# A Review on Role of Biomarkers in Myocardial Infarction.

S.Swarnapriya*[1], B.Naveena[1], S.Kowsalya Devi[1], P.Arjun Kumar[2]

*Department of pharmacy practice, Arulmigu Kalasalingam college of pharmacy, Krishnankovil, Srivilliputhur, Tamil Nadu, India.*
*Department of Pharmaceutics, Arulmigu Kalasalingam College of Pharmacy, Krishnankovil, Srivilliputhur, Tamil Nadu, India*

---

---

## ABSTRACT

Myocardial infarction (MI), recognized as "heart attack," is due to reduced or complete cessation of blood flow to a part of the myocardium. The etiology of acute myocardial infarction is decreased coronary blood flow. Biomarkers are measurable and quantifiable biological parameters which function indices for fitness and body structure assessments. The analysis of acute myocardial infarction (AMI) may be made with the detection of a rise/fall of cardiac troponin (as a minimum one fee above the 99th percentile of the top reference limit) and one in every of 1) symptoms of ischemia, 2) electrocardiogram (ECG) modifications of latest ischemia, 3) new pathological Q waves or 4) imaging proof of latest lack of possible myocardium. Two widely known biomarkers in use for prognosis of acute myocardial infarction are Creatine-Kinase-MB isoform and Cardiac Troponin. Generally used strategies consist of drug remedy, thrombolytic remedy, percutaneous coronary intervention [PCI], and coronary artery skip graft[CABG] surgery. The cardiac biomarkers cTnT, cTnI, BNP, and NT-proBNP offer essential data for clinicians with the aid of using supporting withinside the steering of diagnostic, prognostic, and remedy selections for sufferers providing urgently with symptoms and symptoms and signs and symptoms of MI. Rapid and correct diagnosis, chance stratification, and control selections will stay aided through biomarkers. They play a useful position in supplying powerful care whilst minimizing healthcare costs.

**KEY WORDS:** Myocardial infarction, classification, biomarkers, management.

## I.  INTRODUCTION

Myocardial infarction (MI), recognized as "heart attack," is due to decreased or complete cessation of blood flow to a part of the myocardium[1].It is most usually due to a lower or stoppage of blood flow to a part of the heart, leading to cause necrosis of heart muscle. This is normally the end result of a blood clot withinside the epicardial artery that supplies that territory of heart muscle[2]. It is now diagnosed that, primarily based totally on how AMI is defined, not all cases necessarily need a blood clot etiologically. In all living tissue includes heart muscle, the blood supply deliver should identical the oxygen demands of the muscle. This is termed as the supply–demand ratio[3].

It is now liked that an imbalance in this ratio (too little supply or an excessive amount of demand) as may arise with a very rapid heart rate (too much demand) or a drop in blood pressure (too little supply) may additionally lead to cause myocardial damage without the appearances of a blood clot[4]. Myocardial infarction can also additionally "silent" and go undetected, or it may be a catastrophic event leading to hemodynamic deterioration and sudden death[5].

Most myocardial infarctions is associated with underlying coronary artery disease, the leading cause of death[6]. With coronary artery occlusion, the myocardium is deprived of oxygen. Prolonged deprivation of oxygen supply to the myocardium can result to myocardial cell death and necrosis[7]. Patients can present with chest discomfort or pressure that may radiate to the neck, jaw, shoulder, or arm. In addition to the history and physical examination, myocardial ischemia may be associated with ECG changes and elevated biochemical markers such as cardiac troponins[8]. Acute myocardial infarction can be classified into two categories, non-ST-segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI). Unstable angina is similar to NSTEMI. However, cardiac markers are not elevated[9].

An MI results in irreversible damage to the heart muscle due to a lack of oxygen. An MI may result to impairment in diastolic and systolic function and make the patient prone to arrhythmia[10]. In addition, an MI can result to a number of serious complications. The key is to reperfuse the heart and restore blood flow. The earlier the treatment (less than 6 hours from symptom onset), the better the prognosis[11].

---

An MI is diagnosed when two of the following criteria are met:
1. Symptoms of ischemia
2. New ST-segment changes or a left bundle branch block (LBBB).
3. Presence of pathological Q waves on the ECG
4. Imaging study showing new regional wall motion abnormality
5. Presence of an intracoronary thrombus at autopsy or angiography.

## ]ETIOLOGY

The etiology of acute myocardial infarction is decreased coronary blood flow. The available oxygen supply cannot meet oxygen demand, resulting in cardiac ischemia. Decreased coronary blood flow is multifactorial. Atherosclerotic plaques classically rupture and lead to thrombosis, contributing to acutely decreased blood flow in the coronary. Other etiologies of decreased oxygenation/myocardial ischemia include coronary artery embolism, which accounts for 2.9% of patients, cocaine-induced ischemia, coronary dissection, and coronary vasospasm[12].

**Non-modifiable Risk Factors**
- Sex
- Age
- Family history
- Male pattern baldness

**Modifiable Risk Factors**
- Smoking
- Dyslipidemia
- Diabetes mellitus
- Hypertension
- Obesity
- Sedentary lifestyle
- Poor oral hygiene
- Presence of peripheral vascular disease
- Elevated levels of homocysteine

**Other Causes of MI**
- Trauma
- Vasculitis
- Drug use (cocaine)
- Coronary artery anomalies
- Coronary artery emboli
- Aortic dissection
- Excess demand on the heart (hyperthyroidism, anemia)
1. Abdominal obesity (waist/hip ratio) (greater than 0.90 for males and greater than 0.85 for females)
2. Psychosocial factors such as depression, loss of the locus of control, global stress, financial stress, and life events including marital separation, job loss, and family conflicts
3. Lack of daily consumption of fruits or vegetables
4. Lack of physical activity
5. Alcohol consumption (weaker association, protective)[13]

The INTERHEART study showed that all the above risk factors were significantly associated with acute myocardial infarction except for alcohol consumption, which showed a weaker association. Smoking and abnormal apolipoprotein ratio showed the strongest association with acute myocardial infarction. The increased risk associated with diabetes and hypertension were found to be higher in women, and the protective effect of exercise and alcohol was also found to be higher in women.

Other risk factors include a moderately high level of plasma homocysteine, which is an independent risk factor of MI. Elevated plasma homocysteine is potentially modifiable and can be treated with folic acid, vitamin B6, and vitamin B12[14].

## CLASSIFICATION OF MYOCARDIAL INFARCTION

Type 1 Myocardial infarction is a medical proof of ischemia because of atherosclerotic plaque disruption ensuring in coronary thrombosis and detection of upward thrust and/or fall of cTn values with as a minimum one cost above the 99th percentile upper-reference limit [URL] [15,16]. In addition, sufferers should additionally showcase one of the following signs and symptoms of myocardial ischemia conditions: new ischemic electrocardiogram changes, improvement of pathological Q waves, proof of latest lack of feasible myocardium or new nearby wall movement abnormality in a sample regular with ischemic etiology through imaging and identify of a coronary thrombus via way of means of angiography or autopsy[15].

Type 2 Myocardial infarction additionally consist of the aforementioned symptoms, however is because of a supply-call for mismatch of myocardial oxygen with inside the absence of coronary thrombosis[15,16]. Prior to 2017, differentiating sufferers with kind 1 and sort 2 MI- primarily based totally through scientific coding turned into now no longer viable due to the fact an ICD code for every unique MI subtype did now no longer exist[17].

Type 1 MI may be similarly divided into classifications: ST- elevation myocardial infarction [STEMI] and non-ST- elevation infarction[NSTEMI]. STEMI is described as an

acute coronary thrombosis or chronic ST-Phase elevation ≥1 mm in ≥2 contagious electrocardiographic leads[15,17] NSTEMI is described as ischemic signs at relaxation from an acute coronary plaque rupture or erosion, lasting ≥10 mins, happening inside 24 hours earlier than health center admission, and showing both extended cardiac biomarkers [both creatine kinase or cTn] inside 24 hours after preliminary presentation[17].

## BIOMARKERS

Biomarkers are measurable and quantifiable biological parameters which function indices for fitness and body structure assessments[18]. This consists of sickness hazard and analysis. The analysis of acute myocardial infarction (AMI)[15] may be made with the detection of a rise/fall of cardiac troponin (as a minimum one fee above the 99th percentile of the top reference limit) and one in every of 1) symptoms of ischemia, 2) electrocardiogram (ECG) modifications of latest ischemia, 3) new pathological Q waves or 4) imaging proof of latest lack of possible myocardium.

Both the ECG and cardiac troponin are biomarkers, but the point of interest of this overview may be on serum proteins/markers that have turn out to be more and more critical to enhance our analysis of myocardial infarction, in some instances figuring out humans liable to having an infarct and in others to are expecting long time diagnosis following an actual event.

## What makes an excellent biomarker?

A desirable biomarker is something this is without problems measured and may be used as a surrogate marker for sickness and its severity[19]. For instance, blood sugar maybe used to diagnose diabetes[18] while glycosylated hemoglobin (HbA1c) video display units blood sugar control. Because cardiovascular sickness is still a large burden in most countries, it's miles critical to pick out excessive hazard sufferers in order to save you morbidity or mortality in later life. Medications and remedies additionally come at a fee and therefore easy and reasonably-priced exams have turn out to be more and more important to determine a way to goal treatment. A desirable biomarker will diagnose or are expecting hazard accurately (this is, excessive specificity and sensitivity), directly offer inexpensive but significant results, and ought to offer this incrementally over current markers or medical characteristics.

## Biomarkers in acute myocardial infarction

Some of those more recent biomarkers and their dating to diverse pathophysiological procedures are depicted in Figure 1[20].
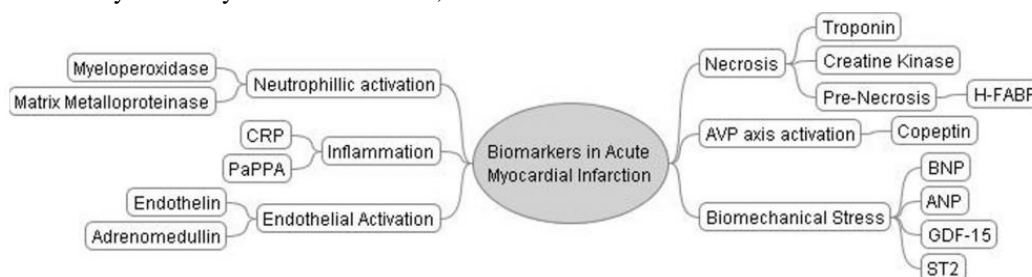


**Figure 1. Pathophysiological procedure of biomarkers in MI**

## Diagnostic biomarkers

Two widely known biomarkers in use for prognosis of acute myocardial infarction are Creatine-Kinase-MB isoform and Cardiac Troponin. In 2000, Cardiac Troponin changed CK-MB because the biomarker of preference for diagnosing a myocardial infarction[21]. Troponin is a protein launched from myocytes whilst irreversible myocardial harm occurs. It is tremendously precise to cardiac tissue and as it should be diagnoses myocardial infarction with a historyof ischemic ache or ECG modifications reflecting ischemia.

Cardiac troponin stage is depending on infarct size[22], as a consequence giving clinicians an concept of the analysis following an infarct. However, following reperfusion therapy, the real troponin stage may be deceptive because of the washout phenomenon. Troponin tiers top at 12 hours, and live extended for 10 days or extra. Whilst using Troponin for diagnosing AMI and threat stratification to aid choice making has revolutionized the control of sufferers imparting with chest ache, the 12-hour wait for the tiers to top stays the Achilles heel of this biomarker.

Newer,extra touchy troponin assays[23] have been brought to rectify this weakness. A nice Troponin is related to accelerated threat of an unfavorable final results at 30 days (HR 1.96, P = 0.003). In addition, the following biomarkers might also additionally assist facilitate early prognosis of AMI, despite the fact that neither has been in comparison with the more modern excessive sensitivity troponin assays.

### C-terminal-provasopressin (Copeptin)

Copeptin is the extra solid surrogate of arginine vasopressin (AVP), with famous outcomes on osmoregulation and cardiovascular homeostasis[24]. Post AMI, vasopressin is idea to[25] boom peripheral vasoconstrictor pastime for that reason growing afterload and ventricular stress[26]; (1) boom protein synthesis in myocytes main to hypertrophy[27] and (2) vasoconstriction of coronary arteries.

These outcomes are mediated thru the V1 receptor, while outcomes at the V2 receptor mediate water retention with inside the renal tubules. These receptors are now objectives for pharmacological therapy[28,29]. Copeptin islaunched in stoichiometric share to vasopressin and is strong and without difficulty assayed.

Copeptin can rule out MI in advance similarly to a terrible Troponin T test[30]. At the time of presentation a copeptin degree of < 14 pg/ml and a Trop T degree of < 0.01 ought to rule out a myocardial infarction with a place under the curve (AUC) of receiver working characteristic curve (ROC) of 0.97 (terrible predictive cost of 99.7%), for this reason obviating the want for tracking and serial blood checks in a majority of patients.

Copeptin is a superb marker of neurohormonal stress, making it additionally beneficial in risk stratification in sepsis[31] and different illnesses and hence isn't particular to the cardiovascular system.

### Heart-Type Fatty Acid Binding Protein (H-FABP)

H-FABP is a low molecular weight protein worried in myocardial fatty-acid metabolism[32]. It is likewise discovered in small portions in brain, kidney and skeletal tissue and degrees can cross up in acute ischemic strokes and intense exercise. It is swiftly launched early in myocardial infarction and necrosis into the cytosol.

H-FABP has been proven in mouse research to be an early marker of ischemia[33] (earlier than morphological proof of myocardial necrosis) and might consequently assist with analysis of MI earlier[33-35]. However, research trying to use H-FABP on my own for early analysis of AMI has produced disappointingresults. One overview of six research discovered that the pooled wonderful predictive cost to be 65.eight% and pooled bad predictive cost to be 82.0%[36].

Other more latest research verified that H-FABP degrees have been honestly related to the composite quit factor of demise, myocardial infarction and coronary heart failure at 10 months[37,38]. When degrees of H-FABP have been measured postACS and divided into quartiles, the pinnacle quartile become related to all-reason mortality 6.59 instances better than the lowest quartile, after adjusting for hsCRP and Troponin. In fact, whilst introduced to Troponin for hazard stratification, a bad troponin and H-FABP level < 5> 5.8 mcg/L become associated with a 4.93-fold growth in hazard of demise and 7.93-fold growth in hazard if Troponin become wonderful and H-FABP >5.8 eight mcg/L.

### Prognostic biomarkers

Before broaching the situation of biomarkers it's far essential to be aware that because of diverse randomized control trials and registry studies, diverse threat elements have been diagnosed and entered into scoring structures that permit a clinician to threat stratify disease[39].

Popular gear include the TIMI rating[40], derived from the Thrombolysis in Myocardial Infarction study, and the PURSUIT rating[41] (from Platelet glycoprotein IIb/IIIa in risky angina: Receptor suppression the usage of Integrally Therapy).

The GRACE rating is any other especially sturdy medical tool[42], which makes use of medical signs to calculate threat, (from the Global Registry of Acute Coronary Events study), using weighted facts approximately renal dysfunction, hemodynamic fame, age, Killip Class, cardiovascular records, and records of a cardiac arrest, in addition to elevated cardiac enzymes and form of ECG changes. On its own this rating has an brilliant c-statistic of 0.eighty four for predicting in-health facility death. Newly added biomarkers must supplement and have incremental prognostic price over and above these easy threat scores.

It is consequently no wonder that biomarkers presenting prognostic facts following an acute coronary syndrome mirror the diverse physiological pathways defined with inside the GRACE rating (for example, hemodynamic fame vs. biomechanical pressure and neurohumoral pathways). Currently, the handiest regular biomarker affecting an alternate in control of a

patient with an acute coronary syndrome is the cardiac troponin.

## Other biomarkers

C-Reactive protein [CRP]. CRP is a beneficial prognostic indicator in sufferers with ACS, as expanded CRP ranges are impartial predictors of cardiac death, AMI and congestive coronary heart failure[43]. It is a maximum extensively used inflammatory markers in habitual medical practice.

## Inflammation Biomarkers

Interleukin-6 in addition to CRP, is a critical irritation biomarker that can be implicated withinside the diagnosis, hazard stratification, and diagnosis of sufferers with AMI. IL-6 expression is proven to be improved in induced myocardial infarction via way of means of Trans-coronary ablation of septal hypertrophy, suggesting its diagnostic role[44].

Cardiac myosin binding protein C[cMyC] is one of the three isoforms of myosin binding protein C expressed withinside the cardiac tissue while the alternative isoforms are expressed withinside the skeletal muscle[45] Following cardiac myocyte necrosis, cMyC seems withinside the circulation in advance as compared to hs-cTn[46]. Notably, the cMyC has a better efficacy for ruling out and ruling in patients than hs-cTn, whilst the diagnostic accuracy is similar.

## TREATMENT

The remedies of myocardial infarction in particular awareness at the recanalization of the occluded coronary artery to repair perfusion and save you myocardial necrosis. To do this, generally used strategies consist of drug remedy, thrombolytic remedy, percutaneous coronary intervention [PCI], and coronary artery skip graft[CABG] surgery.

Traditional drug treatment plans consist of angiotensin-changing enzyme inhibitors[ACEI], angiotensin receptor blocker[ARBs], aldosterone receptor antagonists, beta receptor blockers and so on[47-49].The principal reason of those remedies is the prevention of left ventricular remodeling.

Thrombolytic remedy is currently the principle technique for the remedy of myocardial infarction. Principles of thrombolytic remedy in treating acute myocardial infarction are recanalization of the occluded coronary artery and recovery of the perfusion as quickly as possible.

A huge wide variety of scientific research indicated that thrombolytic remedy that taken inside 6 hours after the onset of myocardial infarction completed the quality healing effect and the sooner remedy is started, the higher the healing effect[50].

## Percutaneous Coronary Intervention

Take the restrictions of thrombolytic remedy into consideration, percutaneous coronary intervention [PCI] has progressively grow to be some other desire to repair perfusion. This process efficaciously restore the blood glide and recovers the characteristics of Coronary heart muscle through putting a unique catheter right into the blood vessel and inflated on the narrowed location of the coronary artery. Compared with thrombolytic remedy, PCI eliminated the thrombus and the reperfusion price after the intervention is 95%-99%. But PCI additionally has a few feasible risk, which include bleeding or contamination of the catheter insertion site, hypersensitive reaction to the assessment dye use, blood clot dealt with blood vessel , rupture with coronary artery and whole remaining of the coronary artery.

Coronary Artery Bypass Grafting [CABG] is an powerful surgical remedy of coronary heart sickness and myocardial ischemia, which could successfully relieve symptoms. It is likewise an powerful approach for the remedy of restenosis and acute head ache in suferrers after PCI. Once a intense headache arise after surgery,emergency CABG will limit myocardial harm and decrease help centre mortality and detrimental events. CABG is an essential opportunity or mixture remedy to PCI[51].

## II.    CONCLUSION

The cardiac biomarkers cTnT, cTnI, BNP, and NT-proBNP offer essential data for clinicians with the aid of using supporting withinside the steering of diagnostic, prognostic, and remedy selections for sufferers providing urgently with symptoms and symptoms and signs and symptoms of MI. cTnT and cTnI have developed through numerous assay revisions and presently the touchy and excessive sensitivity variations of those assays are the exceptional to be had exams for medical use in MI diagnosis.Currently, clinicians commonly degree both cTn or BNP/NT-proBNP while encountering sufferers with suspected acute coronary syndromes or coronary heart failure, primarily based totally at the suggestions posted via way of means of the

European Society of Cardiology or American Heart Association.

These laboratory exams becomes of growing significance throughout the world and especially in Southeast Asia with the converting demographics and healthcare landscape. The developing international epidemic of weight problems and diabetes mellitus will bring about extra sufferers offering to the emergency branch with the diagnostic quandary of MI as opposed to different reasons in their symptoms and symptoms and symptoms. Rapid and correct diagnosis, chance stratification, and control selections will stay aided through biomarkers. They play a useful position in supplying powerful care whilst minimizing healthcare costs.

We nonetheless want to perceive greater novel biomarkers to complement ECG or X-rays and offer greater correct and touchy strategies for cardiovascular disorder diagnosis, threat stratification, and management.

## REFERENCES

[1]. Thygesen K, Alpert JS, White HD, ESC J, ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of the myocardial infarction. Kardiologiapolska. 2008 Jan;66(1):47-62.

[2]. Nascimento BR, Brant LC, Marino BC, Passaglia LG, Ribeiro AL. Implementing myocardial infarction systems of care in low/middle-income countries. Heart. 2019 Jan 1;105(1):20-6.

[3]. Thygesen K, Alpert JS, White HD, Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction. Universal definition of myocardial infarction. Journal of the American College of Cardiology. 2007 Nov 27;50(22):2173-95.

[4]. Reimer KA, Jennings RB, Tatum AH. Pathobiology of acute myocardial ischemia: metabolic, functional and ultrastructural studies. The American journal of cardiology. 1983 Jul 20;52(2):72-81

[5]. Apple FS, Sandoval Y, Jaffe AS, Ordonez-Llanos J. Cardiac troponin assays: guide to understanding analytical characteristics and their impact on clinical care. Clinical chemistry. 2017 Jan 1;63(1):73-81.

[6]. Goodman SG, Steg PG, Eagle KA, Fox KA, López-Sendón J, Montalescot G, Budaj A, Kennelly BM, Gore JM, Allegrone J, Granger CB. The diagnostic and prognostic impact of the redefinition of acute myocardial infarction: lessons from the Global Registry of Acute Coronary Events (GRACE). American heart journal. 2006 Mar 1;151(3):654-60.Mar;

[7]. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. The lancet. 2004 Sep 11;364(9438):937-52.7;

[8]. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. European heart journal. 2008 Apr 1;29(7):932-40.

[9]. Stampfer MJ, Malinow MR, Willett WC, Newcomer LM, Upson B, Ullmann D, Tishler PV, Hennekens CH. A prospective study of plasma homocyst (e) ine and risk of myocardial infarction in US physicians. Jama. 1992 Aug 19;268(7):877-81.

[10]. Nielsen M, Andersson C, Gerds TA, Andersen PK, Jensen TB, Køber L, Gislason G, Torp-Pedersen C. Familial clustering of myocardial infarction in first-degree relatives: a nationwide study. European heart journal. 2013 Apr 21;34(16):1198-203.

[11]. BHF Family Heart Study Research Group. A genomewide linkage study of 1,933 families affected by premature coronary artery disease: The British Heart Foundation (BHF) Family Heart Study. The American Journal of Human Genetics. 2005 Dec 1;77(6):1011-20

[12]. Wang Q, Rao S, Shen GQ, Li L, Moliterno DJ, Newby LK, Rogers WJ, Cannata R, Zirzow E, Elston RC, Topol EJ. Premature myocardial infarction novel susceptibility locus on chromosome 1P34-36 identified by genomewide linkage analysis. The American Journal of Human Genetics. 2004 Feb 1;74(2):262-71.

[13]. Writing Group Members, Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics

Subcommittee. Circulation. 2006 Feb 14;113(6):e85-151.

[14]. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. Circulation. 2018 Mar 20;137(12):e67-492.;

[15]. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Mickley H, Crea F, Van de Werf F, Bucciarelli-Ducci C. Fourth universal definition of myocardial infarction (2018). European heart journal. 2019 Jan 14;40(3):237-69.

[16]. McCarthy CP, Vaduganathan M, Singh A, Song Z, Blankstein R, Gaggin HK, Wasfy JH, Januzzi JL. Type 2 myocardial infarction and the hospital readmission reduction program.Journal of the American College of Cardiology. 2018 Sep 4;72(10):1166-70.

[17]. Anstey DE, Li S, Thomas L, Wang TY, Wiviott SD. Race and Sex Differences in Management and Outcomes of Patients After ST-Elevation and Non–ST-Elevation Myocardial Infarct: Results From the NCDR. Clinical cardiology. 2016

[18]. Chan D, Ng LL. Biomarkers in acute myocardial infarction. BMC medicine. 2010 Dec;8(1):1-1.

[19]. Vasan RS: Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation 2006, 113:2335-2362

[20]. WHO Expert Committee on Diabetes Mellitus: Second report. World Health Organ Tech Rep Ser 1980, 646:1-80.

[21]. Alpert JS, Thygesen K, Antman E, Bassand JP: Myocardial infarction redefined--a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am CollCardiol 2000, 36:959-969.

[22]. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E: Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. N Engl J Med 1996, 335:1342-1349.

[23]. Keller T, Zeller T, Peetz D, Tzikas S, Roth A, Czyz E, Bickel C, Baldus S, Warnholtz A, Frohlich M, Sinning CR, Eleftheriadis MS, Wild PS, Schnabel RB, Lubos E, Jachmann N, Genth-Zotz S, Post F, Nicaud V, Tiret L, LacknerKJ, Münzel TF, Blankenberg S: Sensitive troponin I assay in early diagnosis of acute myocardial infarction. N Engl J Med 2009, 361:868-877.

[24]. Itoi K, Jiang YQ, Iwasaki Y, Watson SJ: Regulatory mechanisms of corticotropin-releasing hormone and vasopressin gene expression in the hypothalamus. J Neuroendocrinol 2004, 16:348-355.

[25]. Tunstall-Pedoe H, Vanuzzo D, Hobbs M, Mahonen M, Cepaitis Z, Kuulasmaa K, Keil U: Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA Project populations. Lancet 2000, 355:688-700.

[26]. Goldsmith SR: Vasopressin as Vasopressor. American Journal of Medicine 1987, 82:1213-1219.

[27]. Fukuzawa J, Haneda T, Kikuchi K: Arginine vasopressin increases the rate of protein synthesis in isolated perfused adult rat heart via the V1 receptor. Mol Cell Biochem 1999, 195:93-98.

[28]. Gheorghiade M, Gattis WA, O'Connor CM, Adams KF Jr, Elkayam U, Barbagelata A, Ghali JK, Benza RL, McGrew FA, Klapholz M, Ouyang J, Orlandi C, Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) Investigators: Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. JAMA 2004, 291:1963-1971.

[29]. Abraham WT, Shamshirsaz AA, McFann K, Oren RM, Schrier RW: Aquareticeffect of lixivaptan, an oral, non-peptide, selective V2 receptor vasopressin antagonist, in New York Heart Association functional class II and III chronic heart failure patients. J Am CollCardiol 2006, 47:1615-1621.

[30]. Reichlin T, Hochholzer W, Stelzig C, Laule K, Freidank H, Morgenthaler NG, Bergmann A, Potocki M, Noveanu M, Breidthardt T, Christ A, Boldanova T, Merki R, Schaub N, Bingisser R, Christ M, Mueller C: Incremental value of copeptin for rapid rule

out of acute myocardial infarction. J Am CollCardiol 2009, 54:60-68.

[31]. Jochberger S, Morgenthaler NG, Mayr VD, Luckner G, Wenzel V, Ulmer H, Schwarz S, Hasibeder WR, Friesenecker BE, Dunser MW: Copeptin and arginine vasopressin concentrations in critically ill patients. J ClinEndocrinolMetab 2006, 91:4381-4386.

[32]. Glatz JF, Luiken JJ, van Nieuwenhoven FA, Van derVusse GJ: Molecular mechanism of cellular uptake and intracellular translocation of fattyacids. Prostaglandins LeukotEssent Fatty Acids 1997, 57:3-9.\

[33]. Glatz JF, van Bilsen M, Paulussen RJ, Veerkamp JH, van derVusse GJ, Reneman RS: Release of fatty acid-binding protein from isolated rat heart subjected to ischemia and reperfusion or to the calcium paradox. BiochimBiophysActa 1988, 961:148-152.

[34]. Chan CP, Sanderson JE, Glatz JF, Cheng WS, Hempel A, Renneberg R: A superior early myocardial infarction marker. Human heart-type fatty acid-binding protein. Z Kardiol 2004, 93:388-397.

[35]. Chen L, Guo X, Yang F: Role of heart-type fatty acid binding protein in early detection of acute myocardial infarction in comparison with cTnI, CK-MB and myoglobin. J HuazhongUnivSciTechnolog Med Sci 2004, 24:449-451. 459

[36]. Body R: Towards evidence based emergency medicine: Best BETs fromthe Manchester Royal Infirmary. Bet 2. Heart Fatty Acid binding protein for rapid diagnosis of acute myocardial infarction in the emergency department.Emerg Med J 2009, 26:519-522.

[37]. O'Donoghue M, de Lemos JA, Morrow DA, Murphy SA, Buros JL, Cannon CP, Sabatine MS: Prognostic utility of heart-type fatty acid binding protein in patients with acute coronary syndromes. Circulation 2006, 114:550-557

[38]. Kilcullen N, Viswanathan K, Das R, Morrell C, Farrin A, Barth JH, Hall AS: Heart-type fatty acid-binding protein predicts long-term mortality after acute coronary syndrome and identifies high-risk patients across the range of troponin values. J Am CollCardiol 2007, 50:2061-2067.

[39]. de AraujoGoncalves P, Ferreira J, Aguiar C, Seabra-Gomes R: TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization

in NSTE-ACS. Eur Heart J 2005, 26:865-872.

[40]. Scirica BM, Cannon CP, Antman EM, Murphy SA, Morrow DA, Sabatine MS, McCabe CH, Gibson CM, Braunwald E: Validation of the thrombolysis in myocardial infarction (TIMI) risk score for unstable angina pectoris and non-ST-elevation myocardial infarction in the TIMI III registry. Am J Cardiol 2002, 90:303-305.

[41]. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, Akkerhuis KM, Harrington RA, Deckers JW, Armstrong PW, Lincoff AM, Califf RM, Topol EJ, Simoons ML: Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients.The PURSUIT Investigators. Circulation 2000, 101:2557-2567.

[42]. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, Van De Werf F, Avezum A, Goodman SG, Flather MD, Fox KA: Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med 2003, 163:2345-2353.

[43]. R. P. Tiwari, A. Jain, Z. Khan et al., "Cardiac troponins I and T: molecular markers for early diagnosis, prognosis, and accurate triaging of patients with acute myocardial infarction," Molecular Diagnosis & Therapy, vol. 16, no. 6, pp. 371–381, 2012.

[44]. C. Liebetrau, J. Hoffmann, O. Dörr et al., "Release kinetics of inflammatory biomarkers in a clinical model of acute myocardial infarction," Circulation Research, vol. 116, no. 5, pp. 867–875, 2015.

[45]. Carrier L, Bonne G, Bahrend E, Yu B, Richard P, Niel F, Hainque B, Cruaud C, Gary F, Labeit S, Bouhour JB. Organization and sequence of human cardiac myosin binding protein C gene (MYBPC3) and identification of mutations predicted to produce truncated proteins in familial hypertrophic cardiomyopathy. Circulation research. 1997 Mar 1;80(3):427-34.

[46]. Kaier TE, Alaour B, Marber M. Cardiac myosin-binding protein C—from bench to improved diagnosis of acute myocardial

infarction. Cardiovascular drugs and therapy. 2019 Apr;33(2):221-30.

[47]. González-Cambeiro MC, López-López A, Abu-Assi E, Raposeiras-Roubín S, Peña-Gil C, García-Acuña J, González-Juanatey R. Mortality benefit of long-term angiotensin-converting enzyme inhibitors or angiotensin receptor blockers after successful percutaneous coronary intervention in non-ST elevation acute myocardial infarction. Revista Portuguesa de Cardiologia (English Edition). 2016 Dec 1;35(12):645-53.

[48]. Eyuboglu M. Effects of new antiplatelet agents and aldosterone receptor antagonists on mortality in patients with myocardial infarction. Cardiovascular Drugs and Therapy. 2015 Oct;29(5):495-.

[49]. Er F, Dahlem KM, Nia AM, Erdmann E, Waltenberger J, Hellmich M, Kuhr K, Le MT, Herrfurth T, Taghiyev Z, Biesenbach E. Randomized control of sympathetic drive with continuous intravenous esmolol in patients with acute ST-segment elevation myocardial infarction: The BEtA-Blocker Therapy in Acute Myocardial Infarction (BEAT-AMI) Trial. JACC: Cardiovascular Interventions. 2016 Feb 8;9(3):231-40.

[50]. Jariwala P, Chandra S. Diagnosis and management of failed thrombolytic therapy for acute myocardial infarction.Indian Heart Journal. 2010 Jan 1;62(1):21-8.

[51]. Peng X, Zhou J, Wu XS. New strategies for myocardial infarction treatment.Journal of Cardiology and Therapy. 2017 Jun 3;4(3):664-70.