure 11A)** and a decrease on POD-1 (2.5±0.7 L/min/m^2, $p<0.001$). CPI and CPO **(Figure 11F, G)** remained almost constant across the three time points. GGI slightly increased post-PPCI (pre-PPCI: 11.8±3.8 to post-PPCI: 12.1±4) **(Figure 11D)** but decreased on POD-1 (10.3±2.9, $p<0.001$). In contrast to GGI, both TPR (from 1408.9±528.7 dynes-sec/cm^5 to 1282.1±693.6 dynes-sec/cm^5, $p<0.05$) and TPRI (from 2712.6±943.2 dynes-sec/cm^5-m^2 to 2433.8±963.9 dynes-sec/cm^5-m^2, $p<0.05$) **(Figure 11I)** decreased in post-PPCI and increased on POD-1 (TPR 1511.3±532.3 dynes-sec/cm^5 and TPRI 2906.4±978.5 dynes-sec/cm^5-m^2, $p<0.05$).

The average lactate level was 1.9±1.6 mmol/L prior to PPCI, and decreased to 1.5±1.3 mmol/L ($p<0.05$) post-PPCI **(Figure 11C)**. SBP ($p<0.001$, **Figure 11B**), lactate ($p<0.05$, **Figure 11C**), and TPRI ($P<0.05$, **Figure 11I**) demonstrated significant reductions post-PPCI. However, hemodynamic parameters did not demonstrate any significant alteration post-PPCI, although upward trends were noted for CI **(Figure 11A)** and GGI **(Figure 11D)**, while SI **(Figure 11E),** CPI **(Figure 11F),** CPO **(Figure 11G),** HR **(Figure 11H),** and TBW **(Figure 11J)** remained unchanged from pre-PPCI to post-PPCI.

In the context of TIMI flow assessment, prior to PPCI, 126/200 individuals (63%) displayed TIMI flow 0, 36/200 individuals (18%) displayed TIMI flow 1, while 31/200 (15.5%) and 7/200 (3.5%) individuals exhibited TIMI flow 2 and 3, respectively. Subsequent to PPCI, none of the individuals displayed TIMI flow 0, while 3/200 (1.5%), 50/200 (25%), and 147/200 (73.5%) individuals displayed TIMI flow 1, 2, and 3, respectively. The average left ventricular end-diastolic pressure (LVEDP) of STEMI patients is 20.3±7.7 mmHg (n-197) with a median of 20 mm of Hg and range (4-43) mm of Hg, and mean left ventricular ejection fraction (LVEF) (n=180) is 53.5±0.1% with a median of 55% and range (15-89) %.

Considering Killip classification, a marker of adverse outcome, 168 individuals (82.4%) were classified as Killip class-I, 19 individuals (9.3%) were classified as Killip class-II, 10 individuals (4.9%) were classified as Killip class-III, and 7 individuals (3.4%) were classified as Killip class-IV.

Table 4. *All-comer STEMI patients' characteristics pre-PCI, post-PCI and POD-1* ***[p <0.05 (*), p <0.001 (**), α = Pre- and Post-PPCI and β = Pre- and POD-1 comparison]***

Patients' characteristics (n=204)	**Normal value**	**Pre-PCI**	**Post-PCI**	**POD-1**
		Mean ± SD **Range** **Median (IQR)**	**Mean ± SD** **Range** **Median (IQR)**	**Mean ± SD** **Range** **Median (IQR)**
SBP (mm of Hg)	120	121.6 ± 27.1 57-199 117 (103-139)	113.3 ± 21.9 ** α 62-196 110 (97-126.8)	118.0 ± 16.4 β 78-167 118 (107-127)
DBP (mm of Hg)	80	69.5 ± 15.5 39-120 70 (58-78)	66.4 ± 14.2 * α 37-110 66.5 (56-75)	68.2 ± 11.7 37-100 68 (59-76)
HR (beats/min)	60-90	79.3 ± 19.7 34-228 78 (67-90)	80.9 ± 18.6 39-183 78 (68-92)	75.6 ± 15.2 * β 42-164 73 (66-83)
SV (ml)	60-130	71.4 ± 23.1 14.8-120 68.5 (53.7-88.1)	73.5 ± 23.6 14.3-120 71.1 (57.7-91.4)	66.1 ± 19.1 * β 18.5-120 64.2 (52.9-78.9)
SI (ml/m^2)	35-65	36.2 ± 10.6 8.6-65.4 35.9 (28.3-43.1)	37.3 ± 10.5 6.7-65 36.8 (31.3-43.5)	33.8 ± 8.8 * β 9.6-57.2 33.3 (28.1-39.6)
CO (L/min)	4.0-8.0	5.6 ± 2.0 1.6-12 5.4 (4.1-6.8)	5.8 ± 1.9 0.6-10.8 5.8 (4.5-7.2)	4.9 ± 1.5 ** β 1.6-10.4 4.8 (3.9-5.8)
CI (L/min/m^2)	2.5-4.0	2.8 ± 0.9 0.9-6.8 2.8 (2.2-3.4)	2.9 ± 0.9 0.3-6.2 2.9 (2.4-3.6)	2.5 ± 0.7 ** β 0.8-4.9 2.5 (2.0-2.9)
CPI (Watt/m^2)	0.45-0.85	0.6 ± 0.2 0.1-1.5 0.5 (0.4-0.7)	0.5 ± 0.2 0.03-1.3 0.5 (0.4-0.7)	0.5 ± 0.2 ** β 0.1-1.3 0.5 (0.4-0.6)
CPO (Watt)	>1	1.1 ± 0.5 0.2-2.8 1.1 (0.7-1.4)	1.1 ± 0.5 0.1-2.5 1.0 (0.8-1.3)	0.9 ± 0.3 ** β 0.3-2.1 0.9 (0.7-1.1)

Table 4. continues				
GGI	>10	11.8 ± 3.8 2.8-28 11.5 (9.4-13.9)	12.1 ± 4.0 0.9-32 11.98 (9.8-14.3)	10.3 ± 2.9 ** β 3.0-25.7 10.1 (8.5-12)
TPRI (dynes-sec/cm^5-m^2)	1600-3000	2712.6 ± 943.2 700-6647 2588 (2020.5-3310.5)	2433.8 ± 963.9 * α 679-7125 2295.5 (1774.5-2781)	2906.4 ± 978.5 * β 1151-8362 2734 (2292.3-3333.3)
TPR (dynes-sec/cm^5)	770-1500	1408.9 ± 528.7 532-3701 1324.5 (1001.8-1674)	1282.1 ± 693.6 * α 508-8010 1148.5 (899.5-1476.5)	1511.3 ± 532.3 659-4321 1378.5 (1178.3-1773.8)
TBW (% weight)	44.4-57.6	50.0 ± 8.5 31.1-76 49.1 (44.4-55.2)	49.9 ± 8.7 31.1-76.1 49.1 (44.1-55.1)	51.3 ± 9.6 10.1-79.6 50.5 (45.4-57.4)
TIMI flow, n (%) (n=200)	TIMI-0 TIMI-1 TIMI-2 TIMI-3	126 (63%) 36 (18%) 31 (15.5%) 7 (3.5%)	0 (0%) 3 (1.5%) 50 (2.5%) 147 (73.5%)	
EDP (mm of Hg) (n=197)	5-12	20.3 ± 7.7 4-43 20 (15-25)		
Killip classification, n (%)	Killip-I Killip-II Killip-III Killip-IV	168 (82.4%) 19 (9.3%) 10 (4.9%) 7 (3.4%)		
CS score (n=176)	Range: 1-9	2.25 ± 1.3 1-6 2 (1-3)		
EF % (n=180)	>50	53.5 ± 0.1 15-89 55 (50-60)		
pH (n=200)	7.35-7.45	7.39 ± 0.1 7.17-7.59 7.39 (7.35-7.43)	7.36 ± 0.1 7.14-7.53 7.37 (7.34-7.40)	
PCO2 (mm of Hg) (n=200)	35-35	38.4 ± 7.8 16-56 40 (34.1-44.0)	40.5 ± 6.7 24-95 40 (37-43)	

Table 4. continues				
PO2 (mm of Hg) (n=200)	70-100	132.4 ± 50.5 28-352 128 (98-158)	124.5 ± 54.9 47-404 111 (91-142.5)	
Glucose (mmol/L) (n=200)	3.6-6.0	9.5 ± 3.9 3.0-23.2 8.3 (7.0-10.7)	9.0 ± 3.7 1.4-25 7.9 (6.7-10.2)	
Lactate (mmol/L) (n=200)	0.5-1.6	1.9 ± 1.6 0.5-16 1.5 (1-2.2)	1.5 ± 1.3 ***** α 0.4-11.1 1.2 (0.8-1.7)	

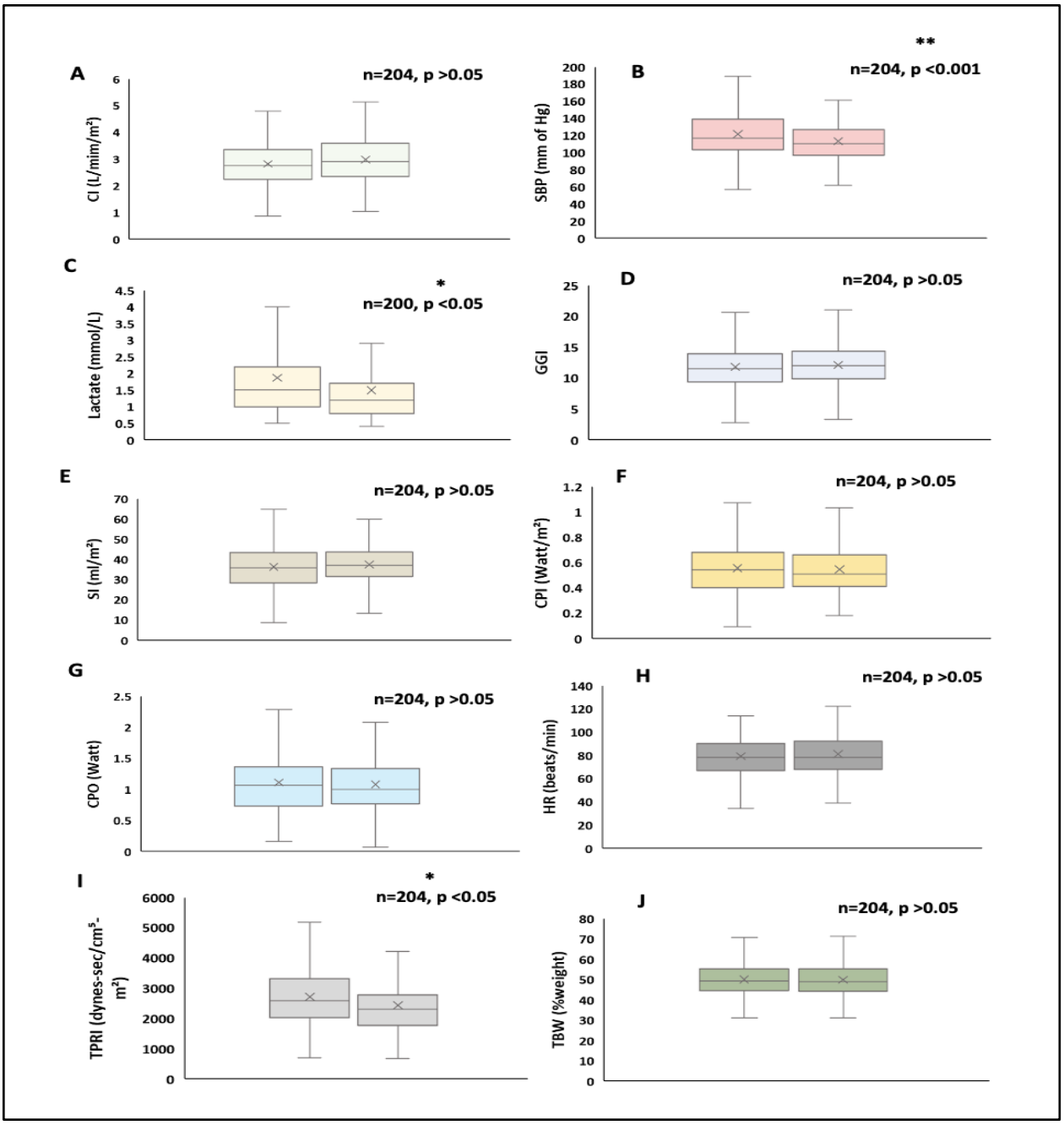

Figure 11: Box and Whisker plot displaying pre-PPCI and post-PPCI measurements of A) CI, B) SBP, C) arterial lactate, D) GGI, E) SI, F) CPI, G) CPO, H) HR, I) TPRI, J) TBW. *In the box plot, the bottom line illustrates the 25th percentile, the middle line illustrates median, the top line represents the 75th percentile and the cross mark (x) represents mean value. Error bar shows 10th and 90th percentile. Here, n= 204 (for lactate n=200 as ABG samples could not be collected from 4 patients). P-values were obtained by student's T-test using Excel. CI, cardiac index; SBP, systolic blood pressure; GGI, Granov-Goor Index; SI, stroke index; CPI, cardiac power index; CPO, cardiac power output; HR, heart rate; TPRI, total peripheral resistance index; TBW, total body water; PPCI, primary percutaneous coronary intervention; ABG, arterial blood gas. p <0.05 (*), p <0.001 (**).*

4.5. Hemodynamic profiles of STEMI patients based on SCAI cardiogenic shock classification

STEMI patients were classified according to SCAI classification (A, B, C, D, E), as judged by the treating interventional cardiologist. We have described their hemodynamic profiles pre-PPCI and post-PPCI in **Table 5 and 6.** Prior to PPCI, the mean SBP for SCAI-A patients was 126.3±25.9 mmHg, while the values for SCAI-B, C, D, and E patients were 122.1±24.9 mmHg, 92.6±20.1 mmHg, 95.9±22.1 mmHg, and 98.3±19.2 mmHg, respectively **(Table 5).** After PPCI, the SBP values decreased in SCAI-A (116.5±21.1 mmHg), SCAI-B (105.5±25.3 mmHg), and SCAI-C (103.2±17.3 mmHg) patients, but increased in SCAI-D (108.2±18.2 mmHg) and SCAI-E (104.6±12.7 mmHg) patients **(Table 6).**

In contrast, CI increased in all patients after PPCI, with values for SCAI-A, B, C, D, and E patients increasing from (A) 2.9±0.8 L/min/m^2 to 3.1±0.9 L/min/m^2, (B) 2.8±1.3 L/min/m2 to 3.0±1.1 L/min/m^2, (C) 2.2±0.7 L/min/m2 to 2.4±0.7 L/min/m2, (D) 2.4±0.9 L/min/m2 to 2.5±1.1 L/min/m2, and (E) 2.2±0.7 L/min/m^2 to 2.2±1.0 L/min/m^2, respectively **(Table 5, 6).**

Similar patterns were observed in lactate levels, which decreased after PPCI, except for SCAI-E patients, where they slightly increased. Prior to PPCI, lactate levels were 1.5±0.9 mmol/L (SCAI-A), 2.1±1.0 mmol/L (SCAI-B), 3.2±1.6 mmol/L (SCAI-C), 5.6±4.6 mmol/L (SCAI-D), and 2.0±0.5 mmol/L (SCAI-E) **(Table 5),** while after PPCI, they were 1.2±0.8 mmol/L (SCAI-A), 2.0±1.8 mmol/L (SCAI-B), 2.4±0.9 mmol/L (SCAI-C), 3.4±2.5 mmol/L (SCAI-D), and 2.2±0.5 mmol/L (SCAI-E) **(Table 6).**

Interestingly, SI increased after PPCI in all SCAI classes (SCAI-A: from 38.2±9.9 ml/m2 to 39.2±9.2 ml/m2; SCAI-B: from 33.6±10.3 ml/m2 to 35.8±11.5 ml/m2; and SCAI-D: from 27.8±13.3 ml/m^2 to 30.9±12.8 ml/m^2) except for SCAI-C and SCAI-E, in which SI decreased from 29.9±5.5 ml/m^2 to 29.4±6.6 ml/m^2 and from 29.4±10.2 ml/m^2 to 25.1±12.9 ml/m^2 consequently **(Table 5,6)**.

Table 5: *Pre-PPCI hemodynamic parameters of STEMI patients according to SCAI classification*

Hemodynamic Parameters (n=204)	**SCAI-A (144)**	**SCAI-B (33)**	**SCAI-C (10)**	**SCAI-D (9)**	**SCAI-E (8)**
	Mean ± SD Range Median (IQR)	**Mean ± SD Range Median (IQR)**	**Mean ± SD Range Median (IQR)**	**Mean ± SD Range Median (IQR)**	**Mean ± SD Range Median (IQR)**
SBP (mm of Hg)	126.3 ± 25.9 68-199 120 (108-141.8)	122.1 ± 24.9 79-195 119 (103.5-138)	92.6 ± 20.1 73-147 86.5 (80-96.8)	95.9 ± 22.1 57-136 95 (80-112.5)	98.3 ± 19.2 68-133 100 (82.3-112)
DBP (mm of Hg)	71.6 ± 14.6 40-116 71 (61.3-80.8)	68.1 ± 16.3 39-120 70 (56-78)	57.5 ± 16.9 42-104 55 (44.8-60.3)	62 ± 14.4 39-90 58 (54-73)	61.9 ± 13.0 44-88 59.5 (50.8-71.3)
HR (beats/min)	77.9 ± 14.9 34-126 76.5 (67.0-87.8)	82.8 ± 32.3 41-228 83 (63-91.5)	76.6 ± 27.3 44-129 72 (46-98.3)	91 ± 13.9 68-114 87 (79.5-103)	82.0 ± 15.0 65-105 75.5 (69.3-101)
SV (ml)	75.1 ± 22.2 30.4-120 73.3 (56.7-91.4)	66.5 ± 22.1 21.9-112 63.3 (53.3-83.5)	57.0 ± 13.8 40.3-85.3 56.3 (43.7-66.7)	54.7 ± 29.7 14.8-107 52.4 (28.8-83.7)	61.3 ± 20.2 33.8-105 55.5 (49.8-73.6)
SI (ml/m^2)	38.2 ± 9.9 18.9-65.4 38.1 (30.1-45.1)	33.6 ± 10.3 12.2-61.8 32.2 (26.4-39.9)	29.9 ± 5.5 20.6-37.3 29.3 (25.7-35.4)	27.8 ± 13.3 8.6-52.3 26 (16.2-38.5)	29.4 ± 10.2 14.4-52.1 29.6 (22.5-31.9)

Table 5. continues					
CO (L/min)	5.8 ± 1.9 2.2-12 5.6 (4.4-6.8)	5.4 ± 2.3 1.78-10.4 5.2 (3.5-7.2)	4.4 ± 1.9 1.9-8.2 4.6 (2.7-5.6)	4.6 ± 2.0 1.6-7.4 4.1 (2.8-6.9)	4.9 ± 1.7 3.3-8.0 4.6 (3.4-6.7)
CI (L/min/m^2)	2.9 ± 0.8 0.9-6.8 2.8 (2.4-3.4)	2.8 ± 1.3 0.86-6.1 2.5 (1.8-3.5)	2.2 ± 0.7 1.2-3.4 2.5 (1.5-2.8)	2.4 ± 0.9 0.9-3.6 2.1 (1.6-3.4)	2.2 ± 0.7 1.5-3.6 2.3 (1.5-2.6)
CPI (Watt/m^2)	0.6 ± 0.2 0.2-1.45 0.6 (0.5-0.7)	0.5 ± 0.3 0.1-1.3 0.5 (0.3-0.7)	0.4 ± 0.2 0.2-0.7 0.3 (0.2-0.5)	0.4 ± 0.2 0.1-0.8 0.4 (0.3-0.6)	0.4 ± 0.1 0.2-0.6 0.4 (0.3-0.5)
CPO (Watt)	1.2 ± 0.5 0.3-2.7 1.1 (0.9-1.4)	1.1 ± 0.6 0.3-2.8 0.9 (0.6-1.4)	0.7 ± 0.4 0.3-1.4 0.6 (0.3-1.0)	0.8 ± 0.4 0.2-1.5 0.8 (0.4-1.2)	0.8 ± 0.3 0.5-1.5 0.7 (0.5-1.0)
GGI	12.5 ± 3.6 6.0-28 12 (9.9-14.5)	10.7 ± 3.6 3.4-17.6 10.3 (7.8-13.7)	9.8 ± 2.4 5.3-13 9.8 (8.4-11.6)	9.5 ± 4.6 2.8-17.5 9.6 (5.5-13.4)	9.1 ± 3.3 4.3-15.8 9.3 (6.3-10.4)
TPRI (dynes-sec/cm^5-m^2)	2647.0±865.9 1130-6647 2532 (2108-3155)	2957.2±1130.2 700-6244 2805 (2001-3673)	2676.3±875.2 1655-4226 2352 (1847-3544)	2771±875.9 1708-4031 2695 (1812-3677)	2863.8±1321.5 1449-5456 2377.5 (1757-4010)
TPR (dynes-sec/cm^5)	1380.7±495.9 619-3701 1291.5 (1016.3-1629.3)	1508.9±606.1 532-3012 1422 (1040-1836.5)	1472.4±613.6 684-2666 1309.5 (906.3-2001.3)	1493.7±563.4 722-2370 1592 (916.5-2033.5)	1328.5±530.4 716-2322 1150 (857-1808.5)

Table 5. continues					
TBW (%)	50.4 ± 8.3 33.4-76 49.7 (44.5-55.5)	48.9 ± 8.5 31.1-70.6 48.9 (41.9-53.4)	52.6 ± 8.8 40-68.5 50.7 (46.1-60.1)	48.5 ± 6.9 38.9-61.6 47.1(43.5-54.2)	47.1 ± 10.6 35.8-71.3 46(37.8-51.2)
Lactate (mmol/L) (n=200)	1.5 ± 0.9 0.5-8.6 1.3 (1.0-1.7)	2.1 ± 1.0 0.6-4.6 2.1 (1.1-2.9)	3.2 ± 1.6 1.3-5.9 2.8 (1.6-5.1)	5.6 ± 4.6 2.3-16 3.8 (2.4-8.2)	2.0 ± 0.5 1.2-2.9 2.1 (1.6-2.4)

Table 6: Post-PPCI hemodynamic parameters of STEMI patients according to SCAI classification

Hemodynamic Parameters (n=204)	**SCAI-A (144)**	**SCAI-B (33)**	**SCAI-C (10)**	**SCAI-D (9)**	**SCAI-E (8)**
	Mean ± SD Range Median (IQR)	**Mean ± SD Range Median (IQR)**	**Mean ± SD Range Median (IQR)**	**Mean ± SD Range Median (IQR)**	**Mean ± SD Range Median (IQR)**
SBP (mm of Hg)	116.5±21.1 80-196 113 (101-130)	105.6±25.3 62-190 101 (91-122)	103.2±17.3 73-139 99.5 (93.3-116)	108.2±18.2 83-141 104 (92.5-124)	104.6±12.7 88-129 104.5(91.3-113.5)
DBP (mm of Hg)	67.6±13.9 38-106 67 (57.3-75)	65±16.5 37-110 63 (52-80.5)	60.8±10.9 41-76 64 (51.8-67.8)	61.3±11.3 45-84 60 (52-69)	63.5±10.9 41-75 67 (54.8-73.3)
HR (beats/min)	79.2±15.7 45-122 78 (67-87)	85.7±22.7 58-183 85 (71-95)	82.7±24.2 43-135 81.5 (64.8-95)	84.2±23.2 53-129 73 (67.5-105)	87±26.7 39-131 89.5(68.5-106.3)
SV (ml)	77.3±21.8 26.7-120 75.7 (61.1-93.3)	70.9±24.6 21.4-120 67.1 (57.5-79.9)	56.2±17.4 38.2-100 52.6 (42.4-63.9)	60.9±26.6 21.5-98.6 61 (31.4-84.9)	52.1±25.2 14.3-107 48.3 (36.2-63.1)
SI (ml/m^2)	39.2±9.2 16.6-65 39.1 (33.6-45.2)	35.8±11.5 11-65 34.4 (30.8-39.5)	29.4±6.6 19.7-41.4 30.4 (22.7-33.8)	30.9±12.8 11.1-49.2 35.8 (16.6-41.4)	25.1±12.9 6.7-52.8 22.3 (16-30.9)

Table 6. continues					
CO (L/min)	6.1±1.9 2.0-10.6 5.9 (4.7-7.3)	5.9±2.0 2.2-10.8 5.7 (4.2-7.5)	4.6±1.8 2.5-9.2 4.3 (3.2-5.1)	4.8±2.0 2.1-7.9 4.3 (2.6-7.1)	4.6±2.1 0.6-7.3 4.7 (3.3-6.5)
CI (L/min/m^2)	3.1±0.9 1.3-5.8 3.0 (2.5-3.6)	3.0±1.1 1.0-6.2 2.9 (2.2-3.6)	2.4±0.7 1.4-3.8 2.4 (1.6-2.8)	2.5±1.1 1.1-4.3 2.5 (1.5-3.5)	2.2±1.0 0.3-3.6 2.5 (1.4-3.2)
CPI (Watt/m^2)	0.6±0.2 0.2-1.2 0.5 (0.4-0.7)	0.5±0.2 0.2-1.3 0.5 (0.3-0.7)	0.4±0.1 0.2-0.6 0.4 (0.2-0.5)	0.4±0.2 0.2-0.9 0.4 (0.2-0.6)	0.4±0.2 0.03-0.7 0.4 (0.3-0.6)
CPO (Watt)	1.1±0.5 0.3-2.5 1.1 (0.8-1.4)	1.0±0.5 0.3-2.3 0.9 (0.6-1.3)	0.8±0.3 0.4-1.5 0.7 (0.5-1.0)	0.8±0.4 0.4-1.6 0.8 (0.4-1.2)	0.8±0.4 0.1-1.3 0.7 (0.6-1.3)
GGI	12.7±3.7 0.9-32 12.5(10.8-14.6)	11.7±4.2 3.9-23.6 11.3 (8.9-13.7)	9.7±2.7 5.2-15.5 9.5 (8.0-11.1)	10.2±5.1 3.3-19.3 10.2 (4.6-14.7)	7.5±3.8 2.2-15.5 6.9 (4.8-9.5)
TPRI (dynes-sec/cm^5-m^2)	2345.4±780.0 1012-5132 2236 (1750.5-2708.3)	2357.6±1120.1 679-6752 2176 (1648.5-2685.5)	2684.7±854.3 1407-4382 2676.5 (2162-3066.8)	2979.1±1329.5 1367-5882 2424 (1942-3881.5)	3413.3±1735.2 1760-7125 2501 (2116.3-4654.5)
TPR (dynes-sec/cm^5)	1224.0±478.8 519-3195 1143 (899.5-1414)	1201.2±566.5 508-3256 1019 (791-1466)	1424.6±435.6 650-2129 1394 (1178.3-1742)	1546.7±703.7 750-2918 1425 (911.5-2149.5)	2185.3±2239.6 869-8010 1336 (976.3-2003)

Table 6. continues					
TBW (%)	50.3±8.4 31.7-76.1 49.7 (44.3-55.4)	48.9±8.7 31.1-70.7 48.9 (42.3-54.9)	51.4±10.4 33.7-68.7 51.2 (44.1-60.1)	48.1±8.2 39-64.9 45.9 (41.1-54.7)	46.6±10.6 35.4-71.2 45.4 (37.8-50.4)
Lactate (mmol/L) (n=200)	1.2±0.8 0.4-7.1 1.0 (0.7-1.3)	2.0±1.8 0.5-11.1 1.6 (0.9-2.3)	2.4±0.9 1.3-4.2 2.2 (1.7-2.9)	3.4±2.5 1.3-9.4 2.2 (1.7-4.5)	2.2±0.5 1.6-2.8 2.2 (1.7-2.7)

4.6. Comparison of hemodynamic profiles of STEMI patients pre-PPCI, post-PPCI and POD-1 based on outcome

Table 7 compares the hemodynamic profiles of STEMI patients at three different time points (pre-PPCI, post-PPCI and POD-1) who had adverse outcome (hospital stay >4 days and death at 30-day) versus those who did not. Among 204 patients, 44 (21.6%) patients had adverse outcome [7 (3.43%) death at 30-day and 42 (20.6%) in-hospital stay >4 days], and 160 (78.4%) patients had uneventful course.

The mean SBP in patients with adverse outcome were 112.7±32.2 mm of Hg (pre-PPCI), 116.2±23.7 mm of Hg (post-PPCI) and 112.3±19 mm of Hg (POD-1), while in the patients without adverse events the SBP values were 123.9±25 mm of Hg (pre-PPCI), 112.5±21.3 mm of Hg (post-PCI) and 119.6±15.2 mm of Hg (POD-1). The comparison of SBP values between patients with adverse outcomes and those without was statistically significant (* $p < 0.05$) in pre-PPCI and POD-1 **(Table 7)** but not in post-PPCI.

Similarly, the comparison of CI values between the two groups showed a statistically significant difference, both pre-PPCI [adverse outcomes: 2.4±0.9 L/min/m^2 vs. no adverse outcomes: 2.9±0.9 L/min/m^2; $p<0.05$], as well as post-PPCI [adverse outcomes: 2.6±0.9 L/min/m^2 vs. no adverse outcomes: 3.1±0.9 L/min/m^2; $p<0.001$] **(Table 7)**. However, no significant statistical difference was found in POD-1.

The lactate levels also showed a significant difference between the two groups, both pre-PPCI (adverse outcomes: 2.6±2.8 mmol/L vs. no adverse outcomes: 1.7±1.1 mmol/L; $p<0.05$), as well

as post-PPCI (adverse outcomes: 2.1±1.6 mmol/L vs. no adverse outcomes:1.3±1.1 mmol/L; p<0.001) **(Table 7)**.

Table 7. *Comparison of hemodynamic parameters of STEMI patients pre-PPCI, post-PPCI and POD-1 based on outcome* ***[p <0.05 (*), p <0.001 (**)]***

Parameters (n=204)	**Pre-PPCI**		**Post-PPCI**		**POD-1**	
	Adverse outcome (n=44)	**Uneventful course (n=160)**	**Adverse outcome (n=44)**	**Uneventful course (n=160)**	**Adverse outcome (n=44)**	**Uneventful course (n=160)**
	Mean ± SD Range Median (IQR)	**Mean ± SD Range Median (IQR)**	**Mean ± SD Range Median (IQR)**	**Mean ± SD Range Median (IQR)**	**Mean ± SD Range Median (IQR)**	**Mean ± SD Range Median (IQR)**
SBP (mm of Hg)	112.7± 32.2 57-195 105 (89.5-131.3)	123.9±25.0 * 73-199 120 (106-139.8)	116.2±23.7 83-190 115 (96.5-130.8)	112.5±21.3 62-196 110 (97-125)	112.3±19 78-167 111.5 (100-121.8)	119.6±15.2 * 90-163 118 (109-128.8)
DBP (mm of Hg)	66.6±19.2 39-120 61 (51.3-81.8)	70.3-14.2 40-116 70 (59-78)	69.8±14.9 41-110 68 (60-79.5)	65.5±13.9 37-103 65 (56-73)	65.1±12.1 43-99 66 (55-72.8)	69.1±11.5 * 37-100 68 (60-77.8)
HR (beats/min)	86.7±19.9 44-129 88.5 (71-103.8)	77.3±19.2 * 34-228 76.5 (66-87)	87.8±23.3 39-135 89 (70.5-103.8)	79.0±16.5 * 50-183 77.5 (67-87)	83.3±15.3 52-123 81 (73.3-97)	73.5±14.4 ** 42-164 71 (64-81)
SV (ml)	56.6±19.1 14.8-117.0 55.1 (45.5-64.3)	75.4±22.4 ** 21.9-120 75.4 (57.3-91.4)	57.9±21.7 14.3-120 57.2 (44.1-69.9)	77.8±22.2 ** 21.4-120 75.7 (61.7-95.1)	56.1±19.4 18.5-107 54.9 (43.8-68.1)	68.9±18.0 ** 24.9-120 66.3 (54.6-81.6)

Table 7. continues						
SI (ml/m^2)	28.9±9.5 8.6-59.3 28.6 (23.1-32.6)	38.2±9.9 ** 12.2-65.4 38.1 (31.0-44.9)	29.4±10.5 6.7-52.8 30.1 (22.5-35.9)	39.5±9.5 ** 11.9-65 39 (33.7-45.2)	28.7±9.5 9.6-52.9 28.4 (22.8-34.1)	35.3±8.1 ** 13.9-57.2 34.6 (29.1-40.8)
CO (L/min)	4.9±1.9 1.6-9.7 4.9 (3.5-5.9)	5.8±1.9 * 2.2-12.0 5.6 (4.3-7.1)	5.1±2.1 0.6-10.3 4.9 (3.5-6.5)	6.1±1.9 * 2.0-10.8 6.0 (4.6-7.4)	4.6±1.7 1.6-7.9 4.6 (3.3-5.7)	5.0±1.4 2.1-10.4 4.9 (3.9-5.9)
CI ($L/min/m^2$)	2.4±0.9 0.86-4.6 2.4 (1.8-2.9)	2.9±0.9 * 0.9-6.8 2.8 (2.3-3.5)	2.6±0.9 0.3-5.0 2.5 (2.0-3.1)	3.1±0.9 ** 1.3-6.2 3.0 (2.6-3.7)	2.4±0.8 0.8-4.0 2.3 (1.9-2.9)	2.6±0.7 1.2-4.9 2.5 (2.1-2.9)
CPI ($Watt/m^2$)	0.5±0.3 0.1-1.3 0.4 (0.3-0.6)	0.6±0.2 * 0.2-1.5 0.6 (0.5-0.7)	0.5±0.2 0.03-1.2 0.4 (0.3-0.6)	0.6±0.2 0.2-1.3 0.5 (0.4-0.7)	0.4±0.2 0.1-0.9 0.5 (0.3-0.5)	0.5±0.2 * 0.2-1.3 0.5 (0.4-0.6)
CPO (Watt)	0.9±0.6 0.2-2.8 0.9 (0.5-1.2)	1.2±0.5 * 0.3-2.7 1.1 (0.8-1.4)	0.9±0.5 0.1-2.5 0.9 (0.6-1.3)	1.1±0.4 0.3-2.4 1.0 (0.8-1.4)	0.8±0.4 0.3-2.1 0.8 (0.6-1.1)	0.9±0.3 0.4-2.1 0.9 (0.7-1.1)
GGI	9.5±3.6 2.8-23.2 9.4 (7.2-11.0)	12.4±3.6 ** 3.4-28 12 (9.9-14.5)	9.5±3.8 2.2-19.8 9.3 (6.8-11.8)	12.8±3.8 ** 0.9-32 12.6 (10.8-14.6)	8.7±2.6 3-14 8.8 (7-10.4)	10.7±2.8 ** 4.5-25.7 10.6 (8.8-12.3)
TPRI (dynes-sec/cm^5-m^2)	2916.9 ±1018.4 1223-6244 2732 (2069.8-3586.8)	2656.4 ±913.4 700-6647 2493.5 (2011.5-3270.8)	3005.3 ±1295.5 1211-7125 2629 (2294.3-3560.3)	2276.7 ±776.4 ** 679-5132 2144 (1710.3-2694.8)	3091.3 ±1251.2 1426-8362 2845.5 (2320.3-3421.8)	2855.6 ±882.2 1151-6249 2711 (2286-3321)
TPR (dynes-sec/cm^5)	1505 ±534.2 619-3012 1397.5 (1083.3-1813.8)	1382.5 ±524.1 532-3701 1274 (984.8-1641.3)	1638.3 ±1140.1 613-8010 1410 (997.5-1787.8)	1184.1 ±459.8 ** 508-3195 1114.5 (862.3-1377.5)	1610.8 ±696.6 758-4321 1463 (1113-1879.3)	1483.9 ±473.7 659-3085 1369.5 (1179.8-1734)

Table 7. continues						
TBW (%)	47.4±9.2 31.1-71.3 46 (40.1-53.7)	50.7±8.1 ***** 36.3-76 49.1 (45-55.6)	47.2±9.6 31.1-71.2 45.3 (40.2-54.1)	50.6±8.3 ***** 33.7-76.1 49.7 (44.7-55.5)	50.1±11.5 30.8-79.6 48.5 (42.4-56.2)	51.7±9.0 10.1-78.4 50.9 (45.9-57.7)
Lactate (mmol/L)	2.6±2.8 0.7-16 1.9 (1.1-2.6)	1.7±1.1 ***** 0.5-8.6 1.4 (1.0-2.0)	2.1±1.6 0.5-9.4 1.7 (1.0-2.6)	1.3±1.1 ****** 0.4-11.1 1.1 (0.8-1.6)	-	-

Figure 12A-F depicts a correlation between various parameters pre- and post-PPCI in STEMI patients among two patient groups: those who experienced adverse events and those who did not. The trendlines of SBP and CI for uneventful groups were found to be horizontal in both pre- and post-PPCI, with R^2 values of 0.0002 and 0.0348, respectively. In contrast, for adverse patient groups, the trendlines exhibited a slight upward slope, with R^2 values of 0.1904 and 0.0012 for pre-PPCI and post-PPCI, respectively **(Figure 12A, B).** It is worth noting that the association between CI and SBP was poor in all cases. These findings describe that even for similar systolic blood pressure, patients experiencing adverse outcomes had low CI, suggesting incorporating both of these parameters are likely to identify sicker patients or the ones who may experience adverse outcomes.

In terms of lactate and CI, poor association was observed in both patient groups, with R^2 values of 0.023 and 0.1242 in uneventful and eventful patients, respectively, for pre-PPCI, and R^2 values of 0.0219 and 0.0461 for uneventful and eventful patients, respectively, for post-PPCI **(Figure 12C, D).**

Similarly, poor association was observed in both patient groups for lactate and SBP in pre- and post-PPCI **(Figure 12E, F).** The statistical significance of the p-values was observed to be less than 0.001 in all cases **(Figure 12A-F).**

Observed discrepancies between such correlations were more pronounced in the pre-PPCI setting in comparison to the post-PPCI times.

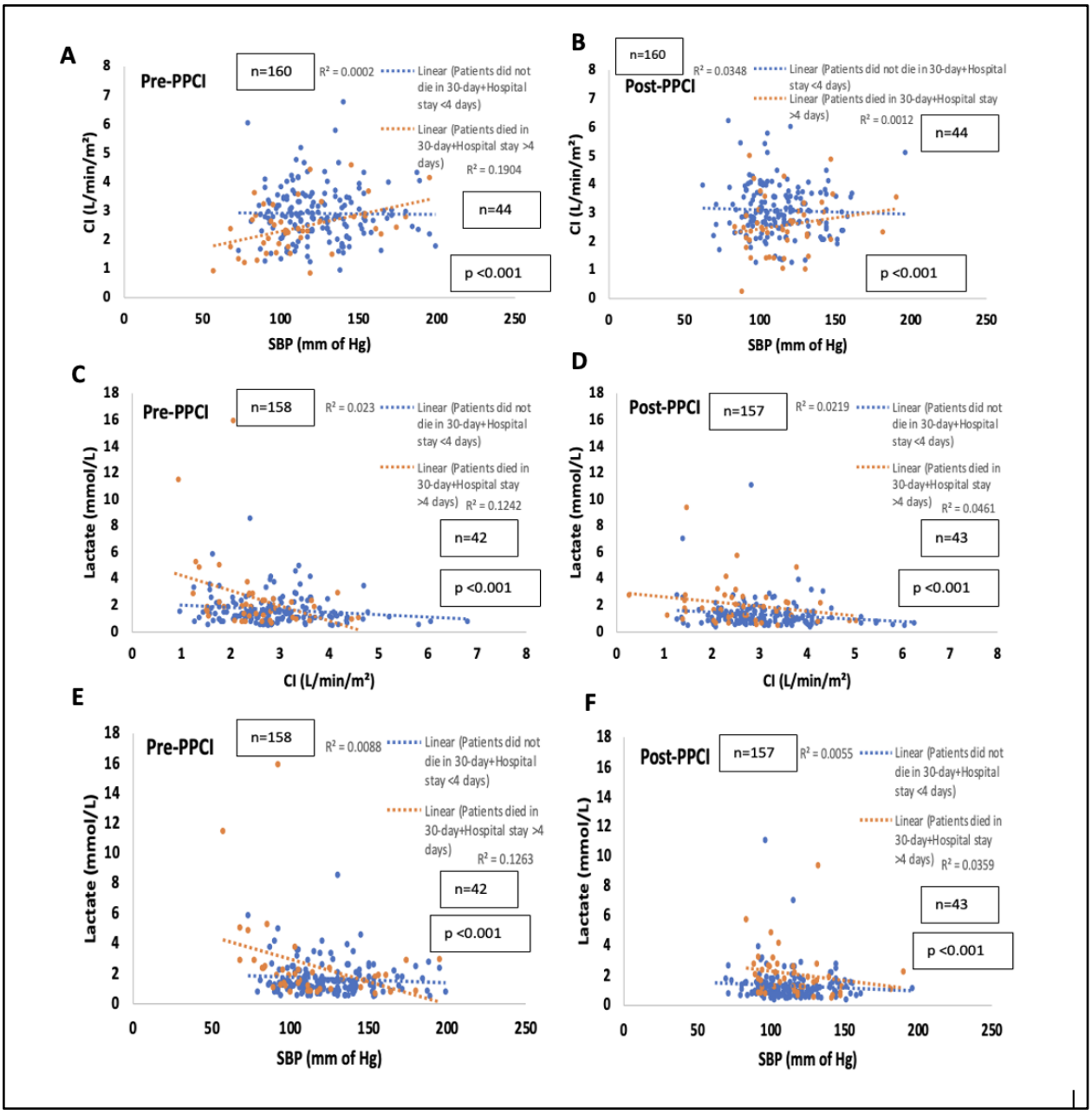

Figure 12: Scatterplots depicting the association between CS defining parameters pre and post PPCI in STEMI patients comparing outcome [adverse outcome (patient die at 30-day+hospital stay >4 days) vs uneventful course]. *A) Association between CI and SBP pre-PPCI, B) Association between CI and SBP post-PPCI, C) Association between Lactate and CI pre-PPCI, D) Association between Lactate and CI post-PPCI, E) Association of SBP and Lactate pre-PPCI, F) Association between SBP and Lactate post-PPCI. Blue line represents trendline for those patients who had adverse outcome and Orange line indicates trendline for uneventful course. P-values were obtained by one-way anova using excel. R^2 indicates linear regression. CI, cardiac index; SBP, systolic blood pressure; STEMI, ST Elevation Myocardial Infarction; CS, cardiogenic shock; PPCI, primary percutaneous coronary intervention*

4.7. Outcomes

The mean hospitalization duration was 5.6 ± 10.2 days, and the median duration was 3 days, with a range of 1 to 103 days, as reported in **Table 8**. Among the 204 patients, 42 (20.6%) remained hospitalized for more than 4 days. Of these patients, 186 (91.17%) were discharged, while 12/204 (5.89%) were transferred to other medical facilities. During the hospitalization, 7/204 (3.43%) patients passed away within 30 days. One-year follow-up data was available for 119 patients, with a mortality rate of 8.4% (10/119) recorded **(Table 8, Figure 13).** Among the patients who stayed in hospital for more than 4 days, 44/204 (21.6%) died within 30 days, and 46/119 (38.7%) died within one year of their admission.

Table 8. *Outcome of STEMI patients at 30-day and 1-year*

Variable (n=204)	**Median ± SD Range (Minimum-Maximum) Median (IQR)**
Total hospital- stay, (days)	5.6 ± 10.2 1-103 3 (2-4)
Hospital stay >4 days, n (%)	42 (20.6%)
Discharged home, n (%)	186 (91.17%)
Transferred to another health facility, n (%)	12 (5.89%)
Death at 30-day, n (%)	7 (3.43%)
Death at 1-yr, n (%) (n=119)	10 (8.4%)
Death at 30-day and hospital stay >4 days, n (%)	44 (21.6%)
Death at 1-yr and hospital stay >4 days, n (%) (n=119)	46 (38.7%)

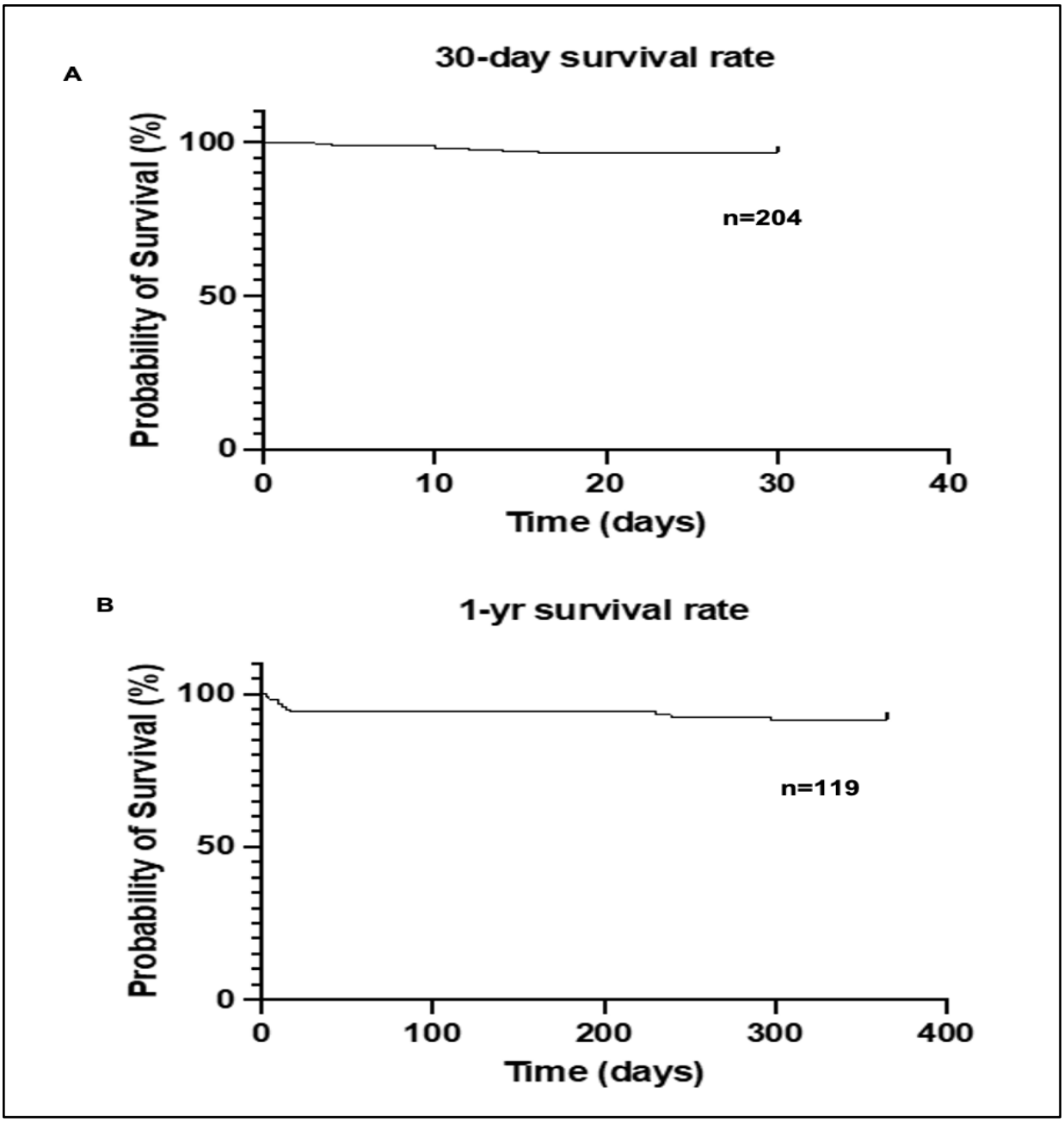

Figure 13: Kaplan-Meyer curve estimates the survival of STEMI patients at *A) 30-day and B) 1-year*

Chapter 5.

Discussion

Our study was designed to provide a comparison of the incidence of CS in STEMI patients based on three widely accepted parameters, namely SBP, lactate levels, and CI, and also to evaluate the impact of PPCI on these parameters. Key findings of our study are: (1) significant variability in the incidence of each CS defining parameter, with poor agreement within, (2) marked improvement in each of these CS defining parameters post PPCI, and (3) a range of hemodynamic differences in patients experiencing adverse outcomes (death and prolonged in-hospital stay).

Demographics of our patient cohort were comparable to previously published research [114]. these included age, biological sex, body mass index, and prevalence of cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus, and prior myocardial infarction [32,115]. Moreover, similar to previously published studies, we also noted that inferior STEMI with the RCA being the culprit artery was the most commonly encountered STEMI [116,117].

Our data revealed that the current criteria used to define CS in STEMI patients, including SBP, CI, and lactate, cannot be used interchangeably. Despite being commonly used in guidelines to identify CS patients [29,49], these parameters exhibit minimal overlap in our study. Elevated lactate was the most commonly observed parameter in our study. In early 1960s, elevated lactate [> 4mmol/L] was described to be associated with adverse outcome in patients with undifferentiated shock state [118] or even all comer in-hospital patients [119]. Although various organs can produce lactate under anaerobic conditions, as an end product of glycolysis, skeletal muscle is the

predominant source of generally observed lactate rise [120]. Usually, liver rapidly metabolizes this elevated lactate from circulation, whereas kidney is also able to clear lactate albeit to a smaller extent followed by cardiomyocytes [121]. Although multiple conditions in addition to cardiogenic shock can result in increased lactate production, such as septic shock, mitochondrial dysfunction [122], patients brought to the catheter laboratory with STEMI were absolutely fine till they started having chest pain due to occluded coronary artery. Hence, only tissue hypoperfusion irrespective of being hypo/normotensive state and alternative aetiologies are unlikely to be responsible.

Some STEMI patients are hypoxic at the time of arrival due to either reduced cardiac output and/or pulmonary congestion, however, majority of patients maintain normal level of hypoxia at the time of arrival to the hospital. Intense chest pain and/or fear in STEMI patients may result in sympathetic overdrive [123] and resultant catecholamine elevation [124]. Although, not described in STEMI setting, elevated catecholamines are reported to be responsible for exaggerated cellular glycolysis to generate energy and producing excess lactate rather than going through normal oxidative phosphorylation in tumor cells, also known as "Warburg effect". Catecholamines are thought to be responsible for tumor cell-specific alterations. Although not described in acute setting, role of catecholamine in lactate production in STEMI setting requires further exploration. Additionally, we noted significantly higher proportion of STEMI patients were noted to have elevated lactate level, and without doubt this value is unlikely to be representative of cardiogenic shock, we do not have clear explanation to this observed phenomenon.

When production is higher than clearance capacity, lactate accumulates and this depresses myocardial contractility and also blunts vasopressor effectiveness. Bicarbonate therapy to mitigate

lactate mediated acidic environment is described to exacerbate lactate production and associated mortality [125]. Published literature describes various cut off levels for elevated lactate; here we have used lactate >2.0 mmol/L as an elevated lactate. Elevated lactate is considered to be a sensitive marker of tissue perfusion than systolic or even mean blood pressure. Similarly SHOCK trial demonstrated a phenotype of normotensive cardiogenic shock [73].

We observed cardiac output to be in lower in patients experiencing adverse outcomes in our study. Although, it did not correlate well with systolic blood pressure, it's correlation with systolic blood pressure correlated with uncomplicated in-hospital and 30-day as well as 1-year mortality. this supports the concept that CI or SBP alone cannot be used as an independent parameter of adverse outcomes in STEMI patients. However, patients experiencing adverse outcomes were noted to have markedly low stroke index (a surrogate marker of myocardial contractility) and to compensate to maintain adequate output, the same patient cohort was noted to have elevated heart rate, likely secondary to elevated sympathetic drive. Low stroke index ($\leq$35 mL/m^2) irrespective of left ventricular contractility or systolic function is described to be a low-flow state [126]. Although this is well known to the structural heart disease team focusing on trans-catheter aortic valve implantation (TAVI), low flow state is associated with adverse outcomes. In contrast to perceived general consensus, patients undergoing TAVI, with 'low-flow' but preserved left ventricular contractility (preserved EF) were noted to have excess heart failure and 1-year mortality whereas the patients with 'low-flow' and impaired ventricular contractility (low EF) had outcome similar to the ones with normal flow [126]. Similarly, in contrast to earlier data described excess mortality only associated with low ejection fraction[127], emerging data describe excess mortality with hyperdynamic left ventricular contractility in heart failure and other settings [128,129]. Although, left

ventricular ejection fraction is not available in our study cohort, it appears that low SI pre-PPCI, immediately post-PPCI as well as the next day appears to be a strong marker associated with adverse outcomes.

We observed that patients experiencing adverse outcomes were noted to have low CPI and CPO, similar to described by others, including SHOCK study [73]. Although CPO/CPI are described to be independent hemodynamic parameters associated with adverse outcome, due to technical challenges (calculation requires cardiac index value) with measurement, such parameters are not measured in routine clinical practice. We also observed GGI (a patented marker only limited to NICaS system); a surrogate marker of effective ventricular contraction was noted to be markedly low at all 3 time points, in patients experiencing adverse outcomes [130].

Given the emergence of non-invasive and wearable technologies, utility of technologies similar to NICaS that provides continuous non-invasive monitoring, including a range of hemodynamic parameters in routine clinical practice warrants further evaluation.

Our analysis has indicated that while the incidence of low CI reduced after intervention, the incidence of low SBP remained unchanged, or rather increased immediately post-PPCI. Such increment could be due to (1) coronary flow restoration associated pain relief and normalization of sympathetic overdrive, and/or (2) nitrate and other vasodilator use mediate peripheral vasodilation, hence reduction in SBP despite improvement in cardiac output and cardiac index. It is notable that low SBP alone should not be used as a surrogate for low CI. Most trials have used a subjective definition of CS rather than objective criteria [29]. Various combinations of these CS defining parameters identified different incidence rate in our STEMI patient cohort. It appears that

any single parameter is not directly suggestive of CS, but which combination may provide more objective description of CS remains unclear. Given challenges with these single parameter-based CS identification, suggest that we clinicians should focus on identifying high-risk patients experiencing adverse outcomes using these parameters. In our study we chose death and 30-days and 1 year, and patients needing prolong in-hospital stay as these parameters. Majority of STEMI patients are discharged within 3-4 days from their presentation, unless some other issues complicate their in-hospital course; heart failure, arrhythmias are the most commonly encountered complications post-STEMI.

The incidence of these parameters changes very quickly immediately post PPCI. Given significant dynamicity in these parameters due to underlying hemodynamic fluctuations, it is possible that value obtained at one point in time may not provide useful value, rather continuum of these parameters may provide clinical useful details. Patients with quickly improving hemodynamics with PPCI are likely to have a trajectory towards improved outcomes, whereas the ones, who fail to demonstrate such an improvement, may experience adverse outcomes. Identification of such outcome-associated parameter information is likely to allow the currently stretched healthcare system to focus on such high-risk patients with intention to provide close monitoring and plausibly improve their outcomes. Our findings of dynamic change in hemodynamic parameters is unique, as previous studies did not employ defined time points to measure parameters for defining CS [29].

We also investigate the incidence of CS in relation to the type of STEMI; inferior versus non-inferior. The myocardial blood supply is maintained through three major arteries, namely the LAD, the RCA, and the LCx [131]. The LAD and LCx primarily supply blood to LV, whereas RCA is the primary provider of the RV myocardium. LV systolic impairment due to direct myocardial damage

results in low CO/CI and cardiogenic shock, whereas primary RV impairment compromises systemic ventricular pre-fill and hence compromise effective cardiac output. Although, majority of our study cohort were noted to have inferior STEMI, published literature findings remain conflicting. Previous research has shown that anterior STEMI has a higher mortality rate owing to LV dysfunction, CS, and ultimately, death [29,30,54,65,77]; likely linked to a decrease in SBP/CI and/or an increase in lactate levels [29]. We found higher incidence rate of CS defining parameters in inferior STEMI patients in comparison to the ones with anterior STEMI.

The data indicate notable variations in the hemodynamic profiles of STEMI patients. Although PPCI appears to improve CI, this improvement is not statistically significant. Similarly, we noted marginally improved, but statistically non-significant SI and GGI after PPCI. Nevertheless, the observed significant reduction in lactate levels and TPRI after PPCI suggests restoration of peripheral blood flow and tissue perfusion. Observed improvement in hemodynamic parameters and normalization of lactate imply that PPCI is likely aborting impending CS, potentially leading to improved mortality rates [76].

The realm of CS encompasses the entire spectrum of the condition, spanning from the pre-shock to its advanced stages; the SCAI classification aims at increasing utility of such staging in routine clinical practice. Our hemodynamic characteristic of patients in various classes describes gradual deterioration with worsening SCAI CS class. Our research findings also suggest that a low SBP measuring below 90 mm Hg is likely a late-stage marker of CS. It is likely that if all parameters are carefully not considered and incorporated in a timely fashion, by the time physicians initiate intervention including initiation of pharmaco-mechanical circulatory support, end-organ damage

has already set-in and any of these interventions may not improve outcomes, as shown by evidences till date [current day CS definition includes many end-organ damage parameters, such as cold skin, reduced urine output, altered sensorium, etc.].

5.1. Outcomes

Our study's results also indicate the comparability of the median hospital stay, 30-day mortality rate, and 1-year mortality rate to those reported in prior research. Specifically, our investigation reports a median hospital stay of 3 days, a 30-day mortality rate of 3.43%, and a 1-year mortality rate of 8.4%, which are consistent with previously documented rates of 3 days, 3.52%, and 7.4%, respectively [116,132,133].

5.2. Limitations

Our research work was heavily compromised due to COVID-19 pandemic; as we have to come in direct contact with patients, we could not recruit patients for a long period of time. NICaS derived hemodynamic parameter measurements were adversely influenced in patients with tremor or agitated and continued moving, significant PVD, pedal edema, or amputee [91].

5.3. Significance of the study

Our study aims to facilitate early identification of high-risk patients before the onset of clinically evident CS. Prompt and timely identification of such patients can provide sufficient opportunity for intervention, leading to improved outcomes and enhanced quality of life among this significantly vulnerable patient group.

5.4. Future directions

We have not identified outcome-associated demographic, hemodynamic and other parameters. We plan to continue recruiting STEMI patients and perform statistical analysis to identify outcome-associated parameter/s with different hazard ration to identify significant parameters before designing a formula to identify high-risk patients that can be validated in a separate STEMI Patient cohort. Moreover, we have also enrolled 110 patients with NSTEMI and 57 patients with UA. We will compare their hemodynamic parameters pre- and post-PPCI to compare with STEMI cohort to identify similarities and differences. Additionally, we are aiming to identify potential biomarkers, which can be used for the diagnosis of CS and to predict outcomes, by utilizing a non-targeted lipidomic/metabolic approach which would provide valuable insights into the pathophysiology and biomarkers of STEMI, and enhance the current understanding of CS and its associated outcomes.

Chapter 6.

Conclusion

Our study highlights limitations in the current approach to CS, and utility of non-invasive technologies in providing continuous hemodynamic monitoring. We have also demonstrated PPCI mediated improvement in these parameters, and identified outcome-associated differences.

References

1. Jensen, R. V., Hjortbak, M. V. & Bøtker, H. E. Ischemic Heart Disease: An Update. *Semin. Nucl. Med.* **50**, 195–207 (2020).
2. Libby, P. *et al.* Atherosclerosis. *Nat. Rev. Dis. Prim.* **5**, 1–18 (2019).
3. Falk, E. Pathogenesis of Atherosclerosis. *J. Am. Coll. Cardiol.* **47**, 0–5 (2006).
4. Molina, D. K. & Dimaio, V. J. M. Normal organ weights in men: Part I-the heart. *Am. J. Forensic Med. Pathol.* **33**, 362–367 (2012).
5. Duncker, D. J. & Bache, R. J. Regulation of coronary blood flow during exercise. *Physiol. Rev.* **88**, 1009–1086 (2008).
6. Neumann, F. J. *et al.* 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *Eur. Heart J.* **41**, 407–477 (2020).
7. Fihn, S. D. *et al.* 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, a. *J. Thorac. Cardiovasc. Surg.* **149**, e5–e23 (2015).
8. Álvarez-Álvarez, M. M., Zanetti, D., Carreras-Torres, R., Moral, P. & Athanasiadis, G. A survey of sub-Saharan gene flow into the Mediterranean at risk loci for coronary artery disease. *Eur. J. Hum. Genet.* **25**, 472–476 (2017).
9. Devon, H. A., Mirzaei, S. & Zègre-Hemsey, J. Typical and atypical symptoms of acute coronary syndrome: Time to retire the terms? *J. Am. Heart Assoc.* **9**, 1–4 (2020).
10. Thygesen, K. *et al.* Fourth Universal Definition of Myocardial Infarction (2018). *J. Am. Coll. Cardiol.* **72**, 2231–2264 (2018).
11. Nichols, M., Townsend, N., Scarborough, P. & Rayner, M. Cardiovascular disease in

Europe 2014: Epidemiological update. *Eur. Heart J.* **35**, 2950–2959 (2014).

12. Khan, M. A. *et al.* Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study. *Cureus* **12**, (2020).
13. Cohen, R. *et al.* Significance of a positive family history for coronary heart disease in patients with a zero coronary artery calcium score (from the multi-ethnic study of atherosclerosis). *Am. J. Cardiol.* **114**, 1210–1214 (2014).
14. Virani, S. S. *et al.* Associations between lipoprotein(a) levels and cardiovascular outcomes in black and white subjects: The Atherosclerosis Risk in Communities (ARIC) study. *Circulation* **125**, 241–249 (2012).
15. Meadows, T. A. *et al.* Ethnic differences in cardiovascular risks and mortality in atherothrombotic disease: Insights from the reduction of atherothrombosis for continued health (REACH) registry. *Mayo Clin. Proc.* **86**, 960–967 (2011).
16. Ralapanawa, U. & Sivakanesan, R. Epidemiology and the magnitude of coronary artery disease and acute coronary syndrome: A narrative review. *J. Epidemiol. Glob. Health* **11**, 169–177 (2021).
17. Schultz, A. S. H. *et al.* Index coronary angiography use in Manitoba, Canada: A population-level descriptive analysis of First Nations and non-First Nations recipients. *BMJ Open* **8**, 1–10 (2018).
18. Bonaccio, M. *et al.* Ultra-processed food consumption is associated with increased risk of all-cause and cardiovascular mortality in the Moli-sani Study. *Am. J. Clin. Nutr.* **113**, 446–455 (2021).
19. La Rosa, J. C. & Conti, C. R. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *ACC Cardiosource Rev. J.* **15**, 97–99 (2006).

20. England, T. N. Numb Er 18 of Cardiovascular Disease. *English J.* **345**, 1291–1297 (2001).

21. Rea, T. D. *et al.* Smoking status and risk for recurrent coronary events after myocardial infarction. *Ann. Intern. Med.* **137**, 494–500 (2002).

22. Malakar, A. K. *et al.* A review on coronary artery disease, its risk factors, and therapeutics. *J. Cell. Physiol.* **234**, 16812–16823 (2019).

23. Sirajuddin, A. *et al.* Ischemic heart disease: Noninvasive imaging techniques and findings. *Radiographics* **41**, 990–1021 (2021).

24. Virani, S. S. *et al. Heart disease and stroke statistics—2020 update a report from the American Heart Association*. *Circulation* vol. 141 (2020).

25. Henderson, C. & Lapu-Bula, R. Heart Disease: Heart Disease. *Jama* **289**, 236 (2003).

26. Government of Canada. Heart disease in Canada: highlights from the Canadian chronic disease surveillance system. *Public Heal. Agency Canada* **200**, 0–5 (2017).

27. Dyck, J., Tate, R., Uhanova, J. & Torabi, M. Social determinants and spatio-temporal variation of Ischemic Heart Disease in Manitoba. *BMC Public Health* **21**, 1–15 (2021).

28. Reed, G. W., Rossi, J. E. & Cannon, C. P. Acute myocardial infarction. *Lancet* **389**, 197–210 (2017).

29. Vahdatpour, C., Collins, D. & Goldberg, S. Cardiogenic Shock. *J. Am. Heart Assoc.* **8**, 1–12 (2019).

30. Samsky, M. D. *et al.* Cardiogenic Shock after Acute Myocardial Infarction: A Review. *JAMA - J. Am. Med. Assoc.* **326**, 1840–1850 (2021).

31. Kolte, D. *et al.* Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States. *J. Am. Heart Assoc.* **3**, 1–17 (2014).

32. Martínez, M. J. *et al.* Non-STEMI vs. STEMI Cardiogenic Shock: Clinical Profile and Long-Term Outcomes. *J. Clin. Med.* **11**, (2022).

33. Michael A., G. J. & Guillermo, G.-C. Endothelial cell dysfunction and the pathobiology of atherosclerosis. *Circ. Res.* **176**, 139–148 (2016).

34. Amsterdam, E. A. *et al. 2014 AHA/ACC Guideline for the management of patients with non-st-elevation acute coronary syndromes: Executive summary: A report of the American college of cardiology/American heart association task force on practice guidelines*. *Circulation* vol. 130 (2014).

35. Anderson, J. L. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: Executive summary: A report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* **127**, 529–555 (2013).

36. Ibanez, B. *et al.* 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur. Heart J.* **39**, 119–177 (2018).

37. Hinohara, T. T. & Rao, S. V. Current State of Radial Artery Catheterization in ST-Elevation Myocardial Infarction. *Prog. Cardiovasc. Dis.* **58**, 241–246 (2015).

38. Valgimigli, M. *et al.* Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: A randomised multicentre trial. *Lancet* **385**, 2465–2476 (2015).

39. Cannon, C. P. *et al.* Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *J. Am. Med. Assoc.* **283**, 2941–2947 (2000).

40. Jung, R. G. *et al.* Implications of myocardial infarction on management and outcome in

cardiogenic shock. *J. Am. Heart Assoc.* **10**, (2021).

41. Collet, J. P. *et al.* 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur. Heart J.* **42**, 1289–1367 (2021).

42. Amsterdam, E. A. *et al.* 2014 AHA/acc guideline for the management of patients with Non-ST-Elevation acute coronary syndromes: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J. Am. Coll. Cardiol.* **64**, e139–e228 (2014).

43. Levine, G. N. *et al.* 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarctionAn update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the. *Circulation* **133**, 1135–1147 (2016).

44. Levine, G. N. *et al.* 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients with ST-Elevation Myocardial Infarction An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for th. *J. Am. Coll. Cardiol.* **67**, 1235–1250 (2016).

45. Wald, D. S. *et al.* Randomized Trial of Preventive Angioplasty in Myocardial Infarction. *N. Engl. J. Med.* **369**, 1115–1123 (2013).

46. Engstrøm, T. *et al.* Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3 - PRIMULTI): An open-label, randomised controlled trial. *Lancet* **386**, 665–671 (2015).

47. Gershlick, A. H. *et al.* Randomized trial of complete versus lesion-only revascularization in

patients undergoing primary percutaneous coronary intervention for stemi and multivessel disease: The CvLPRIT trial. *J. Am. Coll. Cardiol.* **65**, 963–972 (2015).

48. Spencer, F. A., Sekercioglu, N., Prasad, M., Lopes, L. C. & Guyatt, G. H. Culprit vessel versus immediate complete revascularization in patients with ST-segment myocardial infarction - A systematic review. *Am. Heart J.* **170**, 1133–1139 (2015).

49. England, T. N. Complicated By Cardiogenic Shock. **341**, 625–634 (1999).

50. Hochman, J. S. *et al.* One-year survival following early revascularization for cardiogenic shock. *J. Am. Med. Assoc.* **285**, 190–192 (2001).

51. Sabatine, M. S. *et al.* Implications of Upstream Glycoprotein IIb/IIIa Inhibition and Coronary Artery Stenting in the Invasive Management of Unstable Angina/Non-ST-Elevation Myocardial Infarction: A Comparison of the Thrombolysis in Myocardial Infarction (TIMI) IIIB Trial and th. *Circulation* **109**, 874–880 (2004).

52. Trial, a R. C., Cayla, G. & Steg, P. Immediate vs Delayed Intervention. **302**, 947–954 (2014).

53. Pinto, D. S. *et al.* Hospital delays in reperfusion for ST-elevation myocardial infarction: Implications when selecting a reperfusion strategy. *Circulation* **114**, 2019–2025 (2006).

54. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* **343**, 311–322 (1994).

55. Wallentin, L. *et al.* Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: The assessment of the safety and efficacy of a new thrombolytic regimen (ASSENT)-3

PLUS randomized tr. *Circulation* **108**, 135–142 (2003).

56. Mohr, F. W. *et al.* Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. *Lancet* **381**, 629–638 (2013).

57. Yadav, M. *et al.* Prediction of coronary risk by SYNTAX and derived scores: Synergy between percutaneous coronary intervention with taxus and cardiac surgery. *J. Am. Coll. Cardiol.* **62**, 1219–1230 (2013).

58. James, S. *et al.* Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: Results from the platelet inhibition and patient outcomes (PLATO) trial. *Circulation* **122**, 1056–1067 (2010).

59. Gibson, C. M. *et al.* Percutaneous Coronary Intervention in Patients Receiving Enoxaparin or Unfractionated Heparin After Fibrinolytic Therapy for ST-Segment Elevation Myocardial Infarction in the ExTRACT-TIMI 25 Trial. *J. Am. Coll. Cardiol.* **49**, 2238–2246 (2007).

60. Nowbar, A. N., Gitto, M., Howard, J. P., Francis, D. P. & Al-Lamee, R. Mortality from ischemic heart disease: Analysis of data from the world health organization and coronary artery disease risk factors from NCD risk factor collaboration. *Circ. Cardiovasc. Qual. Outcomes* **12**, 1–11 (2019).

61. Lozano, R. *et al.* Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **380**, 2095–2128 (2012).

62. Amini, M., Zayeri, F. & Salehi, M. Trend analysis of cardiovascular disease mortality, incidence, and mortality-to-incidence ratio: results from global burden of disease study

2017. *BMC Public Health* **21**, 1–12 (2021).

63. Samsky, M. *et al.* Clinical and regulatory landscape for cardiogenic shock: A report from the Cardiac Safety Research Consortium ThinkTank on cardiogenic shock. *Am. Heart J.* **219**, 1–8 (2020).

64. Thiele, H., Ohman, E. M., De Waha-Thiele, S., Zeymer, U. & Desch, S. Management of cardiogenic shock complicating myocardial infarction: An update 2019. *Eur. Heart J.* **40**, 2671–2683 (2019).

65. Zeymer, U. *et al.* Acute Cardiovascular Care Association position statement for the diagnosis and treatment of patients with acute myocardial infarction complicated by cardiogenic shock: A document of the Acute Cardiovascular Care Association of the European Society of Card. *Eur. Hear. J. Acute Cardiovasc. Care* **9**, 183–197 (2020).

66. Delmas, C. *et al.* Baseline characteristics, management, and predictors of early mortality in cardiogenic shock: insights from the FRENSHOCK registry. *ESC Hear. Fail.* (2021) doi:10.1002/ehf2.13734.

67. Henry, T. D. *et al.* Invasive Management of Acute Myocardial Infarction Complicated by Cardiogenic Shock: A Scientific Statement from the American Heart Association. *Circulation* E815–E829 (2021) doi:10.1161/CIR.0000000000000959.

68. Thiele, H. *et al.* Management of cardiogenic shock. *EuroIntervention* **17**, 451–465 (2021).

69. Thiele, H. *et al.* Intraaortic Balloon Support for Myocardial Infarction with Cardiogenic Shock. *N. Engl. J. Med.* **367**, 1287–1296 (2012).

70. Bauer, T. *et al.* Use and outcomes of multivessel percutaneous coronary intervention in patients with acute myocardial infarction complicated by cardiogenic shock (from the EHS-PCI registry). *Am. J. Cardiol.* **109**, 941–946 (2012).

71. Ponikowski, P. *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur. Heart J.* **37**, 2129-2200m (2016).

72. Lee, J. M. *et al.* Multivessel Percutaneous Coronary Intervention in Patients With ST-Segment Elevation Myocardial Infarction With Cardiogenic Shock. *J. Am. Coll. Cardiol.* **71**, 844–856 (2018).

73. Menon, V. *et al.* Acute myocardial infarction complicated by systemic hypoperfusion without hypotension: Report of the SHOCK trial registry. *Am. J. Med.* **108**, 374–380 (2000).

74. Investigations, O. Criteria for De fi ning Stages of Cardiogenic Shock Severity. **80**, (2022).

75. Baran, D. A. *et al.* SCAI clinical expert consensus statement on the classification of cardiogenic shock: This document was endorsed by the American College of Cardiology (ACC), the American Heart Association (AHA), the Society of Critical Care Medicine (SCCM), and the Societ. *Catheter. Cardiovasc. Interv.* **94**, 29–37 (2019).

76. Webb, J. G. *et al.* Implications of the timing of onset of cardiogenic shock after acute myocardial infarction: A report from the SHOCK Trial Registry. *J. Am. Coll. Cardiol.* **36**, 1084–1090 (2000).

77. Kaddoura, R. & Elbdri, S. Current evidence in the diagnosis and management of cardiogenic shock complicating acute coronary syndrome. *Rev. Cardiovasc. Med.* **22**, 691–715 (2021).

78. Harjola, V. P. *et al.* Clinical picture and risk prediction of short-term mortality in cardiogenic shock. *Eur. J. Heart Fail.* **17**, 501–509 (2015).

79. Thiele, H. *et al.* PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. *N. Engl. J. Med.* **377**, 2419–2432 (2017).

80. Van Diepen, S. *et al. Contemporary Management of Cardiogenic Shock: A Scientific Statement from the American Heart Association*. *Circulation* vol. 136 (2017).

81. McCallister, B. D., Christian, T. F., Gersh, B. J. & Gibbons, R. J. Prognosis of myocardial infarctions involving more than 40% of the left ventricle after acute reperfusion therapy. *Circulation* **88**, 1470–1475 (1993).

82. Shah, A. H., Puri, R. & Kalra, A. Management of cardiogenic shock complicating acute myocardial infarction: A review. *Clin. Cardiol.* **42**, 484–493 (2019).

83. Jacobs, A. K. *et al.* Cardiogenic shock caused by right ventricular infarction: A report from the SHOCK registry. *J. Am. Coll. Cardiol.* **41**, 1273–1279 (2003).

84. VanDyck, T. J. & Pinsky, M. R. Hemodynamic monitoring in cardiogenic shock. *Curr. Opin. Crit. Care* **27**, 454–459 (2021).

85. Shah, M. R. *et al.* Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness (ESCAPE): Design and rationale. *Am. Heart J.* **141**, 528–535 (2001).

86. Fincke, R. *et al.* Cardiac Power Is the Strongest Hemodynamic Correlate of Mortality in Cardiogenic Shock : A Report From the SHOCK Trial Registry. *J. Am. Coll. Cardiol.* **44**, 340–348 (2004).

87. Saxena, A. *et al.* Value of Hemodynamic Monitoring in Patients with Cardiogenic Shock Undergoing Mechanical Circulatory Support. *Circulation* 1184–1197 (2020) doi:10.1161/CIRCULATIONAHA.119.043080.

88. Hadian, M. & Pinsky, M. R. Evidence-based review of the use of the pulmonary artery catheter: Impact data and complications. *Crit. Care* **10**, (2006).

89. Chioncel, O. *et al.* Epidemiology, pathophysiology and contemporary management of cardiogenic shock – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur. J. Heart Fail.* **22**, 1315–1341 (2020).

90. Porter, T. R. *et al.* Guidelines for the use of echocardiography as a monitor for therapeutic intervention in adults: A report from the american society of echocardiography. *J. Am. Soc. Echocardiogr.* **28**, 40–56 (2015).

91. Cotter, G. *et al.* Accurate, noninvasive continuous monitoring of cardiac output by whole-body electrical bioimpedance. *Chest* **125**, 1431–1440 (2004).

92. PedramHassan-Tash. Correlation of impedance cardiography-derived and cardiac magnetic resonance-derived stroke volumes. (2022).

93. Hassan-Tash P. Validation of Non-invasive Cardiac System (NICaS) Derived Stroke Volume With Cardiac Magnetic Resonance. *Circulation* (2019).

94. Zhang, Y. B. *et al.* Application of pulse index continuous cardiac output system in elderly patients with acute myocardial infarction complicated by cardiogenic shock: A prospective randomized study. *World J. Clin. Cases* **7**, 1291–1301 (2019).

95. Jones, T. W. *et al.* Bioreactance is a reliable method for estimating cardiac output at rest and during exercise. *Br. J. Anaesth.* **115**, 386–391 (2015).

96. Rali, A. S. *et al.* Non-Invasive Cardiac Output Monitoring in Cardiogenic Shock: The NICOM Study. *J. Card. Fail.* **26**, 160–165 (2020).

97. Lavie, A. *et al.* Maternal cardiovascular hemodynamics in normotensive versus preeclamptic pregnancies: A prospective longitudinal study using a noninvasive cardiac system (NICaS^{TM}). *BMC Pregnancy Childbirth* **18**, 1–12 (2018).

98. Beck, R., Milella, L. & Labellarte, C. Continuous non-invasive measurement of stroke volume and cardiac index in infants and children: comparison of Impedance Cardiography NICaS® vs CardioQ® method. *Clin. Ter.* **169**, e110–e113 (2018).

99. Taniguchi, Y. *et al.* Noninvasive and simple assessment of cardiac output and pulmonary

vascular resistance with whole-body impedance cardiography is useful for monitoring patients with pulmonary hypertension. *Circ. J.* **77**, 2383–2389 (2013).

100. Matsuda, Y. *et al.* Perioperative sequential monitoring of hemodynamic parameters in patients with pheochromocytoma using the Non-Invasive Cardiac System (NICaS). *Endocr. J.* **61**, 571–575 (2014).

101. Levy, B., Perez, P., Perny, J., Thivilier, C. & Gerard, A. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Crit. Care Med.* **39**, 450–455 (2011).

102. Richard, C., Ricome, J. L., Bottineau, G. & Auzepy, P. Combined Hemodynamic. *Circulation* **67**, 620–626 (1983).

103. Albert Schweitzer Hospital, Lambarene, Gabon, and Institute of Tropical Medicine, University of Tübingen, Tübingen, G. 需要引用的霍奇金第二肿瘤new England Journal. *N. Engl. J. Med.* **365**, 687–696 (2011).

104. Levy, B. *et al.* Epinephrine Versus Norepinephrine for Cardiogenic Shock After Acute Myocardial Infarction. *J. Am. Coll. Cardiol.* **72**, 173–182 (2018).

105. Zhu, W., Tilley, D. G., Myers, V. D., Tsai, E. J. & Feldman, A. M. Increased vasopressin 1A receptor expression in failing human hearts. *J. Am. Coll. Cardiol.* **63**, 375–376 (2014).

106. Jolly, S. *et al.* Effect of Vasopressin on hemodynamics in patients with refractory cardiogenic shock complicating acute myocardial infarction. *Am. J. Cardiol.* **96**, 1617–1620 (2005).

107. Blumer, V., Marbach, J., Veasey, T. & Kanwar, M. Role of medical management of cardiogenic shock in the era of mechanical circulatory support. *Curr. Opin. Cardiol.* **37**,

250–260 (2022).

108. Mathew, R. *et al.* Milrinone as Compared with Dobutamine in the Treatment of Cardiogenic Shock. *N. Engl. J. Med.* **385**, 516–525 (2021).

109. Dhruva, S. S. *et al.* Use of Mechanical Circulatory Support Devices Among Patients With Acute Myocardial Infarction Complicated by Cardiogenic Shock. *JAMA Netw. open* **4**, e2037748 (2021).

110. Thiele, H. *et al.* Intraaortic Balloon Pump in Cardiogenic Shock Complicating Acute Myocardial Infarction: Long-Term 6-Year Outcome of the Randomized IABP-SHOCK II Trial. *Circulation* **139**, 395–403 (2019).

111. Napp, L. C., Kühn, C. & Bauersachs, J. ECMO bei Herz-Kreislauf-Stillstand und kardiogenem Schock. *Herz* **42**, 27–44 (2017).

112. Guglin, M. *et al.* Venoarterial ECMO for Adults: JACC Scientific Expert Panel. *J. Am. Coll. Cardiol.* **73**, 698–716 (2019).

113. Cheng, R. *et al.* Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: A meta-analysis of 1,866 adult patients. *Ann. Thorac. Surg.* **97**, 610–616 (2014).

114. Camacho, X. *et al.* Relative contribution of trends in myocardial infarction event rates and case fatality to declines in mortality: an international comparative study of 1·95 million events in 80·4 million people in four countries. *Lancet Public Heal.* **7**, e229–e239 (2022).

115. Boyer, N. M. *et al.* Trends in Clinical, Demographic, and Biochemical Characteristics of Patients With Acute Myocardial Infarction From 2003 to 2008: A Report From the American Heart Association Get With The Guidelines Coronary Artery Disease Program. *J. Am. Heart Assoc.* **1**, 1–18 (2012).

116. Omer, M. A. *et al.* Clinical Characteristics and Outcomes of STEMI Patients With Cardiogenic Shock and Cardiac Arrest. *JACC Cardiovasc. Interv.* **13**, 1211–1219 (2020).

117. Newman, J. D. *et al.* Trends in myocardial infarction rates and case fatality by anatomical location in four united states communities, 1987 to 2008 (from the atherosclerosis risk in communities study). *Am. J. Cardiol.* **112**, 1714–1719 (2013).

118. Broder, G. & Weil, M. H. Excess Lactate : An Index of Reversibility of Shock in Human Patients Author (s): George Broder and Max H . Weil Published by : American Association for the Advancement of Science Stable URL : http://www.jstor.org/stable/1713106. *Am. Assoc. Adv. Sci.* **143**, 1457–1459 (1964).

119. Kruse, O., Grunnet, N. & Barfod, C. Blood lactate as a predictor for in-hospital mortality in patients admitted acutely to hospital: A systematic review. *Scand. J. Trauma. Resusc. Emerg. Med.* **19**, 74 (2011).

120. Bier, M. & Gerich, J. E. Contribution of liver and skeletal muscle to alanine and lactate metabolism in humans. (2023).

121. Connor H.a · Woods H.F.a · Ledingham J.G.G.b · Murray J.D.c. A Model of L(+)-Lactate Metabolism in Normal Man. **26**, 4 (1982).

122. Andersen, L. W. *et al.* Etiology and therapeutic approach to elevated lactate levels. *Mayo Clin. Proc.* **88**, 1127–1140 (2013).

123. Jagan, N. *et al.* Sympathetic stimulation increases serum lactate concentrations in patients admitted with sepsis: implications for resuscitation strategies. *Ann. Intensive Care* **11**, (2021).

124. Release, C. Catecholamines in Myocardial Ischemia.

125. Kim, H. J., Son, Y. K. & An, W. S. Effect of Sodium Bicarbonate Administration on

Mortality in Patients with Lactic Acidosis: A Retrospective Analysis. *PLoS One* **8**, (2013).

126. Diego De Stefani, Maria Patron, and R. R. 乳鼠心肌提取 HHS Public Access. *Physiol. Behav.* **176**, 139–148 (2015).

127. Solomon, S. D. *et al.* Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation* **112**, 3738–3744 (2005).

128. Wehner, G. J. *et al.* Routinely reported ejection fraction and mortality in clinical practice: Where does the nadir of risk lie? *Eur. Heart J.* **41**, 1249–1257 (2020).

129. Toma, M. *et al.* The relationship between left ventricular ejection fraction and mortality in patients with acute heart failure: Insights from the ASCEND-HF Trial. *Eur. J. Heart Fail.* **16**, 334–341 (2014).

130. Rozenman, Y., Rotzak, R. & Patterson, R. P. Detection of left ventricular systolic dysfunction using a newly developed, laptop based, impedance cardiographic index. *Int. J. Cardiol.* **149**, 248–250 (2011).

131. Vernon, S. T. *et al.* ST-Segment–Elevation Myocardial Infarction (STEMI) Patients Without Standard Modifiable Cardiovascular Risk Factors—How Common Are They, and What Are Their Outcomes? *J. Am. Heart Assoc.* **8**, (2019).

132. Vogel, B. *et al.* ST-segment elevation myocardial infarction. *Nat. Rev. Dis. Prim.* **5**, 1–20 (2019).

133. Jäger, B. *et al.* One-year mortality in patients with acute ST-elevation myocardial infarction in the Vienna STEMI registry. *Wien. Klin. Wochenschr.* **127**, 535–542 (2015).