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Myocardial Infarction

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Meet the editor

Burak Pamukcu (MD) obtained a doctorate degree in Cardiology from Istanbul University Faculty of Medicine, Istanbul, Turkey. Dr Pamukcu made his post doctorate fellowship (European Society of Cardiology Atherothrombosis Research Fellowship) in the University Department of Medicine, Centre for Cardiovascular Sciences, City Hospital, Birmingham, England, United Kingdom. He is mainly interested in atherothrombosis, atherosclerotic heart vessel disease, antithrombotic therapy and interventional cardiology. Currently Dr Pamukcu is working as a Consultant Cardiologist and Associate Professor of Cardiology in Acibadem Healthcare Group. He has published 98 scientific publications and served as referee for more than thirty different medical journals indexed in SCI expanded. He is serving as associate editor and editorial board member at peer reviewed medical scientific journals.

Contents

Preface

Atherosclerosis is an inflammatory disease. Atherosclerotic cardiovascular diseases and myocardial infarction are still the most common cause of death among adults and their prevalence are increasing in the developing countries. Diabetes mellitus, systemic hypertension, dyslipidemia, cigarette smoking, increased emotional stress, physical inactivity and obesity are known risk factors for atherosclerotic vascular diseases. We are living in an era where deaths from metabolic disorders, including over nutrition, obesity, diabetes and hypercholesterolemia are more prominent than deaths from a shortage of food.

Myocardial infarction is one of the clinical presentations of atherosclerotic coronary artery disease. Silent ischemia, sudden cardiac death, and stable and unstable angina are other clinical forms. However, myocardial infarction is the dominant form and it requires quick diagnosis and accurate treatment. In recent years, there have been important advances in both diagnostic and therapeutic strategies of myocardial infarction. Today we have a very strong armamentarium when compared to the 1980s. A few decades ago, we were using only aspirin and nitrates for the treatment of acute myocardial infarction. There was no interventional therapy and immediate revascularization nor strong medicines (anti-aggregants, anticoagulants, beta blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, statins and more). Today we have a wide spectrum of medical and interventional therapy and thus a better prevention strategy. Since the majority of deaths occur because of ventricular fibrillation in patients experiencing a myocardial infarction today, we have automated external defibrillators at several airports, airplanes, metro-train stations, and in crowded places. It is even possible to send an AED with a drone to a place of need. Emergency medical services are also organized in order to more quickly reach the patients and to bring them to medical centres where primary percutaneous interventions can be performed as soon as possible.

In this book, we aimed to provide, at the beginning, epidemiological data on myocardial infarction and atherosclerotic cardiovascular diseases. Then in the following chapters, we aimed to overview current diagnostic biochemical tools. Current management strategies and interventional therapies are also addressed. And finally we aimed to provide information on 'how to manage myocardial infarction in a specific patient group; the children'.

Today, despite all advances in the management of myocardial infarction, the morbidity and mortality from atherosclerotic cardiovascular diseases and especially myocardial infarction are still high. Recent developments in interventional therapies established an important decrease in morbidity and mortality from myocardial infarction. I think that more can be achieved by the prevention of atherosclerotic processes and efforts should be focused on the early stages of the disease since it may be very late for some of the patients experiencing myocardial infarction.

I hope this book attracts the attention of the readers in a different way to myocardial infarction and finally I would like to acknowledge all contributing authors and our author service manager Ms. Romina Skomersic for their contributions to the project.

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Introductory Section

Chapter 1

Introductory Chapter: Atherosclerotic Cardiovascular Disease

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Additional information is available at the end of the chapter

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1. Introduction

Atherosclerotic cardiovascular disease is still the most common cause of death among adults [1]. Its prevalence is increasing in developing countries and despite all advances in both diagnostic tools and treatment modalities, it is still very common in the developed world. The nutritional and metabolic problems especially obesity, diabetes mellitus, hypercholesterolemia and also overuse of dietary salt play a pivotal role in increased cardiovascular morbidity and mortality worldwide [1, 2].

The atherosclerotic cardiovascular disease has got a wide clinical spectrum from silent ischemia to sudden cardiac death [3]. Myocardial infarction (MI) is at the center of this clinical spectrum, and a majority of current clinical efforts are mainly focused on the diagnosis and treatment of myocardial infarction. There are still scientific efforts to provide more comprehensive and realistic definition for myocardial infarction. The latest expert consensus document including experts from the main cardiovascular societies including European Society of Cardiology (ESC), American College of Cardiology (ACC), American Heart Association (AHA) and World Heart Federation (WHF) established the most comprehensive definition and classification of myocardial infarction to date [4]. Five major types of MI include type 1 MI—MI associated with occlusive or nonocclusive athero-thrombotic coronary lesions, type 2 MI—MI associated with mismatch between oxygen supply and demand, type 3 MI—MI in patients with ischemia-associated cardiac death, type 4a, 4b, and 4c—MI associated with percutaneous coronary intervention (PCI), and type 5 MI—MI associated with coronary artery bypass grafting surgery [4].

From the very beginning of human life in earth, three major issues including contagious diseases, shortage of food, and wars diminished human population for several years. To date, for the first time in history, modern medicine is providing us great success against contagious

diseases and advances in agriculture have almost finished the scarcity of food. In our era, deaths from over nutrition, obesity, diabetes, and hypercholesterolemia appear to overwhelm deaths from shortage of food. Furthermore, increased life expectancy and aging of the population have also increased cardiovascular diseases.

The management of ST-segment elevation myocardial infarction (STEMI) is very dynamic and several changes are recommended by the current guidelines from 2012 to 2017 [5]. There are more evidence to prefer radial access and drug-eluting stents (DESs) in primary preventions. Complex revascularizations during primary percutaneous intervention (PCI) were accepted as contraindicated (class III indication) in 2012; however, the 2017 guidelines recommend complete revascularization during index primary PCI in STEMI patients in shock with class IIa indication. Thrombus aspiration is no more recommended during primary PCI according to the new guidelines. The use of enoxaparin and early hospital discharge are encouraged in the new guidelines (class IIa). Additional lipid lowering therapy is recommended (class IIa) if low density lipoprotein levels are over 70 mg/dL despite maximum tolerated statins [5].

Current European revascularization guidelines also recommend radial access as standard approach in both angiography and PCI, use of DES instead bare metal stents (BMS) in any PCI, use of SYNTAX score in revascularization procedures involving left main coronary artery or multivessel disease, use of the same revascularization strategy in patients with non-STEMI after stabilization of the patient, use of radial artery grafts over saphenous vein grafts in patients with severe coronary stenosis, and to prefer CABG surgery for patients with coronary artery disease, heart failure, and left ventricular ejection fraction <35% [6].

In this book, we aimed to provide at the beginning epidemiological data on myocardial infarction and atherosclerotic cardiovascular disease. Then, in the following chapters, we aimed to address the role of current diagnostic biochemical markers in the diagnosis of acute MI. We also aimed to overview current management strategies and the role of interventional therapies in patients with acute coronary syndromes. At the end of the book, we aimed to provide information on "how to manage myocardial infarction in a specific patient group; the children."

Recent developments in interventional therapies, drugs, and devices lead to important decrease in morbidity and mortality from myocardial infarction. Despite all advancements in the management of myocardial infarction, morbidity and mortality from atherosclerotic cardiovascular diseases and especially myocardial infarction are still high. We think that more glory can be achieved by the prevention of atherosclerotic processes, and efforts should be focused on the early stages of the disease since it may be very late for some of the patients experiencing myocardial infarction.

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Section 2

Epidemiology of Atherosclerotic Cardiovascular Diseases and Myocardial Infarction

Chapter 2

Epidemiology of Myocardial Infarction

Joshua Chadwick Jayaraj, Karapet Davatyan,
S.S. Subramanian and Jemmi Priya

Additional information is available at the end of the chapter

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Abstract

Coronary heart disease (CHD) is the leading cause of morbidity and mortality throughout the world. The most common form of CHD is the myocardial infarction. It is responsible for over 15% of mortality each year, among the vast majority of people suffering from non-ST-segment elevation myocardial infarction (NSTEMI) than ST-segment elevation myocardial infarction (STEMI). The prevalence of myocardial infarction (MI) is higher in men in all age-specific groups than women. Although the incidence of MI is decreased in the industrialized nations partly because of improved health systems and implementation of effective public health strategies, nevertheless the rates are surging in the developing countries such as South Asia, parts of Latin America, and Eastern Europe. The modifiable risk factors represent over 90% of the risk for acute MI. The risk factors such as dyslipidemia, smoking, psychosocial stressors, diabetes mellitus, hypertension, obesity, alcohol consumption, physical inactivity, and a diet low in fruits and vegetables were strongly associated with acute MI.

Keywords: myocardial infarction, epidemiology, prevalence, incidence, risk factors

1. Introduction

The widely accepted definition of epidemiology is "the study of the distribution and determinants of health-related states or events in specified populations, and the application of this study to the control of health problems" [1]. The overarching aim of epidemiology is to improve the control of disease through both prevention and treatment that will decrease morbidity and mortality due to the disease and will increase the quality of life of those who have a severe illness like coronary artery diseases, e.g., myocardial infarction.

1.1. Coronary heart disease

The most common cause of coronary heart disease (CHD) is atherosclerosis of coronary arteries [2]. Atherosclerosis causes an inadequate supply of oxygen for a given a myocardial demand leading to myocardial hypoxia.

1.2. Atherosclerosis

The sequence of endothelial dysfunction, plaque formation consisting of lipids and smooth muscles, and associated inflammation causes atherosclerotic plaque [3]. Over these plaques rupture and thrombosis causing further narrowing of arteries and occlusion of blood flow can occur.

Although beyond the scope of this chapter, atherosclerosis implies disturbances in the coronary circulation as well as the microcirculation dysfunction.

1.3. Burden of coronary heart disease

Globally, cardiovascular diseases (CVDs) are the number one cause of mortality. According to the World Health Organization (WHO), it is estimated that 7.4 million deaths were due to coronary heart disease in 2015. Eighty-two percent of deaths in low- and middle-income countries are accountable for CVD. **Figure 1** shows the age-standardized estimate of mortality by cardiovascular diseases and diabetes per 100,000 people. It is estimated that 23.6 million people will die from CVDs by 2030. These are projected to remain the leading cause of mortality.

1.4. Geographic variations in coronary heart disease

Worldwide the prevalence of CHD is increasing albeit there are regional variations due to the influence of economies, industrialization, and advancement in healthcare systems [5]. Data from the USA suggest about 25% of deaths in the USA are associated with heart disease each year [6]. An American dies due to myocardial infarction (MI) every 60 seconds [6]. The incidence of CHD in the western world is decreasing even though the risk factors for CHD such as hypertension, diabetes mellitus, and obesity are increasing. The decline is due to strengthening healthcare systems due to relative advancement in therapeutic and invasive interventions. As a result, CHD costs the USA about $200 billion each year [7]. The total cost includes not only the cost of healthcare services or medications, but it also includes the loss of productivity [7].

As Asia comprises over one-third of the world population, its experience on the prevalence of CHD is significant. In India, CHD may not be explained due to the traditional risk factors [8], whereas in China, CHD remains the second most cause of the deaths. Chinese cardiovascular medicine focusses centrally on prevention by shifting its focus from symptom-based therapy to lifestyle-guided improvement [9]. Trends in mortality from CHD were favorable in European Union countries, whereas in Eastern European countries, mortality from CHD

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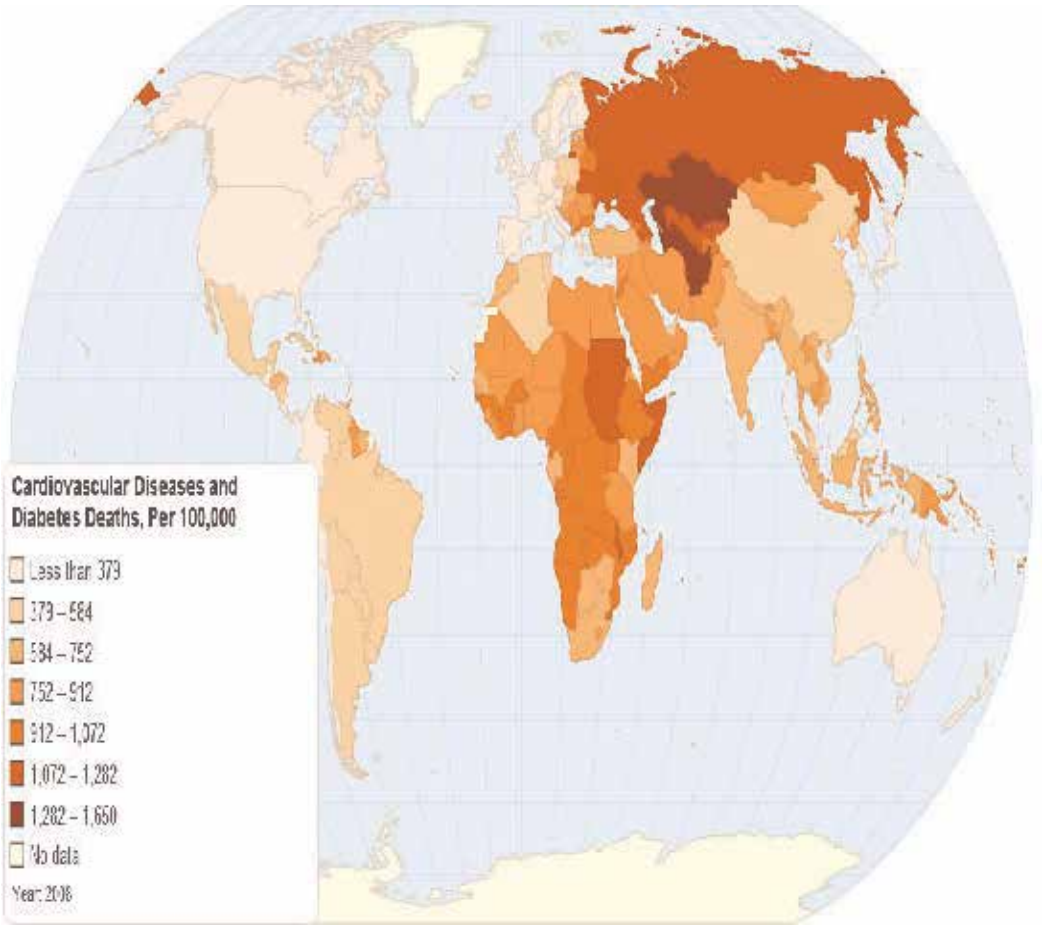

Figure 1. Cardiovascular diseases and diabetes, deaths per 100,000 people. Source: Global Health Observatory data repository and World Health Organization [4].

remains exceptionally high [10]. CVD death rates have been significantly decreasing in most of the countries of Latin America despite the disparities in current trends [11].

The WHO has identified very cost-effective interventions that are feasible to be implemented even in low resource settings for averting the global epidemic of CVDs.

2. Myocardial infarction

2.1. Defining myocardial infarction

The most common form of CHD is the myocardial infarction (MI) [12]. MI occurs when a coronary artery is occluded or almost occluded, which creates a severe reduction in the blood flow, causing some of the heart muscle being supplied by that artery to become infarcted [13].

There are two clinical settings of MI—ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI). STEMI is recognized by characteristic changes on the electrocardiography (ECG) [14]. One of those ECG changes is the typical elevation in the "ST segment" which is called as STEMI. On the contrary the absence of ST-segment elevation and the presence of positive cardiac biomarker such as troponin are called NSTEMI [15].

In the following sections, prevalence and incidence of myocardial infarction are elaborated. Prevalence is defined as the number of diseased individuals present in the population at a specific time. The incidence rate is determined as the number of new cases of a disease that occur during a specific time. The estimates are reported from various data sources such as general practice registries and self-reported by the patient through the national survey. The reliability of the data is based on the data source.

2.2. Prevalence of myocardial infarction

According to 2014, based on the self-reported national survey of the UK, the prevalence of MI was reported as 640,000 in men and 275,000 in women; this represents about 915,000 people that have suffered an MI in the UK. In 2013, the prevalence of MI in men was about three times higher than for women in the UK [16]. As shown in **Figure 2**, the prevalence of age-specific MI extends from 0.06% of men <45 years of age to 2.46% of those ≥75 years old.

In contrast to these developed countries, South Asian countries (India, Pakistan, Sri Lanka, Bangladesh, and Nepal) have the highest prevalence of MI seen in younger than 45 years of age compared to those older than 60 years.

2.3. Incidence of myocardial infarction

Prevalence reflects first (acute) MI and MI in patients who had a previous MI. The incidence of MI only reflects the former. The incidence of MI has been declining in developed countries, including the USA and the UK.

The recent estimates of the incidence of MI in the USA are about 525,000 based on AHA data [18]. The Mozaffarian Study reported data comparing and contrasting the incidence of myocardial infarction in white men and women versus and black men and women. The study concludes that the incidence of myocardial infarction was more significant among black men (12.9/100,000 males) who are in the age group 75–84 years of age than whites for both men (9.1/100,000 males) and women (7.8/100,000 females). Similar trends exist in other age groups and their counterparts (**Figure 3**) [19]. It is essential to assess the effectiveness of public health strategies to fight MI.

Regarding the clinical type of MI, it has been estimated that incidence rates (per 100,000) of STEMI decreased appreciably (121 to 77), whereas those incidence rates of NSTEMI declined slightly (126 to 132) [20]. In a landmark study, no variation was seen in all-cause mortality for both STEMI and NSTEMI between 6 months and 4 years of follow-up. But, STEMI patients

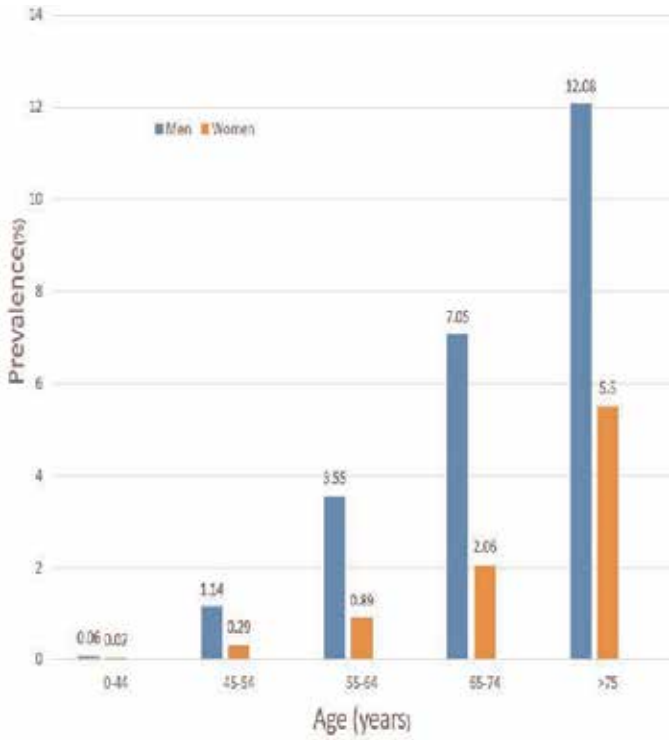

Figure 2. Age-specific prevalence of MI in the UK, 2014 [17]. Adapted from Clinical Practice Research Datalink (CPRD), 2014. Evaluations are based on records from a sample of general practices in each of the constituent nations of the UK.

have a worse long-term prognosis matched to NSTEMI patients [21]. Other studies have shown a worse 7-year mortality rate for NSTEMI patients than STEMI patients [22].

2.4. Risk factors

The INTERHEART study evaluated the prevalence of nine potentially modifiable risk factors in more than 15,000 cases with the first acute MI and matched with about 15,000 asymptomatic age- and sex-matched controls [23]. Nine risk factors were strongly associated with acute MI in the 52 countries included in the trial. The modifiable risk factors represent over 90% of the risk for acute MI. Diabetes mellitus is a significant predictor of adverse cardiac outcomes, especially in women. It is considered to be a coronary heart disease equivalent (**Tables 1–4**) [24, 25].

2.5. Summary

It is evident that MI is the leading cause of morbidity and mortality worldwide. It is responsible for over 15% of mortality each year, among the vast majority of people suffering from NSTEMI than STEMI. The prevalence of MI is higher among men in all age-specific groups than women. Although the incidence of MI is decreased in the industrialized nations partly

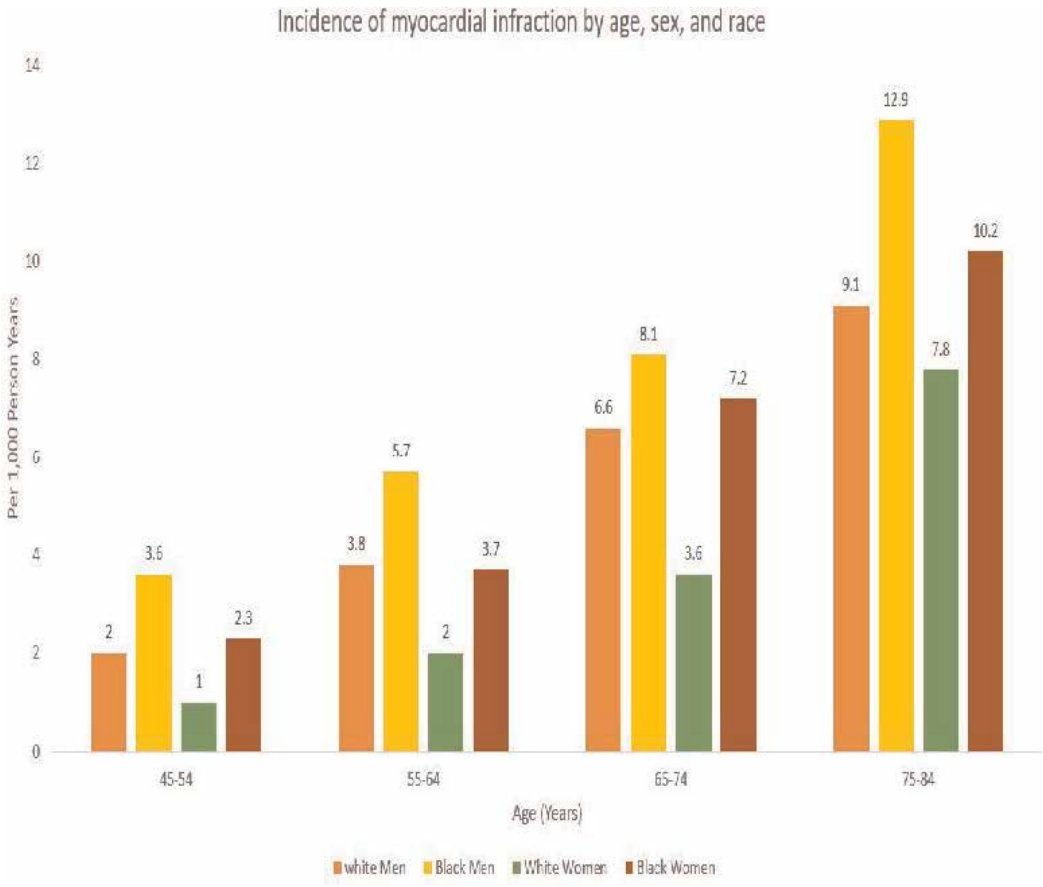

Figure 3. Incidence of myocardial infarction by age, sex, and race in the USA, 2015 [19]. Adapted from Heart Disease and Stroke Statistics—2015 update: A report from the American Heart Association.

CHD risk equivalents	• Noncoronary atherosclerotic disease (e.g., carotid, peripheral, abdominal aortic aneurysm) • Diabetes mellitus • Chronic kidney disease
CHD-established risk factors	• Dyslipidemia, smoking, psychosocial stressors, diabetes mellitus, hypertension, obesity, alcohol consumption, physical inactivity, and diet low in fruits and vegetables • Age (especially >50 in men and postmenopausal women) • Family history of CHD in first-degree relative age < 50 (men) and age < 60 (women)

Table 1. Risk factors for coronary heart disease (CHD).

because of improved health systems and implementation of effective public health strategies, nevertheless the rates are surging in the developing countries such as South Asia, parts of Latin America, and Eastern Europe. The modifiable risk factors account for more than 90% of the risk for acute MI. Nine risk factors such as dyslipidemia, smoking, psychosocial stressors,

Involved myocardium	Occluded vessel	ECG leads involved
Anterior MI	LAD	Some or all of leads V1–V6
Inferior MI	RCA or LCX	ST elevation in leads II, III, and aVF
Right ventricular MI (occurs in ½ of inferior MI)	RCA	ST elevation in leads V4–V6R
Posterior MI	LCX or RCA	ST depression in leads V1–V3 ST elevation in leads I and aVL (LCX) ST depression in leads I and aVL (RCA)
Lateral MI	LCX, diagonal	ST elevation in leads I, aVL, V5, and V6 ST depression in leads II, III, and aVF

Table 2. Myocardial infarction location based on coronary artery involvement.

Test	Onset of abnormality	Duration of abnormality
ECG	Immediately at onset of chest pain	ST elevation progresses to Q-waves over several days to weeks
Myoglobin	1–4 hours	1–2 days
CK-MB	4–6 hours	1–2 days
Troponin	4–6 hours	1–2 weeks

Table 3. Diagnostic tests.

Mechanical complication of acute MI	Coronary artery typically involved	Time course	Clinical findings	Echocardiography
RV failure	RCA	Acute	• Hypotension and clear lungs • Kussmaul sign	• Hypokinetic RV
Papillary muscle rupture	RCA	Acute and within 3–5 days	• Acute severe pulmonary edema • New holosystolic murmur	• Severe mitral regurtitation with fail leaflet
Interventricular septal rupture/defect	LAD: Apical septal rupture RCA: Basal septal rupture	Acute and within 3–5 days	• Shock and chest pain • New holosystolic murmur • Biventricular failure	• Left-to-right shunt at the level of rupture • Step-up oxygen level between the right atrium and ventricle
Free wall rupture	LAD	Within first 5 days to 2 weeks	• Shock and chest pain • Jugular venous distention • Distant heart sounds	• Pericardial effusion with tamponade

Table 4 Evaluation of chest pain in the acute setting.

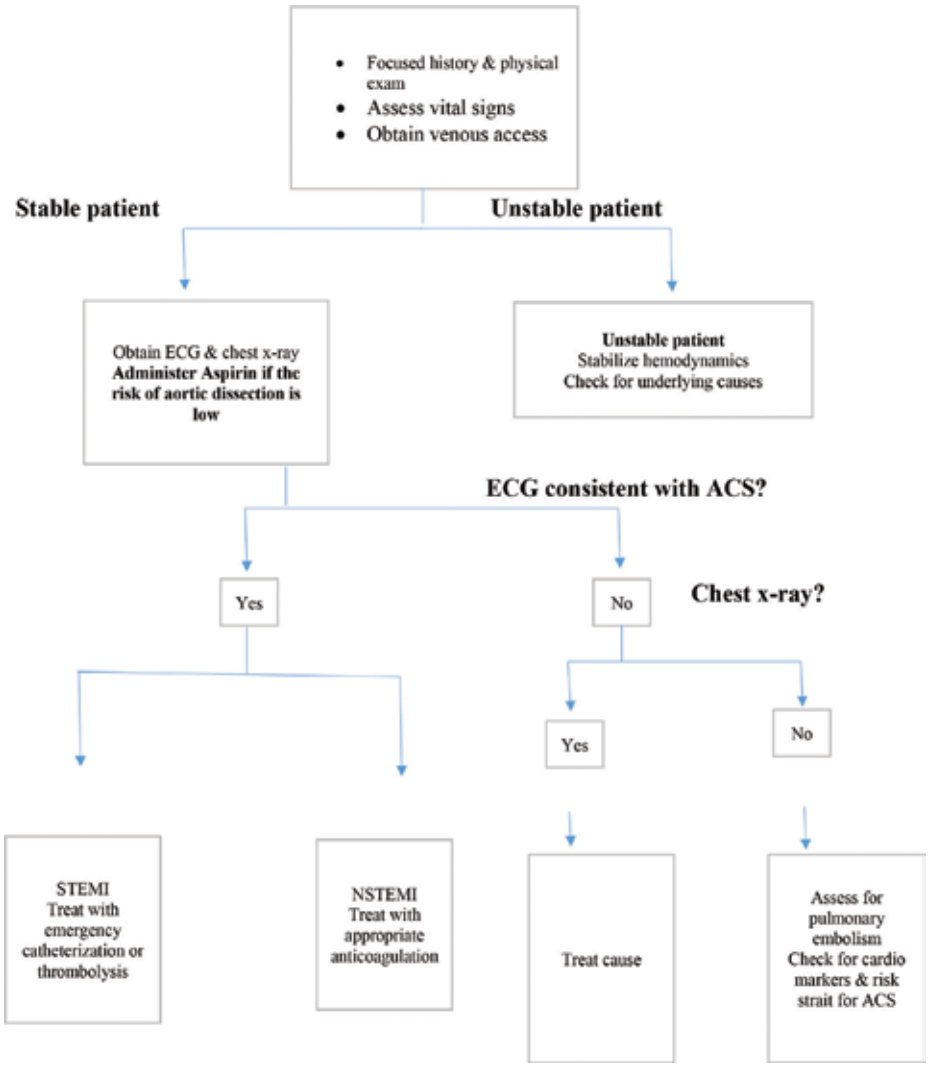

Chart 1 Evaluation of chest pain in the acute setting.

diabetes mellitus, hypertension, obesity, alcohol consumption, physical inactivity, and a diet low in fruits and vegetables were strongly associated with acute MI in the 52 countries (**Chart 1**).

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Conflict of interest

No conflict of interest.

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Section 3

Biochemical Markers in the Diagnosis of Myocardial Infarction

Chapter 3

The Diagnostic Value of Biochemical Cardiac Markers in Acute Myocardial Infarction

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Additional information is available at the end of the chapter

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Abstract

Cardiovascular disease is the leading cause of death worldwide. The role of cardiac markers in the diagnosis, risk stratification, and treatment of patients with chest pain is vital. Patients with elevated cardiac troponin levels but negative CK-MB who were formerly diagnosed with unstable angina or minor myocardial injury are now reclassified as non–ST-segment elevation MI (NSTEMI) even in the absence of diagnostic ECG changes. CK-MB is both a sensitive and specific marker for myocardial infarction. Cardiac troponin T is a cardio-specific, highly sensitive marker for myocardial damage. Cardiac troponin I is a contractile protein exclusively present in the cardiac muscle. The absolute cardiospecificity of cTnI allows the diagnosis of myocardial infarction distinct from muscle lesions and non-cardiac surgery. In 2000, the European Society of Cardiology and the American College of Cardiology redefined AMI with a particular advocacy on troponin. The 2002/2007 American College of Cardiology (ACC) and the American Heart Association (AHA) Guideline Update for the management of these patients strongly recommend to include cTnI. Specifically, with rare exception, the diagnosis cannot be made in the absence of elevated biomarkers of cardiac injury.

Keywords: acute myocardial infarction, unstable angina, CK-MB, cardiac troponin T, cardiac troponin I

1. Introduction

Cardiovascular disease is the foremost cause of death globally, accounting for an estimated 16.7 million deaths per year [1]. The prevalence of coronary artery disease (CAD) varies

between different geographical locations around the world. For example among South Asian populations, Pakistani people have the highest known rate of CAD. According to careful estimates nearly 100,000 individuals suffered from acute myocardial infarction (AMI) in Pakistan, in 2002 [2].

Acute MI is commonly presented with chest pain or discomfort, weakness, sweating, nausea, vomiting, and arrhythmias, sometimes loss of consciousness and syncope. It occurs with the sudden interruption of coronary blood flow and it is a life-threatening medical emergency which requires quick management [3, 4].

2. Pathophysiology

Myocardial ischemia may occur either from increased demand of oxygen by the myocardium, or decreased oxygen supply to the myocardium, or both. During exercise, tachycardia or emotions, myocardial oxygen requirement is increased and if there is coronary obstruction, it will lead to a transitory imbalance. This condition is often termed demand ischemia and is responsible for most episodes of chronic stable angina. In other conditions, this imbalance occurs due to acute decrease of oxygen supply because of increased coronary vascular tone (i.e., coronary vasospasm) or obvious reduction or occlusion of coronary artery as a result of platelet aggregates or thrombi. This condition which is known as supply ischemia may lead to MI and unstable angina (UA). In many conditions, ischemia is a result of both an increase in oxygen demand and a reduction in supply [5–8].

The leading cause of MI, by far, is atherosclerosis, a progressive accumulation of cholesterol and fibrous tissue in plaques present within the arterial wall, spanning over decades [9–12]. Nevertheless atherosclerotic plaques may become unstable, rupture, and form a thrombus that occludes the artery. When a significant plaque rupture occurs in the coronary vessels, it leads to thrombosis and total vascular occlusion which concludes with the occurrence of MI [13, 14].

Total coronary occlusion leading decreased myocardial oxygen supply results with the damage of myocytes [15, 16].

This decreased blood supply has the following consequences:

- After 10–15 min of coronary occlusion necrosis of the myocardial tissue starts and since myocardial cells are strongly differentiated cells they have so weak regenerative abilities. Thus, according the size of the necrotic tissue the heart becomes a permanently weaker pump for the rest of the individual's life;
- The injured myocardial tissue may cause ventricular arrhythmias (e.g. ventricular tachycardias or ventricular fibrillation) by re-entry mechanism. This is the most common underlying mechanism of the sudden cardiac death resulting from MI [17, 18].

3. Histopathological findings

Examination of the heart shows that there is a well-defined circumscribed area of ischemic necrosis (coagulative necrosis). In the first 12–48 h, myocardial fibers are still well delineated with concentrated eosinophilic cytoplasm, but lose their transversal striations and the nucleus along with red blood cells which infiltrate the interstitial space. Later (5–10 days after the initial event), during healing of the myocardial tissue, the area with coagulative necrosis shows histologically preserved myocardial fibers with intensely eosinophilic cytoplasm, transverse striations and nuclei which are completely lost. The interstitium of the infarcted area is primarily infiltrated with neutrophils, then later with lymphocytes and macrophages to phagocytose the necrotic myocyte debris. The necrotic area is peripherally surrounded and gradually infiltrated by granulation tissue, which ultimately replace the infarct with a fibrous scar [19].

4. Risk factors

Atherosclerotic risk factors are also the most common risk factors for MI. These risk factors are old age, obesity, smoking, hypertension, hypercholesterolemia more precisely hyperlipoproteinemia particularly high low density lipoprotein (LDL) and low high density lipoprotein (HDL), diabetes mellitus [20–23].

Furthermore, intense exertion, especially if the exertion is unusually more intense as compared to the usual performance, and emotional stress are other risk factors. Recent studies established that quantitatively, the duration of strenuous exercise and following recovery is associated with 6-fold higher MI rate in comparison to the more comfortable time frames for people who are physically more fit. For individuals with poor physical health, the rate differential is over 35-fold higher. Since the increased arterial pulse pressure results in stretching and relaxation of arterial vasculature with each heart beat thereby increasing the mechanical stress on atheromas, hence it significantly enhances the susceptibility of plaque ruptures [16, 24].

Increased spasm/contraction of coronary artery in association with cocaine abuse can also precipitate MI [25–29]. Gender is also another risk factor and male individuals are more prone to suffer from MI [30, 31].

5. Diagnosis

The diagnosis of acute MI depends on both clinical and laboratory findings including electrocardiogram, and cardiac biomarkers for myocyte injury [32]. Biochemical cardiac markers are the signals from the injured myocardium (**Figure 1**) and are released in case of damage at the

cardiac muscle. The most common causes of injury are acute coronary syndromes (MI, non Q-wave MI, unstable angina pectoris) and other conditions affecting cardiac muscle including trauma, cardiac surgery, myocarditis etc. The level of cardiac biomarkers can be detected/measured in blood samples in these cases [33–35].

The role of cardiac biomarkers in the process of diagnosis, risk evaluation, and management of patients with chest pain has continued to evolve. The initial electrocardiogram (ECG) may be non-diagnostic. Although physicians awareness and diagnostic utilities increase the rate of missed MI continues to remain between 1.5 and 2%. Determination of cardiac biomarkers plays an increasingly important role for the evaluation and diagnosis of patients with chest pain. The guidelines for the diagnosis of MI have recently been upgraded and have incorporated the results of cardiac marker estimation in the clinical definition of MI [36–39]. Creatine kinase-MB (CK-MB), cardiac troponin T (cTnT), cardiac troponin I (cTnI), myoglobin, homocysteine and C-reactive protein (CRP) are all used for evaluation of the suspected acute MI. CK-MB, cTnT, and cTnI may also be used to detect and manage high-risk patients [36–39].

In early 1990s, the diagnosis of MI was primarily based on an elevated serum CK-MB level. Though, the introduction of troponin markers significantly increased the sensitivity and specificity for the diagnosis of myocardial injury and for this reason succeeded CK-MB as the gold standard for the diagnosis. A consensus guideline from both the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) has redefined acute MI [40]. According to these associations, acute MI is now typically termed as a typical rise and fall of serum biochemical markers (e.g., Troponin, CK-MB), associated with symptoms of ischemic injury, new pathologic Q waves on ECG, ischemic ECG changes (ST-segment elevation or depression), coronary artery intervention or histologic findings of AMI [41, 42].

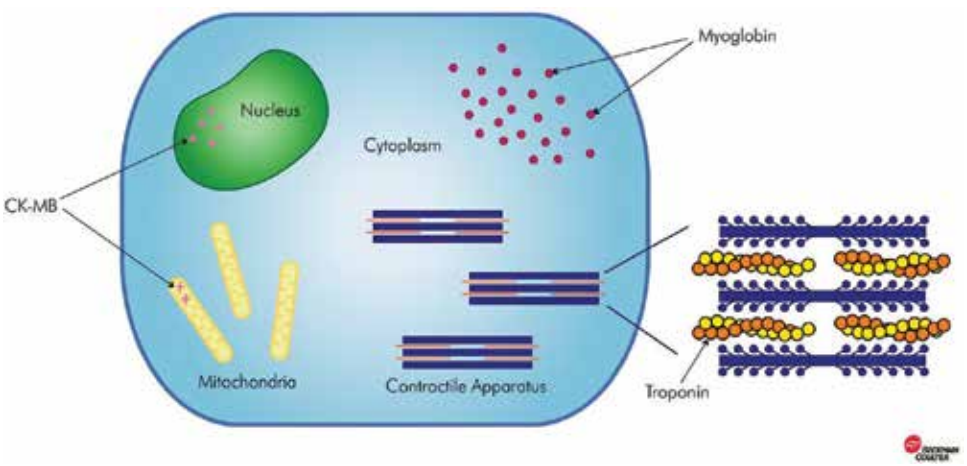

Figure 1. Cardiac muscle cell. Biochemical markers (troponin T, CK-MB, and myoglobin) in myocardium; adopted by Cummins.

Patients with elevated cardiac troponin levels but negative CK-MB who were previously diagnosed as unstable angina or minor myocardial injury are now re-stratified as non–ST-segment elevation MI (NSTEMI) even in the absence of diagnostic ECG changes [43].

5.1. Operational definition for acute myocardial infarction

The term MI should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
- Symptoms of ischemia;
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
- Development of pathological Q waves in the ECG;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality [43–46].

5.2. Types of myocardial infarctions

The most recent guidelines recognize five distinct types of MI [43–48].

- Type 1: Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection. This would be the typical ST elevation or non-ST elevation MI.
- Type 2: Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.
- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Type 4: MI associated with percutaneous coronary interventions, and there are two types of this category: one associated with the procedure itself, and one associated with subsequently verified stent thrombosis.
- Type 5: Myocardial infarction associated with CABG [43–48].

6. Biochemical markers of myocardial necrosis

Myocardial cell death can be documented by the appearance in the blood of different proteins released into the blood circulation from the ischemically injured myocytes: including myoglobin, cardiac troponin T and I, CK, LDH, besides many others (e.g. heart fatty acid binding protein). Myocardial infarction is diagnosed when blood levels of sensitive and specific cardiac biomarkers such as cardiac troponin or CK-MB are elevated in the clinical setting of acute myocardial ischemia [33, 49, 50]. Even though elevated biomarkers reflect myocardial damage and necrosis, they do not designate its underlying mechanism. Hence, an elevated value in the absence of clinical findings of ischemia triggers a need to search for other causes of cardiac damage, for example myocarditis [43, 45, 48].

6.1. Creatine kinase and CK-MB isoenzyme

Creatine kinase is a regulator of high-energy phosphate production, that is utilized in contractile tissues [51]. In addition it also has a more general role in shuttling high-energy phosphate bonds via creatine phosphate from the site of ATP production in the mitochondria to the site of utilization within the cytoplasm [51].

Cytoplasmic CK is a dimer, composed of both M and/or B subunits, that produce CK-MM, CK-MB and CK-BB iso-enzymes. CK has also a dimeric mitochondrial form consisting of both sarcomeric and non-sarcomeric subunits [52]. Mitochondrial CK is unstable in human serum, and that's why it is difficult to measure. CK-MM is the main isoenzyme found in striated muscle constituting about 97% of the total CK. CK-MB is found principally in cardiac muscle comprising approximately 15–40% of the total CK activity, with the remainder being CK-BB. CK-BB is the predominant iso-enzyme found in brain, intestinal and urinary systems. The skeletal muscle CK-MB produce 2–3% of the total CK activity; the patients with skeletal muscle injury may have increased CK and CK-MB levels [53].

The antibodies in turn inhibit M-subunit activity, with remaining enzyme activity being derived from B-subunits only; CK-BB is not detectable by activity measurement in serum, except the patient has suffered a serious cerebrovascular accident, so the residual activity represents CK-MB activity. Although antibodies had been developed to the B- and M-subunits of CK, it was thought that MB did not have its own unique antigenicity. However, specific antibodies were developed in the mid- 1980s, allowing the development of direct immunological assays for CK-MB. Serum total CK activity and CK-MB concentration rise simultaneously following myocardial injury [54, 55].

For CK-MB, two forms of the MB iso-enzyme were eventually recognized and isolated from plasma; the tissue form is designated CK-MB2; removal of the lysine residue from the carboxy terminus of the single M-subunit, catalyzed by the action of carboxypeptidase-N giving rise to the CK-MB1 isoform. Elimination of the lysine residue, which is positively charged, leaves a more negatively charged isoform thereby leaving a basis for isolation of the isoforms by electrophoresis [56]. The B-subunit is not sensitive to enzymic degradation, so only two isoforms of CK-MB exist. In normal plasma, CK-MB isoforms exist with each other in

balance ratio of 1:1. Release of tissue CK-MB2 increases its fraction in plasma; a change in the ratio of CK-MB2:CK-MB1 from 1:1 to 2:1 can be identified using high-voltage gel electrophoresis, even though there is no noticeable change in the plasma concentration of CK-MB [56, 57]. Significant fluctuations in the ratio of both the isoforms in plasma can be detected between 2 and 4 h after myocardial injury. Systematic prospective studies have confirmed that CK-MB isoforms act as an early marker of myocardial injury, and have also established a CK-MB2:CK-MB1 ratio above 1.5:1 as a diagnostic criterion [57–59]. The isoform ratio returns to normal within 18–30 h after injury. It has been proposed that a normal 1:1 isoform ratio in a sample collected at least 6 h after an event effectively excludes a diagnosis of myocardial infarction. The rapid return to normal values makes the CK-MB isoforms the best available laboratory investigation for the confirmation of re-infarction. Unfortunately, the analytical procedure used (high-voltage gel electrophoresis) requires specially designed equipment and a great deal of technical expertise, and is therefore unfeasible for daily/routine use. CK-MB is a sensitive as well as specific marker for myocardial infarction. CK-MB usually becomes abnormal 3–4 h after an event of myocardial infarction, peaks in 10–24 h, and returns to normal within 72 h [60–62].

Besides, skeletal muscle contains trace amounts of CK-MB, so an elevated serum CK-MB may be observed in people with severe skeletal muscle damage and/or renal failure. In such cases, the CK index that is CK-MB divided by total CK is very useful. If the index is lower than 4%, a non-myocardial etiology of a high CK-MB should be suspected [60–62].

6.2. Troponin T

The troponins are regulatory proteins found in both cardiac and skeletal muscles. They have 3 subunits; troponin I (TnI), troponin T (TnT), and troponin C (TnC). The genes that code for the skeletal and cardiac isoforms of troponin C (TnC) are similar. The skeletal and cardiac subforms for troponin I (TnI) and troponin T (TnT) are distinct, and immunoassays have been developed to distinguish subtypes [63, 64]. Skeletal TnI and TnT are structurally diverse. No cross-reactivity arises between skeletal and cardiac TnI and TnT with the current assays [63, 64].

Troponin is adhered to the protein tropomyosin and structurally lies within the groove between actin filaments in muscular tissue. In a relaxed muscle, tropomyosin blocks the site of attachment for the myosin cross-bridge thereby consequently preventing contraction. When the muscle cell is triggered to contract by an action potential, calcium channels get open in the sarcoplasmic reticulum hence releasing calcium into the sarcoplasm. A portion of this calcium gets attach to troponin resulting in conformational change that displaces tropomyosin so that the cross bridges can attach to actin and ensue muscle contraction [63, 64].

Troponin can originate from both skeletal and cardiac muscles, but the specific forms of troponin vary between types of muscle. The main difference is that the TnC in skeletal muscle has four binding sites for calcium ion, whereas in cardiac muscle there are only three. The process of contraction in both cardiac and skeletal muscles is controlled by variation in the intracellular calcium concentration. When calcium level rises the muscles contract, and when calcium drops the muscles relax. Smooth muscle does not contain troponin [65].

Individual subunits play different roles:

- Troponin C binds to calcium ions to create a conformational change in TnI
- Troponin T binds to tropomyosin, interlocking them to constitute a troponin-tropomyosin complex
- Troponin I binds to actin in thin myofilaments in order to hold the troponin-tropomyosin complex in place [66].

Cardiac troponin T (cTnT) is a cardio-specific, highly sensitive marker for myocardial injury. Cardiac troponin T rises approximately 3–4 h after acute myocardial infarction (AMI) and may continue up to 2 weeks thereafter [65, 66]. In comparison to ST-elevation myocardial infarction (STEMI), the diagnosis of non-ST elevation myocardial infarction (NSTEMI) mainly relies upon level of cardiac troponin T [66]. The diagnosis of MI can be made when blood levels of cTnT are above the 99th percentile of the accepted limit along with an evidence of myocardial ischemia [67]. Cardiac troponin T is an independent prognostic marker which can forecast the near-, mid-, and even long- term outcome of events in patients with acute coronary syndrome (ACS). Cardiac troponin T is also ideal marker of myocardial injury in the diagnosis and management of non-ST elevation acute coronary syndromes [43, 68] (**Figure 2**).

6.3. Cardiac troponin I

Cardiac troponin I is the contractile part and it is only present inside the myocardium [69, 70]. It is a part of the troponin complex (I, T, C) that along with the tropomyosin is bound to actin within the thin myofibril filament. cTnI is acquired as free TnI, as well as intricated with troponin C with troponin T termed as binary IT or with both the troponin C and troponin T where it is called as ternary ITC. Its physiological function is to hinder the ATPase activity of the actin-myosin complex during lack of calcium, and thus, to avert muscular contraction [71].

Three types of tissue isoforms are found. Fast and slow troponin I (19,800 Da) participating in fast and slow twitch skeletal muscle fibers and cTnI (24,000 Da). All the three isoforms of troponin I are encoded by the different genes. The human cTnI reveals merely 54 and 52% amino acid sequence homology with human slow and fast skeletal troponin I, respectively [72]. cTnI specific monoclonal antibody pair is selected. Moreover it is found that skeletal muscles do not express cTnI, neither during development nor in response to a stimuli [72]. cTnIs can differentiate cardiac and skeletal muscle injuries, and facilitates the diagnosis of MI discrete from the skeletal muscle injuries (e.g. rhabdomyolysis, polytraumatism or from the non-cardiac surgery) [72–75]. Increased troponin I levels are also determined in unstable angina [76] and congestive cardiac failure [77]. In acute MI serum concentrations of both cTnI and CK-MB show similar increase and decrease patterns. It is recommended that at least three blood samples should be collected during the early triage period [78]. In the cardiac muscles the level of cTnI is 13 times more than that of CK-MB. Moreover cTnI does not circulate in the

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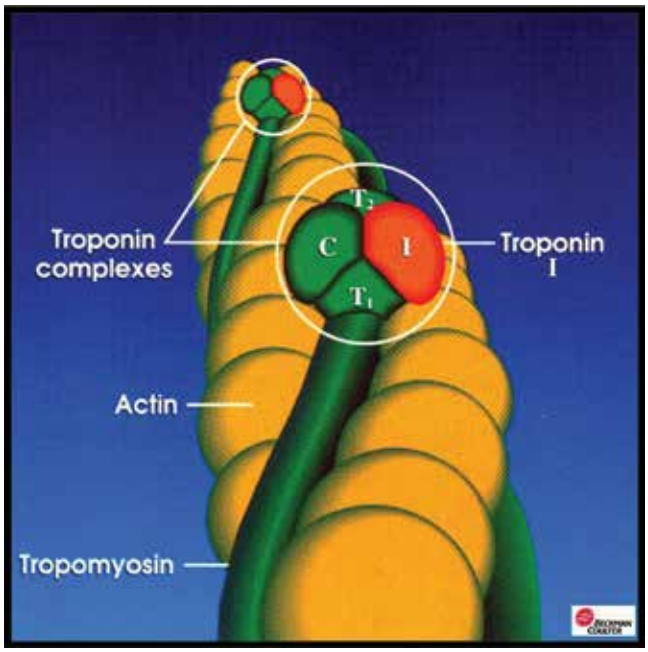

Figure 2. The troponin regulatory complex; adopted by Roger Cummin.

blood in normal circumstances, therefore elevated serum levels of c TnI are more significant for the diagnosis of myocardial necrosis [79]. Data obtained from recent studies specify that the troponin I concentration can be determined within the first 3–6 h after the onset of chest pain. The levels of Troponin I reach the peak level at approximately 12–16 h and remain elevated for 4–9 days after acute MI. The time to attain the peak concentration of cTnI was found to be more among patients who did not underwent thrombolytic therapy [73, 80, 81].

Recent studies have found that in patients after AMI the predominant form of cTnI exhibited in blood is the binary troponin IC complex with slight concentrations of ternary ITC complex, binary IT complex and free cTnI [82–85]. The release pattern of these forms in MI is still under investigation. Commercially available laboratory methods can identify complexed and free cTnI subforms [82, 86, 87]. Some of the assays have the same responses to different forms of cTnI. The second type may result in over or under estimation of troponin I concentrations in complex biological settings. The equimolar binding characterized as the ability to determine both the complexed and free cTnI forms uniformly leads to an unbiased estimation of the total cTnI found in the samples from same subject in MI. The Access AccuTnI assay identifies the binary troponin IC or IT or ternary troponin ITC complexes and free cTnI evenly. The assay detects both the phosphorylated and dephosphorylated forms of cTnI complex [88].

The American College of Cardiology (ACC) and the European Society of Cardiology (ESC) guidelines advocate that the different laboratories define their own reference range and also

an elevated level of cTnI be identified as an amount above the 99th percentile of a normal control group, that is, 99th percentile of the upper reference limit [89, 90].

Conversely in patients with unstable angina and acute MI without the evidence of ST segment elevation (NSTEMI) the expectation of suffering from an adverse event is reported to be quite difficult. The advancement as well as commercialization of more specific and more sensitive cardiac troponin I (cTnI) immunoassays have considerably added to the accurate diagnosis of MI and to the risk stratification of NSTEMI/UA patients.

The definition of MI was formally redefined in 2000 by the European Society of Cardiology and the American College of Cardiology to realign evidence of myocardial injury as defined by biomarkers with a particular advocacy on troponin [32]. The 2000/2002 American College of Cardiology (ACC) and the American Heart Association (AHA) Guideline Update evocatively advocate to incorporate the estimation of cTnI for the management of AMI patients and also for the risk stratification of patients presenting with symptoms suggestive of acute coronary syndromes [40, 91]. This definition was updated in 2007 [43] to reflect the progress that had been made in understanding assays. It again relied heavily on a definition based on troponin. Specifically, with rare exception, the diagnosis cannot be made in the absence of elevated biomarkers of cardiac injury [43, 68].

Considering the potential adverse outcomes the estimation of the prognosis should aid clinicians in identification and management of high risk patients. Eventually the evaluation of the prognosis will be helpful in both the identification of site of care as well as in distinguishing patients most likely to get benefit from specific therapeutic interventions.

7. Conclusion

Acute myocardial infarction usually presents with discomfort or chest pain, weakness, sweating, nausea, vomiting, and arrhythmias. Common risk factors include old age, obesity, smoking, hypertension, hypercholesterolemia and diabetes mellitus. Myocardial ischemia may result either from increased demand or decreased supply of oxygen to the myocardium or both.

A consensus guideline from both the American College of Cardiology (ACC) and the European Society of Cardiology (ESC) has redefined AMI as a typical rise and fall of serum biochemical markers (e.g., Troponin, CK-MB), associated with symptoms of ischemic injury, new pathologic Q waves on ECG, ischemic ECG changes (ST-segment elevation or depression), coronary artery intervention or histological findings of AMI.

Biochemical cardiac markers include myoglobin, cardiac troponin T, cardiac troponin I, CK-MB, LDH, and many others like ischemia modified albumin, Glycogen phosphorylase BB and fatty acid binding protein. Cardiac markers are vital not only from diagnostic but also from the prognostic viewpoint.

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Section 4

Managemant of Myocardial Infarction

Chapter 4

Interventional Therapies for Post-Cardiac Arrest Patients Suffering from Coronary Artery Disease

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Additional information is available at the end of the chapter

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Abstract

Acute myocardial infarction and coronary artery disease (CAD) are the most common causes for the development of malignant arrhythmia often leading to cardiogenic shock and cardiac arrest. Structural heart disease represents the main pathology in older patients, whereas young adults mostly suffer from cardiomyopathies and channelopathies. This book chapter delineates modern interventional therapies for patients with cardiogenic shock or aborted cardiac arrest. Epidemiological data on the incidence of malignant arrhythmia depending causing cardiac arrest depending on the presence or absence of CAD and myocardial infarction are presented. Realistic difficulties within clinical decision-making are counterbalanced for and against an early, aggressive and invasive therapeutic approach including early coronary angiography with percutaneous coronary intervention (PCI), targeted temperature management and mechanical cardiac assist devices, depending on the individual clinical presentation and underlying cardiac arrhythmia.

Keywords: cardiac arrest, assist device, shock, ventricular fibrillation, ventricular tachycardia, coronary artery disease

1. Introduction

In recent decades, cardiovascular mortality has been reduced by effective prevention of risk factors and development of coronary heart disease (CAD) or progressive heart failure syndrome [1]. Nevertheless, cardiovascular disease accounts for 17 million deaths per year, of which 25% are related to cardiac arrest with consecutive sudden cardiac death (SCD) [1]. The risk of SCD was shown to be higher in men and increasing age, alongside with an increasing age-dependent

prevalence of CAD. European guidelines estimate SCD occurring in about 1.40/100,000 person-years in women, and even higher in about 6.68/100,000 person-years in men. Accordingly, the estimated annual death rate ranges in between 1100 and 9000 in Europe [1].

There are multiple varying causes for development of cardiac arrest. Structural heart diseases are present at older age, including CAD, heart valve diseases and heart failure syndrome, whereas in younger adults, cardiac arrest is more often caused by cardiomyopathies, channelopathies, myocarditis and substance abuse [1].

This chapter summarizes current knowledge of patients with cardiac arrest and concomitant CAD. Current knowledge about epidemiological data on the incidence of malignant arrhythmias causing cardiac arrest depending on the presence or absence of CAD is presented. Furthermore, the potential benefits of an early coronary revascularization as well as of a prompt complete coronary revascularization compared to treatment of coronary culprit lesion only are outlined. Finally, the advantages of invasive therapies for patients surviving cardiac arrest, such as targeted temperature management and mechanical cardiac assist devices, are elucidated.

2. Prevalence of CAD in patients with malignant cardiac arrhythmia

This chapter subsumes asystole, ventricular tachycardia, ventricular storming and ventricular fibrillation under the term malignant arrhythmia.

Prior structural heart disease may be present in almost 50% of patients suffering from cardiac arrest, whereas an even higher rate of subclinical CAD is suspected in these patients. Over decades, medical research has focused on the detection of reliable risk markers for the development of malignant arrhythmia in order to reliably estimate the chance for their individual occurrence. The most robust indicator represents the degree of left ventricular (LV) dysfunction according to LV ejection fraction (LVEF). In addition, screening includes all known cardiovascular risk factors, such as increases of low-density lipoprotein (LDL) cholesterol, smoking status, presence of diabetes mellitus, arterial hypertension and obesity. The implementation of screening methods to assess patients′ individual cardiovascular risk, as well as effective diagnostics and treatment of CAD and heart failure has helped to prevent approximately 40% of SCD cases [2].

The overall rate of primary ventricular fibrillation or pulseless ventricular tachycardia (pVT) as the initial documented heart rhythm in clinical arrest settings varies between 25 and 79% in US registries in 2007, especially when occurring in public daily life [3]. In contrast, an increase of pulseless electrical activity (PEA) and asystole was documented alongside with a decrease of ventricular fibrillation and pVT. This inversion may be explained by improved medical care including improved guideline-based drug treatment for CAD and heart failure, percutaneous coronary intervention (PCI), implantable cardioverter-defibrillators (ICD), and the associated increasing prevalence of end-stage heart failure syndrome, which is associated with a higher prevalence of combined PEA or asystole at final disease stages [4, 5]. Survival rates are higher after cardiac arrest when a shockable ventricular arrhythmia (pVT or ventricular fibrillation) is documented (30.5%), whereas survival is lower in the presence of PEA or asystole (only 7.5–8%) [6].

- The risk of SCD is higher for men and increases with age.
- Incidence of SCD: approx. 1.40/100,000 person-years in women, whereas 6.68/100,000 person-years in men.
- The annual death rate of SCD ranges from 1100 to 9000 in Europe.
- Causes:
  - Young adults: cardiac channelopathies, cardiomyopathies, myocarditis and substance abuse.
  - Older adults: degenerative heart disease such as CAD, valvular heart disease and heart failure.
- Structural heart disease is already known in about 50% of patients.
- Active screening for cardiovascular risk factors and early detection and treatment of CAD and heart failure prevents 40% of SCD cases.
- A shockable initial rhythm (VF, pVT) is associated with a higher survival rate compared to asystole and PEA.
- The rates of asystole and PEA as initial arrhythmia in cardiac arrest are increasing.
- CAD requiring intervention is present in up to 75% of patients with survived cardiac arrest.
- Patients with persistent coma after cardiac arrest are associated with a higher mortality of up to 50%.

Table 1. Empirical data on coronary artery disease (CAD), malignant cardiac arrhythmia and cardiac arrest.

Clinically relevant CAD with critical coronary arterial stenoses requiring PCI was shown in approximately 75% of patients with cardiac arrest [7, 8]. In the presence of an acute coronary syndrome, about 6% of these patients sustain pVT or ventricular fibrillation within the first 24 h after symptom onset [1]. There is currently no detailed information available on the exact prevalence of CAD depending on the different types of malignant arrhythmia. This is partly due to lack of representative prospective studies or registries including either preselected cohorts with smaller patient numbers and short follow-up periods. Currently running registries are:

- Parisian Region Out of Hospital Cardiac Arrest (PROCAT; [9]),
- Minnesota Resuscitation Consortium (MRC; [10]),
- Resuscitation Outcomes Consortium (ROC; [11]),
- Emergency Cardiopulmonary Bypass (ECPB; [12, 13]),
- Registry of Malignant Arrhythmias and Sudden Cardiac Death – Influence of Diagnostics and Interventions (RACE-IT; clinicaltrials.gov identifier: NCT02982473),
- Extracorporeal Life Support Organization (ELSO; https://www.elso.org).

Furthermore, empirical data about the influence of CAD specific therapies on the different malignant arrhythmia are inconclusive. This implies in particular the influence of coronary revascularization by PCI or aortocoronary bypass surgery (CABG), targeted catheter-based ablation of ventricular tachycardia or supply by ICD on long-term course of patients with aborted cardiac arrest. Accordingly, mortality data depending on the underlying cardiac arrhythmia in patients being treated by modern cardiological therapies are not well represented in recent studies [1]. **Table 1** summarizes the most important empirical data on CAD, malignant arrhythmia and cardiac arrest.

3. Value of early invasive coronary diagnostics and therapies after cardiac arrest

The biological processes that cause an arrested heart either to regain a regulated sinus rhythm with sufficient myocardial contraction and stroke volume or not to recover adequately after an acute myocardial infarction are still unclear [4]. The reperfusion-damage theory is often debated, which has to be prevented by coronary revascularization and reperfusion. Still vital myocardium is threatened not only by cell death under circumstances of ongoing ischemia, but also by changes in cell metabolism and the sudden resupply of oxygen and other substrates after reperfusion [14]. Whether re-exposure to normal concentrations of oxygen, calcium or a balanced pH value may have beneficial or even fatal effects following successful reperfusion of a closed coronary artery is poorly understood and very controversial [15, 16]. It is assumed that the reperfusion damage is subject to temporal dynamics. After a prolonged ischemic phase, there is a critical time frame in which reperfusion may cause even more harm than benefit [17]. This has been proven in studies investigating ischemic preconditioning. Here, repetitive periods of iatrogenic induced complete ischemia may reveal myocardial protection and may reduce the reperfusion damage [18].

Today, emergency PCI combined with an extracorporeal bypass is one of the favored revascularization strategies. Emergency bypass requires rapid cannulation of a large central artery and vein, typically femoral artery and vein, and can be inserted out-of-hospital already [12, 19]. Since 2000, those concepts have been pushed forward. For instance, more than 30 cardiac arrest centers were created in Japan to establish full cardiovascular support and emergency PCI support within 15 min, achieving a survival rate of more than 15% in cardiac arrest patients with good neurological function [7]. The administration of additional intravenous drug combinations as a so-called "anti-perfusion-damage cocktail" is another concept that has so far only been evaluated in experimental work [4, 20].

In case of an established emergency bypass protected emergency PCI can be performed safer. Emergency PCI represents the decisive therapy in cardiac arrest patients, which may prevent ongoing myocardial necrosis. In addition, the baseline neurological status of each individual patient is directly related to mortality after cardiac arrest. About two-thirds of all patients with out-of-hospital cardiac arrest caused by ST segment elevation myocardial infarction (STEMI) are in a comatose state. In particular, this group of patients is associated with a significantly higher mortality of 50%, compared with a mortality of only 5% in awake patients after being successfully resuscitated [21].

About 50% of patients surviving out-of-hospital cardiac arrest and with proven CAD reveal acute coronary artery occlusion [7]. Therefore, European guidelines recommend primary PCI in patients with a successfully restored spontaneous circulation (ROSC) after cardiac arrest, cardiopulmonary resuscitation (CPR) in the presence of STEMI, regardless of baseline neurological status (recommendation class I, level of evidence B) [1, 7, 9]. In contrast, coronary angiography should also be performed independently of ECG findings in survivors of cardiac arrest with an intermediate pretest probability, which is estimated on the basis of age, gender and symptoms (recommendation grade IIa, level of evidence B-C [1, 22, 23]. This also includes patients with "ventricular storming" (recommendation grade IIa, level of evidence C [22]). According to various mostly nonrandomized studies, early invasive coronary

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angiography may lead to increasing one-year survival in up to 60%. Still 58% of patients without ST-segment elevation reveal a critical coronary arterial stenosis ("culprit lesion") [6, 9, 24, 25]. Again, most studies investigating patients suffering from acute coronary syndrome and malignant arrhythmia were observational and heterogeneous including both patients with STEMI and NSTEMI [26]. Invasive coronary angiography with PCI should be performed either immediately or as early as possible based on careful clinical assessment [6]. This concept is also supported by animal studies demonstrating an improvement of both survival and neurological function after immediate reperfusion therapy in pigs with induced ischemia-driven ventricular fibrillation [27]. A fortiori, further clinical parameters become considerably important, which in turn may limit the use of an early PCI in the individual (**Table 2**).

These parameters include the following: [6]

- unwitnessed cardiac arrest;
- absence of ventricular fibrillation as primary arrhythmia;
- absence of bystander CPR;
- prolonged or repeated CPR;
- CPR period longer than 30 min;
- lactate value >7 mmol/L, pH value <7.2 both being associated with severe tissue hypoxia and multiple organ failure;
- age > 85 years;
- terminal renal failure requiring renal replacement therapy; and
- presence of noncardiac causes leading to cardiac arrest.

• Unwitnessed cardiac arrest
• Absence of ventricular fibrillation as primary arrhythmia
• Absence of bystander CPR
• Prolonged or repeated CPR
• CPR period longer than 30 min
• Lactate value >7 mmol/L, pH value <7.2 both being associated with severe tissue hypoxia and multiple organ failure
• Age > 85 years
• terminal renal failure requiring renal replacement therapy
• Presence of noncardiac causes leading to cardiac arrest
• Patients with noncardiac causes of cardiac arrest
• Advanced dementia
• Persistent ventilation
• Frailty
• Multisystem disorders

Table 2. Important clinical parameters limiting prognosis and the additional benefit of an early aggressive invasive treatment strategy by PCI.

Other factors to consider include comorbidities such as advanced dementia, persistent mechanical ventilation, respiratory failure, frailty, physical or neurological disability and multisystemic disorders. All these factors should be taken into account independently of the documented primary arrhythmia on ECG because they postpone the indication for early invasive diagnostics and therapies.

Figures 1 and **2** show two emergency complex multiple PCIs in two patients in cardiogenic shock after impending or survived cardiac arrest using two different cardiac/ventricular assist devices (VAD) as extracorporeal life support (ECLS).

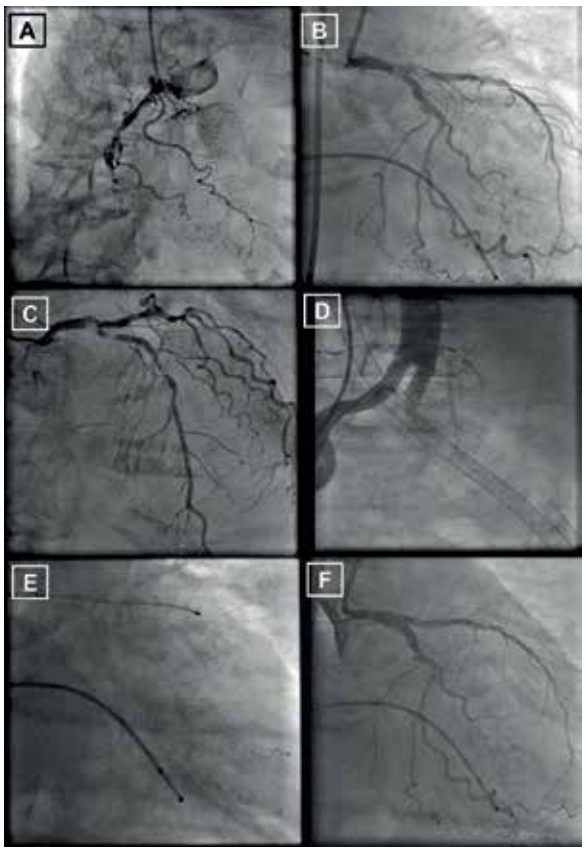

Figure 1. Emergency coronary angiography of a 82-year-old female patient surviving out-of-hospital cardiac arrest with immediate nonprofessional resuscitation. Ventricular fibrillation was documented as primary arrhythmia, with consecutive 15-min of CPR, multiple external electrical defibrillations and final ROSC. Severe coronary 3-vessel disease was found, with a chronic total occlusion of the right coronary artery (CTO) with ipsilateral and contralateral retrograde collateral connections (A). The left coronary artery shows a critical 99% stenosis at the distal main trunk (LMT), progressing into the central left circumflex (CX) (B) and left artery descending (LAD). LAD additionally shows sequential high-grade 99% proximal and mid-stenoses (C). By implantation of a venous-arterial extra-corporal membrane oxygenation (VA-ECMO) via the left femoral artery and vein hemodynamic collapse was rapidly stabilized and complex multivessel PCI could have been initiated (D). First, rotablation (1.25 mm burr) from the LMT into the middle LAD (E). Secondly, single PCI/DES implantation was performed at mid-LAD (Boston Syndrome II 2.5/16 mm). Finally, bifurcational PCI of LMT-CX-RIVA T-stenting with antegrade protrusion (TAP) technique and final balloon kissing was performed (LMT in CX, Boston Synergy 4.0 / 24 mm; LMT in LAD protruded, Boston Synergy II 3.0/16 mm; final kissing with non-compliant balloons, Boston Emerge 4.0/20 and 3.5/15 mm) (F). Weaning from VA-ECMO and mechanical ventilation succeeds on the following day and the patient could have been discharged from hospital at day 9 in stable neurological and cardiopulmonary status.

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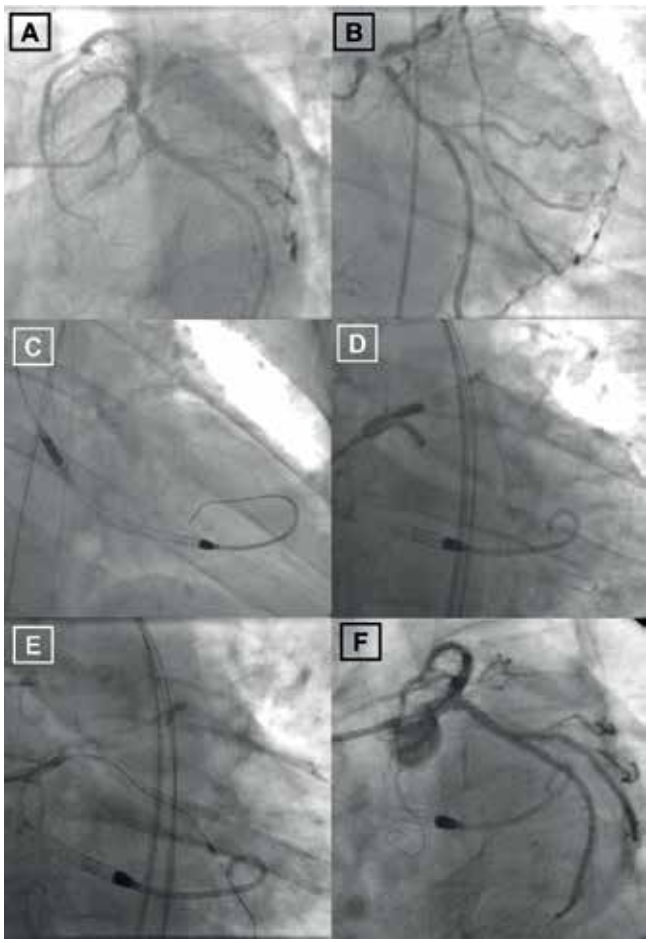

Figure 2. Severe coronary artery disease of a 50-year-old male patient with ST segment elevation myocardial infarction (STEMI) of the anterior wall, consecutive cardiogenic shock and prolonged cardiac arrest. Coronary angiography showed a subtotal stenosis of the mid and distal LMT, LAD showed long and critical stenosis, CX and first marginal branch were also highly stenosed (A&B). Right coronary artery was normal (not shown). Firstly, percutaneous and central intracardiac LVAD (Impella 2.5) was inserted into the left ventricle (C). Secondly, the LMT-LAD-CX bifurcation was predilated by a kissing balloon technique (D). Thirdly, rotablation (1.25 mm burr) of the mid CX was performed (E). Finally, complex multivessel PCI of marginal branch, CX and LAD. Final result showed sufficient TIMI-III flow with complete emergency revascularization (F). Impell device was removed after PCI due to recovery of circulation.

4. Emergency PCI with complete coronary revascularization or treatment of the coronary "culprit lesion" only?

European guidelines recommend immediate coronary revascularization in patients with recurrent ventricular tachycardia or fibrillation, in order to prevent suspected myocardial ischemia. However, graduation of recommendation is based on expert consensus only (grade of recommendation I, level of evidence C; [1, 22]). On the other hand, the SYNTAX trial demonstrated that complete compared to incomplete coronary revascularization (either by PCI or CABG) significantly improves long-term survival of patients with coronary three-vessel

disease [28]. In cardiogenic shock, early coronary revascularization was associated with improved long-term survival compared to drug therapy [29, 30]. However, early PCI in cardiogenic shock or in patients with aborted cardiac arrest is applied in 50–70% of patients only [31], although most of these patients reveal coronary multivessel disease being associated with significantly higher mortality compared to coronary one-vessel disease [32, 33]. Depending on hemodynamic instability and complexity of multivessel coronary disease according to the SYNTAX level, either a PCI or CABG may be the recommended treatment option in cardiogenic shock (Grade I, Level B evidence) [22]. The "CULPRIT-SHOCK" study recently demonstrated a prognostic benefit for a staged PCI of the "culprit lesion" at first in patients with cardiogenic shock and coronary multivessel disease compared to "ad-hoc" multivessel PCI directly at presentation. This prognostic benefit was attributed to fewer amount of contrast use and consecutive fewer rates of renal failure, when the culprit lesion was treated at first presentation and all other critical coronary artery stenoses underwent PCI some days later after hemodynamic recovery [34, 35]. Comparative studies evaluating CABG versus PCI in patients suffering from cardiac arrest or cardiogenic shock are lacking [36]. However, the advantages for immediate PCI consist of a better accessibility of cardiac catheterization laboratories compared to cardiac surgery units, including rapid feasibility of PCI with minimally invasive access. This has led to an almost lower prevalence of emergency CABG in post-cardiac arrest patients of less than 5% [31].

5. Additional benefit of interventional and surgical treatment options after cardiac arrest

Beside revascularization therapy of all critical coronary artery stenoses or occlusion, further interventional and surgical therapeutic option have become available for patients after cardiac arrest. These advanced therapies reveal two main therapeutic goals:

1. cerebral neuroprotection and myocyte protection after episodes of ongoing hypoxemia during cardiac arrest; and
2. restoration of hemodynamic stability in cardiogenic shock.

5.1. Targeted temperature management

Cerebral and myocardial protection can be achieved by myocardial reperfusion and targeted temperature management (TTM). The TTM may attenuate various signaling pathways leading to cell death by revealing anti-apoptotic and anti-inflammatory effects [37]. Smaller cohort studies demonstrated that invasive treatment after cardiac arrest including TTM and coronary angiography with reperfusion therapy by PCI can reduce myocardial infarction size [38]. In addition, it could have been shown that TTM alone without reperfusion reveals adverse effects because the extent of myocardial infarction was comparable independently of treatment with TTM. TTM plus reperfusion resulted in the best recovery

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of cardiac function with the lowest myocardial infarction size [39]. This experimental evidence confirms the disadvantage of delayed coronary revascularization and limits the benefit of sole TTM after cardiac arrest.

In contrast, Mooney et al. demonstrated that delayed initiation of TTM in patients with out-of-hospital cardiac arrest was associated with a 20% increase of mortality. However, the rate of invasive coronary angiography was 72% with a PCI rate of 40% only [40]. It is well documented from several cohort studies that a combined PCI plus TTM improves survival and neurological outcome in patients with cardiac arrest and persistent coma [6].

TTM consists of controlled intravenous infusion systems (e.g., Bogard XP® Temperature Management System, ZOLL Medical Corporation, Asahi Kasei Corp, Japan) in combination with cool packs. TTM may not be initiated out-of-hospital only in order to achieve potentially best possible prognostic and neurological outcome [41, 42]. The target temperature is aimed between 32 and 36°C, whereas even lower target temperatures were shown to have no additional prognostic or neurological benefit [37, 43, 44]. Regardless of the documented primary arrhythmia, TTM is always recommended for at least 24 h duration in patients with persistent coma [37].

5.2. Cardiac assist devices for extracorporeal life support (ECLS)

Despite successful CPR and consecutive ROSC, there are still 30–40% of patients revealing hemodynamic instability and prolonged cardiogenic shock. In this situation, cardiac ventricular assist devices (VAD) may achieve stabilization or normalization of circulation. Cardiac index may be normalized, myocardial oxygen consumption and perfusion of secondary organs including brain and kidneys will be improved [25]. The presence of the acute emergency, in which post-cardiac arrest patients with prolonged cardiogenic shock are situated, favors minimally invasive or percutaneous VAD. Depending on the device type, each individual VAD increases cardiac output either with left (LV) or right ventricular (RV) mechanical support.

Currently available VAD systems for percutaneous access include the following:

- Intra-aortic balloon pump (IABP);
- LVAD – central:
  - LV to aorta: non-pulsatile axial Impella® 2.5/5.0 (Abiomed Europe, Aachen, Germany; Abb. 3a),
  - Left atrium (LA) to aorta: TandemHeart® LVAD KIT (CardiacAssist, Inc., Pittsburgh, USA; Abb. 3b);
- RVAD – central:
  - Vena cava inferior (VCI) to pulmonary artery (PA): non-pulsatile axial Impella RP® (Abiomed Europe, Aachen, Germany; 3a),

- RA to PA: TandemHeart® RVAD KIT with 2 cannulas (CardiacAssist, Inc., Pittsburgh, USA; Abb. 3c),
- RA to PA: TandemHeart® RVAD PROTEKDuo® double lumen cannula (CardiacAssist, Inc., Pittsburgh, USA; Abb. 3d);

- Extracorporeal membrane oxygenation (VA [veno-arterial]-ECMO) – peripheral:
  - V. femoralis to *A. femoralis* (VA): CARDIOHELP system (MAQUET GETINGE GROUP, Rastatt, Germany) or LIFEBRIDGE® 2.0 Systemccar- dio (ZOLL Medical Deutschland GmbH; Abb. 3e).

Unfortunately, scientific evidence about clinical benefits of the various VAD in patients with cardiogenic shock, aborted cardiac arrest or persistent ventricular tachycardia or fibrillation ("ventricular storming") is still insufficient and not sound [1, 22, 25, 45]. Recommendation for mechanical circulatory support in cardiogenic shock caused by myocardial infarction is based purely on expert opinion (grade of evidence IIb, level of evidence C; [22]). VAD were shown to stabilize patients suffering from hemodynamically unstable ventricular tachycardia. In contrast, VAD may also complicate the therapeutic management in emergency situations because clinical application of VAD demands more members of stuff. Additionally, mechanical assist devices were also shown to alleviate the incidence of ventricular tachycardia by the VAD itself [1].

Combining PCI with IABP was not associated with a significant reduction of infarct size [46]. In particular, IABP was not associated with a reduction of 30-day or 1-year mortality in patients surviving cardiogenic shock due to myocardial infarction [47, 48]. Therefore, the use of IABP is recommended only in case of mechanical complications in order to bridge the patient for cardiac surgery [22, 49].

More and more meta-analyses have recently been published, which conclusively analyzed smaller studies evaluating the benefit of VAD in patients after cardiac arrest or with cardiogenic shock. Ouweneel et al. [50] demonstrated that, after cardiac arrest, the use of VA-ECMO significantly improves both survival and neurological outcome at 30 days compared to patients treated with IABP or Impella® (n = 219). Even after cardiogenic shock, patients treated with VA-ECMO showed a higher survival rate at 30 days compared to patients with IABP or Impella® (n = 151) [50]. In contrast, the direct comparison between IABP and Impella® showed differences of survival in patients with acute myocardial infarction and cardiogenic shock [51, 52]. However, it could have been shown that the earliest possible use of Impella® reveals an independent prognostic factor for improved survival after cardiogenic shock [53–55]. Vase et al. described in a small case series (n = 8) that the use of the Impella® after cardiac arrest and mean CPR duration with "low-flow-time" of about 50 min is associated with a comparable survival rate to cardiogenic shock [56, 57].

Data for VAD between LA and aorta, such as TandemHeart®, are not available for patients surviving cardiac arrest or cardiogenic shock. Therefore, no evidence-based recommendation can be given. However, TandemHeart® was shown as a safe and feasible

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mechanical circulatory support during high-risk PCI [45]. Specifically, for TandemHeart® a transseptal puncture is needed during implantation with trans-septal sheath diameters ranging from diameters of 15–16 French. However, transseptal puncture is rarely performed on a regular basis and only by a smaller number of interventional cardiologists. This makes the application of TandemHeart® limited for a widespread use in clinical practice especially in emergency situations of patients with cardiac arrest and cardiogenic shock [45]. In addition, dislocation of the LA cannula into pulmonary veins or left atrial appendage during relocation maneuvers or during intensive care transports are potential complications.

Data on VA-ECMO in cardiac arrest or cardiogenic shock patients are based on many smaller cohort studies published in 2006 in cardiac surgery settings. Here, a meta-analysis demonstrated a survival rate of 50% [11]. The abovementioned ELSO registry reports about a survival rate of 27% post cardiac arrest [58]. In 2013, Takayama et al. reported on 50% survival rate for patients with cardiac arrest or cardiogenic shock after implantation of VA-ECMO. Half of these patients needed a permanent surgical VAD at follow-up. Also in this cohort, prolonged duration of CPR was associated with increased mortality despite the use of VA-ECMO [59].

Modern medical technologies have been developed in recent years, which make VAD applicable for percutaneous access in critical and unstable situations. It should be emphasized that mechanical support after cardiac arrest and consecutive cardiogenic shock is not limited to the left heart only. In principle, and always depending on the underlying individual clinical condition, RV support can also be performed by another RVAD at the same time. The femoral access route is usually preferred for implantation of the LVAD. For RVAD, both the femoral and the transjugular access routes are possible. Direct and central unload of the congested heart is always recommended, but depends on technical applicability in each individual clinical situation. In contrast, insertion of cannulas at peripheral femoral vessels will always provide indirect unload for the congested heart because extracorporeal blood re-circulated to peripheral vessels. As a result, contrary effects were recently demonstrated for peripheral assist devices (**Figure 3d**, **e**, **left**; [45]). The increasing amount of peripherally recirculated blood volume automatically raises wall tension in the peripheral arterial system. In turn, this leads to considerable increase of afterload, which may be harmful for the congested, severely impaired LV after cardiac arrest. Therefore, the implantation of peripheral VA-ECMO systems additionally requires the placement of LA transseptal cannulas, which leads to "central unload" at the level of left atrium and the left ventricle (**Figure 3e**, **middle**; [60]). "Central unload" within the LA was more effective compared to RA because LV filling can be reduced from the left atrial level, while at the same time systemic perfusion is maintained more effectively. In contrast, unloading at the right atrium was associated with a significant increase of LV wall tension and LV unloading becomes even less effective [60]. Direct unloading within LA or LV (e.g., in the TandemHeart®) therefore represents the most effective way for mechanical circulatory support by VAD [49]. Additional unloading is usually achieved by an additionally inserted cannula, which is positioned in the LA after transseptal puncture, while it can be integrated into the peripheral VA-ECMO circuit via Y-connectors (**Figure 3e**, **right**).

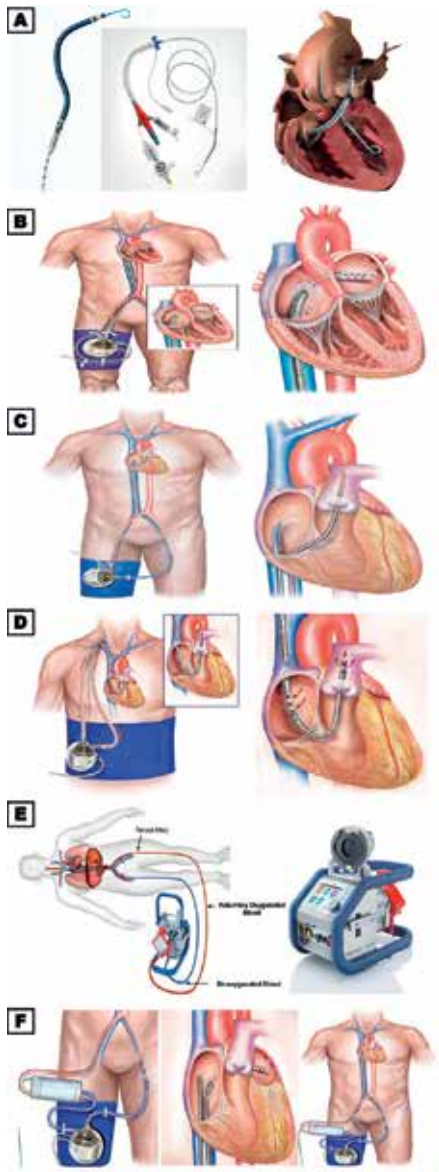

Figure 3. Graphical illustration of different ventricular assist devices (VAD) for extracorporeal life support (ECLS): Central left ventricular assist device (LVAD): (A) LV (left ventricular) to aorta: non-pulsatile axial Impella® 2.5/5.0 (Abiomed Europe, Aachen, Germany). (B) LA (left atrial) to aorta: Tandem Heart® VLAD KIT (Cardiac Assist, Inc., Pittsburgh, USA). Central right ventricular assist device (RVAD): (A) Vena cava inferior (VCI) to PA: nonpulsatile axial Impella RP® (Abiomed Europe, Aachen, Germany). (C) RA (right atrial) to PA (pulmonary artery): Tandem Heart® RVAD KIT with 2 cannulas (Cardiac Assist, Inc., Pittsburgh, USA). (D) RA to PA: Tandem Heart® RVAD PROTEKDuo® dual lumen cannula (Cardiac-Assist, Inc., Pittsburgh, USA). Peripheral ECLS: (E) extracorporeal membrane oxygenation (VA [veno-arterial] - ECMO): peripheral femoral vein to femoral artery (VA) - ECLS: CARDIOHELP System (MAQUET GETINGE GROUP, Rastatt, Germany). (F) Placement of LA cannula (trans-septal) in addition to the VA-ECMO: improved "unload" of the congested heart, the additional cannula can be integrated into the VA-ECMO circuit via Y-connectors. Unfavorable effects on the cardiovascular system due to peripherally placed assist devices can be reduced.

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6. Conclusions for daily clinical practice

- The grade of recommendation for early invasive coronary angiography with immediate PCI in post cardiac arrest patients is still based only on non-randomized cohort studies or expert opinions, depending on the pretest probability and on the type of myocardial infarction (i.e., NSTEMI or STEMI).
- Decision-making for either an interventional-invasive or surgical approach should always include important prognostic cofactors.
- A staged PCI including emergency PCI of the coronary "culprit lesion" only in the emergency setting was shown to be safer and associated with improved survival compared to "ad-hoc" emergency PCI of all critical coronary stenoses in patients suffering from cardiogenic shock and coronary multivessel disease.
- The benefit of emergency CABG compared to emergency PCI after cardiac arrest requires further evaluation.
- Advanced interventional and operative therapies include targeted temperature management in combination with coronary revascularization and extracorporeal mechanical cardiac support systems, which include intra-aortic counter pulsation (IABP), central LVAD and RVAD, as well as peripheral ECMO systems.
- Randomized prospective studies comparing the use of VAD in post cardiac arrest patients is lacking. Use of VAD is still limited to specialized centers and a widespread routine application is still a long way off.

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Chapter 5

Non-ST Elevation Myocardial Infarction: Diagnosis and Management

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Additional information is available at the end of the chapter

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Abstract

Cardiovascular disease is expected to be the main cause of death globally due to the rapidly increasing prevalence of obesity, hypertension and diabetes mellitus. Atherosclerotic lesions and plaque rupture are the most common cause of myocardial infarction. Resting 12-lead ECG is the first diagnostic test for patients with chest pain and should be performed and interpreted within the first 10 min of the patient's admission to the emergency department. Cardiac biomarkers preferably, high-sensitivity cardiac troponin, is mandatory in all patients with suspected NSTEMI for the diagnosis, risk stratification and treatment. Rapid, efficient diagnosis and risk stratification of patients with chest pain will help to administer the appropriate medication and plan for the timing of invasive strategy and the choice of revascularization. This chapter helps to simply but elaborately discuss the diagnosis, risk stratification and the management of patients with non-ST elevation of myocardial infarction.

Keywords: myocardial infarction, percutaneous intervention, antiplatelet

1. Introduction

1.1. Definition of acute coronary syndrome

Acute coronary syndrome (ACS) is a term that describes an acute ischemic insult to the myocardium resulting from sudden reduction in coronary blood flow. The findings on the ECG will help to categorize patients into two major subdivision of major diagnostic and therapeutic consequences [1]:

1. Patients with acute chest pain and persistent >1 mm ST-segment elevation in ≥2 anatomically contiguous leads. This condition is termed ST-elevation ACS and generally reflects an acute total coronary occlusion. The mainstay of treatment in these patients is immediate reperfusion with primary angioplasty or fibrinolytic therapy [2]. While biomarkers are useful for confirmatory and prognostic purposes, they are not required for the diagnosis of STEMI and should not delay treatment.
2. Patients with acute chest pain but no persistent ST-segment elevation. This condition is termed non-ST elevation ACS (NSTE-ACS). The ECG may be normal or there may be transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves or pseudo-normalization of T waves. The NSTE-ACS can be subclassified to:

    1. Non-ST elevation myocardial infarction (NSTEMI) which denote cardiomyocyte necrosis and death by a rise in serum troponin levels.
    2. Unstable angina is defined as myocardial ischemia at rest or minimal exertion in the absence of cardiomyocyte necrosis (cardiac biomarkers are not increased) [3, 4].

The application of high-sensitivity cardiac troponin measurements in daily clinical practice instead standard troponin assays showed increased detection of MI (4% absolute and 20% relative increase) and decreased diagnosis of unstable angina [5–7]. In comparison with NSTEMI patients, unstable angina patients do not have necrosis in their myocardial tissue and have a substantially lower risk of death. Unstable angina patients benefit less from intensified antiplatelet therapy and early invasive strategy [5–12]. NSTEMI encompasses a broad spectrum of ischemic injury to the myocardium, which is detected by elevation of serum cardiac biomarkers. It can be distinguished from unstable angina pectoris by normal serial cardiac biomarkers [1].

1.2. Non-ST elevation myocardial infarction

NSTEMI is an acute ischemic event causing cardiomyocyte death by necrosis in a clinical setting consistent with acute myocardial ischemia [8]. The leading symptom that initiates the diagnostic and therapeutic cascade in patients with suspected ACS is chest pain but to make a diagnosis of NTEMI, one major criteria is typical rise and gradual fall in cardiac biomarkers (troponin or CKMB) in addition to one or more of the following:

1. Symptoms of ischemia.
2. ECG changes.
3. Imaging evidence of new or presumed new loss of viable myocardium or regional wall motion abnormality.
4. Intracoronary thrombus detected on angiography or autopsy [8].

1.3. Classification of myocardial infarction

The development of myocardial tissue-specific biomarkers and sensitive cardiac imaging techniques allows for early detection of very small amounts of myocardial injury or necrosis. Consequently MI has been redefined to encompass any necrosis in the setting of myocardial ischemia by any of the following possible etiologies [3, 8, 13]:

Type 1 MI: spontaneous MI caused by atherosclerotic plaque rupture, ulceration, fissure, erosion or dissection with resulting intraluminal thrombus in one or more coronary arteries leading to decreased myocardial blood flow and/or distal embolization and subsequent myocardial necrosis. The patient may have underlying severe CAD but in 5–20% of cases there may be non-obstructive coronary atherosclerosis or no angiographic evidence of CAD, particularly in women [8, 10, 11, 14].

Type 2 MI: MI secondary to an increase in oxygen demand or decrease in supply. The myocardial necrosis results from causes other than coronary plaque instability [8]. Mechanisms include coronary artery spasm, coronary endothelial dysfunction, tachyarrhythmias, bradyarrhythmias, anemia, respiratory failure, hypotension and severe hypertension. In addition, in critically ill patients and in patients undergoing major non-cardiac surgery, myocardial necrosis may be related to injurious effects of pharmacological agents and toxins [9].

Type 3 MI: Sudden unexpected cardiac death before cardiac biomarkers obtained.

Type 4a MI: MI associated with percutaneous coronary intervention (PCI) where there is a greater than 5-fold rise in troponin during the first 48 h following the intervention [8].

Type 4b MI: MI associated with stent thrombosis.

Type 5 MI: MI associated with coronary bypass graft surgery (CABG), a greater than 10-fold rise from normal baseline levels in troponin during the first 48 h following the intervention [8].

2. Epidemiology and pathogenesis

2.1. Epidemiology

Cardiovascular disease (CVD) is the number one cause of death worldwide, accounting for 17.5 million deaths per year. Coronary heart disease mortality is decreasing in many developed countries, but it is increasing in developing and transitional countries, partly as a result of increasing longevity, urbanization, and lifestyle changes. Epidemiological data have shown that acute coronary syndrome cases with STEMI appear to be declining and that NSTEMI occurs more frequently than STEMI [15, 16]. In the United States, it is estimated that >780,000 people will experience an ACS each year, and approximately 70% of these will have NSTEMI [17]. Trends from the world's largest database of patients with ACS show that the percentage of patients with a diagnosis of NSTEMI is rising dramatically [18]. This is likely to be due

to the advent of more sensitive assays for myocardial injury, earlier pharmacotherapy, and reperfusion (and prevention) of STEMI [13, 18].

2.2. Pathophysiology

NSTEMI is a result of an acute imbalance between myocardial oxygen demand and supply, most commonly due to a reduction in myocardial perfusion. Type 1 MI is most commonly caused by a non-occlusive thrombus that develops in a disrupted atherosclerotic plaque, and leads to non-occlusive or near-complete thrombosis of a vessel supplying the myocardium.

Plaque rupture usually occurs at the weakest and thinnest part of the atherosclerotic cap (often at the shoulder region). Ruptured plaques contain large numbers of inflammatory cells including monocytes, macrophages, and T lymphocytes [19, 20]. Although one third of occlusions occur at a site with the greatest stenosis, most (66–78%) arise from lesions with <50% stenosis, and <5% arise from lesions exhibiting >70% stenosis [19]. It is thought that the lack of ST elevation is because the infarct does not involve the full thickness of the myocardium (not a transmural infarction). The severity of myocardial damage in NSTEMI depends on:

- Duration of ischemia and time to reperfusion
- Extent of underlying atherosclerosis
- Presence of collateral blood flow to the affected region
- Diameter of affected coronary vessel
- Degree of occlusion
- Presence of other comorbidities (i.e., diabetes, renal failure, or HTN).

Classically it is thought that NSTEMI patients ultimately have a diagnosis of a non-Q-wave MI; however, 25% of patients with NSTEMI and elevated biomarkers go on to develop Q-wave MI in the weeks to follow [21]. In addition, approximately 25% of patients with a diagnosis of NSTEMI have a 100% occlusion of the affected artery on coronary angiography [22].

NSTEMI may also be caused by other mechanisms, such as dynamic obstruction (i.e., focal coronary artery spasm or Prinzmetal angina), severe progressive atherosclerosis, restenosis following percutaneous coronary intervention, recreational drug use (e.g., cocaine or other stimulants), arterial inflammation (i.e., vasculitis), or extrinsic causes leading to myocardial supply–demand mismatch (such as hypotension, hypovolemia, or hypoxia) [1].

3. Diagnostic approach

3.1. Clinical presentation

Patients presenting with chest pain or discomfort with suspected ACS require urgent evaluation. The clinical spectrum of NSTEMI may range from patients free of symptoms at presentation to individuals with ongoing ischemia, electrical or hemodynamic instability due to large myocardium

in jeopardy or cardiac arrest secondary to malignant ventricular ischemia. Therefore, it is essential to establish if the patient has ACS and if so, what is the likelihood the patient will have adverse clinical event [1]. Physicians will need to stratify the patients according to their risk status and according to the initial risk assessment to choose an appropriate management strategy. The initial risk assessment includes the history, examination, ECG, and cardiac biomarkers [1, 23].

3.2. History and examination

Angina pectoris is a kind of pain described as a sensation of tightness, heaviness, aching, burning, pressure, or squeezing typically localized at the retrosternal region. The pain can often radiate to the left arm but may also radiate to the lower jaw, neck, both arms, back, and epigastrium. It is associated with exertion or emotional stress and relieved by rest or administration of sublingual nitroglycerin [1].

In ACS patients other symptoms including sweating, nausea, abdominal pain, dyspnea and syncope may be present. Atypical presentations are also possible and characterized by epigastric pain, indigestion-like symptoms and isolated dyspnea. Atypical complaints are more often observed in the elderly, in women and in patients with diabetes mellitus, chronic renal disease or dementia [24, 25]. The relief of pain at rest increase the probability of myocardial ischemia while the relief of symptoms after nitrates administration is not specific for angina pectoris [25]. In patients presenting with suspected MI to the emergency department, overall, the diagnostic performance of chest pain characteristics for MI is limited [25].

Risk factors increase the likelihood of NSTEMI include: Older age, male gender, family history of CAD, diabetes, hyperlipidemia, hypertension, renal insufficiency, previous manifestation of CAD as well as peripheral or carotid artery disease.

Physical examination is frequently unremarkable in patients with suspected NSTEMI but may reveal HTN or hypotension, the presence of third and fourth heart sounds, and paradoxical splitting of the second heart sound. Cardiac auscultation may reveal a systolic murmur due to ischemic mitral regurgitation, which is associated with poor prognosis [26] or a mechanical complication (i.e. papillary muscle rupture or ventricular septal defect) of a subacute and possibly undetected MI. Signs of heart failure (raised jugular venous pressure, bilateral crepitation on auscultation of the lungs) or cardiogenic shock may also be present, and these signify a worse prognosis.

3.3. Initial tests

3.3.1. Electrocardiogram

Resting 12-lead ECG is the first diagnostic test for patients with chest pain and should be performed and interpreted within the first 10 min of the initial admission to the hospital [27]. ECG is critical for the diagnosis of STEMI as the cause for the chest pain, this has a tremendous therapeutic implication for the patient.

While the ECG in the setting of NSTEMI may be normal in more than one-third of patients, a serial ECG at 15- to 30-min intervals should be performed to detect the developing abnormalities.

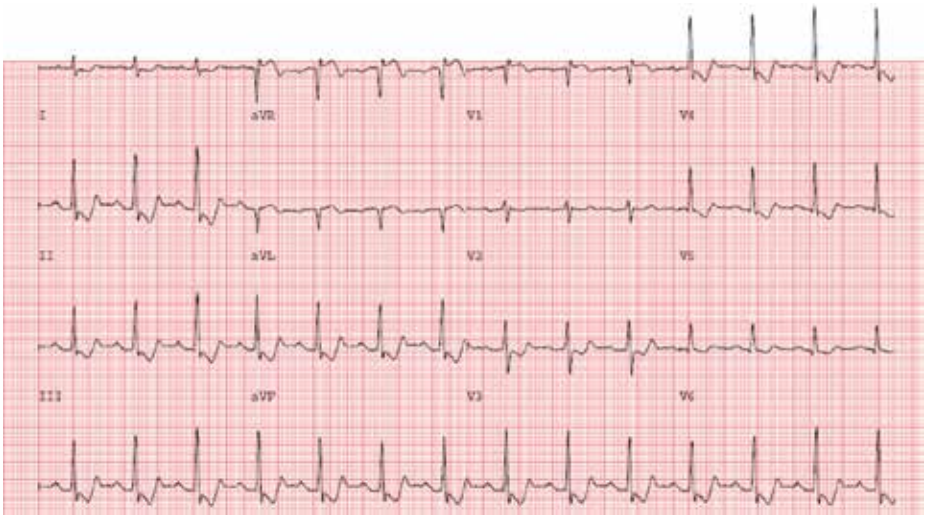

Figure 1. ECG showing ST depression in the inferolateral leads suggestive of inferior-lateral ischemia.

Classic ECG findings of ischemia in NSTEMI include horizontal or down sloping ST depression >0.5 mm and/or symmetrically inverted T waves >2.0 mm (**Figure 1**) [2, 28]. Standard leads may be inconclusive in some patients and additional leads may be necessary (e.g. in case of left circumflex artery occlusion or right ventricular MI may be detected only in V7–V9 and V3R and V4R, respectively) [8]. If it is possible a comparison with previous ECG's may be valuable. Diffuse precordial ST depression more pronounced in leads V4–V6 may indicate a culprit lesion located in the mid left anterior descending coronary artery, while changes more evident in leads V2–V3 may be more suggestive of a culprit lesion located in the left circumflex artery [29]. Diffuse ST depression including both precordial and extremity leads associated with ST-elevation ≥1 mm in lead aVR may indicate either left main coronary artery as the culprit lesion or proximal occlusion of the left anterior descending coronary artery in the presence of severe three-vessel CAD [30, 31].

3.3.2. Blood tests

- CBC: hemoglobin and hematocrit measurements may help to evaluate a secondary cause of NSTEMI (e.g., acute blood loss, anemia) and to evaluate thrombocytopenia to estimate risk of bleeding.
- BUN and serum creatinine: creatinine clearance should be estimated in NSTEMI patients and the doses of renally cleared drugs should be adjusted appropriately. In chronic kidney disease patients undergoing angiography, iso-osmolar contrast agents may be preferred [1, 15].
- Serum electrolytes: electrolyte derangements may predispose to cardiac arrhythmias.
- Liver function tests: useful if treatment with drugs that undergo hepatic metabolism is considered.

- Brain natriuretic peptide (BNP) and N-terminal pro-BNP (NT-pro-BNP): measurement of BNP or NT-pro-BNP may be considered to supplement assessment of global risk in patients with suspected ACS, particularly cardiogenic shock associated with MI type 1 [1].
- Lipid profile: this test is indicated in the first 24 h of admission to the hospital to assess for lipid abnormalities and therefore the need for any lipid-lowering therapy.

3.3.3. Biomarkers

Clinical assessment,12-lead ECG and biomarkers are crucial for the diagnosis, risk stratification and treatment of patients with suspected NSTEMI. Measurement, preferably, high-sensitivity cardiac troponin, is mandatory in all patients with suspected NSTEMI [7–9]. Cardiac troponins are more sensitive and specific markers of cardiomyocyte injury than creatine kinase (CK), its MB isoenzyme (CK-MB) and myoglobin. In patients with suspected myocardial ischemia, a dynamic elevation of cardiac troponin above the 99th percentile of healthy individuals indicates MI. Cardiac troponin levels rise rapidly (i.e. usually within 1 h if using high-sensitivity assays) after symptom onset and remain elevated for several days [8, 9].

The use of high-sensitivity assays, has shortened the time interval to the second cardiac troponin, reduced substantially the delay to diagnosis, translating into shorter stays in the emergency department and lower costs [6–9, 32–35]. In patients presenting very early, the second cardiac troponin level should be obtained at 3 h, due to the time dependency of troponin release; serial cardiac troponin testing should be pursued if the clinical suspicion remains high or whenever the patient develops recurrent chest pain [36, 37]. The negative predictive value for MI in patients assigned 'rule-out 'exceeded 98% [35–41] used in conjunction with clinical and ECG findings. The positive predictive value for MI in those patients meeting the 'rule-in' criteria was 75–80%.

3.3.4. Noninvasive imaging

Transthoracic echocardiography is useful to identify abnormalities suggestive of myocardial ischemia or necrosis (i.e. segmental hypokinesia or akinesia). Strain and strain rate imaging can detect subtle reduced regional function in the absence of overt wall motion abnormalities, which improve the diagnostic and prognostic value of conventional echocardiography [42, 43]. Evaluation of left ventricular systolic function by echocardiography, at the indexed hospital admission, is important to estimate prognosis. Echocardiography can help in discrimination of other pathologies including acute aortic dissection, pericardial effusion, aortic valve stenosis, hypertrophic cardiomyopathy or right ventricular dilatation associated with acute pulmonary embolism. Echocardiography is the diagnostic tool of choice for patients with hemodynamic instability of suspected cardiac origin [44].

3.3.5. Functional stress testing

In patients without ischemic changes on 12-lead ECGs and negative cardiac troponins (preferably high-sensitivity) who are free of chest pain for several hours, stress imaging can be performed during admission or shortly after discharge [1, 45, 46]. The sensitivity and specificity of these tests increase when combined with either nuclear imaging to look for myocardial

perfusion defects or echocardiography to assess wall motion abnormalities. Stress imaging is preferred over exercise ECG due to its greater diagnostic accuracy and superior prognostic value [47]. While studies have shown that normal exercise or pharmacological stress echocardiograms have high negative predictive value for ischemia and are associated with excellent patient outcomes ECG [48–50]. The addition of contrast to improve endocardial border detection and facilitate detection of ischemia [51].

To evaluate the extent of the CAD, a functional assessment using a submaximal exercise testing can be performed at 4 to 7 days after myocardial infarction, while symptom limited testing can be performed at 14 to 21 days post-myocardial infarction, when the patient has been free of active ischemic or heart failure symptoms [52].

3.3.6. Cardiac magnetic resonance

Cardiac magnetic resonance (CMR) can be used in the assessment of myocardial perfusion and wall motion abnormalities. Patients presenting with acute chest pain with a normal stress CMR have an excellent short and midterm prognosis [53]. CMR also permits detection of scar tissue (using late gadolinium enhancement) and can differentiate this from recent infarction (using T2-weighted imaging to delineate myocardial edema) [54, 55]. Moreover, CMR can facilitate the differential diagnosis between infarction and myocarditis or Takotsubo cardiomyopathy [56].

3.3.7. Nuclear myocardial perfusion imaging

Nuclear myocardial perfusion imaging has been shown to be useful for risk stratification in patients with acute chest pain suggestive for ACS. The presence of an area of myocardium that becomes deprived of perfusion during increased myocardial demand and reperfuses on stopping the activity on nuclear imaging stress tests is a reversible defect (**Figure 2**).

Resting myocardial scintigraphy, can be helpful for the diagnosis of patients presenting with chest pain without ECG changes or elevated cardiac troponins [57]. Combined stress–rest imaging may further enhance assessment of ischemia, while a normal study is associated with excellent outcome [58, 59].

4. Anatomical evaluation

Multidetector computed tomography (MDCT) provide noninvasive evaluation of coronary anatomy and atherosclerosis. Due to the high negative predictive value of coronary computed tomography angiography (CCTA), evidence suggests that CCTA is useful in patients with low to moderate risk of NSTEMI where a normal scan excludes CAD. When compared with the standard care (observation, serial enzymes followed by stress testing) for low-risk patients, CCTA reduced time to diagnosis, reduced length of emergency department stay, and had similar safety [60]. CCTA had high negative predictive values to exclude ACS and excellent outcome in patients presenting to the emergency department with low to intermediate pre-test probability for ACS and a normal coronary CT angiogram [61]. CCTA was proven

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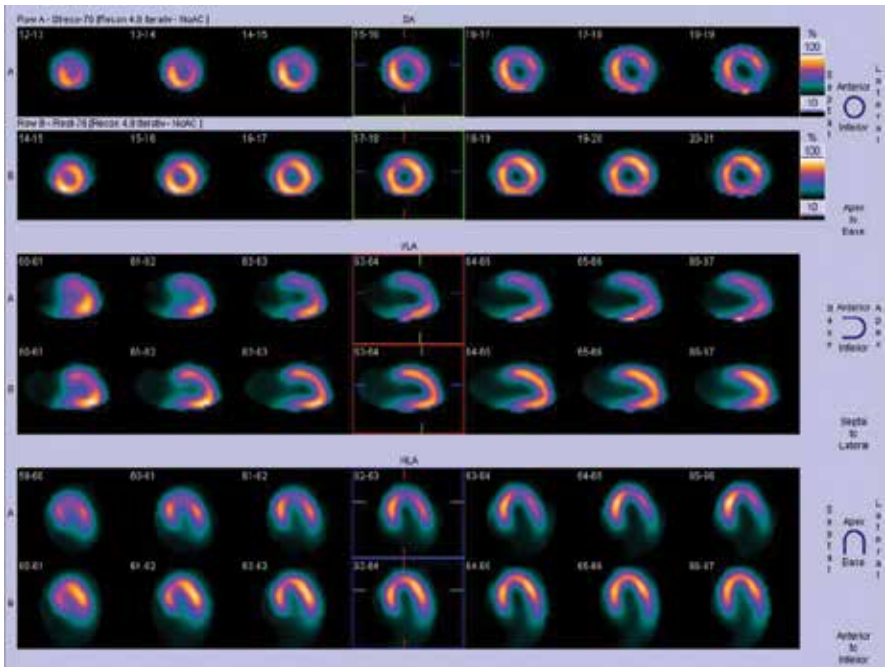

Figure 2. Myocardial nuclear perfusion scan showing anterior, lateral and inferior reversible scan. Coronary angiogram confirmed three vessel disease.

beneficial in the triage of low- to intermediate-risk patients presenting with acute chest pain to emergency departments without signs of ischemia on ECG and/or inconclusive cardiac troponins. At 6 months follow-up, there were no difference in the incidence of MI, post discharge emergency department visits or rehospitalizations, and no deaths in comparison to traditional management. Also, there were reduction in the cost and length of stay associated with MDCT [60, 62–65]. But there was an increase in the use of invasive angiography [65]. CCTA is not indicated for patients with high-risk features and it is not useful in patients with known CAD [66]. Other factors limiting CCTA include severe calcifications and tachycardia. CT imaging can effectively exclude other causes of acute chest pain that, if untreated, are associated with high mortality, namely pulmonary embolism, aortic dissection and tension pneumothorax [67].

5. Risk assessment and outcomes

ACS management requires continuous risk stratification for death or recurrent MI. Quantitative assessment of ischemic risk by means of scores is superior to the clinical assessment alone to further triage and assist in the selection of treatment options [1]. A number of risk scores exist which incorporate a number of variables, the GRACE risk score and the TIMI risk score are examples.

The GRACE risk score provides the most accurate stratification of risk both on admission and at discharge [68, 69]. The GRACE 2.0 risk calculator provides a direct estimation, of mortality

while in hospital, at 6 months, at 1 year and at 3 years. The combined risk of death or MI at 1 year is also provided [70]. Variables used in the GRACE 2.0 risk calculation include age, systolic blood pressure, pulse rate, serum creatinine, Killip class at presentation, cardiac arrest at admission, elevated cardiac biomarkers and ST deviation. The TIMI risk score uses seven variables in an additive scoring system: age ≥ 65 years, three or more CAD risk factors, known CAD, aspirin use in the past 7 days, severe angina (two or more episodes within 24 h), ST change ≥0.5 mm and positive cardiac marker [71]. Patients with a TIMI score of 0–2 are low risk, 3–4 are intermediate risk, and 5–7 are high risk. All-cause mortality, rate of MI, and rate of urgent revascularization at 14 days increase in proportion to the number of risk factors present on the TIMI score. It is simple to use, but its discriminative accuracy is inferior to that of the GRACE risk score [1, 71].

6. Hospital care and standard medical therapies

The aim of initial evaluation is to relieve pain and ischemia, prevent further thrombosis or embolism, and correct hemodynamic abnormalities and treat life-threatening complication.

All patients should undergo early risk estimation based on the medical history, physical exam, ECG findings, and cardiac markers.

7. Initial management

Initial medical therapy is indicated in all patients, with variation in some choices of agent according to risk stratification.

7.1. Cardiac rhythm monitoring

Early revascularization, effective antithrombotic therapy and administration of beta-blockers have reduced the incidence of life threatening arrhythmias in the acute phase of MI to <3%, with most of the arrhythmic events occurring within 12 h of symptom onset [72, 73]. Patients with life-threatening arrhythmias frequently had prior heart failure, low LV ejection fraction (EF < 30%) and triple vessel CAD.

NSTEMI patients at low risk for cardiac arrhythmias require rhythm monitoring for ≤24 h or until coronary revascularization (whichever comes first) in an intermediate or coronary care unit, while individuals at intermediate to high risk for cardiac arrhythmia may require rhythm monitoring for >24 h in an intensive or coronary care unit or in an intermediate care unit, depending on the clinical presentation, degree of revascularization and early post-revascularization course.

All patients require oxygen saturation measurement using pulse oximetry [1]. Although in the past oxygen was routinely given to all patients, there is no evidence to support this practice [74]. Moreover, results of the Air Versus Oxygen in ST-elevation MyocarDial Infarction (AVOID) trial have shown that routine supplemental oxygen may increase myocardial infarct size, and raise rates of recurrent MI and cardiac arrhythmia in patients with ST-elevation

MI but without hypoxia. Guidelines now recommend supplemental oxygen therapy only in patients who are hypoxemic (arterial oxygen saturation < 90%), or in those who have respiratory distress or other high-risk features for hypoxemia [1, 15, 75].

7.2. Pharmacological treatment of ischemia

The goal of pharmacological anti-ischemic therapy is to decrease myocardial oxygen demand (secondary to a decrease in heart rate, blood pressure, preload or myocardial contractility) or to increase myocardial oxygen supply (by administration of oxygen or through coronary vasodilation).

Pain relief is indicated in the initial management of all patients. Those with ongoing ischemic discomfort should receive a trial of sublingual nitroglycerin (0. 4 mg) every 5 min for a total of three doses. Sublingual nitroglycerin reduces myocardial oxygen demand and enhances myocardial oxygen delivery. Intravenous nitroglycerin is recommended in patients with no symptom relief after sublingual nitroglycerin. Under careful blood pressure monitoring, the dose should be titrated upwards until symptoms are relieved, and in hypertensive patients until blood pressure is normalized, unless side effects (notably headache or hypotension) occur. Beyond symptom control, there is no indication for nitrate treatment [76]. In patients with recent intake of a phosphodiesterase type 5 inhibitor (i.e. within 24 h for sildenafil or vardenafil and 48 h for tadalafil), nitrates should not be administered due to the risk of severe hypotension. Nitroglycerin should not be given if systolic BP is <90 mmHg or there is a concern about right ventricular infarction [77]. If the patient does not respond to nitroglycerin, intravenous morphine can be administered in the absence of any contraindications [1]. Morphine causes vasodilation and may produce reductions in heart rate (through increased vagal tone) and systolic BP to further reduce myocardial oxygen demand. It should be given instead of nitroglycerin when nitroglycerin is contraindicated. Morphine should be used with caution, one randomized, double-blind trial found that morphine delays and attenuates ticagrelor exposure and action in patients with myocardial infarction [78, 79].

7.2.1. Beta-blockers

Oral beta-blockers are recommended for routine use in all patients unless contraindicated. Beta-blockers competitively inhibit the myocardial effects of circulating catecholamines and reduce myocardial oxygen consumption by lowering heart rate, blood pressure and myocardial contractility. Randomized trials with threatened or evolving MI have shown lower rates of progression to MI with beta-blocker treatment [80].

The beneficial effects of beta-blockers derived from several meta-analyses were a significant 8 and 13% relative risk reduction for in-hospital and first week mortality following MI respectively with no increase in cardiogenic shock [81, 82].

A registry study of NSTEMI patients found that the use of B-Blocker blockers within 24 h of hospital admission in patients at risk of developing cardiogenic shock (i.e. age > 70 years, heart rate > 110 beats/min, systolic blood pressure < 120 mmHg), the observed shock or death rate was significantly increased [83]. Therefore, early administration of beta-blockers should be avoided in these patients if the ventricular function is unknown.

Contraindications include heart rate <60 bpm, systolic BP <100 mmHg, moderate or severe associated left ventricular failure, PR interval on the ECG >0.24 s, second- or third-degree heart block, active asthma/reactive airways disease, severe COPD, hypotension, right ventricular infarction, and cardiogenic shock. Beta-blockers should not be administered in patients with symptoms possibly related to coronary vasospasm or cocaine use, as they might favor spasm by leaving alpha-mediated vasoconstriction unopposed by beta-mediated vasodilation.

7.3. Initial antiplatelet/anticoagulant

7.3.1. Bleeding risk assessment

The CRUSADE bleeding risk score considered baseline patient characteristics (i.e. female gender, history of diabetes, history of peripheral vascular disease or stroke), admission clinical variables (i.e. heart rate, systolic blood pressure, signs of heart failure) and admission laboratory values (i.e. hematocrit, calculated creatinine clearance) to estimate the patient's likelihood of an in-hospital major bleeding event [84].

The Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) bleeding risk score was derived from a pooled cohort recruited in the ACUITY and HORIZONS-AMI trials [85]. Six independent baseline predictors were identified including: female gender, advanced age, elevated serum creatinine, white blood cell count, anemia and presentation as NSTEMI or STEMI and one treatment-related variable [use of unfractionated heparin and a glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitor rather than bivalirudin alone]. This risk score identified patients at increased risk for non-CABG-related major bleeds at 30 days and subsequent 1-year mortality. However, it has not been validated in an independent cohort.

Changes in interventional practice, such as increasing use of radial access, reduction in the dose of UFH, use of bivalirudin, diminished use of GPIIb/IIIa inhibitors and administration of more effective inhibitors of the platelet adenosine diphosphate (ADP) receptor P2Y12 (P2Y12 inhibitors), may all modify the predictive value of risk scores. Ischemic and bleeding risks need to be weighed in the individual patient, although many of the predictors of ischemic events are also associated with bleeding complications [84, 85]. Overall, CRUSADE and ACUITY scores have reasonable predictive value for major bleeding in ACS patients undergoing coronary angiography, with CRUSADE found to be the most discriminatory [86].

7.4. Platelet inhibition

7.4.1. *Aspirin*

Aspirin (chewed) is indicated immediately for all patients suspected of having an acute coronary syndrome unless contraindicated or already taken [1]. Aspirin should be continued at a daily maintenance dose thereafter [1]. Aspirin, an irreversible COX-1 inhibitor, suppresses thromboxane A2 production preventing platelet aggregation, and reduces the incidence of death and nonfatal MI in patients with unstable angina or acute MI [87, 88]. Aspirin has been shown to achieve a 30–51% reduction in future coronary events [89]. A meta-analysis

suggests that aspirin administration (up to 2 years) is associated with a highly significant 46% odds reduction in major vascular events [90]. There was no difference between higher-dose (300–325 mg/day) and lower dose (75–100 mg/day) aspirin [91].

7.4.2. P2Y12 inhibitors

7.4.2.1. Clopidogrel

Clopidogrel (300–600 mg loading and 75 mg/day maintenance dose) is an inactive prodrug that requires oxidation by the hepatic cytochrome P450 (CYP) system to generate an active metabolite. Clopidogrel is a selective and irreversible inhibitor of platelet P2Y12 receptors and thus inhibits ADP-induced platelet aggregation [92, 93]. Dual antiplatelet therapy (DAPT) comprising aspirin and clopidogrel has been shown to reduce recurrent ischemic events in the NSTE-ACS setting compared with aspirin alone [94, 95]. However, up to 10% of patients treated with the combination of aspirin and clopidogrel will have a recurrent ischemic event in the first year after an ACS, with a rate of stent thrombosis of up to 2% [96]. There is substantial inter individual variability in the antiplatelet response to this drug and an increased risk of ischemic and bleeding events in Clopidogrel hypo- and hyper-responders, respectively [97–100]. There is evidence that key gene polymorphisms are involved in both the variability of active metabolite generation and clinical efficacy of Clopidogrel [101–104].

7.4.2.2. Prasugrel

Prasugrel (60 mg loading and 10 mg/day maintenance dose) is a prodrug that irreversibly blocks platelet P2Y12 receptors with a faster onset and a more profound inhibitory effect than clopidogrel. In the TRITON-TIMI 38, Prasugrel reduced recurrent CV event in ACS patients scheduled for PCI in comparison to clopidogrel, significantly driven by reduction in MI [105]. There were more severe bleeding complications with prasugrel, due to an increase in spontaneous and fatal bleeds [106]. Based on the marked reduction in definite or probable stent thrombosis observed in the TRITON-TIMI 38 prasugrel should be considered in patients with stent thrombosis despite compliance with clopidogrel therapy [100, 107]. Prasugrel is contraindicated in patients with prior stroke/transient ischemic attack due to evidence of net harm in this group in TRITON-TIMI 38. In addition, the study showed no apparent benefit in patients >75 years of age or with low bodyweight (<60 kg) [105].

7.4.2.3. Ticagrelor

Ticagrelor is an oral, reversibly binding P2Y12 inhibitor with a plasma half-life of 6–12 h.

Like prasugrel, ticagrelor has a more rapid and consistent onset of action compared with Clopidogrel, as well as a faster offset of action with more rapid recovery of platelet function [108].

In the PLATO trial, the primary composite efficacy endpoint (death from CV causes, MI or stroke) was significantly reduced with ticagrelor compared with similar reductions for CV and all-cause mortality [109, 110]. There was increased risk of non-CABG-related major bleeds with ticagrelor compared with Clopidogrel but no difference in life-threatening or fatal bleeds [110].

There was a reduction in definite stent thrombosis with ticagrelor in the NSTE-ACS subgroup. In addition to increased rates of minor or non-CABG-related major bleeding events with ticagrelor, adverse effects included dyspnea (without bronchospasm), increased frequency of asymptomatic ventricular pauses and increases in uric acid [109, 111, 112].

All patients should be given dual antiplatelet therapy with a P2Y12 receptor inhibitor in addition to aspirin. If the patient is intolerant of aspirin or it is otherwise contraindicated, a P2Y12 receptor inhibitor can be given instead of aspirin, but two different P2Y12 receptor inhibitors should not be given together. P2Y12 receptor inhibitors can reduce mortality and morbidity, but they are associated with an increased risk of bleeding [113, 114]. Ticagrelor and prasugrel are newer P2Y12 agents, which trials have shown to have a faster onset of action and greater efficacy compared with Clopidogrel [1, 115]. However, the risk of bleeding is also greater with these two P2Y12 agents compared with Clopidogrel [116, 117].

Clinicians need to tailor therapy to strike a balance between a newer agent that may have a faster onset of action and greater antiplatelet effect, but could potentiate bleeding (especially in those with prior TIA or stroke). Regardless of which P2Y12 receptor inhibitor is chosen, a loading dose should be given as soon as possible in most patients and then a maintenance dose continued for a minimum of 12 months [118].

7.5. Anticoagulation

Anticoagulation therapy (subcutaneous low molecular weight heparin, intravenous unfractionated heparin, or the alternative agents fondaparinux or bivalirudin) should be started on earliest recognition of NSTEMI. The anticoagulant is used in conjunction with antiplatelet therapy already started (i.e., aspirin and a P2Y12 receptor inhibitor). If fondaparinux is used during angiography/PCI, guidelines recommend that UFH be used in addition [1].

Anticoagulation should not be given if there are contraindications like major bleeding, history of adverse drug reaction or heparin-induced thrombocytopenia.

The antiplatelet and anticoagulation regimens should be started before the diagnostic angiogram. Triple antiplatelet therapy, in which an intravenous GP IIb/IIIa inhibitor is added to a P2Y12 receptor inhibitor, aspirin, and anticoagulation, can be considered for high-risk patients; however, it should be avoided in patients at high risk of bleeding [1]. Although guidelines recommend the use of GP IIb/IIIa inhibitors in NSTEMI, the level of evidence for their routine use is weak at best, particularly as results from randomized trials are conflicting [119, 120].

8. Conservative approach

Anticoagulation treatment should be added to aspirin and a P2Y12 receptor inhibitor at the earliest recognition of NSTEMI and continued for at least 48 h to hospital discharge and/or until symptoms abide and objective markers demonstrate a trend toward normal [121]. Agents include subcutaneous LMWH, intravenous UFH, or fondaparinux, according to clinician choice.

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9. Ischemia-guided strategy versus early invasive strategies

9.1. Rationale and timing for early invasive strategy

Once initial management is instigated, the decision should be made as to whether the patient requires treatment using an invasive or noninvasive approach. The decision to pursue an invasive approach or medical management is made on an individual basis [122]. Invasive strategy carries risks but the benefit includes diagnostic accuracy, risk stratification and revascularization. The timing for coronary angiography and the selection of the revascularization modality depend on numerous factors, including clinical presentation, comorbidities, risk stratification, presence of high-risk features specific for a revascularization modality, frailty, cognitive status, estimated life expectancy and functional and anatomic severity as well as pattern of CAD. Guidelines recommend that high-risk patients routinely undergo early (12–24 h) coronary angiography and angiographically directed revascularization if possible unless patients have serious comorbidities, including cancer or end-stage liver disease, or clinically obvious contraindications, including acute or chronic (CKD 4 or higher) renal failure or multi-organ failure [1, 123, 124].

9.2. Routine invasive coronary angiography

Invasive coronary angiography allows to confirm the diagnosis of ACS related to obstructive epicardial CAD, to guide antithrombotic treatment, identify the culprit lesions and assess the suitability of coronary anatomy for PCI or CABG. Routine invasive strategy in NSTEMI has been shown to improve clinical outcomes and lower risk of death, reduce recurrent ischemic episodes, subsequent rehospitalization and revascularization [125–127].

Urgent and immediate angiography is indicated if patients do not stabilize with intensive medical treatment [1]. Guidelines recommend that an invasive approach is appropriate if any of the following high-risk features are present [1, 15]:

- Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy
- Rise and fall in cardiac biomarkers (troponin T or I) consistent with MI
- New or dynamic ST-T wave changes
- Signs or symptoms of heart failure, or new or worsening mitral regurgitation
- Hemodynamic instability
- Life-threatening arrhythmia
- PCI within 6 months
- Prior CABG
- High-risk score (i.e., TIMI, GRACE)
- Mild to moderate renal dysfunction

- Diabetes mellitus
- Reduced left ventricular function (ejection fraction <40%).

9.3. Pattern of coronary artery disease

Angiographic patterns of CAD in NSTEMI patients are diverse, ranging from normal epicardial coronary arteries to a severely and diffusely diseased coronary arteries. Up to 20% of patients with NSTE-ACS have no lesions or non-obstructive lesions of epicardial coronary arteries, while among patients with obstructive CAD, 40–80% have multivessel disease [128–130].

Culprit lesions in the infarct-related artery are more often located within the proximal and mid segments, the left anterior descending coronary artery is the most frequent culprit vessel in both STEMI and NSTEMI-ACS (in up to 40% of patients). Left main coronary artery disease may be the underlying condition in 10% and a failure of bypass graft in 5% [128–132].

9.4. Identification of the culprit lesion

Culprit lesion on coronary angiography usually have features suggestive of acute plaque rupture. Vulnerable plaques are usually consisted from thin-cap fibroatheroma, and when rupture of the plaque happens they are characterized morphologically by the presence of at least two of the following features: intraluminal filling defects consistent with thrombus, plaque ulceration (i.e. presence of contrast and hazy contour beyond the vessel lumen), plaque irregularity (i.e. irregular margins or overhanging edges), dissection or impaired flow [132–134]. Multiple complex plaques observed in up to 40% of NSTEMI patients with obstructive CAD [132, 134–138]. One-quarter of NSTEMI patients present with an acute occluded coronary artery and two-thirds of the occlusions are already collateralized at the time of angiographic examination [138, 139].

Identification of the culprit lesion or the differentiation between an acute/subacute and chronic occlusion may sometimes be challenging based solely on angiography data. The additive value of the information from the ECG using lead localization and the regional wall motion abnormalities by Echocardiography can help identify the culprit lesion. Intracoronary imaging like optical coherence tomography can help to identify non-obstructive thin-cap fibroatheroma while vasospasm can be provoked by test such as acetylcholine [140–142]. The value of Fractional flow reserve (FFR) guided PCI in NSTEMI patient has not been properly addressed. The achievement of maximal hyperemia may be unpredictable in NSTEMI because of the dynamic nature of coronary lesions and the associated acute microvascular dysfunction. As a result, FFR may be overestimated and the hemodynamic relevance of a coronary stenosis underestimated [142].

9.5. Timing of invasive strategy

Routine intervention has been associated with an improved outcome [143–146] however, the optimal timing of the intervention has not been well established. Early intervention might

prevent ischemic events that could occur while the patient is awaiting a delayed procedure [147]. Alternatively, by treating a patient with intensive antithrombotic therapy and delaying intervention for several days, procedure-related complications might be avoided with intervention on a more stable plaque [148]. Thus, the question of when to intervene in patients with acute coronary syndromes without ST-segment elevation has not been definitively answered.

Immediate invasive strategy (<2 h from hospital admission) is recommended in very-high-risk NSTE-ACS patients with intent to perform vascularization because of the poor short- and long-term prognosis if left untreated.

Early invasive strategy (<24 h): Early invasive strategy is defined as coronary angiography performed within 24 h of hospital admission. Multiple studies showed no significant difference between early or delayed intervention groups in the rate of death, MI, stroke or major bleeds [130, 149–151].

In the early versus delayed invasive intervention in acute coronary syndromes clinical trial, prespecified analyses showed that early intervention improved the primary outcome in the third of patients who were at highest risk (GRACE risk score > 140) but not in the two thirds at low-to-intermediate risk (GRACE risk score ≤ 140) [129]. Early invasive strategy is recommended in patients with at least one high-risk criterion.

Delayed invasive strategy (<72 h): This is the recommended maximal delay for angiography in patients with low to intermediate risk [127, 149].

9.6. Selective invasive strategy

Patients with no recurrence of symptoms and none of the risk criteria (low risk patient), a non-invasive stress test preferably with imaging for inducible ischemia is recommended before deciding on an invasive strategy [152].

9.7. Conservative treatment

A conservative, early medical management strategy may be appropriate in patients with a low risk score, such subpopulations may not benefit from early invasive management especially low-risk women with NSTEMI [123, 124, 126]. Older patients may be considered at high risk for invasive approach regarding complications, but the benefit may be satisfactory from such approach in this subgroup [153–155]. Patients in whom an invasive strategy may be withheld by the treating physicians may include very elderly or frail patients, patients with comorbidities such as dementia, severe chronic renal insufficiency, or cancer and patients at high risk of bleeding complication. Ultimately patients care should be individualized and left at the discretion of the treating physician.

In the medically managed NSTE-ACS patients, the CURE study demonstrated that treatment with clopidogrel in addition to aspirin for 3–12 months, significantly lower the primary outcome (a composite of death from CV causes, non-fatal MI or stroke at 1 year) but there were significantly more major bleeds [94].

The association between clopidogrel use and the composite of death or MI was significant among patients presenting with NSTEMI compared with those presenting with unstable angina [156].

In the TRILOGY ACS trial, prasugrel was not associated with a statistically significant reduction in the primary endpoint (death, MI or stroke) but there were more frequent TIMI major and minor bleeding [157]. In the PLATO study, the incidence of the primary endpoint was lower with ticagrelor than with clopidogrel, but at the expense of higher incidence of TIMI major bleeds in the ticagrelor-treated patients [158].

10. Percutaneous coronary intervention: technical aspects and challenges

Stent implantation in the setting of NSTE-ACS helps to reduce abrupt vessel closure and restenosis associated with balloon angioplasty and it should be considered the standard treatment strategy (**Figure 3** and movies online). New-generation drug eluting stents are recommended over bare metal stents in NSTE-ACS [159–161]. Dual antiplatelet therapy (DAPT) is recommended for 12 months irrespective of stent type, but DAPT may be extended depending on the number of stents and the total stents' length used, patients with high risk of ischemic events recurrence and if patient's bleeding risk is low. The benefit of thrombectomy has not been assessed prospectively in NSTE-ACS but cannot be recommended, considering the lack of benefit observed in STEMI [162].

Complications of PCI include PCI-induced MI; coronary perforation, dissection, or rupture; cardiac tamponade; malignant arrhythmias; cholesterol emboli; and bleeding from the access site. Contrast-induced nephropathy is a common and potentially serious complication, especially in patients with baseline impaired renal function [163]. Early and late stent thromboses are catastrophic complications. Radial access, performed by experienced operators, is associated with lower bleeding risk and recommended over the transfemoral access in ACS [164, 165].

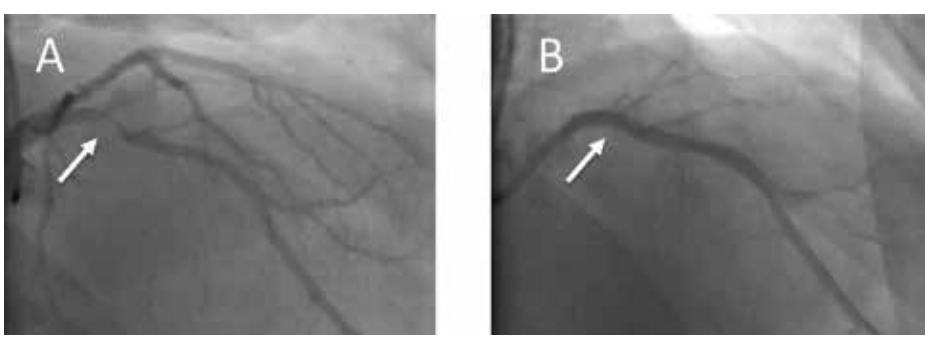

Figure 3. Angiogram of 54 years old gentleman presented with NSTEMI, ECG showed ST depression in the anterior leads. The angiogram confirmed a severe stenotic lesion in the proximal LAD (A) which stented successfully (B). Video clips of the angiogram available online.

11. Revascularization strategies and outcomes

In patients with complex, multivessel disease presenting with NSTEMI, the decision whether to do complete vs. incomplete revascularization and weather to do the complete revascularization at the index admission or to stage it is challenging and need to be tailored to age, general patient condition and comorbidities. A complete revascularization strategy of significant lesions should be pursued in multivessel disease patients with NSTE-ACS based on several studies showing the benefit of early intervention when compared with the conservative approach [143, 166, 167]. Also, recent trials have shown a detrimental prognostic effect of incomplete revascularization [168, 169].

Pursuing completeness of revascularization for some patients with complex coronary anatomy may mean increasing the risk of PCI especially in the presence of complex chronic total occlusions or referring to CABG.

The decision to treat all the significant lesions in the same setting or to stage the procedures should be based on clinical presentation, comorbidities, complexity of coronary anatomy, ventricular function, revascularization modality and patient preference.

With respect to outcomes, periprocedural complications of PCI as well as the long-term ischemic risk remain higher in NSTE-ACS than in stable patients, despite contemporary management. Accordingly, the risk of CV death, MI or stroke in NSTE-ACS patients in recent trials was approximately 10 and 15% at 1 and 2 years follow-up, respectively [110, 170]. For ACS patients who underwent PCI, revascularization procedures represent the most frequent, most costly and earliest cause for rehospitalization [171, 172].

12. Coronary artery bypass surgery

Approximately 10% of NSTEMI patients may require CABG during their index hospitalization [173]. The proportion of patient with NSTEMI undergoing CABG for NSTEMI decreased from 2001 to 2009, while the proportion of patients undergoing coronary angiography and PCI markedly increased [174]. CABG in the setting of NSTEMI is challenging mainly because of the difficulties in balancing ischemic and bleeding risks in relation to the timing of surgery and perioperative antithrombotic therapy. In addition, NSTEMI patients present with a higher proportion of surgical high-risk characteristics, including older age, female gender, left main coronary disease and LV dysfunction compared with patients undergoing elective CABG [175].

13. Percutaneous coronary intervention vs. coronary artery bypass surgery

The main advantages of PCI in the setting of NSTEMI are faster revascularization of the culprit lesion, a lower risk of stroke and the absence of deleterious effects of cardiopulmonary

bypass on the ischemic myocardium, on the other hand, CABG may more frequently offer complete revascularization in advanced multivessel CAD. The decision to perform PCI or CABG was left to the discretion of the investigator. A post hoc analysis of NSTE-ACS patients with multivessel CAD included in the ACUITY trial showed that 78% underwent PCI while the remaining patients were treated surgically [176]. There were no differences in mortality at 1 month and 1 year between the two modalities. PCI treated patients experienced lower rates of stroke, MI, major bleeds and renal injury, but had significantly higher rates of unplanned revascularization than CABG during the periprocedural period and at 1 year [177–179].

While the majority of patients with single-vessel CAD should undergo ad hoc PCI of the culprit lesion, the revascularization strategy in an individual NSTE-ACS patient with multivessel CAD should be discussed in the context of a Heart Team and be based on the clinical status as well as the severity and distribution of the CAD and the lesion characteristics. The SYNTAX score was found to be useful in the prediction of death, MI and revascularization among NSTE-ACS patients undergoing PCI and may help guide the choice between revascularization strategies [180].

14. Long-term management post-stabilization

Cardiac rehabilitation is a structured program that provides heart attack survivors with the tools, motivation, and support needed to change behavior and increase chance of survival. Typically, cardiac rehabilitation programs use group therapy to supervise and promote beneficial exercise, as well as to provide emotional support. The aims of cardiac rehabilitation are to:

- Increase functional capacity
- Stop cigarette smoking
- Modify lipids and lipoproteins
- Decrease body weight and fat stores
- Reduce BP
- Improve psychosocial well-being
- Prevent progression and promote plaque stability
- Restore and maintain optimal physical, psychological, emotional, social, and vocational functioning.

Cardiac rehabilitation should be started on discharge and after clearance by an outpatient physician. The basic prescription should include aerobic and weight-bearing exercise 4–5 times per week for >30 min.

15. Pharmacologic strategies include the following

- Aspirin should be continued indefinitely at a low dose if the patient is tolerant and not contraindicated.

- A P2Y12 receptor inhibitor should be continued for up to 12 months. For patients with aspirin allergy, long-term P2Y12 receptor inhibitor use is suggested [1, 181].
- Oral beta-blockers should be continued indefinitely, especially in patients with reduced left ventricular function.
- All patients with NSTEMI should start high-intensity statin therapy (moderate-intensity if not a candidate for high-intensity statin) in hospital regardless of cholesterol levels, and if there are no contraindications [182]. Two trials demonstrated superior outcomes in patients treated with atorvastatin within 12 h of receiving PCI, and it may provide benefit when given early in NSTEMI [183, 184]. A high-intensity statin is defined as a daily dose that lowers LDL-C by approximately >50%, while a moderate-intensity statin daily dose lowers LDL-C by approximately 30–50%. Statin therapy is particularly important in patients who have hyperlipidemia, diabetes, prior MI, or CAD. Statins inhibit the rate-limiting step in cholesterol synthesis. They may also reduce vascular inflammation, improve endothelial function, and decrease thrombus formation in addition to lowering LDL [185]. The addition of ezetimibe to the statin regimen may also be considered to achieve lower LDL targets [186].
- ACE inhibitors should be started in all patients with left ventricular systolic dysfunction (ejection fraction <40%), heart failure, HTN, diabetes, stable chronic kidney disease [1, 15]. They are started after 24 h. The goal BP is at least <140/90 mmHg (including patients with CKD or diabetes) [187].
- Aldosterone antagonists should be used in all patients with left ventricular dysfunction (ejection fraction ≤40%), a history of diabetes mellitus, or evidence of congestive heart failure. Aldosterone blockade should not be used in patients with serum creatinine >2.5 mg/dL in men or > 2.0 mg/dL in women, as well as in patients with hyperkalemia (potassium >5.0 mEq/L) [188].

16. Prognosis

Patients who have experienced NSTEMI have a high risk of morbidity and death from a future event. The rate of sudden death in patients who have had an MI is 4–6 times the rate in the general population [189]. Life-threatening ventricular arrhythmias (sustained VT or VF) occurring after 48 h from the index acute coronary syndrome portend a poor prognosis, and are most frequently associated with left ventricular dysfunction. The benefit of implantable cardioverter-defibrillators, for both primary and secondary prevention, in patients with significant left ventricular dysfunction has been well demonstrated [190, 191]. Implantation for primary prevention should be considered at a minimum of 40 days following hospital discharge based on current recommendations [192].

Data from the era prior to medical therapy and revascularization suggest that the risk of cardiovascular death following an MI in the absence of treatment is approximately 5% per year, with a death rate after hospital discharge in the first year of about 10%. Pharmacotherapy, lifestyle changes, and cardiac rehabilitation are well demonstrated to be beneficial and together are additive in reducing mortality [193].

17. Monitoring

Patient monitoring after discharge is essential part of patient care. A follow-up should be arranged within the first 1 to 2 weeks of discharge and monthly visits should be scheduled thereafter. Lipids should be monitored at least every 6 months until a target LDL <70 mg/dL is reached in patients who have had an MI or have CAD. The need for follow-up cardiac ultrasounds is at the discretion of the physician. However, cardiac ultrasounds are necessary to evaluate and monitor ventricular function [1].

Smoking cessation, promotion of physical activity and joining the cardiac rehabilitation is extremely helpful. Psychosocial risk factors such as anxiety and depression should be addressed. Depression in particular has been associated with a poor prognosis [194]. All medications should be reviewed at every follow-up visit to encourage patient compliance and optimal dosing [1].

In patients who have undergone direct reperfusion, further noninvasive stress testing or further imaging is indicated only if stenosis of intermediate severity (luminal narrowing of 50–70%) is present in a non-culprit artery. Patients with recurrent ischemic-type pain after reperfusion may need angiography after medical therapy to evaluate for further stenosis or occlusion [195].

All patients, regardless of whether a stent was placed, should be treated with a P2Y12 receptor inhibitor for up to 12 months and low-dose aspirin daily as long as tolerated. This should be given for 1 month after bare-metal stent implantation, 3 months after sirolimus drug-eluting stent implantation, 6 months after paclitaxel drug-eluting stent implantation, and ideally up to 12 months if they are not at high risk for bleeding [195]. A scientific advisory from several major health organizations describes the risks of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents [196].

18. Management of patients with cardiogenic shock

Cardiogenic shock may develop in up to 3% of NSTE-ACS patients during hospitalization and has become the most frequent cause of in-hospital mortality in this setting [197–199]. One or more partial or complete vessel occlusions may result in severe heart failure, especially in cases of pre-existing LV dysfunction, reduced cardiac output and ineffective peripheral organ perfusion. More than two-thirds of patients have three-vessel CAD. Cardiogenic shock may also be related to mechanical complications of NSTEMI, including mitral regurgitation related to papillary muscle dysfunction or rupture and ventricular septal or free wall rupture. In patients with cardiogenic shock, immediate coronary angiography is indicated and PCI is the most frequently used revascularization modality. If the coronary anatomy is not suitable for PCI, patients should undergo emergent CABG. The value of intra-aortic balloon counter pulsation in MI complicated by cardiogenic shock has been challenged [200]. Extracorporeal membrane oxygenation and/or implantable LV assist devices may be considered in selected patients.

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Section 5

Myocardial Infarction in Specific Patient Groups

Chapter 6

Myocardial Infarction in Children

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Additional information is available at the end of the chapter

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Abstract

Myocardial infarction (MI) is a clinical condition that develops associated with a sudden reduction or interruption of the blood flow of the vessels supplying the heart for various reasons. The electrocardiographic, echocardiographic and enzymatic diagnostic criteria of MI have been well defined in adults, in children there are some difficulties. Although seen more often in the presence of congenital heart disease (CHD), MI may also be seen in patients without CHD. Unlike atherosclerotic coronary artery disease in adult patients, ischaemia and infarct in children are often associated with coronary artery anomalies and CHD. In addition, congenital prothrombotic diseases, vasculitis, surgical or interventional procedures may also cause ischaemia and infarct. Subendocardial ischaemia, especially aortic stenosis characterised by hypertrophy in the left ventricle is often seen in hypertrophic cardiomyopathy or hypertensive patients. The most important risk factors in neonates and infants are the presence of CHD, coronary artery anomalies and perinatal asfixia. The most frequently seen causes of pediatric myocardial infarction (PMI) are abnormal left coronary artery originating from the pulmonary artery (ALCAPA) and Kawasaki disease. Another often seen cause of PMI is patients who underwent arterial switch operations.

Keywords: children, myocardial infarction, coronary artery anomalies

1. Myocardial infarction in children

Myocardial infarction (MI) is a clinical condition that develops in association with a sudden reduction or interruption of the blood flow in coronary vessels supplying the heart for various reasons. Coronary artery spasm and myocardial ischaemia are seen in the early stage of occlusion. If the relevant coronary artery is not rapidly re-channelled or cannot be re-vascularised, then MI develops [1]. Myocardial infarction is a common event in adults, but is not common among children. Furthermore, although the electrocardiographic, echocardiographic and

enzymatic diagnostic criteria of MI have been well defined in adults, in children there are some difficulties [2, 3]. As the cardiac structure changes with age, there are sometimes difficulties in the electrocardiographic diagnostic criteria of ischaemia.

Although MI is seen more often in the presence of congenital heart disease (CHD), it may also be seen in patients without CHD. Unlike atherosclerotic coronary artery disease in adult patients, ischaemia and infarct in children are often associated with coronary artery abnormalities and CHD [4]. In addition, congenital prothrombotic diseases, vasculitis, surgical or interventional procedures may also cause ischaemia and infarction [5]. Subendocardial ischaemia, especially aortic stenosis characterised by hypertrophy in the left ventricle is often seen in hypertrophic cardiomyopathy or hypertensive patients [2].

The most important risk factors in neonates and infants are the presence of CHD, coronary artery abnormalities and perinatal asfixia [5, 6]. The most frequently seen causes of Paediatric myocardial infarction (PMI) are abnormal left coronary artery originating from the pulmonary artery (ALCAPA) and Kawasaki disease [7, 8]. Patients undergoing arterial switch operations are also at increased risk for PMI [9].

2. Anamnesis

The anamnesis in Paediatric myocardial infarction (PMI) and Paediatric myocardial ischaemia and physical examination findings show differences from adult cases. The anamnesis of infants and young children is taken from the family and carers [2]. The complaints usually reported in this period are generalised findings such as feeding problems, lack of appetite, irritability, diarrhoea, vomiting, cold extremities, pallor and tachypnea. Older children may be able to describe chest pain well and can explain the spread of pain. A compressive of chest pain spreading to the left arm and shoulder should suggest chest pain with cardiac origin [10, 11]. However, some children may not be able to describe the character of the chest pain.

In the physical examination, patients are generally anxious, pale and interactive. They may have dyspnea or tachypnea. If tachycardia, hypotension or cardiogenic shock develop, these can be determined [2]. In the cardiac examination, rhythm irregularity and gallop rhythm can be determined. Extremities may be cold and the pulse may be weak on the electrocardiography (ECG), ventricular arrhythmia or cardiac block may be determined [2, 12–14]. Patients with ventricular arrhythmias may have symptoms of palpitations, syncope and loss of conscious [12].

3. Cardiac chest pain

The anamnesis has great value in the determination of whether or not the chest pain is from cardiac origin. In the case of a child presenting with chest pain, it must be determined from the family when the pain started, how often the child has experienced chest pain, how long the pain lasts, where the pain radiates to, the relationship with exercise, factors that increase or decrease the pain, whether or not there is any relationship with feeding or respiration, whether there is any trauma anamnesis, whether or not there is any fever, or accompanying

complaints such as shortness of breath, sweating, palpitations or nausea [10, 11]. It must also be determined whether the child or any family member has any CHD and whether or not any family member has recently experienced any chest pain, or MI.

Chest pain, which is one of the most significant symptoms for adults presenting to the Emergency Dept, is generally has a benign character in children. However, it is extremely important to decide whether or not the pain frequently seen in children is of cardiac origin [15]. Chest pain with cardiac origin in childhood can be classified in 3 groups; as structural heart diseases, inflammatory causes and dysrhythmias [10]. Structural heart diseases can lead complaints associated with an increased need for oxygen or a reduction in coronary blood circulation. These include events such as hypertrophic obstructive cardiomyopathy or aortic stenosis because of an obstruction in the left ventricle outlet tractus. Coronary artery abnormalities may also cause coronary ischaemia.

Chest pain with cardiac origin generally presents in situations where an increase in cardiac output is required. It is typically in the precordial or substernal region, in a constricting form and radiates to the left arm, neck and jaw. In some cases, there may also be shortness of breath, sweating, nausea, vomiting or syncope. In infants, the findings may be seen as feeding difficulties, crying and screaming (**Table 1**), [2, 6, 15, 16].

After the anamnesis and physical examination, ECG examination must be made in all patients and X-ray imaging should be applied in order to exclude any respiratory causes [15]. In cases where the pain is thought to be of cardiac origin, troponin and creatine kinase myocardial band (CK-MB) levels must be examined and if necessary echocardiographic evaluation should be made [15, 17, 18].

Neonates	**Older children**
Feeding problems	Fatigue
Lack of interest in surroundings	Lack of appetite
Irritability	Paleness
Diarrhoea	Dyspnoea
Sweating	Tachypnea
Vomiting	Tachycardia
Pallor	Hypotension
Tachypnea	Weak pulse
Dyspnea	Rhythm irregularity
Sudden paroxysmal abdominal pain	Gallop rhythm
	Cold extremities
	Shock
	Ventricular arrhythmia
	Heart block

Table 1. Symptoms and physical examination findings in Paediatric myocardial infarction.

4. Electrocardiography in Paediatric myocardial infarction

The 12-lead ECG is an integral part of the evaluation of coronary artery disease [16]. Elevation of the J point which joins the QRS and the ST segment is the first finding of myocardial ischaemia [7]. Compared to baseline, an elevation of 1–2 mm is seen in the J point and the ST segment in myocardial ischaemia. An elevation of >2 mm should rouse suspicion of MI (**Figures 1** and **2**). When ST elevation is determined, there should be a progression through differential diagnosis of benign early repolarisation, pericarditis, MI, bundle branch block and left ventricle aneurism [18]. While pathological ST elevation does not show variability, J point and ST elevation seen in early repolarisation in healthy adults is generally corrected with isoproteronol infusion or exercise [19].

The presence of PR segment depression is an ECG finding which is valuable in the differentiation of myopericarditis from MI in favour of myopericarditis [18]. The positive predictive value of PR depression seen in chest and extremity derivations has been determined to be 96.7% [19].

T-wave alterations generally accompany ST segment alterations in AMI. Initially, T-waves may be long and sharp (hyperacute T-wave). These changes determined on ECG show myocardial injury (**Figure 3**). ST depression may reflect the reciprocal effect of the region in the derivation corresponding to approximately 180° [7]. The standard leads does not show ST segment elevation in patients with true posterior wall MI. Instead ST elevation, ST segment depression may be seen as a reciprocal change in V4R-V2 on the ECG [20, 21].

Electrocardiographic findings that show recent MI are pathological Q-waves. A long Q-wave from 3 small squares (0.12 secs) in whichever derivation should be evaluated as pathological Q. In addition, broad Q-wave in V1 and V2 may be seen in patients with left ventricle hypertrophy. In short, the evaluation of anamnesis, physical examination and laboratory findings together with the ECG findings is important for every patient.

Generally pathological Q-waves are seen to emerge within the first 12–48 hours on at least 2 adjacent leads, and when they are present at inferior, lateral or anterior derivations, they have

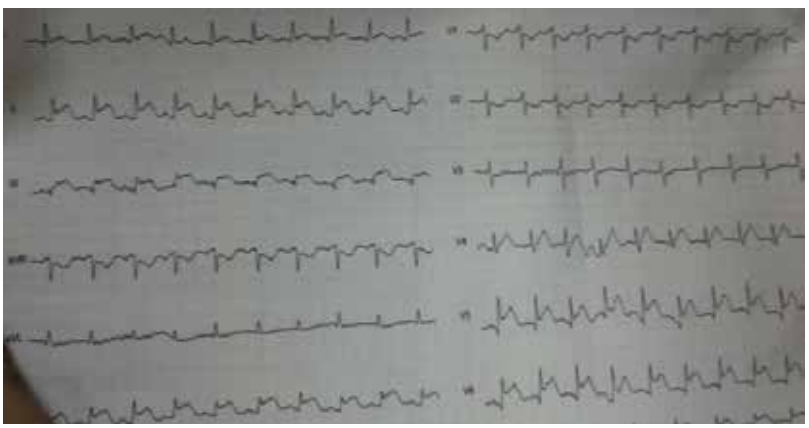

Figure 1. 2–3 mm ST elevations in DII, DIII, aVF, V5, and V6 leads of electrocardiography show that myocardial infarction.

http://dx.doi.org/10.5772/intechopen.74793

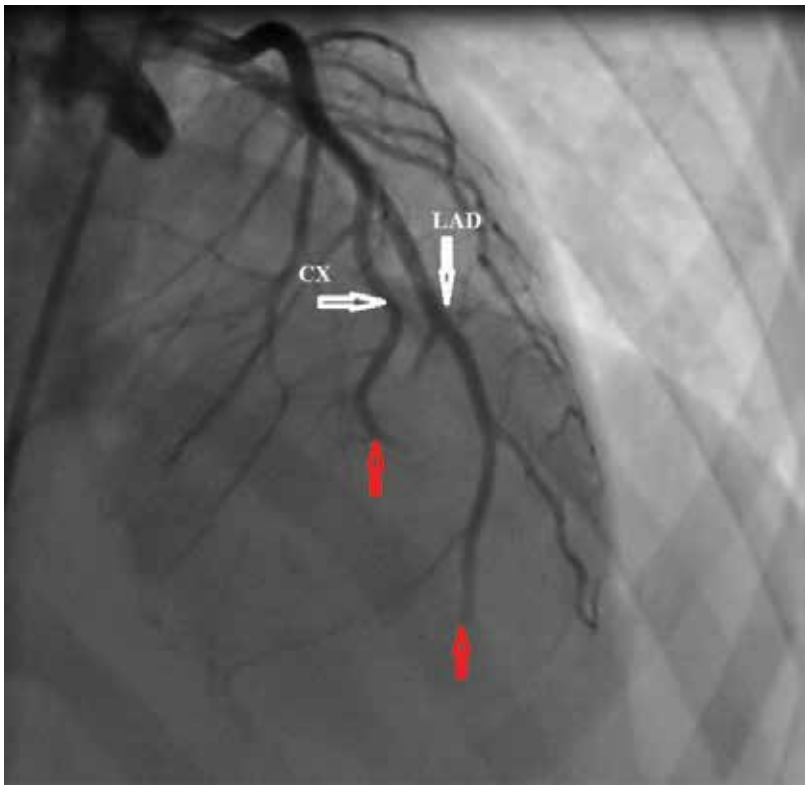

Figure 2. Coronary angiography revealed total occlusion of the left anterior descending [LAD] and distal circumflex (CX) coronary arteries (red arrows).

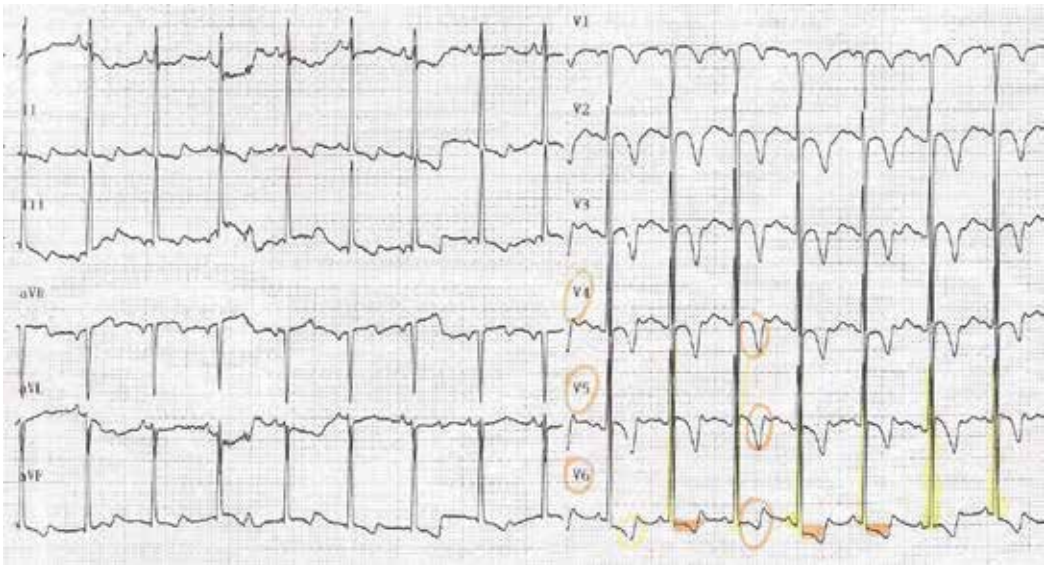

Figure 3. In this patient with aortic stenosis, ST depression on V4–6 and negative T wave show that coronary ischemia.

got extremely high value for the diagnosis of MI [1, 21]. However, in Paediatric patients, the determination of Q-wave in just one derivation could even be sufficient to determine MI [21]. While these Q-waves show infarct of the myocardial wall, high R waves in V1 and/or V2 (negative Q-waves) may represent true posterior wall MI. On the ECG of approximately half of cases, pathological Q-waves have a tendency to regress with time. In newborn infants, the presence of Q-waves in derivations DII, DIII and AVF may be normal. Furthermore, if ECG leads are placed on the upper part of the chest, Q-waves can be incorrectly shown in V5–6 that can cause misinterpretation of an integral part of the evaluation of coronary artery disease [16]. Elevation of the J point that joins the QRS and the ST segment is the first finding of myocardial ischaemia [7]. Compared to baseline, an elevation of 1–2 mm of the J point and the ST segment can be determined in myocardial ischaemia. An elevation of >2 mm should rouse suspicion of MI [7].

When the clinician has suspicions on the resence of pathological Q-wave, ECG in deep inspirium can be helpful. There is a change in the voltage of the Q-waves in physiological cases while there is no change of voltage at deep inspirium in pathological Q waves [7]. Towbin et al. reported that the presence of Q-waves wider than 35 msn on ECG was the most valuable finding for MI and a diagnosis of transmural MI diagnosis should not be made in patients with no Q-wave abnormalities [2].

Towbin et al. evaluated the ECG and clinical findings in the pre-MI records of 37 patients who died because of MI. In this retrospective study, it was reported that findings of MI were determined on the pre-mortem ECG records of 28 children who suffered fatal acute MI, while it was reported in 9 cases who died because of chronic MI [3]. It was also reported by the same authors that when MI was determined in a hypertrophic heart, the infarction was determined at the hypertrophic ventricle. This showed that in PMI, the presence of hypertrophy was a risk factor for MI. At least one of the criteria shown in the **Table 2** was determined to be present in 30 patients included into the study by Towbin et al [2]. Furthermore, no finding was determined on ECG in approximately 19% of the cases in that study, ECG was not sufficient to make a diagnosis of PMI alone. The evaluation of the patient should be made together with the anamnesis, physical examination, ECG and laboratory data.

Furthermore, Nakanishi et al. showed that deep Q-waves were a good marker for MI in Kawasaki patients. It was also determined in the same study that T-wave inversion in derivations II, III and AVF showed MI in the inferior wall [22].

1. New appearance of wide Q waves >35 ms in duration

2. Increased amplitude or duration [>35 ms] of pre-existing Q waves

3. New onset Q waves in serial tracings

4. Q waves notching

5. ST segment elevation [≥2 mm] and prolonged QT interval corrected for heart rate [>440 ms] with any other criteria.

Table 2. Electrocardiographic findings significant for MI in children, as reported by Towbin et al.

In the adult guidelines of MI criteria, it is stated that there should be ECG changes in more than one lead [23]. However, in Paediatric cases, when there are ECG changes in one derivation, there should be suspicion of MI [3]. Moreover, the observation on ECG of more than one of these changes, such as ST elevation, Q-wave changes, ST depression or T-wave inversion should more strongly suggest MI diagnosis.

5. Cardiac enzymes

An increase in the level of enzymes released into circulation from cells exposed to injury is important in the diagnosis of MI. These enzymes are creatine kinase myocardial band (CK-MB) and troponin [7, 10]. In all Paediatric cases thought to have myocardial damage, the troponin level should be examined. Values more than 2 ng/ml value are especially more valuable for cardiac origin [17]. Even in cases of mild damage in myocardial cells, an increase in enzyme levels may be seen [19]. In addition, the events causing an increase in troponin levels must be known (**Table 3**) [6].

6. Echocardiographic evaluation of Paediatric acute myocardial infarction

Acute heart failure
Cardiac contusion
Myopericarditis
Pulmonary embolism
Sepsis
Strenuous exercise
Sympatomimetic drugs
Tachyarrhythmia

Table 3. Non-coronary events which increase troponin.

The increasing experience with echocardiography [echo] in recent decades has greatly facilitated the diagnosis of acute myocardial infarction [AMI], as echo is an inexpensive, readily available, ambulatory, non-invasive method [24]. **Echo is useful, not only in the diagnosis of AMI but also in prognosis, the monitoring of complications and in follow-up.** In Paediatric AMI patients, echo provides very valuable information in the determination of segmentary wall movement abnormalities and in the diagnosis of CHD, pericarditis, myocarditis, Kawasaki disease, cardiomyopathy, aortic stenosis and ALCAPA which often accompanies chest pain. In adult studies, abnormal wall movement findings have been determined in 91% of patients applied with echo in the early stage in

the emergency departments [25]. It has also been shown in studies of adults that a decrease in left ventricular ejection fraction [LVEF] and left ventricle volume loading are significant risk factors for morbidity and mortality [24].

Segmentary wall movement abnormalities are seen in the necrotic region in AMI. If left ventricle function is looked at globally, this finding can be overlooked [24]. The American Society of Cardiology recommends examination of the heart in 16 segments and scoring from 1 to 5 as follows:

1. Normal.
2. Hypokinesis.
3. Akinesis.
4. Dyskinesis.
5. Aneurismal.

A higher score indicates a greater wall abnormality [26]. The score increases in cases with more widespread MI. It has been shown in studies of adults that in addition to segmentary wall movement abnormalities, complications which are rarely seen in children including post-infarct ventricular septal defect, left ventricle free wall rupture, right ventricle failure, and papillary muscle rupture have both value in diagnosis and follow-up of MI [24].

6.1. Aetiology

Paediatric myocardial infarction may be associated with many different diseases (**Table 4**) [2, 3, 5–9, 15]. It has been proposed that the reasons that coronary ischaemia and MI are frequently seen in CHD are multifactorial [27]. Abnormalities in the coronary artery anatomy have been reported to increase the risk of MI. It has been suggested that the stenosis risk after cutting and transfer of coronary arteries could have a potential role in early atherosclerosis and premature coronary artery disease [9]. In addition, congenital heart diseases with right to left shunts may cause paradoxal embolism. A sedentary lifestyle, diabetes mellitus and hypertension are other risk factors for ischaemic heart disease.

In autopsies performed between 1996 and 2010, Bamber et al. determined myocardial necrosis in 1637 patients, and in a group of 187 infant patients with perinatal asphyxia, sepsis, pulmonary disease, cardiomyopathy, tumour, coagulopathy and left ventricle aneurism. The myocardial necrosis was reported to be focal in patients with coronary artery abnormality, while it was diffuse among patients; who died in intensive care unit, with metabolic disease, or myocarditis, the idiopathic group, with mechanical asphyxia and who died during a surgical intervention [6]. In that study, the necrosis in 50% of the cases was determined at the subendocardial region, the papillary muscle and trabeculae. In the same study, CHD, asphyxia and coronary artery abnormalities were reported to be the most common causes of MI seen in this period. It was also strange that there was most frequently ASD, VSD and

- Neonatal Causes
  - Coronary artery abnormalities
  - Congenital heart disease
  - Severe neonatal asphyxia
  - Sepsis
  - Admission to Intensive Care Unit
  - Lung pathologies
  - Pulmonary atresia with intact ventricular septum
  - Metabolic causes
  - Myocarditis
  - Cardiomyopathy
  - Tumours
  - Endocardial fibroelastosis
  - Mediocalsinosis of the coronary arteries
  - Disseminated intravascular coagulation
  - Renal artery thrombosis
  - Idiopathic
  - Coagulopathies
  - Left ventricular aneurisms
- Causes of MI in childhood and adolescence
  - Kawasaki disease
  - Congenital heart disease
  - Coronary artery abnormalities
  - Hypertrophic cardiomyopathy
  - Dilated cardiomyopathy
  - Myocarditis
    - Viral
    - Idiopathic
    - Rheumatic
    - Collagen vascular diseases' induced
  - Substance Use
    - Cocaine
    - Marijuana
    - Bonzai (synthetic cannabis)
  - Previous surgery to the Truncus Arteriosus

Arterial switch operation
Post-transplantation
Post-coronary surgery
Drugs
Epinephrine
Amphetamine
Benzodiazepines
Hyperlipidemia
Blunt Chest trauma
Nephrotic syndrome
Vasculitis
Polyarteritis nodosa
Systemic lupus erythematosus
Behcet's disease
Takayasu arteritis
Atherosclerotic coronary artery disease
Disseminated intravascular coagulation
Genetic diseases
ALKaptonuria
Fabry's disease
Familial hypercholesterolemia (homozygotes or heterozygotes)]
Homocysteinuria
Hurler's syndrome
Hyperbetalipoproteinemia, familial combined hyperlipidaemia, and hypoalphalipoproteinemia
Mucopolysaccharidoses
Pompe's Disease
Progeria
Pseudoxanthoma elasticum
Sepsis
Occult Malignancy
Myocardial bridging
Pulmonary atresia with intact ventricular septum

Table 4. Causes of Paediatric myocardial infarction.

PDA accompanying the CHD. Of 105 cases with acquired or inherited CHD, 63 [60%] were determined to be severe, multiple and complex [6].

In another study conducted in Sweden between 1970 and 1993, the presence of CHD was seen to be a reason for hospitalisation because of ischaemic heart disease (IHD). The risk was reported 16.5 fold increased compared to the control group [27]. These data support that the presence of CHD as an additional risk factor for MI in children. Fedchenko et al. reported the possible mechanisms as; a] a physiological response to a previous surgical procedure could contribute to the development of IHD, b] a predisposition to IHD because of an increased need for oxygen with reduced maximal oxygen re-uptake due to volume and pressure loading in CHD patients, and c] exposure of CHD patients at an early age to radiological procedures and radiation could accelerate atherosclerosis [27].

7. Congenital coronary artery abnormalities

Coronary artery abnormalities generally do not cause clinical findings or the findings are subclinical. However, some coronary artery abnormalities cause serious haemodynamic outcomes [16]. The left coronary artery emerging from the right coronary sinus and the right coronary artery emerging from the left coronary sinus can cause coronary artery circulation problems. The section of the coronary artery that passes between the aorta and the pulmonary artery exposed to pressure at a critical level causes clinical findings [28].

Congenital cardiac abnormalities are a significant cause of MI-related sudden death, most often in the neonatal period (**Table 5**) [28]. Sudden death is often related to exercise especially in patients where the coronary arteries originate from the pulmonary artery and pass between the aorta and the pulmonary artery [28]. Although some cases may show clinical findings with MI in the neonatal period, some cases can remain asymptomatic [29]. In infancy, there may be noticeable findings of heart failure, such as rapid fatigue, sweating, tachypnea and retarded growth and development [2].

Exercise-related death is most often encountered when the left coronary artery emerges from the right coronary sinus, in ALCAPA, and when the right coronary artery emerges from the left coronary sinus [28]. In patients with coronary artery abnormality, the symptoms include chest pain, syncope and findings of heart failure. In infants with ALCAPA, Q-wave seen at DI, AVL or V5–6 on ECG is a good marker for diagnosis [7].

In a Paediatric autopsy study, cardiomegaly was seen in all the cases of children with coronary artery abnormality [30]. The cause of MI seen during exercise in children with coronary artery abnormality has been suggested to originate from an increase in acute angulation of the coronary artery during exercise [29].

Sudden death in the asymptomatic period is a frightening complication of the disease in a significant proportion of cases with coronary artery abnormality [28].

I.	Anomalous origin of ≥1 CA from pulmonary trunk
a.	LMCA or LAD from pulmonary trunk
b.	Both CAS from pulmonary trunk
c.	RCA from pulmonary trunk
II.	Anomalous origin of ≥1 CA from Aortic Sinus
a.	LMCA and RCA from right Aortic Sinus
b.	RCA and LMCA from left Aortic Sinus
c.	LCx and RCA from right Aortic Sinus
d.	RCA and/or LMCA from posterior Aortic Sinus
e.	RCA and LAD from right Aortic Sinus
III.	Single CA ostium from Aorta
IV.	Congenital hypoplastic CAs
V.	CA fistula

LCx: left circumflex, CA: Coronary artery, CAs: Coronary arteryies, LMCA: left main coronary artery, left anterior descending, RCA: right coronary artery.

Table 5. Taylor classification of congenital coronary artery abnormalities.

8. Kawasaki disease

Kawasaki disease is a self-limiting acute vasculitis. Children aged between 5 months and 5 years are especially sensitive to Kawasaki disease. It is one of the most common causes of vasculitis and MI in children [41, 42]. Destruction in the coronary arteries, ectasia and coronary artery aneurisms are frightening complications of the disease [43]. Diagnosis is made from the presence of four of the five diagnostic criteria together with unexplained fever ongoing for at least 5 days. The diagnostic criteria are bilateral non-purulent conjunctivitis, oropharynx changes, cervical lymphadenopathy, persistent oedema in the hands and feet and erythematous rash.

9. Takotsuba cardiomyopathy

Takotsuba cardiomyopathy is a benign clinical condition characterised by chest pain, elevated ST segment on ECG and elevated cardiac enzymes [31]. It is thought to be stress-related. It develops more often with emotional stress and sometimes related to physical stress. Due to chest pain and shortness of breath, it mimics acute myocardial infarction. There is ballooning and/or systolic dysfunction on echo or left ventriculography [32]. Coronary angiography is normal and there is no coronary artery disease. Cardiac enzymes are normal or may be slightly elevated.

10. Myocarditis

As myocarditis is generally seen together with pericarditis, it is known as myopericarditis. Myopericarditis may show differences according to whether the effects of the clinical findings are focal or generalised [19]. Typically, diagnosis is made from the determination of chest pain, the sound of pericardial friction, ST elevation on ECG, high levels of troponin I, cardiomegaly on telecardiography and pericardial effusion on echo (**Table 6**).

Pericardial effusion is observed in 60% of pericarditis patients. Wall movement abnormalities on echo or systolic dysfunction are a warning sign of myocarditis and/or MI. As the ECG findings in myopericarditis are focal in 50% of cases, differential diagnosis from AMI can be difficult. The presence of PR segment depression on II is a valuable finding of myopericarditis [19]. It has been suggested that coronary thrombus, coronary spasm, coronary artery embolism, large vessel and microvascular vasculitis could be reasons for MI seen in myopericarditis [33, 34]. In follow-up,

	Anamnesis	**Physical examination**	**ECG**	**Echocardiography**	**Cardiac angiography**	**Magnetic resonance**	**Telecardiography**	**Biopsy**	**Laboratory**
Myocardial infarction	Sudden onset	Gallop rhythm, ventricular arrhythmia may be seen	ST elevation T-wave changes, pathological Q wave, Ventricular arrhythmia, extended QT distance	Segmentary wall movement abnormalities, reduction in EF, papillary muscle rupture, left ventricle free wall rupture	Coronary artery thrombosis	Increased focal involvement	Normal	Necrosis in the involved area	Elevated levels of Troponin, CKMB
Myocarditis	First there may be findings of viral infection	The sound of pericardial friction, Gallop rhythm, and arrhythmias may be seen	Sinus tachycardia, low voltage, PR segment depression, ST elevation, T-wave changes	Pericardial effusion, reduction in EF, segmentary wall movement abnormalities	Normal	Increased signal in the myocardium and increased contrast involvement in the myocardium and myocardial thickening	Cardiomegaly	Necrosis and inflammatory cells in the involved area	Elevation of troponin, and CKMB levels

Table 6. Differential diagnosis of myocardial infarction and myocarditis.

thinning and fibrosis in the MI area may be seen in echocardiographic examination and in unaffected parts, compensatory hypertrophy may be present. Although it is difficult to apply in infants, endomyocardial biopsy is the gold standard in myocarditis. The death of myocites and inflammatory cells may be seen in biopsy material [36]. Another diagnostic method is cardiac MRI, which requires general anaesthesia. An increase in cardiac signal and increased myocardial contrast involvement is seen on cardiac magnetic resonance imaging [37].

11. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is characterised by a global thickening of the heart muscle. It should be kept in mind especially in children with exercise-related chest pain [36]. The incidence in the general population is 1 per 500 births and genetic transfer is autosomal dominant. Hypertrophy seen in the ventricular septum together with movement of the mitral valve anteriorally causes a narrowing of the left ventricle outlet [36]. Especially during exercise, this narrowness may cause a decrease in cardiac output and sudden death [38]. Shortness of breath and chest pain are frequent complaints. Situations such as exercise which reduces the pre-load and increases the after-load, tachycardia or dehydration, exacerbate the narrowing of the left ventricle outlet [38].

12. Sudden cardiac death

Sudden cardiac death is defined as death occurring within 1 hour without the emergence of any prodromal finding [39]. A significant cause of sudden cardiac death in children is MI. Previous studies have reported that chest pain is seen in few cases of MI-related sudden cardiac death. More frightening is that a large proportion of these cases suffer sudden cardiac death at rest [40]. Cigarette smoking and dyslipidaemia have been determined as significant risk factors for sudden cardiac death related to coronary artery disease in children and young adults [40].

13. Vasculitis

In patients with vasculitis, especially those with coronary artery involvement, anginal complaints may be seen at an early age. Myocardial infarction and unexpected sudden cardiac death can be determined [44–47]. In some cases the clinical findings are non-specific such as abdominal pain, myalgia and muscle pain, and the diagnosis can only be made by postmortem study [46].

Polyarteritis Nodosa (PAN) is a rarely seen severe vasculitis that affects small and medium diameter arteries in particular. Diagnosis of the disease is made according to the criteria defined in 1990 by the American College of Rheumatology (**Table 7**). The disease can cause infarction in the organs by creating transmural necrotising vasculitis mostly in medium diameter arteries [46]. In addition to the heart, the kidneys, the gastrointestinal system, the skin, the nervous system, the joints and the muscles may be affected. The cardiac effect is less compared to the other systems. A coronary involvement alone has been reported in few cases [41].

1.	Arteriographic abnormality
2.	Diastolic blood pressure > 90 mmHg
3.	Elevated blood nitrogen or serum creatinine
4.	Livedo reticularis
5.	Mononeuropathy or polyneuropathy
6.	Myalgias
7.	Presence of hepatitis B reactants in serum
8.	Testicular pain or tenderness
9.	Weight loss
10.	Biopsy-confirmed granulocytic or mixed leukocytic infiltrate in an arterial wall

Table 7. Diagnostic criteria for PAN.

Coronary artery involvement can occasionally be seen in Takayasu arteritis, which tends to involve larger vessels than PAN [48–50]. It has also been reported that Paediatric MI can be seen in Behçet's disease [45].

14. Slow coronary flow phenomenon

Slow coronary flow phenomenon is a microvascular disease characterised by slow progress of the contrast dye within the vessel, which is not obstructive coronary artery flow [51]. Despite evaluation as a benign clinical setting, it is concerning for families and physicians because of the relationship with MI and anginal symptoms. In addition, the mechanism and clinical outcomes of the disease are not yet fully understood.

Occasionally, clinical findings can be seen in children with ST-segment elevation myocardial infarction (STEMI) [51]. On coronary angiography, there is no vessel obstruction or it is close to normal, but the peripheral blood flow is noticeably slow. Studies of these patients have shown cellular oedema, thickening in the capillary endothelium, fibromuscular hyperplasia, myofibril disorganisation and microvascular thickening, causing endothelial dysfunction [52, 53].

15. Atherosclerosis

As atherosclerotic coronary artery disease seen in adults originates in childhood, it is necessary to start taking preventative measures against atherosclerosis in that period. However, as there are few cases related to atherosclerosis within the PMI cases reported in literature it is thought that MI cases developing on an atherosclerotic basis are rare in children [3, 7, 54].

In an autopsy study of 760 murder or accident cases aged 15–34 years, atheroma was determined in males at 2% and was not determined in females [54]. Other risk factors increasing

atherosclerotic changes are known to be familial hypercholesterolemia in particular, and elevated LDL level, substance abuse, smoking, hypertension, obesity and cardiovascular events experienced by a family member at an early age [54].

16. Epinephrine use

Racemic adrenaline is a sympathomimetic drug used in Paediatric bronchiolitis and severe upper respiratory tract obstructions. Although this treatment has been used safely for many years, there is a need for heart rate and ECG monitorisation in cases administered epinephrine consecutively [55]. It has been reported that MI has developed associated with epinephrine not only in cases with racemic epinephrine but also in cases where epinephrine has been used when applying cardiopulmonary resuscitation [56]. The coronary vasospasm of epinephrine is made over alpha 1 and alpha 2 receptors. While low-dose adrenaline shows a beta mimetic effect, at high doses the effect is seen by vasoconstriction, primarily over the alpha 1 and alpha 2 receptors. As there is a relationship between epinephrine used intravenously and a higher complication rate, the selection of intramuscular or subcutaneous routes could contribute greatly to reducing the cardiovascular risks [56] Vasodilators such as nitrate and calcium channel blockers are selected in MI cases related to epinephrine [57, 58].

17. Sickle cell anaemia

In sickle cell anaemia (SCA), because of the sickle cells that develop during the disease, infarcts affect the lungs, heart, spleen, central nervous system, retina, bones and kidneys [59]. SCA is known to create a widening in the left ventricle, hypertrophy, pulmonary hypertension and heart failure. The reason for MI seen in children with SCA is not fully known. However, it has been reported that vasospasm caused by thromboxane expressed from sequestered thrombocytes could play an important role in coronary ischaemia and necrosis [60]. Varying membrane flexibility and varying viscosity in SCA patients have also been reported to be possible causes of ischaemia and infarction.

More detailed examinations should be made of SCA patients especially in conditions of acidosis, deep anaemia, kidney failure and infection. During a vaso-occlusive crisis in SCA children, when there are non-specific ST-T changes on ECG together with chest pain, cardiac enzymes should be examined and the patient should be closely monitored. In patients with suspected myocardial ischaemia, hydration and oxygenation must be provided. It is thought that nitrates could be useful [59]. Although the role of anti-thrombotic treatment is not known, it should be considered in treatment.

18. Substance abuse

The use of marijuana and cocaine should be investigated in adolescents seen with MI. Tramadol, amphetamines, benzodiazepines and opiates are also substances that can cause PMI [61].

The use of a vasoconstrictor substance, especially by those who smoke, increases the risk of ischaemic cardiac complications, even in a healthy heart. [62]. Marijuana stimulates the sympathetic nervous system by expressing epinephrine and the effect is seen with an increase in vasoconstriction, tachycardia, hypertension and cardiac output [63]. Furthermore, by increasing the carboxyhaemoglobin level, the oxygen carrying capacity is reduced [62]. The coronary ischaemia and MI which occur as a result of increased heart rate, vasoconstriction and the increased need for oxygen can be life-threatening for the patient [63–65]. As most substances causing Paediatric MI are illegal, the users may deny having used them. In cases suspected of substance abuse, a toxicology examination must be made. Cardiac ischaemia can also be seen related to the use of bonzai, which is a synthetic cannabinoid [63].

Cocaine with sympathomimetic effect on coronary arteries can cause MI by vasoconstriction. As a result of increasing blood pressure and heart rate, the myocardium has an increased need for oxygen and with the tendency for thrombosis resulting from endothelial dysfunction, MI can develop in patients [4].

In an autopsy examination of 477 cases of sudden cardiac death aged 1–49 years, Bjune et al. determined positive results in the toxicology scan of 57% of the cases [61]. The toxicological substances determined in the blood in that study were benzodiazepines, opioids, antidepressants, anticonvulsants, antipsychotics, ethanol, cannabis, cocaine, amphetamines and gamma hydroxybutyrate. In 39% of the cases with substances determined in the blood, multiple substances were present. Despite the subpharmacological basis of the substances determined and the pharmacological dose, that death occurred was concluded to be due to the interaction of multiple drugs and/or substances.

19. Myocardial bridge

In normal individuals, the coronary arteries have a course over the myocardium. Myocardial bridge [MB] is a clinical event characterised by the course of a section of the coronary arteries within the myocardium [4, 66, 67]. On angiography, the loss in diastole of the narrowing in the vessel lumen that is observed during systole [milking effect] is valuable for diagnosis. The degree of coronary obstruction created by the MB depends on the localisation of the MB, the thickness, length and degree of cardiac contractility [68]. It has been reported to be seen more often in patients with left ventricle hypertrophy such as HCM and aortic stenosis in particular [38]. Other coronary arteries can be affected, but the most commonly affected is the LAD [38, 67, 69].

It has been shown that there is a relationship between the clinical results of MB and ischaemic heart disease, MI, arrhythmia and sudden death and that MB can cause MI even in Paediatric cases [66]. It has not yet been understood how important the haemodynamic effects are of the coronary artery in the intramural region remaining under pressure during systole when >75% of the coronary is in diastole.

Despite the use of beta-blockers at appropriate doses, it has been reported that in symptomatic patients with >75% systolic narrowing, good results can be obtained with supra-arterial myotomy and the risk of MI and sudden death can be prevented [70].

20. Nephrotic syndrome

Nephrotic syndrome is a known condition which increases the tendency to thrombosis [71, 72]. Although the mechanism of the tendency to thrombosis is not completely known, it is thought that lipid abnormalities increase the tendency to thrombosis by increasing haemoconcentration and hypervolemia and the viscosity of full blood and plasma and that hypoalbuminemia stimulates the synthesis of fibronectin, fibrinogen and factors II, V, X, XI, from the liver [73].

21. Antiphospholipid antibody syndrome

Antiphospholipid antibody syndrome is a syndrome characterised by low antiphospholipid antibodies in the blood during pregnancy and arterial and venous thromboses [74, 75]. Just as antiphospholipid antibody syndrome can be seen isolated as primary antiphospholipid antibody syndrome, it may also be seen together with diseases such as systemic lupus erythematosus [4].

22. Diagnosis

When diagnosing MI in children it can be useful to request consultation from adult cardiologists experienced with MI. The anamnesis, laboratory tests and imaging methods should be used to full benefit in diagnosis. Even if the anamnesis does not have such a satisfactory role in Paediatric diagnosis as it does for adults, information must be obtained about the character and radiation of the pain, especially from school-age children and adolescents. The determination of CHD, previous surgical interventions because of the CHD in the anamnesis aortic stenosis, hypertrophic cardiomyopathy, patients underwent operation for transposition of great artery particularly have additional risks for MI [76].

In the physical examination, the determination of weak pulse, dyspnoea, rhythm irregularity, sudden paroxysmal abdominal pain, gallop rhythm, cold extremities and shock should suggest MI [2]. The determination of PR segment depression on ECG, ST segment elevation together with the J point in at least two adjacent derivations, deep and/or wide Q-wave in at least one derivation, T-wave changes, ventricular arrhythmia and cardiac block should suggest a diagnosis of MI [14].

On echocardiography, segmentary wall movement abnormalities, a reduction in left ventricle functions, papillary muscle rupture and left ventricle free wall rupture are valuable for diagnosis [24, 77]. In the laboratory examination, elevation in troponin levels and increased CKMB levels are important for diagnosis.

Coronary angiography is the standard diagnostic method for MI [35]. The application of coronary angiography should be considered in patients with high troponin levels and findings in the anamnesis suggestive of MI. It must also not be forgotten that coronary angiography in MI cases related to vasoconstrictor substance intake, could be normal [63].

23. Treatment

As there are no comprehensive studies related to PMI treatment, the treatment principles of adult MI treatments have been adapted for children and have been formed from experience focussed on cases. Treatment must be organised according to the aetiology and clinical status of the patient. To determine arrhythmia or for early intervention when it has been determined, ECG monitorisation should be applied as soon as possible to all patients with suspected MI [10, 23].

24. Fibrinolytic treatment

24.1. Alteplase

In recent years, alteplase has become the most widely used fibrinolytic drug in children. The most important reasons for selection are that the half-life is short (approximately 5 mins), it is not antigenic and the effect is fibrin-specific [78]. It is a recombinant tissue plasminogen activator. In literature, there is no standard application related to r-tPA dosage in Paediatric patients. There are different applications in different centres. Nakagawa et al. applied intracoronary tPA at the dose of 200,000 unit/kg (0.34 mg/kg) to a patient with Kawasaki disease who suffered MI, but the patient died [79]. Subsequently, doses of 400,000 unit/kg (0.69 mg/kg) and 800,000 unit/kg (1.38 mg/kg) intra-coronary tPA were applied to 2 other patients with Kawasaki disease who suffered MI, and the thrombi and cliinical findings of the patients were determined to have recovered without any complications. In addition to the tPA, Nakagawa et al. also administered urokinase infusion to the first and third of these three patients. Tsubata et al. applied a dose of 300,000 unit/kg tPA to an MI patient with Kawasaki disease as 10% of the total dose in bolus form and the remainder with a 1-hour infusion [80]. After 2 days, a dose of 50,000 unit/kg tPA was administered intra -coronary, but only a partial response was obtained in the thrombus. Krendal et al. treated a 7-year old Kawasaki patient with MI with intravenous 700,000 unit/kg tPA and a response was obtained clinically on echo. The success in that case compared to Tsubata et al. was associated with the administration of high-dose tPA [81].

In cases of intracardiac thrombus and intravascular thrombose**s,** while some centres have used 0.05–0.5 mg/kg/hr. infusion after 0.3–0.6 mg/kg bolus, other centres have administered infusion of 0.01–0.5 mg/kg/hr. without any loading dose, until the thrombus is resolved (max 96 hrs). This has been used and successful results have been obtained in Paediatric cases, especially in the opening of a central venous catheter and in intracardiac or intra-arterial and intravenous thrombus cases [83–86].

After a loading dose of 0.1 mg/kg/10 mins in neonatal infants, some centres have administered maintenance at 0.3 mg/kg/hr. while others have given a loading dose of 0.7 mg/kg in 30—60 mins followed by 0.2 mg/kg/hr. As the infusion time extends, so the possibility of complications developing increases [82, 83]. Major complications that can develop are intracranial bleeding, epistaxis, melena and hematuria and minor complications may be seen as mucosal bleeding or bleeding from the needle entry site. Therefore, patients must be closely

monitored. In patients who develop complications, plasminogen or fibrinogen levels in the blood are examined, and if necessary the treatment must be stopped.

In adult cases, following a 15 mg iv bolus dose, 0.75 mg/kg/hr. is administered in 30 mins. The success of fibrinolytic treatment is evaluated with the correction of ST elevation and the patient symptoms [23].

As Paediatric MI cases are emergencies and the condition is urgent and life-threatening, it may be more appropriate to administer intra-coronary or iv high-dose bolus treatment followed by 0.1–0.5 mg/kg /hr. infusion.

24.2. Reteplase

Unlike alteplase, there is no need for an infusion following the administration of IV bolus. To open blocked catheters in Paediatric patients, 0.1 units was administered and in cases where no response could be obtained, increases were applied of 0.1 units up to a maximum of 0.4 units. Successful results have been obtained with this treatment [85]. In adult coronary thrombo-embolic cases, it is recommended that 10 units are given in the form of 2 doses at a 30-min interval [23].

24.3. Tenecteplase

This is a drug given in bolus form to myocardial infarction patients after diagnosis [23]. Unlike other tissue plasminogen activators, it is a time-saving application as there is no requirement for repeated bolus doses. The recommended doses for adults are 30 mg (6000 unit) for patients <60 kg in weight, 35 mg for those weighing 60–70 kg, and 40 mg for those of 70–80 kg [23].

24.4. Streptokinase

Streptokinase has been used for many years in adult MI patients. Experience related to the efficacy of streptokinase in PMI has been acquired from Kawasaki patients in particular. Studies have shown that in Kawasaki patients with MI, the use of intravenous or intra-coronary streptokinase followed by heparinisation and warfarin or dipyridamol in maintenance, is effective [87, 88]. If Percutaneous Coronary Intervention (PCI) is not applied within the first 2 hours after diagnosis in cases with MI, immediate thrombolytic treatment should be applied with a half-hour infusion. Fibrinolytic treatment can be administered to patients diagnosed with MI within the first 12 hours of diagnosis [23].

25. Percutaneous coronary intervention

In adult patients, it is recommended that PCI is applied within 2 hours of MI diagnosis. In patients where it is predicted that the time from diagnosis to PCI will exceed 2 hours, it is recommended that fibrinolytic treatment is given first in bolus form, after that fibrinolytic treatment catheter unit intake for PCI [23].

26. Anticoagulant treatment

Anticoagulation is recommended for all patients in addition to antiplatelet therapy during primary PCI [23]. The most commonly used drug for this is unfractioned heparin. The initial dose is given in bolus form as 70–100 units/kg and in maintenance, it can be given according to the active clotting time or as 10–15 units/kg/hr. After admission to hospital, it can be terminated within 8 hours of clearance of the coronary occlusion or it can be continued intra venously for 24–48 hrs to heparinisation. The goal is an aPTT value of 50–70 seconds or 1.5–2-fold the control value. It is recommended that the test is repeated at 3, 6, 12 and 24 hours [23].

27. Anti-aggregant treatment

As aspirin is given at the classic anti-aggregant dose (75-100 mg) following classic anti-aggregant dose loading (150-300 mg) in adult MI cases, in Paediatric cases loading is given of 5 mg/kg/day followed by 3-5 mg/kg/day aspirin. Adolescents can benefit from doses similar to those of adults.

The administration of clopidogrel together with aspirin increases the chance of success. The recommended Paediatric dose for clopidogrel is 0.2 mg/kg/day [89]. In adult patients diagnosed with MI, after 300 mg loading, maintenance treatment is given of 75 mg/day clopidogrel. It is recommended that clopidogrel and aspirin treatment is continued for 12 months in adult patients after MI [23].

27.1. Beta blockers

When arrythmia has been determined in MI patients, electrolyte levels must be examined and if the electrolyte levels are normal, beta blockers are preferred in treatment. Metoprolol can be given for this at a single dose of 1-2 mg/kg/day [23]. In addition to the anti-arrhythmic effects of beta blockers, patients who have undergone MI also beenfit from the anti-ischaemic effect because of the vasodilatory properties.

Conflict of interest

Authors declare that they have no conflict of interest to declare.

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Atherosclerotic cardiovascular disease is still the most common cause of death among adults. Its prevalence is increasing in developing countries and despite all advances in both diagnostic tools and treatment modalities, it is still very common in the developed world. Obesity, diabetes mellitus, hypercholesterolemia and overuse of dietary salt play a pivotal role in increased cardiovascular morbidity and mortality worldwide.

Current clinical efforts are mainly focused on the diagnosis and treatment of myocardial infarction. In this book, we provide epidemiological data on myocardial infarction and atherosclerotic cardiovascular disease, current diagnostic biochemical tests and management strategies. A specific patient group, children, experiencing myocardial infarction are also addressed.

Current advances in the management of myocardial infarction have decreased the morbidity and mortality from atherosclerotic cardiovascular disease and especially myocardial infarction; however, more can be achieved by the prevention of atherosclerotic processes via focusing on the early stages of the disease.

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