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UPDATES IN MYOCARDIAL ISCHEMIA IN CHEST PAIN PATIENTS ATTENDING THE EMERGENCY DEPARTMENT

A systematic review submitted to

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Introduction and Rationale

Chest pain is one of the most common reasons people call for emergency medical help. Fortunately, chest pain was not always a signal for a heart attack. Often chest pain is unrelated to any heart problem. But even if the chest pains the patient experience has nothing to do with his cardiovascular system, the problem may still be important — and worth the time spent in an emergency room for evaluation. (1)

Every year emergency doctors evaluate and treat millions of people for chest pain which may be cardiac or non-cardiac in origin. one of the most famous and Dangerous causes is Myocardial Ischemia. Myocardial ischemia, also called cardiac ischemia, can damage heart muscle, reducing its ability to pump efficiently. A sudden, severe blockage of a coronary artery may lead to a heart attack. Myocardial ischemia may also cause serious abnormal heart rhythms. (2)

Myocardial ischemia occurs when the blood flow through one or more of the blood vessels that leads to your heart (coronary arteries) is decreased. This decrease in blood flow leads to a decrease in the amount of oxygen your heart muscle (myocardium) receives. Myocardial ischemia may occur slowly as arteries become blocked over time, or it may occur quickly when an artery becomes blocked suddenly (1)

Painful sensations with ischemic episodes may be due, in part, to mechanical factors such as spasm and/or distention of cardiac vessels. The most common cause of ischemia is coronary artery stenosis due to arteriosclerosis. The lesions present with arteriosclerosis interfere with increases in blood flow necessary to meet increased cardiac demand, which may lead to pain. Spasms in the coronary arteries and vessels are commonly seen in patients with variant angina and Cardiac Syndrome X, but may be important mechanisms in stable and unstable angina (2)

Some patients had chest pain due to other causes, in addition to angina. Angina is typically described by patients as discomfort, tightness, or pressure in the chest with pain radiating to other areas such as the left arm, abdomen, or jaw. Anginal pain is generally associated with some level of exertion and often decreases with rest. In contrast, chest pain of other origins is usually more localized, variable, and described as sharp or burning. Non cardiac chest pain will not typically improve with rest. Determination of the cause of chest pain involves obtaining a careful medical history and diagnostic tests for ischemia such as electro-cardiography (ECG), stress testing, or coronary angiography. There are several types of anginas. Stable angina refers to chest pain that is predictable, reproducible with exertion, and relieved by rest or nitroglycerin. Unstable angina refers to a changing pattern of angina that is often present at rest and requires immediate medical attention. Variant angina usually occurs at rest or without stress, shows ST segment elevations on the ECG, and is due to coronary artery spasm. (3)

Approximately 6.5 million people in the United States suffer from angina, with 400,000 new cases diagnosed each year. The traditional medical model of disease does little to explain the variability seen in pain reporting among patients with angina--ranging from none to moderate to severe pain occurring several times per day. Research has found an inconsistent correlation between the severity of heart disease and the reported level of pain with angina. (4,5) Treatment for myocardial ischemia is directed at improving blood flow to the heart muscle and may include medications, a procedure to open blocked arteries or coronary artery bypass surgery. (6)

AIM OF THE WORK

To update knowledge and review researches in the field of chest pain in the emergency department to be a reference for researchers.

MATERIALS AND METHODS

STUDY DESIGN

This study was carried out as a systematic review. Collection of all possible available data about the chest pain patients in the Emergency department.

MATERIALS

1. Literatures from emergency medicine and intensive care textbooks.
2. Published articles from famous emergency medicine and intensive care journals.
3. Papers, abstracts and texts published on the internet concerned with the acute chest pain patients.
4. Thesis and papers in Egyptian Universities.

SEARCH STRATEGY

A Medline literature search was performed with the keywords "critical care," "emergency medicine," "acute chest pain", "myocardial ischemia". All studies introduced that the myocardial ischemia is a serious pathology that face patients of the emergency and critical care departments. Literature search included an overview of recent definition, causes, pathophysiology, prophylactic and recent therapeutic strategies.

Medline (PubMed), Up to date, Blackwell-synergy, Elsevier, Oxford medicine library and e-medicine was searched using standardized methodological filter for identifying trials, which represent the most famous scientific sites on the internet.

The most famous paid evidence-based web sites journals and internet sites which represent honest references to most of the Emergency medicine physicians and cardiologists will be searched as:

- BMJ evidence based.
- Cochrane.org
- The journal of trauma.
- The New England journal of medicine.
- American Heart journal.
- Coronary Health Care journal.
- Southern medical journal.
- The journal of critical care.

CRITERIA FOR SELECTING THOSE STUDIES

- a. Initial screen to exclude studies not relevant to the review questions.
- b. Second screen determines which of the relevant studies are evidence based and of the highest quality to be included in the systematic review to be as free from bias as possible.

INCLUSION CRITERIA

- Different articles on the myocardial ischemia in chest pain unit and Emergency patients.
- Studies with appropriate research methodology according to the standards of critical appraisal was included.
- Any type of study design including:
 1. Randomized controlled trials.
 2. Open clinical trials.
 3. Review articles.
 4. Systematic review articles.
 5. Meta-analysis.

EXCLUSION CRITERIA:

- All studies that are not relevant to Myocardial ischemia in emergency patients.
- Rejected articles, articles with poorly designed studies were also excluded.

SUMMARIZING THE RESULTS OF RELEVANT STUDIES:

The results of the best available published studies were summarized.

STUDY PREPARATIONS:

- Using paid evidence-based websites for searching about papers & texts.
- Using Microsoft Office Word documents 2007 in typing and preparation of the systematic review.
- Using Internet Explorer Browser version 7 for searching in the internet about papers, abstracts and texts.

NORMAL CORONARIES

Like all organs, the heart is made of tissue and requires a supply of oxygen and nutrients. Although its chambers are full of blood, the heart receives no nourishment from this blood. The heart receives its own supply of blood from an arteries network, called the coronary arteries. (7)

The coronary arteries are distributed so as to bring adequate blood supply. Despite numerous variations, this rule is always met in healthy hearts. An analysis of the total distribution of the coronary arteries in the heart will show that no areas are left devoid of blood supply (8).

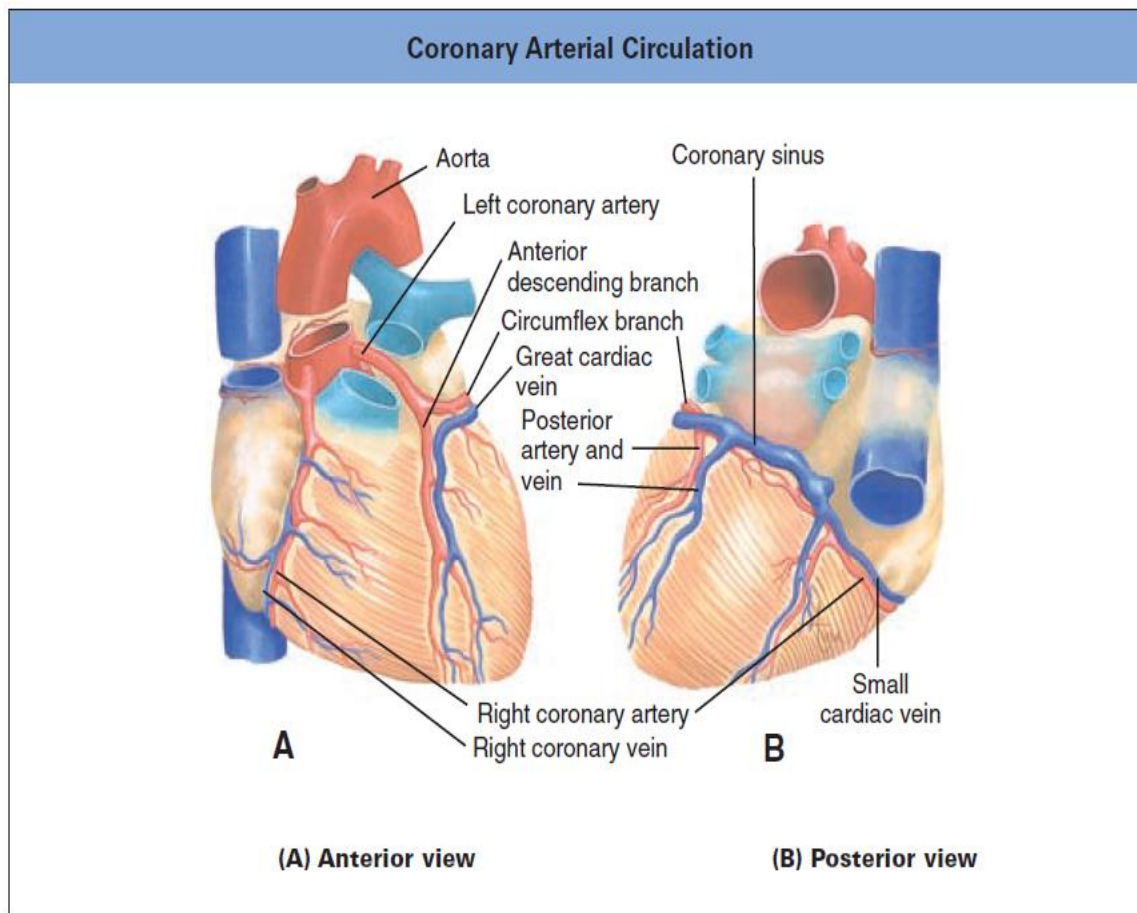


Figure (1): Coronary Artery Anatomy

Left main coronary artery:

The left main coronary artery arises from above the left portion of the aortic valve and then usually divides into two branches, known as the left anterior descending (LAD) and the circumflex (Circ) coronary arteries. In some patients, a third branch arises in between the LAD and the Circ. This is known as the ramus, intermediate, or optional diagonal coronary artery. (7)

(1-2) Left anterior descending artery:

The LAD travels in the groove (known as the **inter-ventricular** groove) that runs in the anterior or front portion of the heart. It sits between the right and the left ventricles or the two lower chambers of the heart. The LAD gives rise to the following two sets of branches: diagonals and septal branches. (7)

The septal branches pass downward into the interventricular septum, which vary in size, number and distribution. Sometimes there is a large first septal branch that is vertically oriented and then breaks into a number of secondary septal branches. In other cases, a more horizontally oriented large septal branch passes parallel to and below the LAD. In still others, a number of septal arteries are roughly comparable in size. These septal branches interconnect with similar septal branches passing upward from the posterior descending branch of the RCA to produce a network of potential collateral channels. The interventricular septum is the most densely vascularized area of the heart, and the first septal branch is its most important potential collateral channel.

The diagonal branches of the LAD pass over the anterolateral aspect of the heart, and it is usually one of these branches, which supplies the apex itself. Although virtually all patients have a single LAD in the anterior interventricular groove, there is a wide variability in the number and size of diagonal branches. More than 90% have one to three such branches. Less than 1% of patients have no diagonal branches. Thus, if none are seen, the angiographer should suspect the possibility that diagonal branches might have originally been present but become totally occluded at its origin from the LAD. (9)

(1-3) The ramus artery:

This vessel is analogous to diagonal branch and usually supplies the free wall along the lateral aspect of the left ventricle. In 78% of patients, the LAD passes all the way around the apex and terminates along the diaphragmatic aspect of the left ventricle. In 22% of patients, however, the LAD fails to reach the diaphragmatic surface, terminating instead either at or even before the cardiac apex. In these cases the posterior descending branch of the RCA is larger and longer than usual, and supplies the apex. Correspondingly, because the LAD doesn't supply the cardiac apex in such cases, its distal segment is smaller and shorter than usual. Early attenuation and narrow distal caliber don't necessarily signify LAD disease if some or the entire cardiac apex is supplied by the posterior descending artery. (10)

(1-4) Left circumflex artery:

The **Circumflex (Circ)** coronary artery is a branch of the left main coronary artery. It travels in the left atrio-ventricular groove that separates the left atrium from the left ventricle. The "Circ" moves away from the LAD and wraps around to the back of the heart. The major branches that it gives off in the proximal or initial portion are known as obtuse marginal or **OM** coronary arteries. As it makes its way to the back or posterior portion of the heart, it gives off one or more left postero-lateral (PL) branches.

In 85% of cases, the Circ terminates at this point and here left coronary artery system is known as a **non-dominant system**. In the other 15% of cases, a **dominant** Circ supplies the PDA or posterior descending artery, which runs in the bottom of the heart within a groove that separates the left from the right ventricle (the posterior inter-ventricular septum).(7)

The left circumflex artery usually gives off one to three large obtuse marginal branches as it passes down the atrio-ventricular groove that supplies the free wall of the left ventricle along its lateral aspect. Beyond the origin of these branches the artery tends to be small. The position of the LCX is best identified in the late phase of coronary injection when the coronary sinus becomes opacified with diluted contrast material that indicates the position of the atrio-ventricular groove and so the LCX as it runs in or near the groove. The LCX also may give rise to one or two left atrial circumflex branches that supply the lateral and posterior aspects of the left atrium.(10)

(1-5) Right coronary artery:

The **right coronary artery (RCA)** originates above the right portion of the aortic valve and runs in the right atrio-ventricular groove towards the crux¹.

The conus artery: it is considered to be the first branch of the RCA. In about 50% of patients this vessel arises at the right coronary ostium or within a few millimeters of the RCA. It passes upward and anteriorly over the right ventricular outflow tract toward the LAD. Its primary importance is to serve as a source of collateral circulation in patients with LAD occlusion. In other 50% of patients, the conus artery arises from a small separate ostium in the right coronary sinus just above the right coronary ostium. (6)

The Sino-atrial branch: it originates from the RCA in 59%, from the LCX in 38% and had a dual blood supply in the remaining 3% of population, it passes obliquely backward through the upper portion of the atrial septum and the antero-medial wall of the right atrium, and send branches to the sinus node and usually to the right atrium or both atria. When it originates from the LCX it may pass backward in the atrial septum or around the postero-lateral wall of the left atrium to reach the sinus node area.(11)

The acute marginal branches: is given off in the proximal to mid portion of the artery, it supplies the anterior wall of the right ventricle; this vessel serves as a source of collateral circulation in cases of LAD occlusion. (8)

The posterior descending artery: this important artery arises from the RCA at the crux in about 85% to make it the dominant artery², and passes forward in the posterior inter-ventricular septum, as it supplies branches to the lower portion of the septum through giving the inferior septal branches and interdigitate with the superior septal branches of the LAD.(10)

The RCA also supplies the postero-lateral artery or PLA to the lower back portion of the left ventricle and the right ventricular branch to the right ventricle.(7)

¹ CRUX: a point on the diaphragmatic surface of the heart where the right atrio-ventricular groove, the left atrio-ventricular groove and the posterior inter-ventricular groove come together.

² The dominant artery is the artery that gives the PDA, and it is the RCA in 85% of population, LCX in 7%, and 8% of population are codominant.(Charles E. Kahn, Jr., MD - CHORUS, 2 February 1995

(1-6) Distribution of the coronary arteries to specific regions of the left ventricular myocardium:

- **The left ventricle:** the diagonal branches of the LAD supply lateral wall of the left ventricle, the terminal portion of the LAD wraps around the apex to supply it and continue to supply the diaphragmatic surface of the left ventricle together with the PDA that anastomose with the termination of the LAD, sometimes when the RCA is dominant the PDA is large that continue in the posterior inter-ventricular septum to the apex to supply all that area. The free posterior wall of the LV is supplied by the OM branches of the LCX; hence the LV is mainly supplied by the left system. .(7)

- **Interventricular septum:** usually the septum receives its blood supply from the anterior inter-ventricular arteries, however; there are two or three other arterial sources for the nourishment of the septum. The LAD supplies the anterior two thirds of the inter-ventricular septum, while the PDA supplies the posterior one third of the inter-ventricular septum. (11)

- **Papillary muscles:** the antero-lateral papillary muscle receives dual blood supply from the diagonal branches of the LAD as well as the LCX, while the postero-medial muscle receives blood supply from the PDA.

- **The sinus node:** receives blood supply from the sinus nodal artery of the RCA in 55% of cases, and from the LCX in 35%, and the sinus node receives dual blood supply in 10% of cases. (12)

- **The atrioventricular node:** receives its blood supply from the atrio-ventricular branch of the PDA in 80% of cases, from the LCX in 10%, and dual blood supply is seen in the last 10% of cases. The presence of collateral circulation from the LAD makes the AVN more prone to ischemia in cases of LAD occlusion than the SAN .(11)

- **His bundle and the bundle branches:** receives blood supply from the AV nodal artery and the septal penetrating branches of the LAD. The anterior fascicle of the left bundle branch receives blood supply from the penetrating septal arteries of the LAD, while the posterior fascicle receives dual blood supply from the septal penetrating branches of the LAD as well as branches from the PDA. .(9)

- **The right ventricle:** it receives its main blood supply from the RCA that gives the anterior ventricular branch to the anterior wall of the right ventricle, the posterior ventricular branch to the diaphragmatic surface of the RV and the PDA that gives blood supply to the RV throughout its course. The anterior inter-ventricular branch gives blood supply to the adjacent parts of the RV while it runs in the anterior inter-ventricular groove. (13)

Chest Pain in Emergency Room

More than 6 million patients present with chest pain and suspected acute coronary syndrome (ACS) to emergency departments (EDs) across the U.S. annually. These patients require rapid and efficient triage to hospitalization versus discharge to maximize appropriate allocation of resources to the highest-risk patients who require timely life-saving therapy.(5) Most commonly repeated Causes are (6)

A. Causes of chest pain that are immediately life-threatening:

- **Heart attack (acute myocardial infarction):** A heart attack occurs when blood flow to the arteries that supply the heart (coronary arteries) becomes blocked. With decreased blood flow, the muscle of the heart does not receive enough oxygen.(6) This can cause damage, deterioration, and death of the heart muscle.
- **Angina:** Angina is chest pain related to an imbalance between the oxygen demand of the heart and the amount of oxygen delivered via the blood. It is caused by blockage or narrowing of the blood vessels that supply blood to the heart. Angina differs from a heart attack in that arteries are not completely blocked, and it causes little or no permanent damage to the heart. (8) Stable angina occurs repetitively and predictably while patient is doing exercise and goes away with rest. Unstable angina results in unusual and unpredictable pain not relieved totally by rest, or pain that actually occurs at rest. (9)
- **Aortic dissection:** The aorta is the main artery that supplies blood to the vital organs of the body, such as brain, heart, kidneys, lungs, and intestines. Dissection means a tear in the inner lining of the aorta. This can cause massive internal bleeding and interrupt blood flow to the vital organs. (11)
- **Pulmonary embolism:** A pulmonary embolus is a blood clot in one of the major blood vessels that supplies lungs. It is a potentially life-threatening cause of chest pain but is not associated with the heart. (14)
- **Spontaneous pneumothorax:** often called a collapsed lung, this condition occurs when air enters the saclike space between the chest wall and the lung tissue. Normally, negative pressure in the chest cavity allows the lungs to expand. When a spontaneous pneumothorax occurs, air enters the chest cavity. When the pressure balance is lost, the lung is unable to re-expand. This cuts off the normal oxygen supply in the body. (19)
- **Perforated viscus:** A perforated viscus is a hole or tear in the wall of any area of the gastrointestinal tract. This allows air to enter the abdominal cavity, which irritates the diaphragm, and can cause chest pain. (22)
- **Cocaine-induced chest pain:** Cocaine causes the blood vessels in the body to constrict. This can decrease blood flow to the heart, causing chest pain. Cocaine also accelerates the progression of atherosclerosis, a risk factor for a heart attack. (24)

B. Causes of chest pain that are not immediately life-threatening

* **Acute pericarditis:** means inflammation of the pericardium, which is the sac that covers the heart.

- **Mitral valve prolapse:** It is an abnormality of one of the heart valves in which the "leaves" of the valve bulge into the upper heart chamber during contraction.

When this occurs, a small amount of blood flows backward in the heart. This may cause chest pain in some people. (26)

- **Pneumonia:** Pneumonia is an infection of the lung tissue. Chest pain occurs because of inflammation to the lining of the lungs. (27)
- **Disorders of the esophagus:** Chest pain from esophageal disorders can be an alarming symptom because it often mimics chest pain from a heart attack. (28)
 - **Acid reflux disease** (gastro-esophageal reflux disease, GERD, heartburn) occurs when acidic digestive juices flow backward from the stomach into the esophagus. Resulting heartburn is sometimes experienced as chest pain. (29)
 - **Esophagitis** is an inflammation of the esophagus. (30)
 - **Esophageal spasm** is defined as excessive, intensified, or uncoordinated contractions of smooth muscles of the esophagus. (31)
- **Costochondritis:** an inflammation of the cartilage between the ribs. Pain is typically located in the mid-chest, with intermittently dull and sharp pain that may be increased with deep breaths, movement, and deep touch. (38)
- **Herpes zoster:** Also known as shingles, this is a reactivation of the viral infection that causes chickenpox. With shingles, a rash occurs, usually only on one small part of the body. (39) The pain, often very severe, is usually confined to the area of the rash. The pain may precede the rash by 4-7 days. Risk factors include conditions in which the immune system is compromised, such as advanced age, HIV, or cancer. (40) Herpes zoster is highly contagious to people who have not had chickenpox or have not been vaccinated against chickenpox for the five days before and the five days after the appearance of the rash. (27)

Chest pressure with dyspnea leads physicians to consider an acute coronary syndrome such as unstable angina or MI, but these symptoms also may represent chest wall pain or PE. Dyspnea is common in patients with heart failure, whereas dyspnea with fever is characteristic of pneumonia and bronchitis. (37) The usual descriptions of peptic ulcer disease and GERD include epigastric discomfort and retrosternal burning, but often it is difficult to distinguish clearly between classic “heart-burn” and classic “chest pressure.” Although it often is thought that symptoms of anxiety can help distinguish pulmonary diseases from other causes of chest pain, this is not a consistent finding and should not be relied upon. (42) There is enough overlap among clinical manifestations of different causes of chest pain to make “classic” symptoms unhelpful in differentiating among diagnoses and ruling out serious causes. (46) However, there are several validated clinical decision rules that combine groups of symptoms. (22) It is important to obtain a clear history of the onset and evolution of chest pain, with particular attention to details as location, quality, duration, and aggravating or alleviating factors. Certain key symptoms and clinical findings help rule in (or) out specific diagnoses. (45)

Determining whether pain is (1) sub-sternal, (2) provoked by exertion, or (3) relieved by rest or nitroglycerin helps to clarify whether it is typical **anginal** pain (has all three characteristics), atypical anginal pain (has two characteristics), or **non-anginal** pain (has one characteristic) (47). Anginal chest pain has a high risk for CAD in all age groups; atypical anginal chest pain carries intermediate risk for CAD in women older

than 50 years and in all men; and non-anginal chest pain carries intermediate risk for CAD in women older than 60 years and men older than 40 years.(14)

The likelihood of MI is higher if there is pain radiating to both arms(5) hypotension,(6). an S3 gallop on physical examination or diaphoresis(9) Other factors predicting MI include age greater than 60 years, male sex, and prior MI.(15) MI is less likely if pain is sharp or pleuritic. If the pain is reproducible by palpation of a specific tender area, the likelihood of MI decreases but chest wall pain may increase. A history of rheumatoid arthritis or osteoarthritis also increases the likelihood of chest wall pain.(16) **The Rouen decision rule** reliably predicts patients with chest pain and normal or nonspecific electrocardiogram (ECG) at higher risk for MI. However, because up to 3 percent of patients initially diagnosed with a non-cardiac cause of chest pain suffer death or MI within 30 days of presentation, patients with cardiac risk factors such as male sex, greater age, diabetes, hyperlipidemia, prior CAD, or heart failure warrant close follow-up (17)

Rouen Decision Rule for Myocardial Infarction

Clinical Characteristics . (One point for each clinical characteristic).

Age greater than 60 years

Diaphoresis

History of MI or angina

Male sex

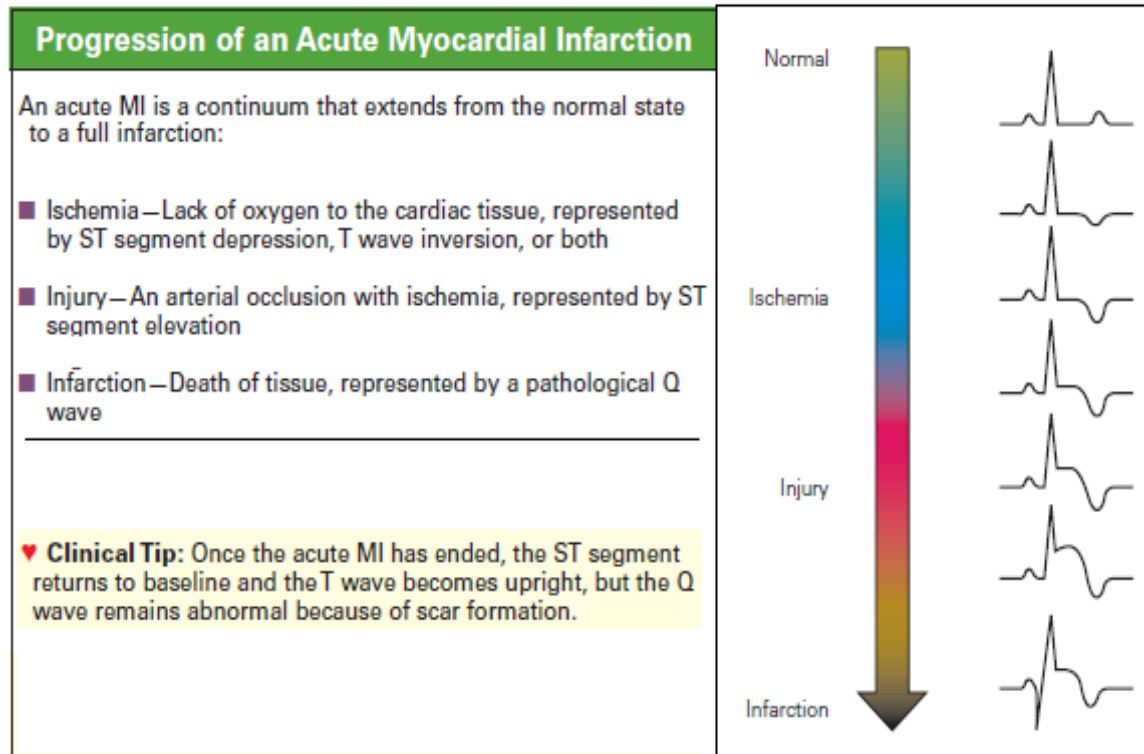
Pain described as pressure

Pain radiating to arm, shoulder, neck, or jaw

NOTE: At no level of risk MI can be completely ruled out

Score*	Risk of MI (%)
0	Up to 0.6
1	Up to 3.4
2	Up to 4.8
3	Up to 12.0
4	Up to 26.0

Heart failure alone is an uncommon cause of chest pain, it may accompany acute coronary syndrome, valve disease or MI. Almost all patients with heart failure have exertional dyspnea, so the absence of exertional dyspnea is helpful in ruling out this diagnosis. Important diagnostic tests when evaluating for acute coronary syndrome in Emergency room include the 12-lead ECG and serum markers of myocardial damage.(7)



Picture 2: ECG progression of Myocardial Ischemia (8)

ECG findings that most strongly suggest MI are ST segment elevation, Q waves and conduction defect, especially if such findings are new compared with a previous ECG. New T-wave inversion increases the likelihood of MI. However, none of these findings is sensitive enough that its absence can exclude MI. (56)

The most common markers of myocardial damage are **creatinine kinase**, the **MB isoenzyme** of creatine kinase (**CK-MB**), **troponin T**, and **troponin I**. A CK-MB level greater than 6.0 ng per mL (6.0 mcg per L) within nine hours of presentation for emergency care modestly increases the likelihood of MI or death in the next 30 days. (34) Elevated levels of either troponin T (i.e., higher than 2 ng per mL [2 mcg per L]) at least eight hours from presentation or troponin I (i.e., higher than 1 ng per mL [1 mcg per L]) at least 6 hours from presentation support the diagnosis of MI or acute coronary syndrome and increase the likelihood of death or recurrent MI within 30 days. (36) A normal level of troponin T or troponin I between 6 and 72 hours after the onset of chest pain is strong evidence against MI and acute coronary syndrome, particularly if the ECG is normal or near normal. (28) In one study (29) of 773 patients who each presented to emergency departments with chest pain and had a normal ECG, researchers found that only 0.3 percent of those with a normal troponin I at six hours and 1.1 percent of those with a normal troponin T at six hours experienced acute MI or death in the 30 days following presentation. Thus, individuals with chest pain who have a history that indicates low risk of cardiovascular disease, a normal or near-normal ECG, and normal troponin levels can safely be evaluated as outpatients. (37)

Patients at low risk usually do not need further testing unless there are other risk factors in their family or medical history that markedly increase their likelihood of CAD.

Patients at intermediate risk for CAD who can exercise and have no left bundle branch block, preexcitation, or significant resting ST depression on their ECG can be evaluated with exercise stress ECG. (27) Patients with baseline ECG abnormalities should have perfusion imaging performed along with a stress ECG, and patients who cannot exercise may be evaluated with a pharmacologic stress or vasodilator test (e.g., dobutamine [Dobutrex], adenosine [Adenocard]). High risk patients for CAD should proceed directly to angiography, which allows definitive assessment of coronary artery anatomy for patients in whom other testing is non-diagnostic and for patients who could benefit from re-vascularization.(30) The exercise electrocardiography (ExECG) role in the ED among patients with intermediate or low risk for ACS has been tested in a number of studies (6,7). On the basis of the collective data, it can be surmised that ExECG is a good and cost-effective test to triage patients with intermediate risk. There are, however, several limitations to ExECG: the percentage of patients who present to the ED and are unable to exercise has been reported to be as high as 35%, the rate of suboptimal exercise is largely unaccounted for in the published studies, the rate of false-positive tests is unacceptably high especially among women. Furthermore, stress imaging testing has been shown to have excellent accuracy and cost-benefit in stratifying patients in the ED (8).

Multiple imaging studies have been performed in the ED and CPU settings in patients with suspected ACS or those who were admitted with the diagnosis of acute myocardial infarction. Resting ECG have been reported to be 90% sensitive and 65% specific for the diagnosis of ACS or acute myocardial infarction (9). A large randomized study of rest nuclear imaging in the ED showed that there was a 10% absolute reduction in hospitalization in patients with chest pain and non-diagnostic ECG when perfusion data was included in the decision-making (8). In contrast echocardiography (CE) compared with a modified Thrombolysis In Myocardial Infarction (TIMI) score for triage of nearly 1,000 patients presenting with chest pain and non-diagnostic ECG. Both regional myocardial function and perfusion were analyzed by rest CE and related to early (in the first 24 h), intermediate (at 30 days), and late (1 year) events. The comparison of CE was performed with the modified TIMI (mTIMI) score, which initially did not include serum troponin levels. Troponin levels became available during CPU stay after CE was performed. The presence of normal regional function (RF) was most efficient in predicting lowest risk in the first 24h. (23)

The lowest mTIMI score failed to identify approximately 4% of ACS (myocardial infarction), which is consistent with previous data. Further, CE also was able to classify patients with an intermediate mTIMI score into low risk (normal RF) and high risk (abnormal RF) for ACS. For a given RF finding, the presence of perfusion abnormality by CE was indicative of the highest risk whereas normal perfusion identified a very low risk (0.4%) for ACS. Even the subsequent complete TIMI score (which included the troponin level) failed to predict up to 5% of early events. These findings are a confirmation that clinical variable plus cardiac enzymes alone are insufficient to adequately triage low- and intermediate-risk patients in CPU, and the reliable discrimination would need an imaging test. (23)

Which imaging test does one choose? In the case of nuclear imaging, the wealth of experience with myocardial perfusion imaging, the safety of adenosine or stress imaging, and the recent approach of using fatty acid imaging to identify ischemic

memory offer tremendous advantages in the ED (11). However, the ability to readily obtain information on left ventricular regional function and perfusion by rest CE at bedside is a significant advantage from a practical and universal applicability. Previous echocardiographic studies in the ED were performed at a time when a significant proportion of transthoracic echocardiograms were suboptimal, thus limiting the clinical applicability of the approach. (11) The advent of CE and new transducer technology has had a tremendous positive impact on image quality, making transthoracic echocardiography interpretable in 90% of studies. Current transducer and equipment technology also allow myocardial perfusion imaging with little additional operator interaction. (26)

The limitations of CE have to do with the traditional arguments of image quality and operator dependency of echocardiography. Contrast echocardiography has made the former problem a rarity and, with CE wall motion and thickening, can be appreciated even by a modestly trained eye. Interpretation of perfusion may be more challenging for the untrained eye. However, the growth of telemedicine means that the expert can both guide the acquisition and read the information in real time. These issues are not prohibitory to the application of CE or, for that matter, any imaging modality in the ED. Recent experimental data from work on targeted imaging using either radioisotopes or micro-bubbles add another exciting dimension to imaging in the ED. (56) For example, annexin-A5 can be bound to polymer micro-bubbles, which can then be insonated with ultrasound to image myocyte apoptosis in the infarcted myocardium (12). It is also possible that the endothelial alterations during ischemic injury will also offer a convenient target for CE in ED in the future(13).

There are challenges to contend with implementation of imaging in the CPU protocol for triage. Patients with chest pain who present after-hours to the ED require additional resources that have to be specifically allocated, readily available, and carefully monitored (e.g., the quality of data obtained during "afterhours").(45) The economics of imaging, whether it be rest or stress imaging in the CPU, is uncertain. Contrast echocardiography will certainly have more resource-based relative value units than standard non-contrast two-dimensional echocardiography but this would still favorably compare with resting or stress nuclear testing. (44) There is a burgeoning interest in studying the role of multislice computed tomography imaging of coronary anatomy in patients presenting to the CPU in the ED. Whether multi-slice computed tomography will cut into or complement CE or nuclear imaging remains to be seen. Cardiac magnetic resonance seems to be least practical because of the time it takes to obtain an image. Finally, the adverse clinical outcome and the fear of litigation of missed ACS in <1% of patients have been strong deterrents to the implementation of any of the early diagnostic protocols in the ED. (51) This issue has been amplified by the uncertainty of marginal elevations of troponin in the setting of atypical symptoms and suspected ACS. All of this has further fueled the practice of watchful waiting in the CPU, with its attendant enormous cost burden. Imaging stress testing may alleviate some of this burden and arguably improve the efficiency and effectiveness of triage of patients in the CPU by bringing the cardiologist into play early in the process of clinical decision-making. (62)

Therefore, it is imperative that we continue to find algorithms that may help to reliably identify the lowest-risk patients who may not even have coronary artery disease (CAD) because the economic burden of hospitalization of these patients is enormous. During the last decade, chest pain units (CPUs) in the ED were born out of such an effort to triage patients with intermediate and low-risk for ACS (5). Typically, these units hold patients for as long as 12 h for clinical observation, during which time serial ECGs and cardiac enzymes are performed. A positive evaluation leads to hospitalization, whereas a negative evaluation leads to stress testing or discharge without stress testing. (18)

RISK FACTORS AND PATHOPHYSIOLOGY

A risk factor for CAD is any characteristic or behavior that increases chances for developing coronary artery disease and its complications. Some risk factors can be controlled, or modified (hypertension, DM, cigarette smoking, excess weight.), but others can not (age, sex, family history). Risk factors interact with each other, the more risk factors; the greater chances of developing coronary disease .

Table (1): Risk factors for coronary artery disease (14)

Modifiable risk factors	Non modifiable risk factors
Hypertension	Advanced Age
Diabetes mellitus	
Dyslipidaemia	Gender (males are more susceptible)
Cigarette smoking	
Excess weight	Race(African Americans tend to have higher blood pressure than other populations)
Metabolic syndrome	
Sedentary life style	
Stress	Family history
Oral contraceptives for women	

Sometimes coronary artery disease develops without any classic risk factors. Researchers are studying other possible factors, including the following:

C- reactive protein.

Homocysteine.

Hyperfibrinogenaemia.

Lipoprotein (a).

(1) Modifiable Risk Factors

a. Hypertension:

The positive relationship between hypertension and coronary artery disease has long been recognized, which is strong, continuous, predictive and etiologically significant for those with or without CAD

Definition of hypertension: A systolic pressure is consistently at 140 or higher or a diastolic pressure consistently at 90 or higher.

Stages of hypertension (346)

- Normal: systolic BP <120 and diastolic BP <80
- Prehypertension: SBP 120-139 or DBP 80-89
- Stage 1 hypertension: SBP 140-159 or DBP 90-99
- Stage 2 hypertension: SBP \geq 160 or DBP \geq 100

Prevalence of hypertension:

The estimated prevalence of hypertension in Egypt was 26.3% compared to approx 1 in 5 or 18.38% or 50 million people in USA i.e. about 25% of population and about 80-85% affected are not treated in England while the world wide prevalence is estimated by 600 million people affected worldwide Hypertension prevalence in Egypt increased progressively with age, from 7.8% in (25-34)-year-olds to 56.6% in those 75 years or older. Hypertension was slightly more common in women than in men (26.9% versus 25.7%, respectively)(15).

The importance of systolic hypertension and its association with increased cardiovascular risk was demonstrated in the Copenhagen City Heart Study.5 which define isolated systolic hypertension as SBP \geq 160 mm Hg and DBP <90 mm Hg. (16)

In those older than age 50, systolic blood pressure (SBP) of >140 mmHg is a more important cardiovascular disease (CVD) risk factor than diastolic BP (DBP); beginning at 115/75 mmHg, CVD risk doubles for each increment of 20/10 mmHg. DBP is a more potent cardiovascular risk factor than SBP until age 50; thereafter, SBP is more important (17)

Effect of hypertension on the CVS:

On blood vessels; The excessive pressure in your arteries from high blood pressure alters the cells of the arteries' inner lining. That launches a cascade of events that make artery walls thick and stiff, to cause what is called arteriosclerosis or hardening of the arteries. Circulating fats pass through the altered cells and accumulate to start the process of atherosclerosis. These changes can affect arteries throughout the body, including coronary arteries. The damage can cause chest pain (angina), heart attack, and heart failure. Through these weak areas of arteries blood can cause a section of it to enlarge and cause aneurysms that may cause life-threatening hemorrhages.

On the heart; Enlarged left heart. High blood pressure forces heart to overexert itself. This causes the left ventricle to enlarge (left ventricular hypertrophy). This enlargement limits the ventricle's ability to expand sufficiently and to completely fill with blood. The ventricle can't pump out as much blood to the body. This condition increases the risk of heart attack, heart failure and sudden cardiac death. (18)

Risk stratification:

this classification is used to determine the cardiovascular risk of the patient, it is determined by the level of blood pressure (based on the average of two or more readings taken, when systolic and diastolic blood pressure falls into two different categories; the higher category should be selected to classify the patient), and the presence or absence of end organ damage or other risk factors such as smoking.

The WHO classification of hypertensive patient:

Risk group A: patient with pre-hypertension or hypertension stage I or II who don't have clinical cardiovascular disease, endorgan damage or other risk factors, they require vigorous life style modification with careful blood pressure monitoring, pharmacological therapy may be added if the goal blood pressure is not achieved. In Stage II hypertensive patients' drug therapy is warranted.

Risk group B : patient with pre-hypertension or hypertension stage I or II who don't have clinical cardiovascular disease or end-organ damage but have one or more risk factors other than diabetes mellitus, require life style modification, drug therapy and management of risk factors.

Risk group C: these are the hypertensive patients with clinical cardio-vascular disease or end organ damage. According to the Joint National Committee criteria; any pre-hypertensive patient with renal insufficiency or diabetes mellitus should be considered for life style modification and drug treatment.

Antihypertensive treatment:

Neal B. and his colleagues showed that antihypertensive therapy has been associated with reductions in [1] stroke incidence, averaging 35–40 %; [2] myocardial infarction (MI), averaging 20–25 %; and [3] HF, averaging >50 % It estimated that in patients with stage 1 hypertension (SBP 140–159 mmHg and/or DBP 90–99 mmHg) and additional cardiovascular risk factors, achieving a sustained 12 mmHg reduction in SBP over 10 years will prevent 1 death for every 11 patients treated. In the added presence of CVD or target organ damage, only nine patients would require such BP reduction to prevent one death (21).

Lowering both SBP and DBP reduces ischemia and prevents CVD events in patients with CAD, in part by reducing myocardial oxygen demand. One caveat with respect to antihypertensive treatment in patients with CAD is the finding in some studies of an apparent increase in coronary risk at low levels of DBP as proven in the SHEP³ study that shows that lowering DBP to <55 or 60 mmHg was associated with an increase in cardiovascular events, including MI. (22)

Unless contraindicated, pharmacologic therapy should be initiated with a BB. BBs will lower BP; reduce symptoms of angina; improve mortality; reduce cardiac output, heart rate and AV conduction. If contraindicated, CCBs are good alternative.

increased risk of cardiac ischemic events was associated with antihypertensive treatment in elderly men whose diastolic pressure was 90 mm Hg or lower. A plausible explanation is that lowering the blood pressure could compromise coronary flow in a subgroup of patients with marginal coronary perfusion. They support the concept of a "J-shaped curve" relationship between diastolic blood pressure and myocardial infarction, and they suggest that lowering blood pressure below an optimal level in elderly patients paradoxically increases the risk of developing cardiac ischemia. (23)

As regarding choice of antihypertensive drugs, the ALLHAT⁴ study, which involved more than 40,000 hypertensive individuals, (26) stated that there were no differences in the primary CHD outcome or mortality between the thiazide-type diuretic,

³SHEP trial: Systolic Hypertension in the Elderly Program Trial.

⁴ ALLHAT study: the Antihypertensive and Lipid Lowering Treatment to prevent Heart Attack Trial.

chlorthalidone; the ACEI, lisinopril; or the CCB, amlodipine, although sub-analysis of the MRFIT⁵ study from which it was inferred that in a subset of 12,866 high-risk men aged 35 - 57 years hypertensive patients (with evidence of ECG abnormality) diuretic treatment have harmful rather than beneficial. (24)

Life style and risk factor modification:

Weight loss also of as little as 10 lbs (4.5kg) reduces BP and/or prevents hypertension in a large proportion of overweight persons, although the ideal is to maintain normal body weight.

BP is benefited by adoption of the Dietary Approaches to Stop Hypertension (DASH) eating plan (25) which is diet rich in fruits, vegetables, and low fat dairy products with a reduced content of dietary cholesterol as well as saturated and total fat. It is rich in potassium and calcium content. Dietary sodium should be reduced to no more than 100 mmol per day (2.4 g of sodium). A met analysis that studied the effect of aerobic exercise on blood pressure recommended that hypertensive patient should engage in regular aerobic physical activity such as brisk walking at least 30 minutes per day most days of the week (35).

The PREMIER clinical trial recommended the combinations of two or more lifestyle modifications to achieve better results with more cardiovascular risk reduction

Table (2): Lifestyle modifications to prevent and manage hypertension (27)

Modification	Recommendation	Approximate SBP Reduction
Weight reduction	Maintain normal body weight (BMI 18.5–24.9 kg/m ²).	5–20 mmHg/10kg
Adopt DASH ⁶ eating plan	Consume a diet of fruits, vegetables, and low fat dairy products with low content of saturated and total fat.	8–14 mmHg
Dietary sodium reduction	Reduce dietary sodium intake to no more than 100 mmol/day (2.4 g sodium or 6 g sodium chloride).	2–8 mmHg
Physical activity	Engage in regular aerobic physical activity such as brisk walking (at least 30 min/day, most days of the week).	4–9 mmHg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks/day (e.g., 24 oz beer, 10 oz wine, or 3 oz 80-proof whiskey) in most men, and to no more than 1 drink/day in women and lighter weight persons.	2–4 mmHg

⁵ MRFIT: Multiple Risk Factor Intervention Trial

⁶ - DASH = Dietary Approaches to Stop Hypertension; SBP, systolic blood pressure

b. Diabetes mellitus:**DM as a CAD risk factor:**

Myocardial ischemia is a major complication in the course of diabetes, causing 75% of diabetes-related deaths. Moreover, patients with diabetes have a higher rate of sudden death and poorer outcomes after myocardial infarction as it increase the risk of CAD by a factor of two to four. (28).

Several large screening studies for silent myocardial ischemia (SMI) in type II diabetic patients have been performed demonstrating variable prevalence rates from 6.4 to 58%. the results that have been updated by DIAD⁷ to instate the prevalence of SMI to be >20% in asymptomatic patients with type II diabetes. (30). While type I diabetic patients have been screened for the incidence of CAD by (EDC)⁸study (31) and Eurodiab⁹(32), reported an incidence of total coronary events (including electrocardiogram [ECG] changes) of 16% over 10 years and 9% over 7 years, respectively, of follow-up in type 1 diabetic patients. As the mean age at baseline was ~30 years, these incidence rates reflect the experience of those aged in their late30s. In EDC, total CAD incidence (including angina and ischemic ECG changes) was >2% per year for those aged >35 years. (33)

▶ A study comparing the incidence of CAD in diabetic and non-diabetic patients revealed that multi-vessel disease was more common in diabetic than non-diabetic patients, three-vessel disease being the most common. Furthermore, 38 of 79 diabetic patients had three-vessel disease compared to 29 of 79 controls. Diabetic patients were also more likely to have more segments diseased in one vessel (34).

▶ Silent ischemia is a particular concern in patients with diabetes.(35.) pain response to ischemia is often absent or blunted in these patients (possibly related to diabetic neuropathy resulting in a lack of symptoms or an atypical presentation. Thus, the first sign of CAD may be acute myocardial infarction or cardiac death. This late presentation contributes to higher mortality rate in diabetic patients. (35.)

▶ A study published in Diabetes journal concluded that; in a direct manner, mean HbA1c over 18 years predicted coronary atherosclerosis in type 1 diabetic patients with no symptoms of coronary heart disease. And that a tighter glycemic control could reduce the well-known premature coronary heart disease in those patients. Silent coronary atheromatosis is highly prevalent as abnormal exercise ECGs were found in 15% of studied patients, and angiographic diameter stenosis of >50% in one or more of the main coronary arteries was found in 34% of patients, so; a special reconsideration of diagnosis and early treatment of this disease in type 1 diabetes should be considered. (36). Also **Elizabeth Anne** found that silent ischemia occurs in > 20% of asymptomatic people with type II diabetes. (37)

⁷DIAD: The Detection of Ischemia in Asymptomatic Diabetics Investigators

⁸ EDC: the Pittsburgh Epidemiology of Diabetes Complications

⁹Eurodiab.: a multicenter, clinic-based study in Europe.

Pathophysiology of CAD in DM:

Insulin receptors are found on endothelial cells of both large and small blood vessels. They are thought to mediate glucose homeostasis and control of vascular tone. Insulin has shown to effect the secretion of the potent vasoconstrictors vascular endothelial growth factor and endothelin 1. Insulin acts as a vasodilator through secretion of endothelial nitric oxide synthase. Interestingly this effect is impaired in diabetes. (38)

Endothelial dysfunction¹⁰ as impaired vasodilatation is associated with increased cardiovascular risk and is apparent in patients with insulin resistance even before the development of overt hyperglycemia. (38)

Prolonged hyperglycemia results in non-enzymatic glycosylation of proteins and lipids, oxidative stress, and protein kinase C activation that leads to irreversible atherosclerosis. (39)

Dyslipidaemia is also involved in the pathogenesis of CAD, as NIDDM is associated with decreased HDL¹¹ and increased synthesis of the highly atherogenic LDL¹², VLDL¹³ and TG¹⁴. In the presence of hyperglycaemia this lipoprotein becomes glycosylated and is poorly recognized by the LDL receptor. It is scavenged by tissue macrophages creating the foam cell, a constituent of the atherosclerotic plaque. (40)

DM is associated with up regulation of systemic acute phase reactants including C reactive protein, which is associated with adverse cardiac outcomes. Circulating leucocytes are recruited at atherosclerotic sites by adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1). During endothelial activation the soluble form of VCAM-1 is shed into the circulation and is found in higher concentrations in patients with NIDDM than in non-diabetic controls. Concentrations of soluble VCAM-1 are also independently associated with increased coronary risk in patients with NIDDM. Increased concentrations of Von Willebrand factor, factor VII,VIII and plasminogen activator inhibitor type 1 are associated with the diabetic state resulting in potentiation of the coagulation cascade and platelet activation. (38)

Natural history of CAD with DM:

Atherosclerosis has more aggressive course in diabetics that is because DM is associated with platelet and endothelial dysfunction that results in accelerated atherosclerosis and plaque instability. Diabetic atheromatous plaques have greater lipid deposits and numbers of phagocytes. Also, endothelial dysfunction is thought to induce negative arterial remodeling in response to atherosclerosis resulting in a decrease in luminal size. Rate of post PCI re-stenosis is higher in diabetics as rate of neointimal proliferation by vascular smooth muscle cells as a consequence of endothelial damage after balloon inflation and stent placement is significantly higher among diabetic patients

¹⁰ Endothelial dysfunction: the vasoconstrictor forces overweigh the vasodilator one.

¹¹ HDL: High-density lipoprotein.

¹² LDL: low-density lipoprotein.

¹³ VLDL: very low density lipoprotein.

¹⁴ TG: triglycerides.

after PCI, it was found also that DM has been shown to be associated with increased severity of CAD more than in non-diabetic. (41)

Concerning sex variability, It is noted that CAD is more severe in diabetic females which is assumed to be due to the effect of diabetes on sex hormones with loss of the pre-menopausal cardio-protection (42)

About ethnicity, some studies stated that mortality rates from CAD are 40% higher than those seen among whites. As **Thomas et al**, examined 106 consecutive angiograms of Arab women undergoing cardiac catheterization. They found that 82 angiograms showed evidence of CAD. Of these, 59 had NIDDM and had an increased severity of disease but as this study has been accused by being relatively small, further studies are needed to confirm these results. (43)

As regarding dyslipidaemia, the severity of angiographic CAD is related to the number of LDL particles and plasma lipoprotein (a) concentration in patients with NIDDM, and positively associated with IDL¹⁵ and negatively associated with a subtype of HDL. (44).

Inflammatory markers - especially C-reactive protein - are also associated with increase CAD risk. Also CAD tends to affect more than one vessel in diabetics, who exhibit small caliber vessels, with high incidence of left main stem affection. (45).

Diabetic patients are associated with increased coronary artery calcification scores with a reduced risk of procedural success and increased risk of MACE¹⁶ after PCI. Unfortunately, collateral vessel development thought to be an important cardio-protective mechanism - has been shown to be impaired in DM.(46).

Increase the percentage of glycosylated haemoglobin A1c, is associated with increased severity of disease, the initial results from the UK prospective diabetes study showed that each 1% reduction in HbA1c was associated with a 14% reduction in risk for myocardial infarction.(47). Prevalence of CAD with type II diabetes, makes the American Diabetes Association (ADA) recommends performing a cardiovascular risk assessment at least yearly.

C. Dyslipidaemia:

Cholesterol is a fatty substance that circulates in blood, which is an important structural component of all human cells. The body obtains cholesterol through 2 methods: via the liver, which produces about 75% of cholesterol, and through food, which accounts for 25%. (48) Cholesterol is of two types HDL, which is the good type and is associated with decrease the CAD risk and the LDL (the bad type), which is associated with an increased risk of heart attacks and strokes.

Dyslipidaemia is elevation of plasma cholesterol and/or TGs or a low HDL level that contributes to the development of atherosclerosis through deposition within the walls of the arteries that eventually form atherosclerotic plaques.(48)

Causes of dyslipidaemia:

Many factors involved in development of acquired dyslipidaemia, which are:

¹⁵ IDL: intermediate density lipoprotein

¹⁶ MACE: Major Adverse Cardiac Events.

–Metabolic causes

- a. Diabetes (that may impair the removal of triglyceride rich Particles).
- b. Obesity..
- c. Hyperuricaemia.
- d. Glycogen storage disease (type I)

–Hormonal influences:

- a. Insulin (as hyperinsulinaemia leads to increased production of VLDL)
- b. Estrogen.
- c. Thyroxin.

- Nutritional influences:

- a. Alcohol.
- b. High carbohydrate intake.

- Disease states:

- a. Renal disease: nephrotic syndrome, renal failure.
- b. Paraproteinaemias.

- Drugs: 1. Diuretics.2. Beta blockers.3. Glucocorticoids.4. Estrogen replacement

Patients with poorly controlled diabetes tend to have higher triglyceride levels than patients with well-controlled diabetes there is growing evidence that postprandial hyperlipidaemia in patients with diabetes is prolonged, which means that the arteries are exposed to atherogenic particles for extended periods. (49)

Many studies have shown that people with elevated total cholesterol are at an increased risk for future heart attacks and death. National guidelines now recommend that, in addition to total cholesterol, everyone should know their LDL and HDL levels because they offer a more specific estimate of the risk of developing arterial blockages. Obesity and nutritional are factors that contribute to hyper-lipidaemia. Insulin resistance with hyperinsulinaemia is common in patients with truncal obesity and may increase VLDL production. Diet may be important in many patients. (50)

The latest guidelines recommend an optional goal of an LDL level of less than 70 mg/dL in persons at very high risk, which is defined as patients with known heart disease and multiple risk factors (especially diabetes), multiple or poorly controlled risk factors (for example, continued cigarette smoking), recent heart attack or acute cardiac chest pain. (51). Persons without heart disease who have other risk factors for developing heart disease (for example, diabetes mellitus, hypertension, family history of heart disease, or smoking) should aim for LDL levels less than 130 mg/dL and, ideally, less than 100 mg/dL.(51)

Oxidatively modified low density lipoprotein (Ox-LDL) plays an important role in the development of atherosclerosis as its uptake by macrophages and smooth muscle cells leads to formation of foam cells which is a critical step in the evolution of the pathological state. (52)

MDA-LDL¹⁷ concentrations are higher in patients with severe disease, such as multi-vessel disease, which shows that not only the MDA-LDL concentrations are raised in patients with CAD but also the concentrations reflect the severity of the pathogenic state. (53)

¹⁷MDA-LDL: malondialdehyde modified LDL.

In studying the topographic distribution of atherosclerosis and their relation to risk factors there was found that high non-HDL cholesterol and low HDL cholesterol concentrations associate with more extensive fatty streaks and raised lesions in all regions of abdominal aorta and RCA. (54)

It has been shown that the greater the concentration of LDL, the greater the risk of developing atherosclerosis. The relationship between LDL and atherosclerosis is becoming clearer, with the revelation of the structure, binding domains and the molecular pathways involved in the production of modified LDL. (55)

Increase LDL level as a result of increased consumption of saturated animal fat leads also to down regulation of the LDL receptors with subsequent increase LDL level that is accumulated sub-intimally. (56)

MIRACL¹⁸ trial examined the fact that early and intensive treatment with high dose atorvastatin therapy begun immediately after the onset of an acute coronary event might produce beneficial clinical effects. (57)

The National Cholesterol Education Program Adult Treatment Panel III (NECP ATP III) has made the recommendations for the treatment of hypercholesterolaemia with target levels depends on overall risk of cardiovascular death or non fatal myocardial infarction to reach LDL cholesterol level >100 mg/dl for high risk patients. (58)

Table (3): Overview of Current Recommendations from the National Cholesterol Education

Hypertriglyceridaemia:

Risk Category	LDL Goal	Initiate Lifestyle Changes When LDL is	Consider drug Therapy When LDL is
Very high risk: ACS, or CHD with DM, multiple risk factors	< 70 mg/dL	70 mg/dL or more	70 mg/dL or more
High risk: CHD or CHD risk equivalents (10-year risk Greater than 20%) if LDL is less than 100 mg/dL	< 100 mg/dL	100 mg/dL or more	100 mg/dL or more
Moderately high risk: at least 2 risk factors (10-year risk 10% to 20%)	< 100 mg/dL	130 mg/dL or more	130 mg/dL or > (100 to 129 mg/dL: consider drug treatment
Moderate risk: at least 2 risk factors (10-year risk < 10%)	< 130 mg/dL	130 mg/dL or more	160 mg/dL or more
Lower risk: 0 to 1 risk factor	< 160 mg/dL	160 mg/dL or more	190 mg/dL or more

¹⁸ MIRACL: the Myocardial Ischaemia Reduction and Aggressive Cholesterol Lowering trial

Triglycerides are major lipids in chylomicrons and very-low-density lipoprotein (VLDL) particles. These particles are closely related to the metabolism of other lipoproteins, including high-density lipoprotein particles. Hypertriglyceridemia is a common disorder that is exacerbated by uncontrolled diabetes mellitus, obesity, and sedentary habits, all of which are more prevalent in industrialized societies than in developing nations.

Hypertriglyceridemia may be a result of either genetic defects (primary causes) or, more commonly, acquired factors (secondary causes) such as obesity, alcohol, diabetes mellitus, hypothyroidism or using of certain medications that increase triglyceride production or decrease its clearance or both. (59)

(a) Chylomicronemia

(a-1) (type I hyperlipoproteinemia):

Deficiency of lipoprotein lipase or apolipoprotein C-II.

Autosomal recessive.

Fasting chylomicronemia.

Triglyceride level 1,000 to 4,500 mg/dL.

In heterozygotes, normal fasting TG levels that increase after fatty meals.

Recurrent pancreatitis.

(a-2) Type V hyperlipoproteinemia:

– Fasting chylomicronemia, elevated VLDL levels.

– Hypertriglyceridemia aggravated by factors that increase VLDL production (i.e., alcohol, estrogens, rapid weight gain, poorly controlled DM).

– Triglyceride levels 500 to 3,000 mg/dL.

– Pancreatitis, neurological symptoms, xanthomas, heart disease.

(a-3) Remnant hyperlipidemia (type III hyperlipoproteinemia, familial dysbetalipoproteinaemia):

– Binding defect of apolipoprotein E.

– Chylomicron and VLDL accumulation.

– Xanthomas, atherosclerotic disease.

(a-4) Familial hypertriglyceridemia:

– Autosomal dominant overproduction of VLDL.

– Isolated hypertriglyceridemia in family members.

– Triglyceride level 200 to 500 mg/dL.

– Associated with metabolic syndrome.

(a-5) Familial combined hyperlipidemia:

– VLDL elevation, LDL elevation, or both.

– Family history of premature atherosclerosis. (60)

(a-6) Hepatic lipase deficiency:

There is a growing awareness of the potential atherogenicity of TG-rich lipoproteins (TGRLPs), including very low density lipoproteins (VLDL), chylomicrons, and their remnants, which is reflected, in part, by HTG. (61).

In Montreal Heart Study, angiographic progression of CHD was directly related to concentration of IDL and inversely related to HDL-C levels. (62)

(b) Metabolic disorders associated with hypertriglyceridaemia:

- Low HDL.
- Small dense LDL.
- Insulin resistance.
- Atherogenic triglycerides rich lipoprotein remnants.
- Increase blood coagulability and blood viscosity.

The VA-HIT¹⁹ emphasized the importance of triglycerides in overall management of lipid disorders.¹⁷ Patients with elevated triglyceride levels must aggressively pursue lifestyle modifications. Exercise, weight loss, smoking cessation, reduction of alcohol intake, and aggressive diabetes control all lower triglyceride levels. (63).

D. Tobacco use:**Facts about smoking:**

Nicotine meets the criteria of a highly addictive drug. Nicotine is a potent psychoactive drug that induces euphoria, serves as a re-enforcer of its use, and leads to nicotine withdrawal syndrome when it is absent.

“By 2020, smoking will be the largest single health problem worldwide.” Tobacco use is a largest single cause of premature death in the developed world among individuals aged 35 years or more. (64).

Also **passive exposure** to smoke in individuals who have never smoked may increase the risk of CAD. **3,785** deaths due to CVD were attributable to smoking among adults ages 35 or older in 2003, also 30% of all cases of ischaemic heart disease are caused by tobacco smoking. (65)

The World Health Organization (WHO) Report for the year 2002 has classified risk factors for cardiovascular diseases, such as tobacco use as being among the top 10 risks to health in all regions of the world.(66) even one cigarette a day increases the chances for developing cardiovascular disease, those who smoked 1-4 cigarettes a day had a 50% increased risk of dying from any cause, as compared to those who never smoked. Light smokers were found to be three times more likely to develop coronary artery disease than non-smokers. (67)

Effect of tobacco:

Nicotine directly activates macrophages via the nicotinic acetylcholine receptor, activating multiple downstream events, enhancing production of pro-inflammatory cytokines by macrophages that leads to NF-B-mediated inflammation in arterial wall and accelerated atherosclerosis. (68)

Long-term cigarette smoking is known to contribute adverse myocardial events in several ways. Smoking causes increased platelet aggregation and thrombus formation, increased myocardial workload, and increased carbon monoxide levels, resulting in less oxygen delivered to the heart, coronary vasoconstriction, and catecholamine release . Smoking causes inflammation and oxidative injury, leading to endothelial dysfunction (69).

Smoking is associated with thrombus formation due to increased platelet aggregation. This is thought to be an important factor in acute coronary and other arterial vascular events. Platelet activation occurs immediately after smoking a single

¹⁹ VA-HIT: The Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial

cigarette. For long-term smokers, a substantial number of activated platelets are constantly present in the circulation. (70)

In otherwise healthy people, smoking a cigarette increases myocardial workload by activating the sympathetic nervous system, thus increasing heart rate, blood pressure, stroke volume, and cardiac output. (71).

Carbon monoxide is present in the inhaled component of cigarettes. It is thought to be harmful in part because it reduces available myocardial oxygen. The increase in carbon monoxide levels may possibly contribute to increased potential for arrhythmias by inducing myocardial ischemia. (71).

Cigarette smoking results in coronary vasoconstriction and decreases coronary blood flow in patients with coronary artery stenosis. (72)

Nicotine-induced sympathetic stimulation may result in myocardial ischemia and arrhythmia potentiation. Nicotine causes catecholamine release and increased heart rate and blood pressure that result in myocardial ischemia, especially if coronary stenosis is present. (73)

There is also evidence that smoking increases vascular production of free radicals, such as super oxide, which react with nitric oxide to decrease its availability, thereby impair endothelium-dependent vasodilatation and promote other processes that accelerate atherosclerosis. (74)

A recently published population-based, cross-sectional study showed that male smokers had higher white blood cell counts, fibrinogen levels, plasma viscosity, and high-sensitivity C-reactive protein levels than patients who had never smoked. (75), The only significant marker of inflammation in female smokers was an elevated white blood cell count. However, others have shown elevated levels of inflammatory markers in female smokers compared with nonsmoking women. (76).

Low-grade inflammation, atherogenic dyslipidaemia and hypercoagulability are present in smokers compared with those who never smoked among subjects without apparent inflammation who underwent coronary angio-graphy on suspicion of coronary artery disease. (77). In smokers the levels of total cholesterol, LDL cholesterol, non-HDL cholesterol and MDA were significantly elevated when compared with the controls. The atherogenic index as indicated by various risk ratios were also found to be increased in smokers as compared to controls (78).

Many studies suggested various mechanisms leading to lipid alteration by smoking which are: (a) nicotine stimulates sympathetic adrenal system leading to increased secretion of catecholamines resulting in increased lipolysis and increased concentration of plasma free fatty acids (FFA) which further result in increased secretion of hepatic FFAs and hepatic triglycerides along with VLDL- C in the blood stream .(b) Fall in estrogen levels occurs due to smoking which further leads to decreased HDL – cholesterol (c) Presence of hyper-insulinemia in smokers leads to increased cholesterol, LDL-C, VLDL-C, and TG due to decreased activity of lipoprotein lipase. (d) Consumption of a diet rich in fat and cholesterol as well as low fiber diet and cereal content by smokers as compared to non-smokers.(79)

Nicotine replacement therapy:

Nicotine replacement therapy is an effective pharmacotherapy for smoking cessation. People with cardiovascular disease who continue to smoke have an increased risk of myocardial infarction, cerebrovascular accident, and other serious vascular events. Studies have indicated no increase in cardiovascular events in those

who use NRT compared with those who continue to smoke. The benefit of NRT to enhance efforts to quit smoking successfully is clear and convincing, and NRT is even more effective if used in conjunction with other cessation approaches. This proven pharmacotherapy as an adjunctive to brief smoking cessation counseling should be considered in this high-risk group of patients. (80),

E. Obesity:

The World Health Organization (WHO) adopted weight classifications developed by the National Institutes of Health (NIH) through an expert panel convened in 1995 that reviewed data from approximately 394 studies to clinically assess association between weight levels and disease risk. These classifications were published in the Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults in 1998. The panel recommended the use of Body Mass Index (BMI), a measure of weight in relation to height. An individual's BMI is calculated as weight in pounds divided by the square of height in inches times 703. (BMI is also calculated as weight in kilograms divided by the square of height in meters.) Using this measure (81)

Table (4): Weight categories by BMI

Underweight	<18.5
Normal	18.5 - 24.9
Overweight	25.0 - 29.9
Obesity Class I	30.0 - 34.9
Obesity Class II	35.0 - 39.9
Obesity Class III	>= 40

Childhood obesity predisposes to insulin resistance and type 2 diabetes, hypertension, hyperlipidaemia, liver and renal disease, reproductive dysfunction and increases the risks of adult obesity and cardiovascular disease.

As Atherosclerosis begins in childhood (5 -10 years) as deposits of cholesterol esters in monocyte-derived macrophage foam cells in the intima of large muscular arteries (fatty streaks), (83)

BMI-for-Age: Participants at a workshop on childhood obesity convened by the International Task Force on Obesity agreed upon the use of BMI as a reasonable index of excess weight in children and adolescents (84).

However, as children grow, their body fat composition changes, so BMI must be applied differently among this population, dependent upon the age of the child. Since boys and girls also differ in their body fatness during the growth period, it is necessary

to plot BMI-for-age by sex. Centers for Disease Control and Prevention growth charts for children and adolescents aged two to 20 are used to indicate the percentile into which the child's BMI falls; it is this percentile that determines whether or not the child is considered underweight, normal weight, or overweight. Cutoff points were established by a committee of experts representing professions that treat obese children and adolescents (85).

Table (5): the cutoff of weight classification.(86)

Underweight	BMI-for-age <5th percentile
At risk of overweight	BMI-for-age >or = 85th percentile
Overweight	BMI-for-age > or = 95th percentile

The combination of urban living and an abundant food supply does not by itself, provide the entire explanation. It is very likely that cultural preference for female plumpness (only recently beginning to change), coupled with physical and cultural barriers to physical activity make the difference. For example, the recent predominance of apartment buildings that requires the installation of elevators, means that fewer families live in buildings requiring or permitting stair climbing. (87)

Obesity and CAD:

Obesity is an important factor associated with alterations in carbohydrate and lipid metabolism as well as in coagulation factors that contribute to increase risk of cardiovascular disease. (88) For many years, investigators have known that obesity is associated with increased risk of mortality, much of which is due to cardiovascular disease. Much of the excess mortality rates in persons of higher-than-average weight were due to CAD. There was a stepwise increase in CAD for each weight index category. (89).

In Egypt Diabetes and heart diseases has been found to be of higher rates in obese women compared with non-obese women. As cardiovascular disease has risen steadily as a proportionate cause of mortality for both men and women, from 5% of deaths to 39.1% for men and from 2.9% to 27.2% of deaths for women from 1961 to 1985, respectively. While body weight may be related to the risk for premature cardiovascular disease, it has also been shown to be associated with most of the known risk factors for atherosclerosis, such as hypertension, cigarette smoking, low levels of high-density lipoprotein (HDL) cholesterol, elevated plasma glucose levels, hypercholesterolemia, and hypertriglyceridemia. (86).

The co-segregation of obesity, dyslipidemia, and hyperinsulinemia among families of obese subjects is well documented; (90) and numerous studies have shown that a preferential accumulation of abdominal fat is associated with a metabolic cluster that may contribute to substantially increase the risk of atherosclerotic cardiovascular disease. (91).

On the other hand, whether hyperinsulinemia, which often accompanies abdominal obesity, is independently associated with ischemic heart disease remains a

matter of debate. Indeed, analyses of the Paris Prospective Study cohort suggested that fasting insulinaemia was no longer independently associated with ischemic heart disease after controlling for the abdomen-to-thigh ratio. (92).

In study of the relation between body fat distribution and risk of CAD development, 146 women aged from 67 to 78 y with a body mass index (BMI) ranging from 18.7 to 50.6 kg/m² and 83 men aged between 67 and 78 y with BMI ranging from 19.8 to 37.1 kg/m². , Body fat distribution was assessed using: waist circumference, SAD²⁰, waist-to-hip ratio (WHR), waist-to-height ratio and SAD-to-thigh ratio. They found that indicators of body fat distribution are associated with CVD risk factors in the elderly independently of BMI. Our data also show that waist and SAD are the anthropometric indicators of fat distribution, which are most closely related to CVD risk factors in old age. (93).

Obesity affects atherosclerosis through unrecognized intervening variables. Emerging risk factors for CHD also associated with obesity are C-reactive protein in adults and children , insulin resistance and fibrinogen . As other physiological variables related to obesity are identified; they may explain a larger proportion of the association of obesity with atherosclerosis through plausible physiological mechanisms. (94)

Importantly, BMI and abdominal panniculus thickness were simultaneously considered in men, a BMI ≥ 30 kg/m² was associated with raised lesions in the RCA only among individuals with a large panniculus thickness (≥ 17 mm), which reinforces the concept that central fat distribution is more important than total fat as a risk factor for atherosclerosis. (95).

There was a modest but statistically significant positive unadjusted correlation between BMI and FRS²¹ in predicting the incidence of CAD in families. (96).

F. Metabolic syndrome:

The constellation of dyslipidemia (hypertriglyceridemia and low levels of high-density lipoprotein cholesterol), elevated blood pressure, impaired glucose tolerance and central obesity is identified as metabolic syndrome now; it is also called insulin resistance syndrome or syndrome X. (97).It is a cluster of risk factors that is responsible for much of the excess cardio-vascular disease morbidity among overweight and obese patients and those persons with type 2 diabetes mellitus (98)

Given the name syndrome X in 1988, each component of the syndrome has been associated with an increased risk of cardiovascular disease (99).

Etiology:

The etiology of has not been established definitively. One hypothesis presumes that the primary cause is insulin resistance. Insulin resistance correlates with visceral fat measured by waist circumference or waist to hip ratio. The link between insulin resistance and cardiovascular disease probably is mediated by oxidative stress, which produces endothelial cell dysfunction, promoting vascular damage and atheroma formation. (101)The second hypothesis blames hormonal changes for the development of abdominal obesity. One study demonstrated that persons with elevated levels of

²⁰ SAD: sagittal abdominal diameter.

²¹ FRS: Framingham Risk Score

serum cortisol (caused by chronic stress) developed abdominal obesity, insulin resistance, and lipid abnormalities. (102)

Risk of metabolic syndrome:

A report from the National Cholesterol Education Program- Adult Treatment Panel (NCEP-ATP III) identified metabolic syndrome as an independent risk factor for cardiovascular disease and considered it an indication for intensive lifestyle modification (103). The metabolic syndrome is a major determinant of ischemic cardiovascular disease among middle-aged Japanese among smokers. (104) The role of smoking in the development of metabolic disease has been attributed to the negative effect of smoking on insulin sensitivity which has been documented in several studies, as cigarette smoking increases the circulating level of insulin antagonistic hormones. (105)

Table (6): new IDF definition (347)

The new International Diabetes Federation (IDF) definition	
According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have:	
Central obesity (defined as waist circumference* with ethnicity specific values)	
plus any two of the following four factors:	
Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Raised blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose	(FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

G. Oral contraceptive pills:

Oral contraceptive pills are combined formulations of a progestin and a synthetic estrogen. (536) Since their introduction in 1960, oral contraceptives have become the most widely used method of contraception among fertile woman. In the last two decades, oral contraceptives with lower estrogen doses were found to be as effective for contraception and much more tolerable. (106)

Oral contraceptives raise both systolic and diastolic blood pressure by 4 to 9 mm Hg. Women who take oral contraceptives are more likely to develop hypertension than women who have never taken them. (107) An addition of another cardiovascular risk factor, smoking for example, increases the risks of serious cardiovascular problems from hormonal contraceptive use such as myocardial infarction and stroke. This is more

evidenced above the age of 35 years. Worthy to know that women who do not smoke and do not have hypertension or DM are not at increased risk of acute myocardial infarction when they take oral contraceptive pills. (108).

Alternative methods of contraception should be advised in women with LDL >160 mg/dL, triglycerides >250 mg/dL, or multiple additional CAD risk factors. (109).

AHA/ACC Consensus Panel Statement (1999) Guide to Preventive Cardiology for Women:

- Use of oral contraceptives is relatively contraindicated in women \geq 35 years old who smoke.
- Women with a family history of premature heart disease are recommended to have a lipid analysis before starting oral contraceptives.
- Women with significant risk factors for diabetes are recommended to have glucose testing before starting hormonal contraceptives.
- If a woman develops hypertension while using oral contraceptives, she should be advised to stop taking them. (110)

Hormone replacement therapy (estrogen and progestin) also increases the risk for heart disease. The landmark Women's Health Initiative (WHI) found that a woman's risk of heart attack almost doubles during her first year of taking hormone replacement therapy (HRT) and levels off to an increased risk of 24% after about 6 years. (111). Smoking dramatically increases the risk of myocardial infarction at the ages when the overall risk of this event begins to rise steeply. The combination of oral contraceptive pill use and smoking has a greater effect on risk than the simple addition of the two factors. Thus, oral contraceptive pills generally are not prescribed to smokers over 35 years of age. (112).

The risk of mortality from cardiovascular disease attributable to oral contraceptive pill use is up to 10 times higher in women 40 to 44 years of age than in women 20 to 24 years of age. (113).

Special considerations:

There are recommendations stated by Peterson H.B. to use oral contraceptive pills in healthy women over 35 years of age who do not smoke, as the benefits of oral contraceptive pills generally exceed the risks. (114).

WHO guidelines for the use of OCP:

Coronary artery disease Structural heart disease Diabetes with complications, Age >35 years, smoking 20 cigarettes or more per day Hypertension (blood pressure of >160/100 mm Hg or with concomitant vascular disease, (115) all are considered by the WHO as category 4 which is comparable to the "Who should not take oral contraceptives" category in the Physicians' Desk Reference. (116).

New oral contraceptives carry a greatly reduced risk of cardiovascular complications compared with other high-dose preparations, but third-generation progestins appear to greatly increase risk of venous blood clots in the leg veins. Overall, the risk/benefit ratio is excellent except for women who smoke. (117).

Older formulations of oral contraceptives containing high doses of estrogen induced hypertension in 5% of users. Newer, lower-dose monophasic oral contraceptives have

been shown to cause minimal elevation in blood pressure, which has not been found to be clinically significant overall. No significant changes in blood pressure have been found with use of multiphasic contraceptives (118).

Therefore, women with well-controlled hypertension can take these agents but should be closely monitored during therapy. Diuretics may be the best choice in women taking oral contraceptives, because the mild increase in blood pressure caused by these agents is thought to be due to volume expansion. (119)

(2) Non modifiable risk factors:

A. Family history:

Family history of CAD is a non-modifiable risk factor, it is defined as having a first-degree²² female (<65 years) or male (<55 years) relative with documented CAD or sudden death. Also; heritable traits contributing to CAD are extremely common in CAD patients, A family history of premature CAD is an independent risk factor for developing CAD, The precise amount of risk attributable to family history is unclear, Risk increases with younger age of onset and greater number of affected first-degree relatives; siblings of probands appear to be at highest relative risk, although being a non-modifiable risk factor; F FH can be helpful in CAD screening and risk reduction in genetically susceptible individuals. (120).

CAD tends to cluster in families because a predisposition to develop cardiac risk factors is often genetically linked, and families often share environmental and behavioral risk factors.(121)

CAD is a multi-factorial disease caused by alterations in numerous metabolic pathways that are often inherited. The penetrance and severity of these metabolic alterations, and ultimately the presence and severity of CAD, are determined by interactions between genetic variations and environmental and behavioral factors. Many of the precise genetic mechanisms contributing to familial risk are unknown. Although there are many single-gene disorders that are associated with a high risk of early CAD and MI, risk segregates in a polygenic rather than Mendelian fashion in most cases of premature CAD.(122).

Numerous studies have found genetic links between CAD and related disorders, including hypertension, obesity, diabetes and dyslipidaemia (123) The presence of heritable traits contributing to cardiac risk is common in CAD patients; Familial CAD is associated with subclinical atherosclerosis as measured by coronary artery calcification approximately 40% of variability of which was attributable to the effects of individual genes. (124).It was found that family history of premature CAD is an independent risk factor for CAD, even after correction for major familial risk factors such as cholesterol, Obesity, hypertension, and diabetes. (125). Because cardiovascular events often occur in families with a history of premature CAD, assessing family history can be a useful tool for diagnosis and risk stratification, particularly in patients with intermediate predicted risk (10% - 20% 10-year risk). (126).

²²First degree relative: parent, sibling, or offspring.

If a patient reports a positive family history for premature CAD (even if low-risk), both the patient and their relatives should be evaluated for the presence of CAD risk factor. (127). **The NCEP Adult Treatment Panel III** recommends lower thresholds for initiating treatment and lower goals for LDL cholesterol for primary prevention in patients with a family history of premature CAD. (128).

B. Gender:

Cardiovascular diseases, and more specifically coronary artery disease presentations in women are different than in men. In addition, pathology and pathophysiology of the disease present significant gender differences, which leads to difficulties concerning diagnosis, treatment and outcome of the female population. (129)

Women are normally protected against CAD as compared with men until elderly age as estrogen has a cardioprotective effect (130), but once they experience an acute myocardial infarction (MI), they have poorer outcomes than their male counterparts, particularly if younger than 60 years (131). a meta-analysis concluded that men are more likely to undergo noninvasive cardiac investigations than women, although subsequent evaluation showed no deference. (132)

The female sex hormone estrogen tends to raise HDL cholesterol, and as a rule, women have higher HDL (good) cholesterol levels than men do. Estrogen production is highest during the childbearing years. This may help explain why pre-menopausal women are usually protected from developing heart disease. (132) Women also tend to have higher triglyceride levels. Triglyceride levels range from about 50 to 250 mg/dL, depending on age and sex. As people get older, more overweight or both, their triglyceride and cholesterol levels tend to rise. (132)

In men, increased total cholesterol, decreased HDL and increased triglyceride are risk factors for CAD in women. However, HDL and triglyceride levels may be more powerful predictors of CAD in women. In the Framingham study, every 10mg/dL increase in HDL resulted in a 40% to 50% decrease in CAD risk for women. Finally, a multivariate analysis of the Framingham study demonstrated that a triglyceride level of greater than 150mg/dL was an independent risk factor for CAD, particularly when the level exceeded 400mg/dL. (133) Hypertension prevalence increases with age in both men and women. After the age of 50, however, more than 2 times as many women as men develop hypertension. (134)

Notably, even if women had had diabetes for fewer than 4 years, their risk of CAD was significantly elevated. Coexistent hypertension and obesity multiplied this risk 3-folds. (135)

In the Framingham Heart Study, smoking was associated with an increase in CAD death in premenopausal women. (136) Some physicians considered angina to have a benign course as evidenced by the long-term data from the Framingham Study showed that 86% of women who presented initially with chest pain did not have an MI complicating their angina. (139), but it is now thought that many women in the Framingham population may have had non-cardiac chest pain and would have had no evidence of obstructive coronary disease on angiography. (140)

The effect of obesity on women's relative risk for CAD has been controversial. The Framingham study noted a relative risk of 2.0%, which was independent of other risks.

(141). A large prospective study of 262,019 women and 62,116 men ages 30 to 85 showed that greater body-mass index was associated with higher mortality from all causes, and from cardiovascular disease up to age 75. (142)

As regarding the coronary artery size, it was found that females has small coronary artery diameter than males of the same age which is refers to the effect of sex hormones on coronary arteries (143), But it was proved that it has nothing to do with the increase of coronary artery disease incidence

(3) Other risk factors:

A. Plasma homocysteine:

Homocysteine (Hcy) is a sulfhydryle- containing amino acid derived from the demethylation of dietary methionine, with a normal level being 5-15 μ mol/L. Plasma Homocysteine concentrations increase with age, and levels are higher in men than in women. This is determined by both genetic and nutritional factors. (144).

Aetiology and types of hyperhomocysteinaemia:It is of two types;

I. Primary hyperhomocysteinaemia has shown a special relation to the early development of CAD (235)this includes:

- Cystathionine beta synthase (CBS) deficiency.
- 5, 10 methylene tetrahydrofolatereductase (MTHFR) deficiency.
- Methylene tetrahydrofolatehomocysteine methyl transferase deficiency.

II. Secondary hyperhomocysteinaemia:

- Physiological :
 - Increasing age.
 - Male sex.
 - Menopause.
- Life-style factors:
 - Tobacco use.
 - Coffee consumption.
- Vitamin deficiency: (such as B12, folic acid and B6 vitamin deficiency)
 - Systemic disorders: examples are SLE, DM, renal impairment, hypothyroidism, severe hepatic impairment ...etc.
- Drugs:
 1. Folate antagonists (methotrexate, phenytoin, carbamazepine).
 2. Vitamin B6 antagonists (theophylline, oestrogen oral contraceptives).
 3. Nicotine.
 4. Metformin, thiazide diuretics, colestipol, nicotinic acid, etc.(236)

Atherosclerosis and homocysteine:

Homocysteine tends to increase the activation of procoagulant factors and inactivation of anticoagulant substances (145).

It also Increases the production of platelet aggregating substances like thromboxane A2, inhibition of natural anticoagulation pathway via protein C, thrombin-thrombomodulin system. (146) High levels of homocysteine impair nitric oxide production by cultured endothelial cells (147), it has a pro-oxidant properties forming hydrogen peroxide in the presence of copper or ceruloplasmin(148).

Also homocysteine leads to increase intimal wall thickness by stimulation of growth of the vascular smooth muscle cells (149). Available data suggest that elevated plasma homocysteine concentrations lead to oxidation of LDL-cholesterol, potentially causing atherosclerosis. An interaction with lipoprotein (a) which promotes binding with fibrin has also been reported. (150) Recently a correlation between systolic blood pressure and plasma homocysteine has been demonstrated in a hypertensive geriatric population. (151)

In a study including type 1 diabetic patients, plasma homocysteine levels were significantly higher in smoking patients than in control subjects. (152). Some studies researching the relationship between plasma homocysteine and diabetes have shown that type 2 diabetic patients have a higher prevalence of hyperhomocysteinemia than control subjects (153)

Elevated plasma homocysteine may be an important cause for atherosclerosis formation. The adverse effects of homocysteine, involve oxidative damage to vascular endothelial cells, increased proliferation of smooth muscle cells, and oxidative modification of low density lipoprotein, all leading to atherosclerosis. (154)

Plasma homocysteine levels were increased significantly in CAD patients when compared to controls. And also homocysteine is the best predictor of CHD risk amongst other conventional risk factor in CAD patients. (155)

Metabolic syndrome patients have elevated homocysteine levels, but these higher levels are not associated with an increased risk for new cardiovascular events. In contrast, elevated homocysteine levels confer increased risk in patients without the metabolic syndrome. (156)

B. Hemostatic factors:

Fibrinogen is a sticky, fibrous coagulant in the blood that plays a key role in blood clotting and also considered to be an acute phase reactant that increases during inflammatory reactions (157). Whereas Fibrin D-dimer is a product of the action of plasmin on cross-linked fibrin and therefore reflects fibrinolytic activity and fibrin turnover. (158). Fibrin D-dimer levels are elevated in patients with established atherothrombotic vascular disease and predict arterial thrombotic events in prospective studies involving healthy, middle-aged subjects. (159)

Fibrinogen (FBG) and total coagulation factor VII (FVIIc) concentrations are higher in those patients with coronary artery disease who are at increased future risk of acute ischemic events. (160). Evidence that “emerging” risk factors such as elevated fibrinogen and CRP levels show associations similar to elevated circulating homocysteine levels with cardiovascular mortality. (161). Fibrin D-dimer reflects the extent of fibrin turnover in the circulation and epidemiological evidences has found D-dimer level to have modest predictive value for vascular events. (162) Also existing atherosclerosis may increase fibrinogen levels, and, thus will lead fibrinogen to predict future CHD events. It is also elevated in population with increased CHD risk, for example, cigarette smokers, people from less favorable socioeconomic backgrounds. (163).

Recent study on patients with documented CAD, showed that C-reactive protein and fibrinogen were predictive for future cardiovascular risk, but did not provide further information on top of that obtained from models including traditional risk factors. Our data emphasize the clinical importance of traditional risk factors in patients with CAD. (264). In patients with coronary artery disease, fibrinogen and D-dimer levels are

independent predictors of subsequent cardiovascular death. These data support a role of impaired coagulation/fibrinolysis process in the complications of coronary artery disease. (164).

It was also observed that elevated concentrations of fibrinogen are found in a dyslipoproteinaemia observed in diabetic, hypertensive, and obese patients in particular; fibrinogen level correlates with elevated serum triglycerides, increased VLDL cholesterol, and reduced HDL cholesterol. (165). Plausible mechanisms that may explain relationship between tPA and atherothrombotic vascular disease are: increased circulating levels of tPA may reflect increased endothelial tPA content and expression and enhanced plasmin-mediated breakdown of the extracellular matrix, resulting in *plaque instability*. In addition, tPA levels reflect the acute phase response given the association between CAD and markers of chronic infection or inflammation. (166)

C. Physical activity:

Physical activity is defined as any bodily movement produced by skeletal muscles that result in energy expenditure beyond resting expenditure, while Exercise is a subset of physical activity that is planned, structured, repetitive, and purposeful in the sense that improvement or maintenance of physical fitness is the objective. (167). Physical activity both prevents and helps treat many established atherosclerotic risk factors, including elevated blood pressure, insulin resistance and glucose intolerance, elevated triglyceride concentrations, obesity and low high-density lipoprotein cholesterol (HDL-C) concentrations (168).

Vigorous physical activity can also acutely and transiently increase the risk of acute myocardial infarction (AMI) and sudden cardiac death (SCD) in susceptible individuals. (169). Exercise training has been documented to reduce depression in clinically depressed patients following an acute myocardial infarction. (170).

Physical activity also reduces insulin resistance and glucose intolerance, postprandial hyperglycemia, and possibly hepatic glucose output. It is also an important adjunct to diet for achieving and maintaining weight loss. (171)

D. Personality and psychological state:

Mental stress is considered a risk factor for cardiovascular disease (CVD) according to experimental and clinical evidence. (172). Mental stress may cause increased sympathetic activity, which could lead to increased ambulatory blood pressure levels and pulse rates, (173) reduced insulin sensitivity, (174) increased platelet aggregation (175) and endothelial dysfunction. (176). Mental stress may trigger the clinical events of coronary heart disease, particularly in the presence of advanced coronary atherosclerosis and can cause coronary vasoconstriction at sites with atherosclerotic plaques. (177). Several mechanisms by which psychological stress may decrease serum levels of HDL cholesterol have been hypothesized. Specifically, both norepinephrine and adrenocorticoids may diminish lipoprotein lipase activity, which in turn lowers HDL cholesterol level that has inverse relationship to the cardiovascular events. (178).

About Personality: Several mechanisms have been proposed linking Type A behavior, or components of it (i.e. hostility), to increased risk of developing coronary

heart disease. In contrast to Type A behavior, Type B behavior is characterized by low levels of competitiveness, time urgency and hostility. It has been suggested, for example, that compared with Type Bs, Type A individuals respond more quickly and strongly to stress both in their overt behavior and in their physiological responses (e.g. increased blood pressure and heart rate), producing more wear and tear on cardiovascular system. (179).

The type A behavior personality is characterized by traits such as impatience, aggressiveness, a sense of time urgency, and the desire to achieve recognition and advancement. People exhibiting Type A behavior have a hyper awareness of time and thus walk, eat and perform most activities rapidly and perfunctorily (180).

Type A personality was associated with a statistically significant 57% increase in risk of nonfatal MI, this was similar for men and women. (181)

Recently, a new personality construct, the type D or 'distressed' personality, has been proposed, characterized by the negative affectivity²³ including depressed mood, anxiety, anger, and hostile feelings. (182).

The inhibition of emotions has been associated with higher cardiovascular reactivity, lower cardiovascular recovery, lower heart rate variability, and, in the long term, carotid atherosclerosis, and increase incidence of coronary heart disease and cardiac mortality. (183)

In a sample of patients undergoing cardiac rehabilitation, deaths from cardiac causes were increased four-fold in those with type D personality, even after controlling for conventional risk factors. (184)

Depression: A number of studies have assessed the relationship of depression and CAD outcomes in patients hospitalized for acute myocardial infarction. These studies suggest that the presence of depression during or shortly after hospitalization confers 2 to 3 times the risk for mortality or nonfatal cardiac events. It also found that depressive symptoms and clinical depression have an unfavorable impact on mortality in CHD patients. (185).

Several biobehavioral mechanisms have been hypothesized to underlie the relationship between depression and CAD, these include: poor adherence to prescribed regimens. (186)

A number of studies have demonstrated that depression is associated with imbalances in HPA axis functioning which is related to many cardiovascular disease risk factors such as truncal obesity, hypercholesterolemia, hypertriglyceridemia, increased blood pressure and elevated heart rate. (187).

ANS dysregulation has been implicated in CAD in the form of hyperactivity of the SNS that leads to hypertension and other risk factors for CAD mortality such as decreased vagal tone and reduced heart rate recovery; it may elicit coronary vessel constriction in CAD patients, resulting in myocardial ischemia. (188)

As emerging evidence suggests that alterations in immune functioning and inflammation may contribute to the development and clinical manifestations of CAD,

²³Tendency to experience negative emotions.

there is an evidence from both population and CAD samples that increased inflammation is associated with depression and with other CAD risk factors such as the metabolic syndrome. (189)

E. Alcohol:

Many epidemiological studies suggest that there is U- or J-shaped association between alcohol consumption and various types of ischemic illness, including myocardial infarction. (306) Low amounts of alcohol when taken on a regular basis have been shown to protect against cardiovascular disease and death whereas heavy drinking constitutes a severe risk condition. (190). The cardioprotective effect of alcohol is supposed to be due to increase HDL level. (191), but Alcohol consumption is associated with obesity, which is a risk factor for hypertension. (192).

Episodic consumption of large amounts of alcohol has been associated with a high risk of coronary heart disease in several studies. (193). In conclusion, we have demonstrated that consumption of 210 g alcohol per week is a risk factor for hypertension in free-living North American populations. (194).

F. Coffee consumption:

Coffee is one of the most widely consumed beverages worldwide. It's a major source of caffeine which is a trimethyl xanthine whose primary biological effect is the antagonism of the A1 and A2 subtypes of adenosine receptors, so all tissues with adenosine receptors may be affected by caffeine exposure. Caffeine stimulates fat oxidation in muscle and increases basal energy expenditure. Also, caffeine stimulates free fatty acid release from peripheral tissues (195) and decreases insulin sensitivity in skeletal muscle. (196) In addition, caffeine might impair insulin action by stimulating the release of epinephrine, which is a potent inhibitor of insulin activity. Finally, caffeine increases blood pressure and homo-cysteine levels. (197)

Coffee intake may trigger myocardial infarction. The association is particularly strong among people with light/occasional intake of coffee (up to a cup/day), those with a sedentary lifestyle, and those with 3 or more risk factors for coronary heart disease. (198)

Although cafestol and kahweol²⁴ in coffee have been implicated in increasing the risk of coronary heart disease by increasing serum cholesterol level after coffee consumption an Indian study suggests that caffeine on its own also increases the risk of coronary heart disease. (199)

Frequent coffee consumption was strongly associated with smoking: 30% of the men and more than half of the women who drank 6 cups per day also smoked cigarettes. In addition, individuals who drank more coffee were more likely to drink alcohol and to use aspirin and less likely to drink tea, to exercise, and to use multivitamin and vitamin E supplements. (200) Whereas others mechanisms could counterbalance the effects of caffeine, for instance, substances in coffee such as potassium, niacin, and magnesium have previously shown to be beneficial for glucose and insulin metabolism. (201).

²⁴cafestol and kahweol : (belonging to the diterpene family) are the active chemicals in coffee

In addition, antioxidants in coffee such as chlorogenic acid and other phenolic compounds might improve insulin sensitivity. (202) Smoking a cigarette while drinking a cup of coffee may damage the heart more than either vice alone. (203). Low-density lipoprotein (LDL) cholesterol levels were significantly higher among persons who smoked cigarettes and consumed five or more cups of coffee per day than among nonsmokers who abstained from coffee. Conversely, high-density lipoprotein (HDL) cholesterol was higher in persons who did not smoke or drink coffee than in coffee-consuming smokers (204).

G. Drug abuse:

Cocaine is the newest and sometimes unrecognized risk factor for cardiovascular disease in young individuals otherwise free of cardiovascular risk factors, (328) Cocaine intake results in marked increase in blood pressure with hypertension related complications, myocardial oxygen demand and heart rate. Coronary blood flow is decreased by cocaine intake. Increased demand of oxygen by the myocardium in the face of decreased supply in subjects with cocaine use, leads to myocardial ischemia, which in turn forms a substrate for most of the cardiovascular complications, namely, myocardial infarction, cardiac arrhythmias and acute pulmonary edema. (205).

Normally, increased myocardial oxygen demand results in dilation of the coronary arteries to allow more blood flow. However, cocaine has a direct vasoconstrictor effect on vascular smooth muscle. This effect is independent of alpha-adrenergic stimulation but is dependent on calcium. Thus, vaso-constriction occurs despite the increase in myocardial oxygen demand. If coronary artery disease is present, the problem is compounded by vaso-constriction at sites of stenosis. (206) Also, the concomitant use of other drugs, such as alcohol, may enhance the cardio-toxic effects of cocaine. (207)

Cocaethylene is the product of the combination of cocaine and alcohol to increase the euphoric effect; it is thought to be responsible for the increased mortality rate among cocaine abusers. The risk of sudden death is 25 times greater in persons who abuse both alcohol and cocaine than in those who use only cocaine. (208) Heavy use of cigarettes and crack cocaine were significantly and inversely associated with obesity in this cohort, which is consistent with previous report linking heavy cocaine use with wasting. (209)

Cocaine's effect on platelets causes increased thromboxane production and platelet aggregation, with a greater potential for intracoronary thrombosis. Finally, cocaine may induce procoagulant effects through transient depletion of protein C and antithrombin III. (210)

Marijuana use on the other hand, a known appetite stimulant, tended to be associated with central obesity in our cohort, although not significantly. (211) Marijuana has several well-described effects on the cardiovascular system with a net increase in myocardial oxygen demand with a decrease in oxygen supply, which is due in part to an increase in carboxy-hemoglobin. (212). The risk of myocardial infarction onset is elevated almost 5-fold in the hour after smoking marijuana. (213) In addition to the hemodynamic effects, smoked marijuana is associated with an increase in carboxyhemoglobin, resulting in decreased oxygen-carrying capacity. (214). The pathophysiology of myocardial infarction after amphet-amine use is unclear. Possible explanations include coronary vasospasm, coronary spasm with intra-coronary

thrombus. (215) Increased myocardial oxygen demand induced by catechol-amines and catecholamine-mediated platelet aggregation with subsequent thrombus formation. (216)

H. Hyperuricemia:

In patients with significant angiographically defined CAD, serum uric acid predicted mortality independent of traditional risk factors. This suggests that elevated serum uric acid may be a risk factor for mortality in patients with significant cardiovascular disease. (217).

These results suggest that elevated uric acid levels are correlated with the presence of coronary heart disease in female rather than in male diabetic patients, independently of hypertension and nephropathy. (218). There have been suggestions that measurement of serum uric acid can enhance the prediction of CHD. (219). A strong association between uric acid and cardiovascular disease in persons without than in persons with hypertension was observed, although this effect was more pronounced for cerebrovascular disease than for coronary heart disease (220)

The bottom line is that measuring uric acid is a useful test for the clinician, as it carries important prognostic information. Uric acid elevation is associated with an increased risk for cardiovascular disease and mortality, especially in women. (221)

Uric acid and Atherosclerosis Non-diabetic atherosclerosis and athero-scleropathy (accelerated atherosclerosis associated with MS, prediabetes, and TIIDM²⁵) are each impacted with the elevation of uric acid. (222)

Hyperuricemia has been associated with increasing body mass index (BMI) in recent studies and are even apparent in the adolescent youth. (223).

Furthermore, hypertriglyceridemia and free fatty acids are related to Hyperuricemia independently of obesity and central body fat distribution. (224)

A direct relation between homocysteine levels and serum uric acid levels is known to occur in patients with atherosclerosis. (225).

Serum uric acid in the early stages of the atherosclerotic process is known to act as an antioxidant and may be one of the strongest determinates of plasma antioxidative capacity, however, later in the atherosclerotic process when serum uric acid levels are known to be elevated (in the upper 1/3 of the normal range >4 mg/dl and outside of the normal range >6 mg/dl in females and 6.5–7 mg/dl in males) this previously antioxidant serum uric acid paradoxically becomes prooxidant. (226).

I. Low circulating level of antioxidants:

The “oxidative modification hypothesis” of coronary heart disease (CHD) proposes that intake of antioxidants, such as carotenoids and vitamin E, protects against atherogenesis by blocking oxidation of low-density lipoprotein cholesterol. (227) Antioxidants may favorably influence plaque stability, vasomotor function, and tendency for thrombosis. (228) as the intake of vitamin E (tocopherol) has been associated with lower risk of CHD in many observational studies of healthy individuals. (229)

Recent study suggested that Vitamin E may be effective in inhibiting earlier stages of atherosclerosis. (230) Ascorbic acid acts as the first line of defense against oxidative stress during the ischemia-reperfusion cycle. It is the only antioxidant in plasma capable

²⁵TIIDM: type II diabetes mellitus.

of completely inhibiting oxidative modification of the low-density lipoprotein by aqueous peroxy radicals. (231) Reactive oxygen species (ROS) include superoxide anion, hydroxyl radical, hydrogen peroxide, hypochlorous acid and peroxynitrites. (232) The excess production of ROS may initiate lipid peroxidation in cell membrane, damage membrane proteins or cause DNA fragmentation, etc. These processes may result in a loss of contractile function of the heart and lead to severe myocardial cell damage, collectively termed as reperfusion injury. (233)

Atherosclerosis is now understood to be a chronic inflammatory disease characterized by excess accumulation of monocyte-derived macrophages within the arterial wall. (234) Compelling evidence points to oxidative stress as an important trigger in the complex chain of events leading to and promoting atherosclerosis. (235) According to the oxidative-modification hypothesis extracellular LDL is oxidized by free radicals to produce the mildly modified LDL that stimulates local vascular cells to produce chemotactic factors to attract and stimulate monocyte recruitment and differentiation to macrophages in arterial walls. (236) Accumulation of oxidized LDL in vascular walls during atherogenesis also impairs vascular endothelial function. (238) As platelets have an important role in the pathogenesis of atherosclerosis and coronary thrombosis, there is now evidence that supplemental concentrations of α -tocopherol inhibit platelet function. (239) Completely oxidized LDL is recognized by scavenger receptors on macrophages and internalized to form so-called foam cells. In addition to promoting the formation of foam cells, oxidized LDL has direct chemotactic activity for monocytes and stimulates the binding of monocytes to the endothelium. (240).

Once monocytes cross the endothelial layer, they become trapped in the subendothelial space, partly because oxidized LDL inhibits their egress from the arterial wall. Oxidized LDL is also cytotoxic to vascular cells, thus promoting the release of lipids and lysosomal enzymes into the intimal extracellular space and enhancing the progression of atherosclerotic lesions. The oxidative-modification hypothesis is supported by evidence that LDL oxidation occurs in vivo and contributes to the clinical manifestations of atherosclerosis. Antibodies raised against oxidized LDL react with atherosclerotic lesions but not with normal arterial segments. (241). Endothelial dysfunction and increased vascular oxidative stress predict the risk of cardiovascular events in patients with coronary artery disease. These data support the concept that oxidative stress may contribute not only to endothelial dysfunction but also to coronary artery disease activity. (242)

J. Autoimmune diseases:

Systemic Lupus Erythematosus (SLE): Lower HDL cholesterol level and diabetes mellitus have a significant influence on abnormal myocardial perfusion results found in asymptomatic patients with SLE. Current vasculitis was associated with abnormal myocardial scintigraphy. These data suggest that abnormal myocardial scintigraphy may be related to subclinical atherosclerosis (243) In patients with systemic lupus erythematosus, the prevalence of coronary-artery atherosclerosis is elevated and the age at onset is reduced. Early detection of atherosclerosis may provide an opportunity for therapeutic intervention. (244) Because the prevalence of myocardial infarction is

increased among patients with lupus, several studies have measured cardiovascular risk factors in this group (245)

Age and presence of hypertension were associated with clinical coronary artery disease (246) Elevated levels of homocysteine have been reported in patients with lupus and have been associated with stroke and arterial thrombotic events. (247)

Hypertension is more frequent in patients with lupus than others and that the patients also had elevated levels of triglycerides and homocysteine .By contrast, the levels of traditional cardiovascular risk factors such as low-density lipoprotein and high-density lipoprotein cholesterol, which are commonly, measured as a means of predicting cardiovascular risk in the general population did not differ significantly between patients and control subjects. (248)

Rheumatoid Arthritis (RA): Patients with rheumatoid arthritis have a significantly higher prevalence of angina pectoris (249), especially women with RA who have a significantly increased risk of myocardial infarction compared with those without RA. (250)

Corticosteroids can cause dyslipidemia, hyperglycemia and hypertension but may also control inflammation in RA. Studies have attempted to define the impact of steroids on mortality in RA but the results are inconsistent. (251)

The inflammatory mechanisms in RA may enhance in several ways athero-genesis. C-reactive protein, a useful marker of disease activity, is elevated in RA and has prognostic value (252) it may also participate directly in endothelial injury by sensitizing endothelial cells to T-cell mediated cytotoxicity. (253)

Indeed, endothelial dysfunction is frequently present in RA patients, even in the absence of identifiable CV risk factors. (254)

3. MI WITH NORMAL CORONARIES

Chest pain may be associated with coronary arteries that appear “normal.” Normal is defined here as no visible disease or luminal irregularities (less than 50%) as judged visually at coronary angiography. (255) Myocardial infarction with ‘normal’ coronary arteries (MINCA) typically occurs in the under the age of 50 years(256). Normal angiography in patients with chest pain is five times more common in women than in men.(257). Since coronary angiography developed, it has been recognized that 1 to 12% of patients may suffer from a myocardial infarction with angiographically normal coronary arteries (MINC).(258)

Usually there is no history of angina or previous myocardial infarction (MI), and risk factors for ischemic heart disease(259) (IHD) may be absent. Symptoms and electrocardiographic (ECG) findings are similar to those of MI with angiographic coronary disease, though infarct sizes tend to be smaller.(260)

The proposed mechanisms for MINCA include coronary vasospasm, coronary thrombosis in situ or embolization from a distal source with spontaneous lysis, cocaine abuse, viral myocarditis, aortic dissection, hypercoagulable states, autoimmune vasculitis and carbon monoxide poisoning(261) The leading cause of myocardial infarction in coronary artery disease patients is plaque rupture.(262)

Most studies of MINC patients have shown that their cardiovascular risk profile is lower than that of patients with CAD. (264) An endothelial dysfunction with a tendency toward increased vasomotor tone has also been implicated in the pathogenesis of MINCA. (265) An interesting finding in another study was the significantly higher number of patients with febrile infections mainly of the upper airways, within 2 weeks prior to infarction in the MINC group.(266)

Mortality rates are similar but morbidity is lower in myocardial infarction patients with absolutely normal coronary angiography compared with those with coronary artery stenosis. The only two independent factors predictive of poor outcome in myocardial infarction patients with normal coronary arteries are left ventricular dysfunction and diabetes. (262) Patients with myocardial infarction and strictly normal vessels have very few ischemic events at follow-up, and may be distinguished from both patients with non-significant lesions as well as those with minor angiographic irregularities. On the other hand, cardiac mortality correlates strongly and independently with a depressed ventricular function.(267) Patients with acute MI and angiographically normal coronary arteries show a bimodal sex and age distribution: a younger age group, all men and uniformly strong cigarette smokers and an older group predominantly women with no significant association with cigarette smoking. Both groups seem to have a favorable prognosis.(268)

Recent study concluded that young patients with myocardial infarction have good prognosis irrespective of the coronary anatomy, as patients with normal coronary angiograms had less risk factors and less frequent new ischaemic events. (264) Q wave and non-Q wave infarctions have both been reported in patients with normal coronary arteries. Younger patients were predominantly men with a strong smoking history and a tendency to develop Q wave infarction. Older patients tended to be women who smoked less and who tended to develop non-Q wave infarcts.(261)

The overall prevalence rate of myocardial infarction with a normal coronary angiogram is low, approximately 3%, but appears to vary with age, with higher rates in young patients.(269)

A. Coronary Spasm:

Coronary artery spasm is a temporary, abrupt, and focal (restricted to one location) contraction of the muscles in the wall of an artery in the heart, which constricts the artery. This spasm slows or stops blood flow through the artery.(270) It has been proposed as a classic aetiological factor of myocardial infarction with normal coronary arteries.(271) Coronary spasm occurs most often from midnight to early morning when the patient is at rest and it is usually not induced by exercise in the daytime. (272)

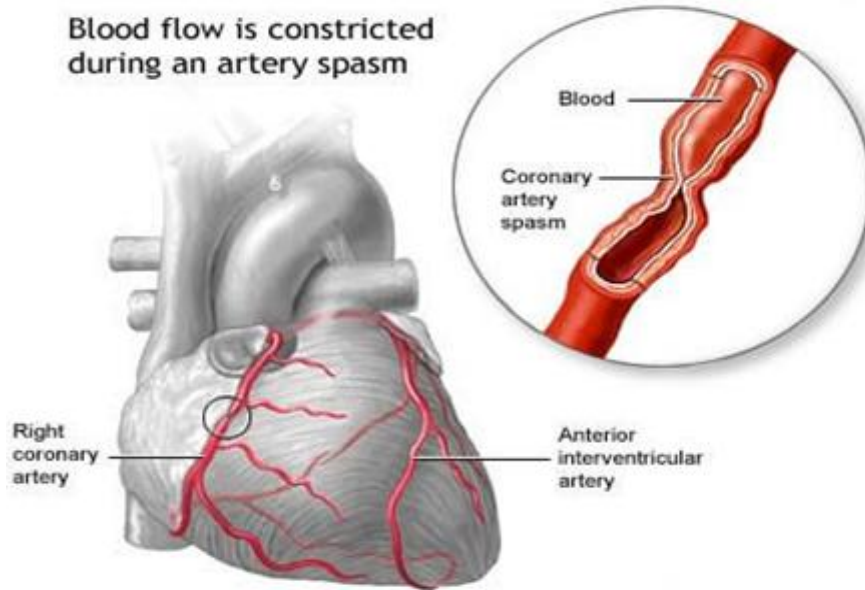


Figure (3): blood flow in coronary artery spasm

Coronary vasospasm can produce myocardial infarction, Most patients with MINCA do not have angina, and it usually affects the epicardial vessels. (273)

Certain angiotensin II type 1 receptor gene polymorphisms have been associated with an increased tendency to vasospasm in angiographically normal coronary arteries challenged with a potent vasoconstrictor. (274)

Cocaine use has been linked with MI in the absence of coronary artery disease. The proposed aetiology is increased myocardial oxygen demand and paradoxical coronary vasospasm and thrombosis as a result of alpha-adrenergic action. (275) This drug may increase concentration of plasminogen activator inhibitor, endothelial permeability to low-density lipoprotein, and platelet activation and aggregability. (276) The fact that smokers show a decreased production of nitric oxide which partly mediates endothelium-dependent vasodilatation, and because most of the patients with MINC are smokers, a pathophysiologic link may seem plausible. (277)

B. Recanalization:

In acute anterior wall myocardial infarction spontaneous coronary artery recanalization is associated with better global and segmental left ventricular systolic function, especially if the occlusion is of pre-septal localization, while collateral circulation is not related to better contractility. In acute inferior wall myocardial infarction one sees the reverse. (278) Patency of the infarct-related artery before thrombolytic therapy or direct coronary artery angioplasty in the absence of heparin or aspirin has ranged from 9% to 28%, and similar prevalence rates have been demonstrated at 90 minutes during heparin infusion. Patients presenting with clinical features of spontaneous coronary reperfusion have a better prognosis and an excellent in-hospital outcome, with evidence of less myocardial damage than patients in whom reperfusion therapy was required to achieve TIMI-3 patency. (279)

The major threat to these patients is reinfarction due to reocclusion of the IRA since the large area of viable myocardium is potentially at risk. (280)

C. Dissection:

Spontaneous coronary artery dissection is a rare and often fatal cause of ischaemic heart disease occurring predominantly in young or middle aged otherwise healthy patients. It is mostly recognized at postmortem examination in young victims of sudden death. (281) Aortic dissection and spontaneous coronary artery dissection can result in an MI with little evidence of coronary artery disease. (282) As the dissection causes a “false lumen” which develops a hematoma that limits the flow of blood through the “true lumen,” it leads to myocardial ischemia and infarction. (283)

While spontaneous coronary artery dissection (SCAD) is well recognized as a rare cause of chest pain, acute coronary syndrome, and sudden cardiac death, its optimal treatment is not established. (284) SCAD is three times more likely to occur in women than in men and is often associated with the peripartum period, defined as the 9 months of pregnancy and up to 3 months postpartum. (285) This was referred to the hormonal and haemodynamic changes that occur during pregnancy and the immediate postpartum period play a role, additionally, increased blood volume and cardiac output during this period increase the shear stress on the wall of the coronary vessel. (286)

About one in four female patients with spontaneous coronary artery dissection are in the peripartum period. Contraceptives and the exceptional hormonal balances in the peripartum period are supposed to weaken the arterial wall and to predispose it to rupture or dissection. Spontaneous coronary artery dissection has also been described in patients with Marfan’s syndrome, with cocaine misuse, and after intense physical exercise. (287)

D. Embolism:

An embolus is a detached intravascular solid, liquid, or gaseous mass that is carried by the blood to a site distant from its point of origin. Most emboli are part of a dislodged thrombus (thromboembolism), but rare forms include fat droplets, air or nitrogen bubbles, atherosclerotic debris (cholesterol emboli), tumor, foreign bodies, (288) The role of distal emboli in the aetiology of MINCA is controversial. Theoretically valvular heart disease, endocarditis and mural thrombosis could predispose to embolic infarcts with subsequent re-canalization of the vessel lumen. In one study an increased incidence of mitral valve prolapse and mitral regurgitation was found in MINCA patients, but the results are hard to interpret because of small numbers and frequency of minor mitral valve prolapse in general population. (262)

Recently, prosthetic heart valves, dilated cardiomyopathy and invasive procedures like coronary angiography have increasingly been associated with embolic occlusion of coronary arteries. (289) Acute myocardial infarction due to coronary thromboembolism from a left ventricular thrombus has been suspected in patients with dilated or aneurysmal left ventricles, but it has rarely been documented. (290) Paradoxical embolism in a coronary artery is a recognized clinical entity, but it is rare and usually definitively established only at autopsy. Calcium embolization of the coronary artery was reported by **Brian D.** et al. in 2001 to be the cause of myocardial infarction in two cases after percutaneous balloon mitral valvuloplasty. (291)

E. Coronary Aneurysm:

Coronary artery aneurysm is an uncommon disease. It is defined as a coronary artery dilatation, and exceeds the diameter of the normal adjacent segment or the diameter of the patient's largest coronary vessel by 1.5-2 times. (292) The aneurysm can be divided into discrete aneurysms (localized dilatation, either saccular or fusiform) or ectasia (diffuse dilatation involving $\geq 50\%$ of the artery). (293) Coronary artery aneurysms are most commonly associated with atherosclerosis but also are reported with Kawasaki's disease, arteritis (polyarteritis nodosa, syphilis, systemic lupus erythematosus, Takayasu's arteritis), mycoses, trauma, connective tissue disorders (Marfan's and Ehlers-Danlos syndromes), metastatic tumors, polycystic kidney disease, and percutaneous coronary interventions. (294)

The pathophysiologic mechanisms that lead to development of these dilatations have not yet been clarified. **Sorrell**, et al suggested there was an association between the chronic stimulation of endogenous nitric oxide, with consequent chronic stimulation of vascular relaxation, and the occurrence of ectatic areas in coronary arteries. (295)

Patients can present with a wide range of symptoms from being asymptomatic to sudden death. Complications include ischemia, myocardial infarction, fistula formation, spontaneous rupture, calcification, and distal embolization as a result of thrombus formation within the aneurysm. (296)

Rupture of a CAA can also cause acute myocardial infarction (AMI) and sudden cardiac death. (297)

E. Hypercoagulability:

One possible mechanism for MINCA is occlusion of the vessel lumen by thrombus that subsequently lyses rapidly. (282) The risk of MI is above normal in people with raised plasma fibrinogen and plasminogen activator inhibitor 1. (298) A raised homocysteine is thought to increase the concentrations of factor VII and thrombin which emphasize its role in MINCA. (299)

Moreover, **A Da Costa** et al. concluded that patients with MI, NCA and congenital coagulation disorder present a high risk of thrombosis recurrence under antiplatelet agent and recommended anticoagulation therapy in this situation. (300) Nephrotic syndrome which is associated with proteinuria that results in the loss of low molecular weight proteins, which in turn alters the concentration and activity of coagulation factors as the liver tries to compensate for the hypoalbuminaemic state, there is an increased synthesis of factors II, VII, VIII, X, XIII and fibrinogen resulting in raised blood levels. (301)

Congenital coagulation abnormalities have been hypothesized as mechanisms of myocardial infarction with angiographically normal coronary arteries. (302)

Recently, a large multicentre study has found a higher prevalence rate of factor V Leiden, a newly described congenital coagulation disorder, in patients with myocardial infarction and normal coronary arteries, compared with myocardial infarction patients

and coronary artery stenosis or healthy subjects. (301) It has been shown that there is increased platelet consumption in young smokers without clinical evidence of coronary artery disease. (303)

This relation is presumably related to the mechanism of enhanced platelet aggregation and adhesion seen after smoking cigarettes that would be expected to increase the thrombotic risk in smokers with normal coronary arteries. (304)

It was observed in essential thrombocytosis and Polycycaemia Vera increase in the incidence of myocardial infarction with normal coronary arteries which explained by increase platelet activity beside increase platelet activation due to endothelial injury. (305)

G. Microvascular Angina:

Myocardial infarction may result from occlusion of the small intramural vessels which causes are listed by Bruce et al. as follow:

- Hypertrophic cardiac disease.
- Friedreich's ataxia
- Progressive muscle dystrophy.
- Progressive myotonic dystrophy.
- Collagen disease.
- Systemic lupus erythematosus.
- Scleroderma.
- Dermatomyositis.
- Diabetes mellitus.
- Hereditary connective tissue disorders.
- Marfan syndrome.
- Hurler' syndrome.
- Infiltrative disease.
- Amyloidosis.
- Neoplasm.
- Coagulopathy.
- Disseminated intravascular coagulation
- Thrombotic Thrombocytopenic purpura.
- Whipple's disease. (306)

Microvascular angina refers to all patients with angina, a normal angiogram, and evidence of impaired coronary microcirculation whether or not there are exercise induced ECG changes. (307)

“Syndrome X” describes patients with angina of exertion, a positive exercise ECG, and a normal coronary angiogram, but excludes coronary artery spasm (Prinz metal's angina). (308) Also in primary amyloidosis, obstructive intramural coronary artery amyloid deposition can cause ischemic symptoms. The epicardial coronary arteries are typically spared. (309) Most patients with primary systemic amyloidosis and cardiac involvement have obstructive intramural coronary amyloidosis and associated microscopic changes of myocardial ischemia. (310) Coronary artery affection by primary systemic amyloidosis is of bad prognosis as it is usually diagnosed during autopsy. (311)

H. Myocardial Bridging:

Myocardial bridging is an anatomic variant not very common in humans, although not rare. It is characterized by the presence of one or more myocardial bundles that cross or surround a coronary artery segment. During systole the bridging causes a strangulation or constriction of the vessel, with subsequent normalization in diastole. (312) The incidence of this anomaly is higher in women than in men. It is found in 5%-86% in anatomic studies but only observed in 0.5% to 12% of patient undergoing coronary arteriography. (313) The occurrence of acute myocardial infarction in myocardial bridging patients with normal coronary arteries is a very rare clinical finding. (314)

In patients with myocardial bridging and normal coronary arteries in coronary cineangiography, and presenting compression of the coronary arteries during systole and decompression and normalization in diastole, the diagnosis of acute myocardial infarction must be consistently based on other associated data. The pain characteristics, electrocardiographic alterations in ST and T segments, early increase in CKMB, troponin and myosin levels should be assessed and valued. (315)

I. Congenital Anomalies:

Overall, anomalies of the coronary arteries are rather rare, they may be seen with hemodynamic or myocardial perfusion abnormalities and may be manifested by sudden death. (316)

Hemodynamically significant congenital Anomalies of coronary arteries are:

- Isolated/primary—without CHD²⁶.
- Anomalous origin of accessory coronary arteries from the pulmonary artery (ALCAPA²⁷, ARCAPA²⁸).
- Ectopic origin of the coronary arteries from aortic sinus.
- Absence of a coronary artery.
- Congenital coronary artery fistula.
- Secondary—with CHD.
- PA²⁹ + IVS³⁰.
- AA³¹ + MS³². (460)

Myocardial ischemia is the consequence of several mechanisms limiting the blood flow in the anomalous CA, including the acute angle take-off from the aorta, the

²⁶CHD: congenital heart disease.

²⁷ALCAPA: anomalous origin of the left coronary artery from the pulmonary artery

²⁸ARCAPA: anomalous origin of the right coronary artery from the pulmonary artery.

²⁹PA: pulmonary atresia.

³⁰IVS: interventricular septum.

³¹AA: aortic atresia.

³²MS: mitral stenosis.

narrowed slit-like lumen with a potential for a flap like closure of the orifice, the proximal intramural course of the anomalous vessel within the aortic tunica media, which may further aggravate the obstruction, and the squeezing of the vessel along its course between the aorta and the pulmonary artery, particularly during exercise when there is an increased cardiac output with expansion of the great vessels. (317)

The origin of the left circumflex coronary artery (LCX) from the right sinus of Valsalva is one of the most common anatomic variations of the coronary artery circulation that is associated with myocardial ischemia. (318) Coronary anomalies have been implicated in chest pain, sudden death, cardiomyopathy, syncope, dyspnea, ventricular fibrillation, and myocardial infarction. (319)

It was found that there is a relationship between anomalous origin of left coronary artery from pulmonary artery [ALCAPA] and acute anterolateral myocardial infarction in newborns) (320) Also if Coronary fistula cause significant coronary steal; that if occurred under resting conditions, it would cause myocardial infarction, hibernation, or resting chest pain. (321)

Left main coronary artery anomalies are rare but are also known as a cause of ischemic heart disease, the magnitude of ischemic risk depends on the degree of angulation of the coronary artery after its origin from the aorta. This acute angulation; is often associated with a slit-like ostium that narrows with the aortic stretch with increasing cardiac output. (322)

J. Hyperthyroidism:

The cardiovascular system and thyroid hormone are closely related. The cardiovascular hemodynamic effects from the excess thyroid hormone result mainly from the direct action of T3 on cardiomyocytes, and indirect action through sympathetic effects such as an increase in sensitivity to catecholamine. (323)

)
The physiopathology mechanisms have not yet been totally explained. There is evidence that the thyroid hormone may affect the factors that determine the consumption of oxygen by the myocardium and that abnormalities in oxygen-hemoglobin dissociation could explain such a fact. (324)

Other possible mechanisms are: ischemia secondary to coronary vasospasm due to an unbalance in the autonomic cardiac innervation, a modification in the concentrations of thromboxane A, and prostacyclin in the coronary circulation, with insufficient vasodilatation to supply the metabolic demand. (325)

4. Myocardial infarction in young adults

Acute myocardial infarction is rare in teenagers and young adults. The pathophysiology of their infarcts is varied but not usually due to athero-sclerotic plaque rupture except for those with genetically predetermined or familial hyperlipidemia. (326) The incidence of CHD is declining in the UK in all age groups. The actual prevalence of the disease was found to be 0.5% in men and 0.18% in women between 35 and 44 years. (327)

causes for MI among patients aged less than 45 can be divided into four groups:

- Atheromatous CHD
- Non-atheromatous CHD
- Hypercoagulable states
- MI related to substance misuse

The pathophysiology of myocardial infarction in the presence of “normal” coronary arteries remains unclear but can be explained on the basis of coronary artery thrombosis, embolization, spasm, or a combination of these processes. (328)

Proteinuria associated with the nephrotic syndrome results in the loss of low molecular weight proteins, which in turn alters the concentration and activity of coagulation factors. Thus factors IX, XI, and XII are decreased due to urinary excretion, increased synthesis of factors II, VII, VIII, X, XIII, and fibrinogen as a compensating mechanism resulting in rise in their blood levels. (323)

Antiphospholipid syndrome (Hughes’ syndrome) Arterial and venous thrombosis is a prominent feature of this syndrome together with antiphospholipid antibodies and miscarriages of pregnancy, Antiphospholipid antibodies are associated with autoimmune diseases such as systemic lupus erythematosus, but when they occur in isolation, this is known as primary antiphospholipid syndrome. The main antiphospholipid antibodies implicated in thrombosis and atherosclerosis are the anticardiolipin antibody, the lupus anticoagulant, and IgG antibodies against plasma-phospholipid binding proteins such as b2-glycoprotein I and prothombin. (329) Cardiac complications include myocardial infarctions and a high prevalence of valvular abnormalities of varying severity. (330)

Also Anticardiolipin antibody increases platelet adhesiveness. (331), it is possible that the antiphospholipid antibodies predisposes to premature atherosclerosis compounding the risk for infarction with this syndrome. (332)

Coronary artery spasm is the predominant mechanism for myocardial infarction with use of cocaine. Cocaine has been associated with angina, myocardial infarction, tachyarrhythmias and bradyarrhythmia, sudden cardiac death and myocardial contraction bands, which act as a substrate for arrhythmias. (333)

The cardiac effects of cocaine are mediated via four main pathways:

(1) increased myocardial oxygen demand due to an acute rise in systemic blood pressure and heart rate; (2) coronary vasoconstriction caused by its α_1 -adrenergic properties and calcium dependent direct vasoconstriction; (3) endothelial dysfunction which predisposes to vasoconstriction and thrombosis; (4) promotion of arteriosclerosis. (334)

Embolization of septic or non septic vegetations from the aortic and mitral valves causing myocardial infarction has been reported. (335)

Myocardial bridging is associated with impeding blood flow during systole that can persist during diastole resulting in myocardial ischemia, which has been associated with

myocardial infarction. Traditionally treatment involved surgical splitting of the band but there are now reports of successful treatment by stent implantation. (336)

Familial hyper- cholesterolaemia, is an autosomal dominant disorder clinically characterized by high serum cholesterol (low density lipoprotein fraction) concentrations, xanthomas, and premature atherosclerosis. (337)

Various other lipid fractions and hyperhomocysteinaemia are implicated in premature atherosclerosis and myocardial infarction. Other risk factors include smoking, hypertension, insulin resistance, obesity, and a family history of premature cardiovascular events. (338)

Spontaneous coronary artery dissection is a rare cause of myocardial infarction. It is a condition with greater prevalence in young women, particularly in the peripartum or early postpartum period. It also has been described in association with atherosclerotic plaque and in an idiopathic group of patients. The left anterior descending artery is often involved, but there are reports of multiple vessel involvement. (339) Aneurysms, ectasia, and anomalous origin of coronary arteries are other causes of myocardial infarction in young adults

In a series of patients who had their MI less than 45 years of age, 69% denied any chest pain before MI. The duration of symptoms was found to be less than a week in most of the patients. (341) Evidence of significant coronary disease (mostly left anterior descending) was found in 93% of patients. (342)

Recommendations

"Prevention is better than cure"

Decline in death rates could be achieved by adopting a healthier lifestyle. That's why it's important for healthcare professionals to implement primary and secondary prevention.

1. Primary Prevention

Risk assessment: Goal: Adults should know the levels and significance of risk factors as routinely assessed by their primary care provider

Smoking: Increasing the awareness, encourage every smoker to quit.

Blood pressure control : Goal: Less than 120/80 mm Hg in non-hypertensive and within the accepted range in hypertensive and diabetics .

Dietary intake : Goal: An overall healthy eating pattern.

Aspirin : Goal: Low-dose aspirin in people at higher risk of coronary heart disease

Blood lipid management

- Keeping LDL, HDL and Cholesterol in levels of the safe zone
- rule out secondary causes of high LDL cholesterol (liver function tests, thyroid function tests, and urinalysis).

Physical activity; Goal: At least 30 minutes of moderate-intensity physical activity, preferably all, days of the week.

Weight management: Goal: maintain desirable weight (body mass index 18.5–24.9 kg/m²).

Diabetes management: Goal: HbA1c of less than 7 percent.

2. Secondary Prevention

Identifying and treating people with established disease and those at very high risk of developing cardiovascular disease.

Smoking: Goal: Complete cessation.

Blood pressure control: Control blood pressure via lifestyle modification and medications

Lipid management: dietary therapy. Reduce intake of saturated fat, *trans*-fatty acids, and cholesterol, medications may be used

Physical activity: Goal: 30 minutes, 7 days per week (minimum 5 days / week) if not contraindicated. Advice medically supervised programs for high-risk patients (e.g., recent acute coronary syndrome or revascularization, heart failure).

Weight management: Goal: Body mass index (BMI) 18.5–24.9 kg/m². Waist circumference less than 40 inches in men and less than 35 inches in women.

Diabetes management: Initiate lifestyle and pharmacotherapy to achieve near normal HbA1c.

Antiplatelet agents/anticoagulants

- Start aspirin at 75 to 162 mg/d and continue unless contraindicated..
- Manage warfarin to international normalized ratio 2.0 to 3.0 for paroxysmal or chronic AF or flutter, and in post–myocardial infarction patients when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus).
- Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely.

Renin-angiotensin-aldosterone system blockers

- for all other patients but for lower-risk patients are low risk and after recanalization , it is optional

Angiotensin receptor blockers:

- Use in ACE inhibitors intolerant having heart failure or myocardial infarction with left ventricular ejection fraction of 40 percent or less. Or it may be used in combination with ACE inhibitors in systolic-dysfunction heart failure.
- **Aldosterone blockade:**
- Use in post-myocardial infarction patients who do not have significant kidney dysfunction or elevated serum potassium, who are already receiving therapeutic doses of an ACE inhibitor and beta blocker, have a left ventricular ejection fraction of 40 percent or less, and have either diabetes or heart failure.

Beta blockers

- Start and continue indefinitely in all patients who have had myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated.
- Consider chronic therapy for all other patients with coronary or other vascular disease or diabetes unless contraindicated.

TREATMENT:

1. INITIAL MEASURES

- Oral nitrates and Aspirin
- ECG within 5 minutes of arrival
- History and examination including BP both arms
- IV cannula

- Oxygen if SaO₂ <98% (unless history of COPD), pain relief with GTN, morphine or diamorphine, metoclopramide if pain still present
- FBC, coagulation, U+E, glucose, lipids, LFT, troponin, CK, CXR
- Consider other diagnoses e.g. PE, aortic dissection, pneumothorax

2. RISK STRATIFICATION Calculate TIMI risk score

2.1 Low risk (TIMI risk score 0-2)

if troponin is not elevated, aim for early discharge:

2.2 Moderate – High Risk (TIMI risk score 3-7)

If ECG or cardiac marker evidence of an ACS or if in the opinion of the admitting physician this is felt to be likely, emergency treatment should be initiated immediately on admission as mentioned above, admit and consult Cardiologist.

- if troponin elevated or dynamic ST depression >1mm should undergo in-patient coronary angiography and revascularisation unless there are contra-indications. Refer to cardiology/cardiologist assessment sisters within 24h .

- Emergency cardiac catheterisation may be required if there are on-going or recurrent symptoms with dynamic ST changes or haemodynamic instability. Consult with a cardiologist

6. ECHOCARDIOGRAPHY

Echocardiography is needed in all patients after MI to assess LV function.

7. GLUCOSE CONTROL

Intensive glucose control offers benefits in patients admitted with MI.

Other Recommendations:

1. Trying to prevent the incidence of myocardial ischemia by proper awareness and life style modification.
2. Early detection of risky patient via risk stratification and early proper management and treatment.
3. Being updated by knowing and following the most recent approved international guidelines in treating myocardial ischemia.
4. Doing more and more studies and researches about myocardial ischemia in chest pain patient in emergency department and sharing the results to help other physicians in helping patients.

Summary

Myocardial Ischemia means narrowing of Coronaries whatever it was transient or permanent, partial or complete, painful or silent, recurrent or firstly experienced, recordable or not. This, Although chambers are full of blood, makes heart muscle blood supply decreases and if it continued it may result in myocardium permanent damage (Myocardial infarction)

PRESENTATION:

Signs and Symptoms

- Symptoms : dyspnea with typical or atypical crushing chest pain, sever or vary in intensity , persisting for 15 minutes or more

- Often accompanied by sweating; may also have nausea, belching or vomiting. Resistant to analgesics or silent, relieved by rest, sublingual nitrates, morphia or not relieved. Patient may give history of similar attacks before and the way it relieved with.

INVESTIGATIONS :

- **ECG** findings: No finding, ST segment elevation, Q-waves, and a conduction defect, if such findings are new compared with a previous ECG. New T-wave inversion also increases the likelihood of MI. **None of these findings is sensitive enough that its absence can exclude MI.**
- Elevated **Cardiac Enzymes and Protein**
 - Creatine kinase (CK)
 - The MB isoenzyme of creatine kinase (CK-MB),
 - Troponin T and troponin I

PREVENTION::

1. Primary Prevention (Risk factor screening)

Goal: Adults should know the levels and significance of risk factors as routinely assessed by their primary care provider.

- Begin risk factor assessment in adults at the age of 20.
- Update family history of coronary heart disease (CHD) regularly.
- Assess smoking status, diet, alcohol intake and physical activity at every routine evaluation.
- Record blood pressure (BP), body mass index (BMI), at each visit (at least every two years).
- Measure fasting serum lipoprotein profile (or total and HDL cholesterol if fasting is unavailable) and fasting blood glucose according to the person's risk for hyperlipidemia and diabetes, respectively (at least every five years; if risk factors are present, every two years).

Smoking

- Increasing the awareness of the danger of smoking among youth through media and campaigns opposing smoking that spreads to include children at schools as the age of smoking has declined to be less than 10 years
- Encourage every smoker to quit.
- Warning against the danger of passive smoking.

Blood pressure control

Goal: Less than 120/80 mm Hg; for people who have been diagnosed with high blood pressure, the goal is less than 140/90 mm Hg; less than 130/80 mm Hg in people with renal (kidney) disease or diabetes.

- Promote healthy lifestyle modification. Advocate reducing weight; reducing sodium (salt) intake to less than 2300 mg a day; eating fruits, vegetables and low-fat dairy products; moderating alcohol intake; and at least 30 minutes of physical activity on most or all days of the week.
- For people with renal (kidney) disease or diabetes, start drug therapy if BP is 130 mm Hg or greater systolic or 80 mm Hg or greater diastolic.
- Start drug therapy for those with BP of 140/90 mm Hg or greater if BP goal is not achieved with lifestyle modifications. Add blood pressure medications,

individualized to the patient's other requirements and characteristics (age, race or need for drugs with specific benefits).

Dietary intake

Goal: An overall healthy eating pattern.:

- Advocate eating a variety of fruits, vegetables, grains, legumes, fat-free or low-fat dairy products, fish, poultry and lean meats.
- Match energy (calorie) intake with energy needs and make appropriate changes to achieve weight loss when needed.
- Modify food choices to reduce saturated and trans fats to less than 10 percent of calories, cholesterol to less than 300 mg per day, and trans fats. (Trans fats result from adding hydrogen to vegetable oils.) Substitute grains and unsaturated fats from fish, vegetables, legumes and nuts.
- Limit salt intake to less than 6 grams per day (2,300 mg of sodium).

Aspirin

Goal: Low-dose aspirin in people at higher risk of coronary heart disease (especially those with a 10-year CHD risk of 10 percent or greater).

- Benefits of reducing cardiovascular risk outweigh these risks in most patients with higher coronary risk.
- Consider 75–160 mg aspirin per day for people at higher risk (especially those with a 10-year CHD risk of 10 percent or greater).

Blood lipid management

- LDL cholesterol less than 160 mg/dL if no more than one risk factor is present.
- LDL cholesterol less than 130 mg/dL (less than 100 mg/dL is an option) if two or more risk factors are present and 10-year CHD risk is less than 20 percent.
- LDL cholesterol less than 100 mg/dL (less than 70 mg/dL is an option for very high-risk patients) if two or more risk factors are present or higher or if person has diabetes. Secondary goals (if LDL cholesterol is at goal range): If triglycerides are greater than 200– 499 mg/dL then use non-HDL cholesterol as a secondary goal:
- Non-HDL cholesterol less than 190 mg/dL for no more than one risk factor.
- Non-HDL cholesterol less than 160 mg/dL for two or more risk factors.
- Non-HDL cholesterol less than 130 mg/dL for diabetes or for two or more risk factors.
- If LDL cholesterol is above goal range,
 - Start therapeutic lifestyle changes diet to lower it: less than 7 percent of calories from saturated fat and less than 200 mg per day of dietary cholesterol.
 - If more LDL cholesterol lowering is needed, add dietary options (plant stanols/sterols not to exceed 2 g per day and/or soluble fiber 10–25 g per day); emphasize weight reduction and physical activity.
 - Rule out secondary causes of high LDL cholesterol (liver function tests, thyroid function tests, and urinalysis).
- After 3 months of TLC, consider LDL-lowering drug therapy if:
 - Two or more risk factors are present, and LDL cholesterol is 130 mg/dL or greater.

- No more than one risk factor is present, and LDL cholesterol is 190 mg/dL or greater.
- Start drugs and advance dose to bring LDL cholesterol into range, usually with a statin, but also consider bile-acid-binding resin or niacin.
- If the LDL cholesterol goal is not achieved, consider combination drug therapy (statin plus resin or statin plus niacin).
- After LDL cholesterol goal has been reached, consider triglyceride level:
 - If triglycerides are 150–199 mg/dL, treat with therapeutic lifestyle changes (TLC).
 - If triglycerides are 200–499 mg/dL, treat high non-HDL cholesterol with TLC and, if needed, consider higher doses of statin or adding niacin or fibrate.
 - If triglycerides are 500 mg/dL or greater, treat with fibrate or niacin to reduce the risk of pancreatitis.
- If HDL cholesterol is less than 40 mg/dL in men and less than 50 mg/dL in women, start or intensify TLC. For higher-risk patients, consider drugs that raise HDL cholesterol (niacin, fibrates, statins).

Physical activity

Goal: At least 30 minutes of moderate-intensity physical activity on most, and preferably all, days of the week.

- If a patient has suspected cardiovascular, respiratory, metabolic, orthopedic or neurological disorders, or is middle-aged or older and sedentary, he or she should consult a physician before starting a vigorous exercise program.
- Moderate-intensity activities (40 to 60 percent of maximum capacity) are equivalent to a brisk walk (15–20 minutes per mile).
- Vigorous-intensity activities (more than 60 percent of maximum capacity) offer added benefits.
- Recommend resistance training with eight to 10 different exercises, 1–2 sets per exercise, and 10–15 repetitions at moderate intensity on two or more days per week.
- Include flexibility training and an increase in daily lifestyle activities to round out the regimen.

Weight management

Goal: Achieve and maintain desirable weight (body mass index 18.5–24.9 kg/m²). When a person's BMI is 25 kg/m² or higher, the waist measurement goal is less than 40 inches for men, and less than 35 inches for women :

- Start a weight-management program through restricting calories in diet and increasing caloric expenditure (exercise) as appropriate.
- For overweight or obese persons, reduce body weight by 10 percent in the first year of therapy.

Diabetes management

Goal: HbA1c of less than 7 percent :

- Start appropriate therapy to achieve near-normal fasting plasma glucose or as indicated by near-normal HbA1c. The first step is diet and exercise.

- Second-step therapy is usually oral hypoglycemic drugs: sulfonylureas and/or metformin with ancillary acarbose and thiazolidinediones. Third-step therapy is insulin.
- Treat other risk factors more aggressively. For example, change BP goal to less than 130/80 mm Hg for patients with high blood pressure, and LDL cholesterol goal to less than 100 mg/dL or lower.

2. Secondary Prevention

Identifying and treating people with established disease and those at very high risk of developing cardiovascular disease.

- Treating and rehabilitating patients who've had a heart attack or stroke to prevent another cardiovascular or cerebrovascular event.

What can secondary prevention achieve?

- extend overall survival.
- improve quality of life.
- decrease need for interventional procedures as angioplasty and bypass grafting.
- reduce the incidence of subsequent heart attack (myocardial infarction).

Heart or stroke patients can do this to help lower their risk of recurring disease:

- An assessment of fasting lipid profile.
- 30–60 minutes physical activity, preferably daily, or at least five days / week.
- Weight adjustment to the ideal, by sticking to a diet and exercise program.
- Checking blood pressure regularly. adjustment by medication. weight control, physical activity, modifying sodium (salt) intake.
- Considering aspirin intake daily or another medication.
- Nicotine replacement methods and formal programs to help quitting smoking.

Smoking

Goal: Complete cessation.

Intervention recommendations

- Ask about tobacco use status at every visit.
- Advise patient and family members to quit.
- Assess the tobacco user's willingness to quit.
- Assist by counseling and developing a plan for quitting.
- Arrange follow-up, referral to special programs, or pharmacotherapy (including nicotine replacement and bupropion).
- Urge avoidance of exposure to environmental tobacco smoke at work and home.

Blood pressure control

Intervention recommendations

- For all patients, initiate or maintain lifestyle modification (weight control, increased physical activity, alcohol moderation, sodium reduction, and emphasis on increased consumption of fresh fruits, vegetables and low-fat dairy products).
- For patients with blood pressure 140/90 mm Hg or greater (or 130/80 mm Hg or greater for individuals with chronic kidney disease or diabetes): As tolerated, add blood pressure medication, initially treating with beta blockers and/or ACE inhibitors, with addition of other drugs such as thiazides as needed to achieve goal blood pressure.

Lipid management

- Start dietary therapy. Reduce intake of saturated fat (to less than 7 percent of calories) *trans*-fatty acids, and cholesterol (to less than 200 mg dietary cholesterol per day).
- Adding plant stanol/sterols (2 grams/day) and viscous fiber (more than 10 grams/day) will further lower LDL-C.
- Promote daily physical activity and weight management.
- Encourage increased intake of omega-3 fatty acids in the form of fish or in capsule form (1gram/day) for risk reduction. For treating elevated triglycerides, higher doses are usually necessary for risk reduction.

For lipid management:

- Assess fasting lipid profile in all patients, and within 24 hours of hospitalization for those with an acute cardiovascular or coronary event. If patients are hospitalized, initiate lipid-lowering medication before discharge as follows:
- If baseline LDL-C is 100 mg/dL or greater, initiate LDL-lowering therapy (typically with a statin).
- If on-treatment LDL-C is 100 mg/dL or greater, intensify LDL-lowering drug therapy (may require LDL-lowering drug combination [statin + ezetimibe, bile acid sequestrant, or niacin*]).
- If baseline LDL-C is 70 to 100 mg/dL, it is reasonable to treat to LDL-C less than 70 mg/dL.
- If triglycerides are 200 to 499 mg/dL, non-HDL-C[#] should be less than 130 mg/dL, and further reduction of non-HDL-C to less than 100 mg/dL is reasonable.

Therapeutic options to reduce non-HDL-C are:

- More intense LDL-C-lowering therapy, or
- Niacin* (after LDL-C-lowering therapy), or
- Fibrate therapy[#] (after LDL-C-lowering therapy)
- If triglycerides are 500 mg/dL or greater, therapeutic options to prevent pancreatitis are fibrate or niacin* before LDL-lowering therapy; and treat LDL-C to goal after triglyceride-lowering therapy. Achieve non-HDL-C to less than 130 mg/dL if possible. Patients with very high triglycerides should not consume alcohol.

*Dietary supplement niacin must not be used as a substitute for prescription niacin. It should not be used for cholesterol lowering because of potentially very serious side effects.

[#]Non-HDL cholesterol is total cholesterol minus HDL cholesterol.

Physical activity

Goal: 30 minutes, 7 days per week (minimum goal, 5 days per week)

Intervention recommendations

- For all patients, assess risk with a physical activity history and/or exercise test, to guide prescription.
- For all patients, encourage minimum of 30 to 60 minutes of moderate-intensity aerobic activity, such as brisk walking, on most, preferably all, days of the week, supplemented by an increase in daily lifestyle activities (e.g., walking breaks at work, gardening, and household work).

- Encourage resistance training two days per week.
- Advise medically supervised programs for high-risk patients (e.g., recent acute coronary syndrome or revascularization, heart failure).

Weight management

Goal: Body mass index (BMI) 18.5–24.9 kg/m². Waist circumference less than 40 inches in men and less than 35 inches in women.

Intervention recommendations

- Calculate BMI and/or waist circumference on each visit and consistently encourage weight maintenance/reduction through appropriate balance of physical activity, caloric intake and formal behavioral programs when indicated to maintain/achieve a BMI between 18.5 and 24.9 kg/m².
- If waist circumference (measured horizontally at the iliac crest) is 35 inches or greater in women and 40 inches or greater in men, initiate lifestyle changes and consider treatment strategies for metabolic syndrome as indicated.
- The initial goal of weight loss therapy should be to reduce body weight by approximately 10 percent from baseline.
- Further weight loss can be attempted if indicated through further assessment.

*A BMI of 18.5 to 24.9 is considered as normal body weight. People with a BMI of 25–29.9 are considered overweight, while people with a BMI of 30 or greater are considered obese.

Diabetes management

- Initiate lifestyle and pharmacotherapy to achieve near normal HbA1c.
- Begin vigorous modification of risk factors (e.g., physical activity, weight management, and blood pressure control and cholesterol management as recommended above).
- Coordinate diabetes care with patient's primary care physician or endocrinologist.

Antiplatelet agents/anticoagulants

- Start aspirin at 75 to 162 mg/d and continue indefinitely in all patients unless contraindicated.
- patients undergoing coronary artery bypass grafting, aspirin should be started within 48 hours after surgery reduces saphenous vein graft closure. Dosing regimens ranging from 100 to 325 mg/d appear to be efficacious. Doses higher than 162 mg/d can be continued for up to one year.
- Start and continue clopidogrel 75 mg/d in combination with aspirin for up to 12 months in patients after acute coronary syndrome or percutaneous coronary intervention with stent placement (one month or more for bare metal stent, three months or more for sirolimus-eluting stent, and six months or more for paclitaxel-eluting stent).
- Patients who have undergone percutaneous coronary intervention with stent placement should initially receive higher-dose aspirin at 325 mg/d for one month for bare metal stent, three months for sirolimus-eluting stent, and six months for paclitaxel-eluting stent.
- Manage warfarin to international normalized ratio 2.0 to 3.0 for paroxysmal or chronic atrial fibrillation or flutter, and in post–myocardial infarction patients when clinically indicated (e.g., atrial fibrillation, left ventricular thrombus).

- Use of warfarin in conjunction with aspirin and/or clopidogrel is associated with increased risk of bleeding and should be monitored closely.

Renin-angiotensin-aldosterone system blockers

Intervention recommendations

Angiotensin-converting enzyme (ACE) inhibitors:

- Start and continue indefinitely in all patients with left ventricular ejection fraction of 40 percent or less and in those with hypertension, diabetes or chronic kidney disease, unless contraindicated.
- Consider for all other patients.
- Among lower-risk patients with normal left ventricular ejection fraction in whom cardiovascular risk factors are well controlled and revascularization has been performed, use of ACE inhibitors may be considered optional.

Angiotensin receptor blockers:

- Use in patients who are intolerant of ACE inhibitors and have heart failure or have had a myocardial infarction with left ventricular ejection fraction of 40 percent or less.
- Consider in other patients who are ACE-inhibitor intolerant.
- Consider use in combination with ACE inhibitors in systolic-dysfunction heart failure.

Aldosterone blockade:

- Use in post-myocardial infarction patients who do not have significant kidney dysfunction or elevated serum potassium, who are already receiving therapeutic doses of an ACE inhibitor and beta blocker, have a left ventricular ejection fraction of 40 percent or less, and have either diabetes or heart failure.

Beta blockers

- Start and continue indefinitely in all patients who have had myocardial infarction, acute coronary syndrome, or left ventricular dysfunction with or without heart failure symptoms, unless contraindicated.

Consider chronic therapy for all other patients with coronary or other vascular disease or diabetes unless contraindicated

TREATMENT:

3. INITIAL MEASURES

- Oral nitrates and Aspirin
- ECG within 5 minutes of arrival
- History and examination including BP both arms
- IV cannula
- Oxygen if SaO₂ <98% (unless history of COPD), pain relief with GTN, morphine or diamorphine, metoclopramide if pain still present
- FBC, coagulation, U+E, glucose, lipids, LFT, troponin, CK, CXR
- Consider other diagnoses e.g. PE, aortic dissection, pneumothorax

4. RISK STRATIFICATION

Calculate TIMI risk score

<u>RISK FACTOR</u>	<u>POINTS</u>
• Age > 65	1
• ≥3 CAD risk factors (↑Chol FHx, HTN, DM, Smoker, PVD)	1
• Known CAD (stenosis ≥50%)	1
• Aspirin use in the past 7 days	1
• Severe angina (≥2 episodes in last 24 hours)	1
• ↑cardiac markers	1
• ST deviation ≥0.5m	1
RISK SCORE = Total Points (0-7)	

2.1 Low risk (TIMI risk score 0-2)

If the TIMI risk score is low and troponin is not elevated, aim for early discharge:

- Normal ECG, age <40 and 0-1 risk factors (DM, smoking, FH premature CAD, HTN, hypercholesterolaemia, PVD) – consider alternative diagnoses. GP follow-up
- Normal ECG, age >40 or ≥2 more risk factors – arrange early exercise test .Refer to cardiac assessment and Discharge with aspirin 75mg and GTN spray with advice to return if recurrent symptoms
- Non-diagnostic (known pre-existing ECG abnormalities) or uninterpretable ECG (e.g. bundle branch block, LVH) – refer to cardiac assessment If angina is suspected. Discharge with aspirin 75mg od and GTN spray with advice to return if recurrent symptoms.

2.2 Moderate – High Risk (TIMI risk score 3-7)

If the patient has ECG or cardiac marker evidence of an ACS or if in the opinion of the admitting physician this is felt to be likely, treatment should be initiated immediately on admission.

Treatment should consist of:

- Aspirin 300 mg then 75 mg od
- Clopidogrel 300 mg then 75 mg od
- Fondaparinux 2.5mg od s/c (see guideline WAHT-CAR-042)
- Beta blocker (e.g. bisoprolol 2.5 – 5mg od) titrated till HR<60 bpm
If beta blocker contra-indicated diltiazem may be used though rate control is less effective
- Statin – the default for ACS cases is Atorvastatin 80 mg od. Use simvastatin 40 mg od if there are concerns regarding tolerability of high dose statin therapy
- ACE inhibitor (e.g. ramipril 1.25 mg bd titrated to 5mg bd) started the day after admission if BP>100 and creatinine<200
- IV nitrates if still in pain or ECG evidence of ischemia

3. ADDITIONAL THERAPIES

- 3.1 IIb/IIIa inhibitors - In the highest risk patients, or if there is evidence of recurrent chest pain with dynamic ECG changes (especially ST depression), use glycoprotein IIb/IIIa inhibitor infusion
- 3.2 Omega-3 fatty acids - Omacor 1gm od improves prognosis when started within 3 months of a myocardial infarction, predominantly by reducing sudden cardiac death.
- 3.3 Aldosterone antagonists
If heart failure with LV impairment present, consider spironolactone 25-50mg od or eplerenone 25-50mg od. **Contra-indicated** in hyperkalaemia or renal failure ($Cr > 200 \mu\text{mol/l}$). Monitor potassium

4. NURSING

- Transfer high risk ACS patients (TIMI risk 5-7) to CCU
- Manage moderate risk ACS patients initially on MAU with ECG monitoring if no cardiology bed available, but aim to transfer to Laurel 1/CCU as soon as possible

5. CARDIAC CATHETERISATION

All patients at high or moderate risk with an elevated troponin or dynamic ST depression $> 1\text{mm}$ should undergo in-patient coronary angiography and revascularization unless there are contra-indications. Refer to cardiology/cardiology assessment within 24 hours.

- Even in the absence of an elevated troponin or dynamic ST changes, patients with a TIMI risk score 3-7 may still be best managed by in-patient coronary angiography. Refer to cardiology assessment within 24 hours.
- Emergency cardiac catheterization may be required if there are on-going or recurrent symptoms with dynamic ST changes or hemodynamic instability. Consult with a cardiologist

6. ECHOCARDIOGRAPHY

Echocardiography should be performed in all patients after MI to assess LV function. If severe LV impairment ($EF < 35\%$), consider Holter monitoring after 3 weeks to look for non-sustained VT (≥ 3 beats at rate > 120) – consider referral for VT stimulation study and possible ICD

If $EF < 30\%$ and $QRS > 120\text{ms}$, consider referral for ICD

7. GLUCOSE CONTROL

Intensive glucose control offers benefits in patients admitted with MI.

IV insulin and glucose in all patients with STEMI and admission glucose $> 11.0\text{mmol/l}$ for 24-48 hours. Contact diabetologist when patients started on insulin. For patients known to have diabetes not treated with insulin, a period of insulin treatment is advised. Convert to s/c insulin (e.g. Novomix 30 bd regime) after 24-48 hours.

For patients known to have diabetes treated with insulin, convert to usual s/c insulin after 24-48 hours and monitor control.

For patients not known to have diabetes, stop infusion after 24-48 hours and monitor blood glucose. Contact diabetologist who will arrange a glucose tolerance test if glucose control is satisfactory.

References

- 1- Amsterdam EA, Kirk JD, Diercks DB, Lewis WR, Turnispeed SD. Immediate exercise testing to evaluate low-risk patients presenting to the emergency department with chest pain *J Am Coll Cardiol* 2002;40:251-256
- 2- Udelson JE, Beshansky JR, Ballin DS, et al. Myocardial perfusion imaging for evaluation and triage of patients with suspected acute cardiac ischemia randomized controlled trial. (published erratum appears in *JAMA* 2003;289:178) *JAMA* 2002;288
- 3- Sabia P, Afrookteh A, Touchstone DA, Keller MW, Esquivel L, Kaul S. Value of regional wall motion abnormality in the emergency room diagnosis of acute myocardial infarction a prospective study using two-dimensional echocardiography. *Circulation* 1991;84(Suppl D):185
- 4- Tong KL, Kaul S, Wang X-Q, et al. Myocardial contrast echocardiography versus Thrombolysis In Myocardial Infarction score in patients presenting to the emergency department with chest pain and a nondiagnostic electrocardiogram *J Am Coll Cardiol* 2005;46:920-927.
- 5- Udelson JE, Bateman TM, Bergmann SR, et al. Proof of principle study of beta-methyl-p-[123I]-iodophenyl-pentadecanoic acid (BMIPP) for ischemic memory following demand ischemia *Circulation* 2003;108:IV405.
- 6- Verjans JW, Haider N, Li P. Targeted ultrasound imaging of apoptosis in acute myocardial injury with annexin-A5 microspheres *Circulation* 2004;110:III509.
- 7- Villanueva FS, Jankowski RJ, Klibanov S, et al. Microbubbles targeted to intercellular adhesion molecule-1 bind to activated coronary artery endothelial cells a novel approach to assessing endothelial function using myocardial contrast echocardiography. *Circulation* 1998;98:1-5.
- 8- Nevas-Nacher EL, Colangelo L, Beam C, et al.: Risk factors for coronary heart disease in men age 18 to 39 years of age. *Ann Intern Med.* 2001; 134:433-439.
- 9- Lloyd W. Klein, Sandeep Nathan: Coronary artery disease in young adults. *J Am Coll Cardiol.* 2003; 41:529-531.
- 10- Williams MJ, Restieaux NJ, Low CJ: Myocardial infarction in young patients with normal coronary arteries. *Heart.* 1998; 79:191-194
- 11- The Cleveland Clinic, heart and vascular institute: How does coronary artery disease develop? (2006).
- 12- King SB III, Douglas FS Jr, Morris DC. New angiographic views for coronary arteriography. In *Hurst Update IV; The Heart*, McConey Hill, New Yourk. (1981), P 615.
- 13- Coronary Artery Anatomy. UAB health system. . 2006.
- 14- Staessen JA, Gasowski J, Wang JG, et al. Risks of untreated and treated isolated systolic hypertension in the elderly: meta-analysis of outcome trials. *Lancet.* 2000; 355: 865-872.
- 15- Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: Results of prospectively designed overviews of randomized trials. *Blood Pressure Lowering Treatment Trialists' Collaboration.* *Lancet* 2000; 356:1955-1964.
- 16- The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *JAMA* 2003; 289: 2560-2571.
- 17- Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the Management of Patients with Chronic Stable Angina). *J Am Coll Cardiol* 2003; 41:159-168.
- 18- Franse LV, Pahor M, Di Bari M, et al. Hypokalemia associated with diuretic use and cardiovascular events in the Systolic Hypertension in the Elderly Program. *Hypertension* 2000; 35(5): 1025-1030.
- 19- Merlo J, et al. Incidence of myocardial infarction in elderly men being treated with antihypertensive drugs: population based cohort study. *BMJ* 1996; 313: 457-461.
- 20- James R. Sowers, George L. Bakris. Antihypertensive Therapy and the Risk of Type 2 Diabetes Mellitus *NEJM.*2000; 342: 969-970.
- 21- Gress TW, Nieto FJ, Shahar E, et al. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *Atherosclerosis Risk in Communities Study.* *N Engl J Med.* 2000; 342: 905-991.
- 22- The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high normal blood pressure. The Trials of Hypertension Prevention, phase II. *Arch Intern Med* 1997; 157:657-667.
- 23- Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. *DASH-Sodium Collaborative Research Group.* *N Engl J Med* 2001; 344: 3-10.

- 24- Vollmer WM, Sacks FM, Ard J, et al. Effects of diet and sodium intake on blood pressure: Subgroup analysis of the DASH-sodium trial. *Ann Intern Med* 2001; 135:1019-1028.
- 25- Chobanian AV, Hill M. National Heart, Lung, and Blood Institute Workshop on Sodium and Blood Pressure: A critical review of current scientific evidence. *Hypertension* 2000; 35:858-863.
- 26- Xin X, He J, Frontini MG, et al. Effects of alcohol reduction on blood pressure: A meta-analysis of randomized controlled trials. *Hypertension* 2001; 38:1112-1117.
- 27- Appel LJ, Champagne CM, Harsha DW, et al. Effects of comprehensive lifestyle modification on blood pressure control: Main results of the PREMIER clinical trial. Writing Group of the PREMIER Collaborative Research Group. *JAMA* 2003; 289:2083-2093.
- 28- Miettinen H, Lehto S, Salomaa V, et al : Impact of diabetes on mortality after the first myocardial infarction. *Diabetes Care* 1998; 21:69-75.
- 29- Haffner SM, Lehto S, Ronnema T, et al: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*.1998; 339:229-234.
- 30- Prior JO, Monbaron D, Koehli M, et al: Prevalence of symptomatic and silent stress-induced perfusion defects in diabetic patients with suspected coronary artery disease referred for myocardial perfusion scintigraphy. *Eur J Nucl Med Mol Imaging*. 2005;32:60-69.
- 31- Fallow GD., Singh J., The prevalence, type and severity of cardiovascular disease in diabetic and non-diabetic patients: a matched-paired retrospective analysis using coronary angiography as the diagnostic tool, 2004; 261(1-2): 263-269.
- 32- Jacoby RM, Nesto RW. Acute myocardial infarction in the diabetic patient: pathophysiology, clinical course, and prognosis. *J Am Coll Cardiol* 1992; 20:736-744.
- 33- Jakob Larsen, Magne Brekke, Leiv Sandvik, et al. Silent Coronary Atheromatosis in Type 1 Diabetic Patients and Its Relation to Long-Term Glycemic Control, *Diabetes* 2002, 51:2637-2641.
- 34- K P Morgan, A Kapur and K J Beatt , Anatomy of coronary disease in diabetic patients: an explanation for poorer outcomes after percutaneous coronary intervention and potential target for intervention, *Heart* 2004;90:732-738.
- 35- Jager A , van Hinsbergh VW, Kostense PJ, et al. Increased levels of soluble vascular cell adhesion molecule 1 are associated with risk of cardiovascular mortality in type 2 diabetes: the Hoorn study. *Diabetes* 2000;49:485-491.
- 36- Marso SP, Giorgi LV, Johnson WL, et al. Diabetes mellitus is associated with a shift in the temporal risk profile of in-hospital death after percutaneous coronary intervention: an analysis of 25,223 patients over 20 years. *Am Heart J* 2003; 145:270-277.
- 37- Cariou B , Bonnevie L, Mayaudon H, et al. Angiographic characteristics of coronary artery disease in diabetic patients compared with matched non-diabetic subjects. *Diabetes Nutr Metab* 2000;13:134-410.
- 38- Maturana MA, Spritzer PM. Association between hyperinsulinemia and endogenous androgen levels in peri- and postmenopausal women. *Metabolism* 2002;51:238-243.
- 39- Thomas CS, Cherian G, HayatNJ, et al. Angiographic comparison of coronary artery disease in Arab women with and without type II diabetes mellitus. *Med Princ Pract* 2002; 11 (suppl 2): 63-68.
- 40- Syvanne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. *Lancet* 1997; 350 (suppl 1): S120-23.
- 41- Blackburn R, Giral P, Bruckert E, et al. Elevated C-reactive protein constitutes an independent predictor of advanced carotid plaques in dyslipidemic subjects. *Arterioscler Thromb Vasc Biol* 2001; 21:1962-1968.
- 42- Cantor WJ, Miller JM, HellkampAS, et al. Role of target vessel size and body surface area on outcomes after percutaneous coronary interventions in women. *Am Heart J* 2002; 144:297-302.
- 43- Waller BF, Palumbo PJ, Lie JT, et al. Status of the coronary arteries at necropsy in diabetes mellitus with onset after age 30 years: analysis of 229 diabetic patients with and without clinical evidence of coronary heart disease and comparison to 183 control subjects. *Am J Med* 1980; 69:498-506.
- 44- WongND, Kouwabunpat D, Vo AN, et al. Coronary calcium and atherosclerosis by ultrafast computed tomography in asymptomatic men and women: relation to age and risk factors. *Am Heart J* 1994; 127:422-430.
- 45- Abaci A, Oguzhan A, Kahraman S, et al. Effect of diabetes mellitus on formation of coronary collateral vessels. *Circulation* 1999; 99:2239-2242.
- 46- Stratton IM, Adler AI, Neil HA, et al., Association of glycaemia with macro-vascular and micro-vascular complications of type II diabetes, (UKPDS 35): prospective observational study. *BMJ* 2000; 321:405-412.
- 47- American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2002; 25:S33-S49.

- 48- Benjamin M. Scirica and Christopher P. Cannon Treatment of Elevated Cholesterol Circulation 2005; 111: 360-363.
- 49- Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239.
- 50- Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. *Nature*, 1993; 362:801–809.
- 51- T Amaki, T Suzuki, F Nakamura, et al, Circulating malondialdehyde modified LDL is a biochemical risk marker for coronary artery disease. *Heart*, 2004;90:1211–1213.
- 52- Henry C. McGill, Jr; C. Alex McMahan; Edward E. Herderick; et al, Strong, Effects of Coronary Heart Disease Risk Factors on Atherosclerosis of Selected Regions of the Aorta and Right Coronary Artery. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2000;20:836.
- 53- Hevonoja T., Pentikäinen M.O., Hyvönen M.T., et al. Structure of low density lipoprotein (LDL) particles: Basis for understanding molecular changes in modified LDL. *Biochemica et Biophysica Acta (BBA) – Molecular and Cell Biology of Lipids*. 2000; 1488: 189-210
- 54- Brown, M.S.& Goldstein, J.L., How LDL receptors influence cholesterol and atherosclerosis. *Sci.American*, 1984; 251: 52- 60.
- 55- Nissen SE, Tuzcu EM, Schoenhagen P, et al: effect of intensive compared with moderate lipid lowering therapy on progression of coronary atherosclerosis. *JAMA*, 2004; 291:1071.
- 56- Stamler J., Daveglus ML., Garside CB, et al. relationship of serum cholesterol in three large cohorts of younger men to long-term coronary, cardiovascular and all cause mortality and to longevity. *JAMA*, 2000; 284:311.
- 57- Campos H., G.O. Roederer, S. Lussier-Cacan, et al: Predominance of large LDL and reduced HDL2 cholesterol in normolipidemic men with coronary artery disease. *Arterioscler. Thromb. Vasc. Biol*. 1995; 15: 1043– 1048.
- 58- Schwartz GG, Olsson AG, Ezekowitz MD, et al: effects of atorvastatin on early recurrent ischaemic events in acute coronary syndromes the MIRACL study: a randomized controlled trial. *JAMA* 2001; 285:1711.
- 59- Hodis HN. Triglyceride-rich lipoprotein remnant particles and risk of atherosclerosis. *Circulation*. 1999; 99:2852–2854.
- 60- Phillips N, Waters D, Havel R., Plasma lipoproteins and progression of coronary artery disease evaluated by angiography and clinical events. *Circulation*. 1993;88:2762–2770.
- 61- Assmann G, Brewer HB Jr. Genetic (primary) forms of hypertriglyceridemia. *Am J Cardiol* 1991;68(3):13A-16A.
- 62- Peto R., Lopez A.D., Boreham J., et al., Mortality from tobacco in developed countries: Indirect estimation from national vital statistics. *Lancet*, 1992;339:1268-1274.
- 63- Steenland, K.: Passive smoking and the risk of heart disease. *JAMA*, 1992;267:94-99.
- 64- Peto R, Lopez A D, Boreham J, et al. Mortality from smoking worldwide. *Br Med Bull* 1996; 52: 12-21.
- 65- World Health Organization, World Health Report . Reducing risks, promoting healthy life. Geneva, 2002.
- 66- Paul P. Lau; Aksam J. Merched; Alan L. Zhang; et al. Nicotine Induces Proinflammatory Responses in Macrophages and the Aorta Leading to Acceleration of Atherosclerosis in Low-Density Lipoprotein receptors, *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2006;26:143.
- 67- M. Cesari, A. C. Pessina, M. Zanchetta, et al. Low plasma adiponectin is associated with coronary artery disease but not with hypertension in high-risk nondiabetic patients. *Journal of Internal Medicine*, 2006; 260 (5) 474.
- 68- Fahim Abbasi, Helke M. F. Farin, Cindy Lamendola, et al. The Relationship between Plasma Adiponectin Concentration and Insulin Resistance Is Altered in Smokers. *The Journal of Clinical Endocrinology & Metabolism*, 2006; 91(12) 5002-5007.
- 69- Blann AD, Steele C, McCollum CN. The influence of smoking and of oral and transdermal nicotine on blood pressure, and haematology and coagulation indices. *Thromb Haemost*. 1997;78:1093-1096.
- 70- Mall T, Grossenbacher M, Perruchoud AP, et al. Influence of moderately elevated levels of carboxyhemoglobin on the course of acute ischemic heart disease. *Respiration*. 1985;48:237-244.
- 71- Nedeljkovic ZS, Gokce N, Loscalzo J. Mechanisms of oxidative stress and vascular dysfunction. *Postgrad Med J*. 2003;79:195-199.
- 72- Frhlich M, Sund M, Lwel H, et al. Independent association of various smoking characteristics with markers of systemic inflammation in men: results from a representative sample of the general population (MONICA Augsburg Survey 1994/95). *Eur Heart J*. 2003; 24:1365-1372.
- 73- Bermudez EA, Rifai N, Buring JE, et al. Relation between markers of systemic vascular inflammation and smoking in women. *Am J Cardiol*. 2002;89:1117-1119.

- 74- Yukio Shimasaki, Yoshihiko Saito, Michihiro Yoshimura, et al; The Effects of Long-term Smoking on Endothelial Nitric Oxide Synthase mRNA Expression in Human Platelets as Detected With Real-time Quantitative RT-PCR , 2007Clinical and Applied Thrombosis/Hemostasis, 2007; 13(1): 43-51.
- 75- L. Grummer-Strawn, M. Hughes and L. K. Khan, "Obesity in Women from Developing Countries,". European Journal of Clinical Nutrition, 2000;54: 247-252.
- 76- Muscat JE, Harris RE. Cigarette smoking and plasma cholesterol. Am Heart J 1991; 121: 141-147.
- 77- Reaven GM. Role of insulin resistance in human disease. Diabetes 1988; 37: 595-607.
- 78- Kimmel SE, Berlin JA, Miles C, et al. Risk of acute first myocardial infarction and use of nicotine patches in a general population. J Am Coll Cardiol. 2001; 37:1297- 1302.
- 79- Dietz WH, Robinson TN. Use of the body mass index (BMI) as a measure of overweight in children and adolescents. Journal of Pediatric 1998;2: 132.
- 80- Barlow SE, Dietz WH. Obesity evaluation and treatment: expert committee recommendations. Pediatrics 1998; 29:102.
- 81- Osman M Galal, The nutrition transition in Egypt: obesity, under-nutrition and the food consumption context, Public Health Nutrition: 2002, 5(1A), 141–148.
- 82- Nutrition Institute. Food Consumption Pattern and Nutrient Intake among Different Population Groups in Egypt, CairoNutrition Institute, 1999.
- 83- Galal OM. Paper presented at the Middle East Studies Association, San Francisco, CA, November 1997
- 84- Basyouny IF. Just a Gaze: Female Clientele of Diet Clinics in Cairo: An Ethno medical Study. Cairo: AmericanUniversity Press, 1998
- 85- Hopkins PN, HuntSC, Wu LL, et al. Hypertension, dyslipidemia and insulin resistance: links in a chain or spokes on a wheel? Curr Opin Lipidol. 1996; 7:241–253.
- 86- Pouliot MC, Despre’s JP, Lemieux S, et al. Waist circumference and abdominal sagittal indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol. 1994; 73:460–468.
- 87- Casassus P, Fontbonne A, Thibult N, et al. Upper-body fat distribution: a hyperinsulinemia-independent predictor of coronary heart disease mortality—the Paris Prospective Study. Arterioscler Thromb. 1992; 12: 1387–1392.
- 88- Turcato E, Bosello O, Di Francesco V, et al. Waist circumference and abdominal sagittal diameter as surrogates of body fat distribution in the elderly: their relation with cardiovascular risk factors. Pubmed, 2000; 24(8): 1005-1010.
- 89- Singh RB, Niaz MA, Agarwal P, et al. Epidemiologic study of central obesity, insulin resistance and associated disturbances in the urban population of North India. Acta cardiol, 1995; 50(3): 215-225.
- 90- Daniel Lesiège, Jean Bergeron, Sital Moorjani , et al. Receptor Gene Assessed Coronary Artery Disease in Men With Known Mutations in the LDL Relationships of Abdominal Obesity and Hyperinsulinemia to Angiographically, Circulation 1998; 97:871-877.
- 91- Alexander JK. Obesity and coronary heart disease. Am. J Med Sci. 2001; 321: 215-224.
- 92- Visser M, Bouter LM, McQuillan GM, et al. Elevated C-reactive protein levels in overweight and obese adults. JAMA. 1999; 282: 2131–2135.
- 93- Ford ES, Galuska DA, Gillespie C, et al. C-reactive protein and body mass index in children: findings from the Third National Health and Nutrition Examination Survey, 1988–1994. J Pediatr. 2001; 138: 486–492.
- 94- Steinberger J, Moran A, Hong CP, et al. Adiposity in childhood predicts obesity and insulin resistance in young adulthood. J Pediatr. 2001; 138: 469–473.
- 95- Zieske AW, Malcom GT, Strong JP. Natural history and risk factors of atherosclerosis in children and youth: the PDAY study. Pediatr Pathol Mol Med. 2002; 21: 213–237.
- 96- Samia Mora, Lisa R. Yanek, et al. Interaction of Body Mass Index and Framingham Risk Score in Predicting Incident Coronary Disease in Families, Circulation. 2005; 111:1871-1876.
- 97- Vega GL. Obesity, the metabolic syndrome, and cardiovascular disease. Am Heart J 2001; 142:1108-1116
- 98- Bjorntorp P. Heart and soul: stress and the metabolic syndrome. Scand Cardiovasc J 2001; 35:172-177
- 99- National Institutes of Health: Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Executive Summary. Bethesda, Md.: National Institutes of Health, National Heart Lung and Blood Institute, 2001 (NIH publication no. 01-3670)
- 100- Hiroyasu Iso, Shinichi Sato, Akihiko Kitamura. Metabolic Syndrome and the Risk of Ischemic Heart Disease and Stroke Among Japanese Men and Women. Stroke, 2007;38:1744
- 101- Tonstad S, Svendsen M., Premature coronary heart disease, cigarette smoking, and the metabolic syndrome. Am J Cardiol. 2005; 96(12):1681-1685

- 102- Tonstad S, Hjermann I. A high risk score for coronary heart disease is associated with the metabolic syndrome in 40-year-old men and women. *J Cardiovasc. Risk*, 2003; 10(2):129-135
- 103- Nakanishi N, Takatorige T, Suzuki K. Cigarette smoking and the risk of the metabolic syndrome in middle-aged Japanese male office workers. *Ind Health*, 2005; 43(2):295-301
- 104- Ronnema T, Ronnema EM, Puukka P et al. Smoking is independently associated with high plasma insulin levels in non diabetic men. *Diabetes Care*, 1996; 19:1229-1232
- 105- David PS, Boatwright EA, Tozer BS, et al. Hormonal contraception update. *Mayo-Clin Proc* 2006; 81(7): 949-954.
- 106- Acute myocardial infarction and combined oral contraceptives: results of an international multi-centre case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet* 1997; 349(9060): 1202-1209.
- 107- Cardoso F, Polonia J, Santos A, et al. Low-dose oral contraceptives and 24-hour ambulatory blood pressure. *Int J Gynaecol Obstet*. 1997;59:237-243.
- 108- Chasan-Taber L, Willett WC, Manson JE, et al. Prospective study of oral contraceptives and hypertension among women in the United States. *Circulation*. 1996;94:483-489.
- 109- Lubianca JN, Faccin CS, Fuchs FD. Oral contraceptives: a risk factor for uncontrolled blood pressure among hypertensive women. *Contraception*. 2003;67:19-24.
- 110- Rosenberg L, Palmer JR, Rao RS, et al. Low-Dose Oral Contraceptive Use and the Risk of Myocardial Infarction. *Arch Intern Med*. 2001; 161:1065-1070.
- 111- Acute myocardial infarction and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. *Lancet* 1997; 349:1202-1209.
- 112- ACOG Practice Bulletin. The use of hormonal contraception in women with coexisting medical conditions. Number 18, July 2000. *Int J Gynaecol Obstet*. 2001;75:93-106.
- 113- Mosca L, Grundy SM, Judelson D, et al. Guide to Preventive Cardiology for Women. *Circulation*. 1999;99:2480-2484.
- 114- Douglas PS. Coronary artery disease in women. In Braunwald et al., eds., *Heart Disease: A Textbook of Cardiovascular Medicine*, 2001, 6th ed., vol. 2, 2038–2051.
- 115- Christopher Hess, Kathleen M. Ariss, Michele Cronen, et al. Birth control pills, hormone replacement therapy, and coronary artery disease, Start a team today, 2006.
- 116- Peterson HB. A 40-year-old woman considering contraception. *JAMA* 1998; 279:1651-1658.
- 117- Improving access to quality care in family planning: medical eligibility criteria for contraceptive use. Geneva: World Health Organization, 1996:13-26.
- 118- Montvale, N.J., Physicians' desk reference. Medical Economics, 1999.
- 119- Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD). Available at: <http://www.ncbi.nlm.nih.gov/omim/>. 2003.
- 120- Krushkal J, Ferrell R, Mockrin SC, et al. Genome-wide linkage analyses of systolic blood pressure using highly discordant siblings. *Circulation*. 1999;99:1407-1410.
- 121- Deng HW, Deng H, Liu YJ, et al. A genomewide linkage scan for quantitative-trait loci for obesity phenotypes. *Am J Hum Genet*. 2002;70:1138-1151.
- 122- Lindgren CM, Mahtani MM, Widen E, et al. Genomewide search for type 2 diabetes mellitus susceptibility loci in Finnish families: the Botnia study. *Am J Hum Genet*. 2002;70:509-516.
- 123- Peacock JM, Arnett DK, Atwood LD, et al. Genome scan for quantitative trait loci linked to high-density lipoprotein cholesterol: The NHLBI Family Heart Study. *Arterioscler Thromb Vasc Biol*. 2001;21:1823-1828.
- 124- Nasir K, Michos ED, Rumberger JA, et al. Coronary artery calcification and family history of premature coronary heart disease: sibling history is more strongly associated than parental history. *Circulation*. 2004; 110:2150-2156.
- 125- Eaton CB, Bostom AG, Yanek L, et al. Family history and premature coronary heart disease. *J Am Board Fam Pract*. 1996;9: 312-318.
- 126- Lloyd-Jones DM, Nam B-H, D'Agostino RB, et al. Parental Cardiovascular Disease as a Risk Factor for Cardiovascular Disease in Middle-aged Adults: A Prospective Study of Parents and Offspring. *JAMA*, 2004; 291:2204-2211.
- 127- Pohjola-Sintonen S, Rissanen A, Liskola P, et al. Family history as a risk factor of coronary heart disease in patients under 60 years of age. *Eur Heart J*. 1998; 19:235-239.

- 128- Leander K, Hallqvist J, Reuterwall C, et al. Family history of coronary heart disease, a strong risk factor for myocardial infarction interacting with other cardiovascular risk factors: results from the Stockholm Heart Epidemiology Program (SHEEP). *Epidemiology*. 2001;12:215-221.
- 129- Murabito JM, Pencina MJ, Nam B-H, et al. Sibling Cardiovascular Disease as a Risk Factor for Cardiovascular Disease in Middle-aged Adults. *JAMA*. 2005;294:3117-3123.
- 130- Sundquist K, Li X. Differences in maternal and paternal transmission of coronary heart disease. *Am J Prev Med*. 2006; 30:480-486.
- 131- Wienke A, HolmNV, Skyttthe A, et al. The heritability of mortality due to heart diseases: a correlated frailty model applied to Danish twins. *Twin Res*. 2001; 4:266-274.
- 132- Grundy SM, Pasternak R, Greenland P, et al. AHA/ACC scientific statement: Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *J Am Coll Cardiol*. 1999, 34:1348-1359.
- 133- Vaccarino V, Krumholz HM, Yarzebski J, et al. Sex differences in 2-year mortality after hospital discharge for myocardial infarction. *Am Intern Med J*. 2001;134:173-181.
- 134- Raine R. Does gender bias exist in the use of specialist health care, *Journal of Health Service Research and Policy*. 2000;5:237-249.
- 135- Castelli WP., Epidemiology of triglycerides: A view from Framingham. *Am J Cardiol* 1992;70:3H-9H.
- 136- Stokes J III, Kannel W, Wolf P, et al: The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham Study. *Circulation*, 1987; 75(6,pt 2):V65-V73.
- 137- Bell MR: Are there gender differences or issues related to angiographic imaging of the coronary arteries? *Am J Card Imaging* 1996;10:44-53.
- 138- Douglas PS, Ginsburg GS: The evaluation of chest pain in women. *N Engl J Med*, 1996;334:1311-1315.
- 139- Bullemer F, Graham K, Pankow J, et al: Gender-related differences in risk factors of young patients with symptomatic coronary artery disease. *J Am Coll Cardiol Special issue*, 1995; (267A).
- 140- Colditz G, Stampfer M, Willett W, et al: A prospective study of parental history of myocardial infarction and coronary heart disease in women. *Am J Epidemiol*, 1986;123:48.
- 141- Hubert H, Feinleib M, McNamara P, et al: Obesity as an independent risk factor for cardiovascular disease: A 26-year follow-up of participants in the Framingham Heart Study. *Circulation* 1983;69:1065-1069.
- 142- Stevens J, Cai J, Pamuk ER, et al: The effect of age on the association between body-mass index and mortality. *N Engl J Med*,1998;338:1-7.
- 143- Lapidus L, Bengtsson C, Larsson B, et al: Distribution of adipose tissue and risk of cardiovascular disease and death: A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. *Br Med J*, 1984;289:1257-1261.
- 144- New G, Timmins KL, Duffy SJ, et al. Long-term estrogen therapy improves vascular function in male to female transsexuals. *J Am Coll Cardiol* 1997;29:1437-1444.
- 145- Gilligan DM, Quyyumi AA, Cannon RO. Effects of physiological levels of estrogen on coronary vasomotor function in postmenopausal women. *Circulation* 1994;89:2545-2551.
- 146- Robinson K, Mayer E, Jacobsen DW. Homocysteine and coronary artery disease. *Cleveland Clinic Journal of Medicine* 1994; 61: 438-450
- 147- Kang SS, Wong PWK, Malinow MR. Hyperhomocysteinemia as a risk factor for occlusive vascular disease. *Ann Rev Nutr*1992; 12: 279-298
- 148- Kluijtmans LA, van den Heuvel LP, Boers GH, et al. Molecular genetic analysis in mild hyperhomocysteinemia: a common mutation in the methylenetetrahydrofolate reductase gene is a genetic risk factor for cardiovascular disease. *Am J Hum Genet* 1996; 58: 35-41.
- 149- NS Neki. Hyperhomocysteinemia – An Independent Risk factor for Cardio-vascular Diseases, *Journal, Indian Academy of Clinical Medicine*, 2003; 4: 1.
- 150- Stamler JS, Osborne JA, Jaraki O et al. Adverse vascular effects of homocysteine are modulated by endothelium derived relaxing factor and related oxides of nitrogen. *J Clin Invest* 1993; 91: 308-318.
- 151- Starkebaum G, Harlan JM. Endothelial cell injury due to copper – catalysed hydrogen peroxide generation from homocysteine. *J Clin Invest* 1993; 77:1370-1376.
- 152- Megnien JL, Garipey J, Saudubray JM et al. Evidence of carotid wall hypertrophy in homozygous homocystinuria. *Circulation* 1998; 98S: 2276-2281.
- 153- Robinson K, Mayer E, Jacobsen DW. Homocysteine and coronary artery disease. *Cleveland Clinic Journal of Medicine* 1994; 61: 438-450.

- 154- Fiorina P, Lanfredini M, Montanari A, et al. Plasma homocysteine and folate are related to arterial blood pressure in type 2 diabetes mellitus. *AJH* 1998; 11: 1100-1107.
- 155- Targher G, Bertolini L, Zenari L, et al. Cigarette smoking and plasmatotal homocysteine levels in young adults with type 1 diabetes. *Diabetes Care*, 2000;23: 524-528.
- 156- Hoogeveen EK, Kostense PJ, Jakobs C, et al. Hyperhomo-cysteinemia increases risk of death, especially in type 2 diabetes. 5-year follow-up of the Hoorn study. *Circulation*, 2000;101: 1506-1511.
- 157- JC Fruchart, MC Nierman, ESG Stroes, et al. New risk factors for atherosclerosis and patient risk assessment. *Circulation*. 2004; 109 (suppl III): III 15-19.
- 158- Margaglione M. Cappucci G. Colaizzo D. et al: fibrinogen plasma levels in an apparently healthy general population: relation to environmental and genetic determinants. *Thromb Haemost*, 1998;80:805.
- 159- Lowe GD, Yarnell JW, Rumley A et al. C-reactive protein, fibrin D-dimer, and incident ischemic heart disease in the Speedwell study: are inflammation and fibrin turnover linked in pathogenesis? *Arterioscler Thromb Vasc Biol*. 2001; 21: 603–610.
- 160- Lowe GDO. Circulating inflammatory markers and risks of cardiovascular and non-cardiovascular disease. *J Thromb Haemost* 2005; 3:1618-1627.
- 161- Wilhelmsen L, Svardsudd K., Korsan-Bengtson K, et al: fibrinogen as a risk factor stroke and myocardial infarction. *N Engl J Med* 1984; 311:501.
- 162- Brunner E, Davey Smith G, Marmot M, et al. Childhood social circumstances and psychosocial and behavioural factors as determinants of plasma fibrinogen. *Lancet*. 1996; 347: 1008– 1013.
- 163- Vittorio Palmieri , Aldo Celentano , Mary J. Roman , et al, Relation of fibrinogen to cardiovascular events is independent of preclinical cardiovascular disease: The strong heart study, 2003; Volume 145 Issue 3,467-474.
- 164- Stefanick ML, Mackey S, Sheehan M, et al. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. *N Engl J Med*. 1998; 339: 12–20.
- 165- Sinning JM; Bickel C; Messow CM; et al, Impact of C-reactive protein and fibrinogen on cardiovascular prognosis in patients with stable angina pectoris: the AtheroGene study, *Eur Heart J*. 2006;27(24):2962-2968.
- 166- Martin Halle; Aloys Berg; Joseph Keul,et al, Association Between Serum Fibrinogen Concentrations and HDL and LDL Subfraction Phenotypes in Healthy Men ;, *Arteriosclerosis, Thrombosis, and Vascular Biology*. 1996;16:144-148.
- 167- Ganda OM, Arkin CF. Hyperfibrinogenemia: an important risk factor for vascular complications in diabetes. *Diabetes Care*. 1992; 15:1245-1250.
- 168- Gram J, Bladbjerg EM, Moller L. Tissue-type plasminogen activator and C-reactive protein in acute coronary heart disease: a nested case-control study. *J Intern Med*. 2000; 247: 205–212.
- 169- Steins MB, Padro T, Mesters RM et al. Overexpression of tissue-type plasminogen activator in atherosclerotic human coronary arteries. *Atherosclerosis*. 1999; 145: 173–180.
- 170- Joseph D. Mills; Michael W. Mansfield; Peter J. Grant, Tissue Plasminogen Activator, Fibrin D-Dimer, and Insulin Resistance in the Relatives of Patients With Premature Coronary Artery Disease, *Arteriosclerosis, Thrombosis, and Vascular Biology*. 2002;22:704.
- 171- Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA*. 1995; 273: 402–407.
- 172- Lee IM, Paffenbarger RS Jr, Hennekens CH. Physical activity, physical fitness and longevity. *Aging (Milano)*. 1997; 9: 2–11.
- 173- Albert CM, Mittleman MA, Chae CU, et al. Triggering of sudden death from cardiac causes by vigorous exertion. *N Engl J Med*. 2000; 343: 1355–1361.
- 174- Blair SN, LaMonte MJ, Nichaman MZ. The evolution of physical activity recommendations: how much is enough? *Am J Clin Nutr*. 2004; 79: 913S–920S.
- 175- Taylor, J. Sallis, and R. Needle. The relationship of exercise and physical activity to mental health. *Public Health Rep.*,1985; 100:195-202.
- 176- Leon AS, Rice T, Mandel S, et al. Blood lipid response to 20 weeks of supervised exercise in a large biracial population: the HERITAGE Family Study. *Metabolism*. 2000; 49: 513–520.
- 177- Thompson PD, Crouse SF, Goodpaster B, et al. The acute versus the chronic response to exercise. *Med Sci Sports Exerc*. 2001; 33 (6 suppl): S438–S445.
- 178- Wing RR, Hill JO. Successful weight loss maintenance. *Annu Rev Nutr*. 2001; 21: 323–341.
- 179- GreenwoodDC, Muir KR, Packham CJ, et al. Coronary heart disease: areview of the role of psychosocial stress and social support. *J Public Health Med*. 1996; 18:221–231.
- 180- Moberg E, Kollind M, Lins P-E, et al. Acute mental stress impairs insulin sensitivity in IDDM patients. *Diabetologia*. 1994; 37:247–251.

- 181- Ghiadoni L, Donald AE, Cropley M, et al. Mental stress induces transient endothelial dysfunction in humans. *Circulation*. 2000; 102:2473–2478.
- 182- Niaura R, Stoney CM, Herbert PN. Lipids in psychological research: the last decade. *Biol Psychol*. 1992; 34:1-43.
- 183- M Myrtek. Meta-analyses of prospective studies on coronary heart disease, type A personality, and hostility. *International Journal of Cardiology* 2001 79: 245-251.
- 184- Lachar, Barbara L. Coronary Prone Behavior, *Texas Heart Institute Journal* 1993; 20: 143-151.
- 185- Horsten M, Ericson M, Perski A, et al. Psychosocial factors and heart rate variability in healthy women. *Psychosom Med* 1999; 61:49–57.
- 186- Denollet J, Sys SU, Stroobant N, et al. Personality as independent predictor of longterm mortality in patients with coronary heart disease. *Lancet* 1996; 347:417–421.
- 187- Jürgen Barth, Martina Schumacher and Christoph Herrmann-Lingen. Depression as a Risk Factor for Mortality in Patients With Coronary Heart Disease: A Meta-analysis, *Psychosomatic Medicine* 2004; 66:802-813.
- 188- DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med* 2000; 160:2101–2107.
- 189- Nemeroff CB, Musselman DL. Are platelets the link between depression and ischemic heart disease? *Am Heart J* 2000; 140(4 Suppl):57–62.
- 190- Rosmond R, Bjorntorp P. The hypothalamic-pituitary-adrenal axis activity as a predictor of cardiovascular disease, type 2 diabetes and stroke. *J Intern Med* 2000; 247:188–197.
- 191- Glassman AH, O'Connor CM, Califf RM, et al, SADHEART Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA* 2002;288:701–709.
- 192- Writing committee for the ENRICH investigators. Effects of treating depression and low social support on clinical events after myocardial infarction: The enhancing recovery in coronary heart disease patients (ENRICH) randomized trial. *JAMA* 2003;289:3106–3116.
- 193- Maclure M. Demonstration of deductive meta-analysis: ethanol intake and risk of myocardial infarction. *Epidemiol Rev*. 1993;15:328–351.
- 194- Di Castelnuovo A, Rotondo S, Iacoviello L, et al. Meta-analysis of wine and beer consumption in relation to vascular risk. *Circulation* 2002;105:2836-2844.
- 195- De Oliveira Silva E. R., Foster D., Alcohol Consumption Raises HDL Cholesterol Levels by Increasing the Transport Rate of Apolipoproteins A-I and A-II. *Circulation*. 2000; 102:2347-2352.
- 196- Breslow RA, Smothers BA. Drinking patterns and body mass index in never smokers: National Health Interview Survey, 1997–2001. *Am J Epidemiol*. 2005; 161:368–376.
- 197- Hiroyasu Iso, Akihiko Kitamura, Takashi Shimamoto, Alcohol Intake and the Risk of Cardiovascular Disease in Middle-Aged Japanese Men, (*Stroke*. 1995;26:767-773.
- 198- Castelli WP, Doyle JT, Gordon T, et al. Alcohol and blood lipids: the cooperative lipoprotein phenotyping study. *Lancet*. 1977; 2:153-155.
- 199- Rehm J, Greenfield TK, Rogers JD. Average volume of alcohol consumption, patterns of drinking, and all-cause mortality: results from the US National Alcohol Survey. *Am J Epidemiol* 2001; 153:64-71.
- 200- Flávio Danni Fuchs, Lloyd E. Chambless, Paul Kieran Whelton. Alcohol Consumption and the Incidence of Hypertension : The Atherosclerosis Risk in Communities Study *Hypertension* 2001;37:1242-1250.
- 201- Spriet LL, MacLean DA, Dyck DJ, et al. Caffeine ingestion and muscle metabolism during prolonged exercise in humans. *Am J Physiol*. 1992;262(part 1):E891– 898.
- 202- Ryu S, Choi SK, Joung SS, et al. Caffeine as a lipolytic food component increases endurance performance in rats and athletes. *J Nutr Sci Vitaminol (Tokyo)*. 2001;47:139–146.
- 203- Keijzers GB, De Galan BE, Tack CJ, et al. Caffeine can decrease insulin sensitivity in humans. *Diabetes Care*. 2002; 25:364–369.
- 204- Verhoef P, Pasma WJ, Van Vliet T, et al. Contribution of caffeine to the homocysteine-raising effect of coffee: a randomized controlled trial in humans. *Am J Clin Nutr*. 2002;76:1244–1248.
- 205- Hartley TR, Lovallo WR, Whitsett TL. Cardiovascular effects of caffeine in men and women. *Am J Cardiol*. 2004;93:1022–1026
- 206- Frary CD, Johnson RK, Wang MQ. Food sources and intakes of caffeine in the diets of persons in the United States. *J Am Diet Assoc*. 2005;105: 110–113
- 207- J.O. Adebayo, A.O. Akinyinka, G.A. Odewole, et al; effect of caffeine on the risk of coronary heart disease – a re-evaluation, *Indian Journal of Clinical Biochemistry*, 2007 ; 22 (1) 29-32

- 208- Esther Lopez-Garcia, Rob M. van Dam, Walter C. Willett, Coffee Consumption and Coronary Heart Disease in Men and Women. A Prospective Cohort Study, (*Circulation*. 2006;113:2045-2053)
- 209- Natella F, Nardini M, Giannetti I, et al. Coffee drinking influences plasma antioxidant capacity in humans. *J Agric Food Chem*.2002; 50:6211– 6216
- 210- Arnlov J, Vessby B, Riserus U. Coffee consumption and insulin sensitivity. *JAMA*. 2004;291:1199 –1201
- 211- Vlachopoulos C, Kosmopoulou F, Panagiotakos D et al. Smoking and caffeine have a synergistic detrimental effect on aortic stiffness and wave reflections. *J Am Coll Cardiol* 2004;44:1911-1917
- 212- S Heyden, G Heiss, C Manegold The combined effect of smoking and coffee drinking on LDL and HDL cholesterol, *circulation*, 1979;(60) 22-25
- 213- Cregler LL, Cocaine: the newest risk factor for cardiovascular disease. *Cli Cardiol*; 1991; 14(6):449-56
- 214- Das G, Cardiovascular effects of cocaine abuse *Int J Clin Pharmacol Ther Toxicol*. 1993; 31(11):521-8
- 215- Flores ED, Lange RA, Cigarroa RG, et al. Effect of cocaine on coronary artery dimensions in atherosclerotic coronary artery disease: enhanced vasoconstriction at sites of significant stenoses. *J Am Coll Cardiol* 1990; 16:74-9
- 216- Campa, A., Z. Yang, S. Lai, et al. HIV-related wasting in HIV-infected drug users in the era of highly antiretroviral therapy. 2005. *CID*.;41. In press.
- 217- Murray A. Mittleman, Rebecca A. Lewis, Malcolm Maclure, et al, Triggering Myocardial Infarction by Marijuana, *Circulation*. 2001;103:2805-2809
- 218- Hollister LE. Health aspects of cannabis. *Pharmacol Rev*. 1986; 38:1–20
- 219- Javier Waksman, Richard N. Taylor, Geza S. Bodor, Acute Myocardial Infarction Associated With Amphetamine Use, *Mayo Clin Proc*. 2001;76:323-326
- 220- Rich MW (2000) Uric acid: Is it a risk factor for cardiovascular disease? *Am J Cardiol* 85: 1018–1021
- 221- Conen D, Wietlisbach V, Bovet P, et al: Prevalence of hyperuricaemia and relation of serum uric acid with cardiovascular risk factors in a developing country. *BMC Public Health* 2004, 4(1):9
- 222- Bonora E, Targher G, ZenereMB, et al: Relationship of uric acid concentration to cardiovascular risk factors in young men. The role of obesity and central fat distribution, The Verona Young Men Atherosclerosis Risk Factors Study. *Int J Obes Relat Metab Disord* 1996, 20:975-980.
- 223- Hayden MR, TyagiSC: Homocysteine and reactive oxygen species in metabolic syndrome, type 2 diabetes mellitus, and atheroscleropathy: The pleiotropic effects of folate supplementation. *Nutr J* 2004, 3(1):4.
- 224- Nyyssonen K, Porkkala-Sarataho E, Kaikkonen J, et al: Ascorbate and urate are the strongest determinants of plasma antioxidative capacity and serum lipid resistance to oxidation in Finnish men. *Atherosclerosis* 1997, 130(1–2):223-233.
- 225- Steinberg D, Parthasarathy S, Carew TE, et al. Beyond cholesterol: modifications of low-density lipoprotein that increase its atherogenicity. *N Engl J Med*. 1989; 320:915–924
- 226- DiazMN, Frei B, Vita JA, et al. Antioxidants and atherosclerotic heart disease. *N Engl J Med*. 1997; 337:408:416.
- 227- Kushi LH, Folsom AR, Prineas RJ, et al. Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. *N Engl J Med*. 1996; 334:1156–1162.
- 228- Steinberg D, Witztum JL. Is the oxidative modification hypothesis relevant to human atherosclerosis? Do the antioxidant trials conducted to date refute the hypothesis? *Circulation*. 2002; 105:2107–2111.
- 229- Frei, B., Ascorbic acid protects lipids in human plasma and lowdensity lipoprotein against oxidant damage. *Am. J. Clin. Nutr.*, 1991, 54, 1113S–1118S.
- 230- Pushpa Bhakuni¹, M. Chandra² and M. K. Misra¹Levels of free radical scavengers and antioxidants in post-reperused patients of myocardial infarction, *Current Science*.2005, 89, NO. 1, 10.
- 231- Jacobson M. D., Reactive oxygen species and programmed cell death. *Trends Biochem. Sci.*, 1996, 243, 81–119.
- 232- Ross R. Atherosclerosis – An inflammatory disease. *N Engl J Med* 1999; 340:115-126.
- 233- Kunsch C, Medford RM. Oxidative stress as a regulator of gene expression in the vasculature. *Circ Res* 1999; 85:753-766.
- 234- Navab M, Berliner JA, Watson AD, et al. The yin and yang of oxidation in the development of the fatty streak: a review based on the 1994 George Lyman Duff Memorial Lecture. *Arterioscler Thromb Vasc Biol*1996; 16:831-42.
- 235- Marco N. D Iaz , Balz Frei, Joseph A. Vitam. Antioxidants And Atherosclerotic Heart Disease, *N Engl J Med*..1997; 337, (6), 408-416.
- 236- Kugiyama K, Ohgushi M, Sugiyama S, et al. Lysophosphatidylcholine inhibits surface receptor-mediated intracellular signals in endothelial cells by a pathway involving protein kinase C activation. *Circ Res* 1992; 71: 1422-8. [Erratum, *Circ Res* 1993;72:723.

- 237- Freedman JE, Farhat JH, Loscalzo J, et al. a-Tocopherol inhibits aggregation of human platelets by a protein kinase C-dependent mechanism. *Circulation*, 1996; 94:2434-40.
- 238- Frostegard J, Haegerstrand A, Gidlund M, et al. Biologically modified LDL increases the adhesive properties of endothelial cells. *Atherosclerosis* 1991;90:119-26.
- 239- Schwartz CJ, Valente AJ, Sprague EA, et al. The pathogenesis of atherosclerosis: an overview. *Clin Cardiol* 1991;14:Suppl I:11-116.
- 240- Thomas Heitzer, Titus Schlinzig, Karoline Krohn, et al, Endothelial Dysfunction, Oxidative Stress, and Risk of Cardiovascular Events in Patients With Coronary Artery Disease , *Circulation*. 2001;104:2673.
- 241- Sella EM, Sato EI, Leite WA, et al, Myocardial perfusion scintigraphy and coronary disease risk factors in systemic lupus erythematosus, *Ann Rheum Dis*. 2003;62(11):1066-70.
- 242- Yu Asanuma, Annette Oeser, Ayumi K. Shintani, et al, Premature Coronary-Artery Atherosclerosis in Systemic Lupus Erythematosus *N Engl J Med*, 2003; 349:2407-2415.
- 243- Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;44:2331-2337.
- 244- Manzi S, Selzer F, Sutton-Tyrrell K, et al. Prevalence and risk factors of carotid plaque in women with systemic lupus erythematosus. *Arthritis Rheum* 1999;42:51-60.
- 245- Esdaile JM, Abrahamowicz M, Grodzicky T, et al. Traditional Framingham risk factors fail to fully account for accelerated atherosclerosis in systemic lupus erythematosus. *Arthritis Rheum* 2001;44:2331-2337.
- 246- Petri M, Roubenoff R, Dallal GE, et al. Plasma homocysteine as a risk factor for atherothrombotic events in systemic lupus erythematosus. *Lancet* 1996;348:1120-1124.
- 247- McEntegart A, Capell HA, Creran D, et al: Cardiovascular risk factors, including thrombotic variables, in a population with rheumatoid arthritis. *Rheumatology (Oxford)* 2001, 40:640-644.
- 248- Solomon DH, Karlson EW, Rimm EB, et al: Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. *Circulation* 2003, 107:1303-1307.
- 249- Wallberg-Jonsson S, Ohman ML, Dahlqvist SR: Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in Northern Sweden. *J Rheumatol* 1997, 24:445-451.
- 250- Otterness IG: The value of C-reactive protein measurement in rheumatoid arthritis. *Semin Arthritis Rheum* 1994, 24:91-104.
- 251- Nakajima T, Schulte S, Warrington KJ, et al. T-cell-mediated lysis of endothelial cells in acute coronary syndromes. *Circulation* 2002, 105:570-575.
- 252- Abbot SE, Whish WJ, Jennison C, et al. Tumour necrosis factor alpha stimulated rheumatoid synovial microvascular endothelial cells exhibit increased shear rate dependent leucocyte adhesion in vitro. *Ann Rheum Dis* 1999, 58:573-581.
- 253- Raffaele Bugiardini*, Lina Badimon, Peter Collins , et al. Angina, “Normal” Coronary Angiography, and Vascular Dysfunction: Risk Assessment Strategies, *PLoS Med* 2007, 4(2): e12.
- 254- Tun A, Khan IA. Acute myocardial infarction with angiographically normal coronary arteries. *Heart Lung* 2000; 29: 348-50.
- 255- Sullivan AK, Holdright DR, Wright CA, et al. Chest pain in women: Clinical, investigative, and prognostic features. *BMJ* 1994; 308: 883-886.
- 256- Alpert, JS (1994) Myocardial infarction with angiographically normal coronary arteries. *Arch Intern Med* 154,265-269.
- 257- Khan IA, Ansari AW. Myocardial infarction in a pre-menopausal woman with angiographically normal coronary arteries. *Postgrad Med J* 1998; 74: 671-2.
- 258- Da Costa, Issaz K, Moutot S, et al. Clinical characteristics, aetiological factors and long-term prognosis of myocardial infarction with an absolutely normal coronary angiogram; a 3-year follow-up study of 91 patients. *Eur. heart* 2001; 22(16):1459-65.
- 259- Kawai, C Pathogenesis of acute myocardial infarction: novel regulatory systems of bioactive substances in the vessel wall. *Circulation* 1994;90, 1033-1043.
- 260- Fournier, JA, Sanchez-Gonzalez, A, Quero, J, et al: Normal angiogram after myocardial infarction in young patients: a prospective clinical-angiographic and long-term follow-up study. *Int J Cardiol* 1997; 60,281-287.
- 261- Shepherd, JT, Vanhoutte, PM (1986) Mechanisms responsible for coronary vasospasm. *J Am Coll Cardiol* 8, 50-54.
- 262- Peter Ammann, MD; Sabine Marschall, MD; Martin Kraus, et al. Characteristics and Prognosis of Myocardial Infarction in Patients With Normal Coronary Arteries, *CHEST* 2000; 117(2):333-338.
- 263- Meierhenrich R, Carlsson J, Brockmeier J, et al, Acute myocardial infarction in patients with angiographically normal coronary arteries: clinical features and medium term follow-up, 2000 Jan;89(1):36-42.

- 264- Yasue H, Kugiyama K, Coronary spasm: clinical features and pathogenesis. *Internal medicine journal*, 1997; 36(11):760-5.
- 265- Raymond R, Lynch J, Underwood D, et al. Myocardial infarction and normal coronary arteriography: ten year clinical and risk analysis of 74 patients. *J Am Coll Cardiol*, 1988; 11: 471–7.
- 266- Maseri A, Severi S, Nes MD, et al: "Variant" angina: one aspect of a continuous spectrum of vasospastic myocardial ischemia. Pathogenetic mechanisms, estimated incidence and clinical and coronary arteriographic findings in 138 patients. *Am J Cardiol*, 1978 Dec; 42(6): 1019-35.
- 267- Sztajel J, Mach F, Righeti A. Role of the vascular endothelium in patients with angina pectoris or acute myocardial infarction with normal coronary arteries. *Postgrad Med J*, 2000; 76:16 -21.
- 268- Amant C, Hamon M, Bauters C, et al. The angiotensin II type I receptor gene polymorphism is associated with coronary artery vasoconstriction. *J Am Coll Cardiol*, 1997; 29:486 -90.
- 269- Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med* 2001; 345:351 -8.
- 270- Su J, Li J, Li W, et al. Cocaine induces apoptosis in primary cultured rat aortic vascular smooth muscle cells: possible relationship to aortic dissection, atherosclerosis, and hypertension. *Int J Toxicol* 2004;23: 233–7.
- 271- Quyyumi, AA, Dakak, N, Andrews, NP, et al (1995) Contribution of nitric oxide to metabolic coronary vasodilatation in the human heart. *Circulation* 92,320-326.
- 272- Kawano H, Ogawa H. Endothelial dysfunction and coronary artery spasm. *Curr Drug Targets Cardiovasc Haematol Disord*. 2004; 4(1):23-33.
- 273- DeWood MA, Spores J, Notske R. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction. *N Engl J Med* 1980;303: 897-902.
- 274- Nir Uriel, Gil Moravsky, Alex Blatt, et al. Acute Myocardial Infarction with Spontaneous Reperfusion: Clinical Characteristics and Optimal Timing for Revascularization, *IMAJ* 2007; 9: April: 243-246.
- 275- Guerci AD, Gerstenbligh G, Brinker JA, et al. A randomized trial of intravenous tissue plasminogen activator for acute myocardial infarction with subsequent randomization to elective coronary angioplasty. *N Engl J Med* 1987; 317:1613-8.
- 276- Brouwer MA, van den Bergh PJ, Aengevaeren WR, et al. Aspirin plus coumarin versus aspirin alone in the prevention of reocclusion after fibrinolysis for acute myocardial infarction: results of the Antithrombotics in the Prevention of Reocclusion In Coronary Thrombolysis (APRICOT)-2 Trial. *Circulation* 2002; 106:659–65.
- 277- Basso C, Morgagni GL, Thiene G. Spontaneous coronary artery dissection: a neglected cause of acute myocardial ischemia and sudden death. *Heart* . 1996; 75:451–454.
- 278- B Chandrasekaran, and A S Kurbaan, Myocardial infarction with angiographically normal coronary arteries , *J R Soc Med*. 2002 August; 95(8): 398–400.
- 279- Velusamy M, Fisherkeller M, Keenan ME, et al. Management of dissection and other complications: spontaneous coronary artery dissection in a young woman precipitated by retching. *J Invasive Cardiol*. 2002; 14(4):198–201.
- 280- Postpartum multivessel spontaneous coronary artery dissection confirmed by coronary CT angiography Catherine Schroder, Robert C. Stoler, George B. Branning, et al. *Bayl Univ Med Cent*) 2006; 19:338–341.
- 281- Hinojal YC, Di Stefano S, Florez S, et al. Spontaneous coronary dissection during postpartum: etiology and controversies in management. *Ital Heart J* 2004; 5(7):563–565.
- 282- Maeder M, Ammann P, Drack G, et al. Pregnancy-associated spontaneous coronary artery dissection: impact of medical treatment. Case report and systematic review. *Z Kardiol* 2005; 94(12):829–835.
- 283- Jorgensen MB, Aharonian V, Mansukhani P, et al. Spontaneous coronary dissection: a cluster of cases with this rare finding. *Am Heart J* 1994; 127:1382–7.
- 284- Hamilos MI, Kochiadakis GE, Skalidis EI, et al. Acute myocardial infarction in a patient with spontaneous coronary artery dissection. *Hellenic J Cardiol* 2003; 44(5):348–351.
- 285- Michele D. Raible, Hemodynamic Disorders Thrombosis / Embolism / Infarction, *Robbins Pathologic Basis of Disease*, Chapter 5, 119-138.
- 286- Yutani C, Imakita M, Ueda-Ishibashi H, et al. Coronary artery embolism with special reference to invasive procedures as the source. *Mod Pathol*. 1992; 5:244-249.
- 287- Brian D. Powell, David R. Holmes, Jr, Rick A. Nishimura, et al. Calcium Embolism of the Coronary Arteries After Percutaneous Mitral Balloon Valvuloplasty *Mayo Clin Proc*. 2001;76:753-757.
- 288- Aaron Satran, Bradley A. Bart, Christopher R. Henry, et al. Increased Prevalence of Coronary Artery Aneurysms among Cocaine Users, *Circulation*. 2005; 111:2424-2429.
- 289- Demopoulos VP, Olympios CD, Fakiolas CN, et al. The natural history of aneurysmal coronary artery disease. *Heart*. 1997; 78: 136–141.

- 290- Sorrell VL, Davis MJ, Bove AA. Current knowledge and significance of coronary artery ectasia: a chronologic review of the literature, recommendations for treatment, possible etiologies and future considerations. *Clin Cardiol* 1998; 21: 57-60.
- 291- Kumar K, LeporNE, Naqvi TZ. Unusual presentation of an acute inferior myocardial infarction. *Rev Cardiovasc Med* 2002; 3: 152-6.
- 292- Erdol C, Celik S, Baykan M, et al. A coronary aneurysm complicated by acute myocardial infarction: A case report. *J Cardiovasc Surg* 2001; 42: 65-7.
- 293- DeLoughery TG. Coagulation abnormalities and cardiovascular disease. *Curr Opin Lipidol* 1999; 10: 443-8.
- 294- Al-Obaidi M, Philippou H, Stubbs, et al. Relationships between homocysteine, factor VIIa, and thrombin generation in acute coronary syndromes. *Circulation* 2000; 101: 372-7.
- 295- Antoine Da Costa, Brigitte Tardy, Kamel Haouchette, et al. , Long term prognosis of patients with myocardial infarction and normal coronary angiography: impact of inherited coagulation disorders, *Thromb Haemost* 2004; 91: 388-93.
- 296- Mansourati J, Da Costa A, Munier S, et al. Prevalence of factor V Leiden in patients with myocardial infarction and normal coronary angiography. *Thromb Haemost* 2000; 83: 822-5.
- 297- Van de Water NS, French JK, Lund M et al. Prevalence of factor V Leiden and prothrombin variant G2021A in patients age<50 years with no significant stenoses at angiography three to four weeks after myocardial infarction. *J Am Coll Cardiol* 2000; 36: 717-22.
- 298- Fahal IH, McClelland P, Hays CRM, et al. Arterial thrombosis in the nephrotic syndrome. *Postgrad Med J* 1994; 70:905-9.
- 299- Da Costa A, Tardy BR, Isaaz K et al. Prevalence of factor V leiden and other inherited thrombophilias in young patients with myocardial infarction and normal coronary arteries. *Heart* 1998; 80: 338-40.
- 300- G. Lande, V. Dantec, M. Trossaert, et al. Do inherited prothrombotic factors have a role in myocardial infarction with normal coronary arteriogram, *journal of internal medicine* 1998; 244: 543-545.
- 301- Fuster V, Chesebro JH, Frye RL, et al. Platelet survival and the development of coronary artery disease in the young adult: effects of cigarette smoking, strong family history and medical therapy. *Circulation*, 1981; 63:546-51.
- 302- M J A Williams, N J Restieaux, C J S Low, Myocardial infarction in young people with normal coronary arteries, *Heart* 1998;79:191-194.
- 303- Antonio Esteves F^o, Francisco de Assis Costa, Antonio Augusto Guimarães Lima, et al. Essential Thrombocythemia and Acute Myocardial Infarction Treated with Rescue Coronary Angioplasty, *Arq Bras Cardiol*, 1999; 73,1.
- 304- Bruce F. Waller, nonatherosclerotic coronary heart disease, in *Hurst: the heart*, 1997, the fifth edition McGraw-Hill. P990.
- 305- D C Whitaker, M F Tunekar, J E Dussek, Angina with a normal coronary angiogram caused by Amyloidosis, *Heart* 2004;90:e54.
- 306- Kaski JC, Elliott PM. Angina pectoris and normal coronary arteriogram: clinical presentation and haemodynamic characteristics. *Am J Cardiol*, 1995; 76:35-42D.
- 307- Crotty TB, Li C, Edwards WD, et al. Amyloidosis and endomyocardial biopsy: correlation of extent and pattern of deposition with amyloid phenotype in 100 cases. *Cardiovasc Pathol* 1995; 4:39-42.
- 308- Neben Wittich MA, Mueller PS, Larson DR, et al., Obstructive intramural coronary amyloidosis and myocardial ischemia are common in primary amyloidosis. *Am J Med*, 2005 Nov; 118(11):1287
- 309- Yamano S, Motomiya K, Akia Y, et al., Primary systemic amyloidosis presenting as angina pectoris due to intramyocardial coronary artery involvement: a case report. *heart vessels*, 2002 May; 16(4):157-60.
- 310- Mohlenkamp S, Hort W, Ge J, et al. Update on myocardial bridging. *Circulation*. 2002; 106(20): 2616-22.
- 311- Laifer LI, Weiner BH: Percutaneous transluminal coronary angioplasty of a coronary artery stenosis at the site of myocardial bridging. *Cardiology* 1991; 81:198-202.
- 312- Vibhuti N Singh, Prakash Deedwania, Rakesh K Sharma, et al. Coronary Artery Atherosclerosis, *emedicine*; 2005.
- 313- McGill HC Jr, McMahan CA, Herderick EE, et al., Origin of atherosclerosis in childhood and adolescence. *Am J Clin Nutr* 2000; 72(suppl): 1307-15S.
- 314- Ryan TJ, Faxon DP, Gunnar RM, et al., Guidelines for percutaneous transluminal coronary angioplasty. A report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty). *Circulation* 1988; 78:486-502.

- 315- Patrick J. Scanlon, David P. Faxon, Anne-Marie Audet et al., ACC/AHA Guidelines for Coronary Angiography: Executive Summary and Recommendations, *Circulation*. 1999; 99:2345-2357.
- 316- Ellis SG, Vandormael MG, Cowley MJ, et al. Coronary morphologic and clinical determinants of procedural outcome with angioplasty for multivessel coronary disease: implications for patient selection. *Circulation*.1990; 82:1193–1202.
- 317- Reifart N, Vandormael M, Krajcar M, et al. Randomized comparison of angioplasty of complex coronary lesions at a single center: excimer laser, rotational atherectomy, and balloon angioplasty comparison (ERBAC) Study. *Circulation*.1997; 96:91–98.
- 318- Stephen G. Ellis, Victor Guetta, Dave Miller, et al. Relation between Lesion Characteristics and Risk with Percutaneous Intervention in the Stent and Glycoprotein IIb/IIIa Era: An Analysis of Results From 10 907 Lesions and Proposal for New Classification Scheme. *Circulation* 1999; 100; 1971-1976.
- 319- The TIMI Study Group; The thrombolysis in myocardial infarction (TIMI) trial, *N Engl J Med* 1985; 31:932-936.
- 320- Appleby MA, Michaels AD, Chen M, et al. The importance of the TIMI frame count: implications for future trials. *Curr Control Trials Cardiovasc Med* 2000; 1:31-34.
- 321- Lincoff AM, Topol EJ, Califf RM, et al. Significance of a coronary artery with thrombolysis in myocardial infarction grade 2 flow (outcome in the thrombolysis and angioplasty in myocardial infarction trials). Thrombolysis and angioplasty in myocardial infarction study group. *Am J Cardiol* 1995; 75:871-876.
- 322- Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000; 101:125-130.
- 323- Gregorini L, Marco J, Kozakova M, et al. Alpha-adrenergic blockade improves recovery of myocardial perfusion and function after coronary stenting in patients with acute myocardial infarction. *Circulation* 1999; 99:482-490.
- 324- S Osula, G M Bell, R S Hornung ,Acute myocardial infarction in young adults: causes and management, *Postgrad Med J* 2002;78:27–30.
- 325- Office of National Statistics. (Key health statistics from General Office, 2000.[http://www.statistics.gov.uk/health and care](http://www.statistics.gov.uk/health%20and%20care)) infarction in young adults: causes and management, *Postgrad Med J* 2002;78:27–30.
- 326- Espanola-Zavaleta N, Vargas-Barron J, Colmenares-Galvis T, et al. Echocardiographic evaluation of patients with primary antiphospholipid syndrome. *Am Heart J* 1999; 137:973–8.
- 327- Reverter JC, Tassies D, Font J, et al. Effects of human monoclonal anticardiolipin antibodies on platelet function and on tissue factor expression on monocytes. *Arthritis Rheum* 1998; 41:1420–7.
- 328- Stephen G. Ellis, Victor Guetta, Dave Miller, et al. Relation between Lesion Characteristics and Risk with Percutaneous Intervention in the Stent and Glycoprotein IIb/IIIa Era: An Analysis of Results From 10 907 Lesions and Proposal for New Classification Scheme. *Circulation* 1999; 100; 1971-1976.
- 329- Lincoff AM, Topol EJ, Califf RM, et al. Significance of a coronary artery with thrombolysis in myocardial infarction grade 2 flow (outcome in the thrombolysis and angioplasty in myocardial infarction trials). Thrombolysis and angioplasty in myocardial infarction study group. *Am J Cardiol* 1995; 75:871-876.
- 330- Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation* 2000; 101:125-130.
- 331- Ito H, Okamura A, Iwakura K, et al. Myocardial perfusion patterns related to thrombolysis in myocardial infarction perfusion grades after coronary angioplasty in patients with acute anterior wall myocardial infarction. *Circulation* 1996; 93:1993-1999.
- 332- Gregorini L, Marco J, Kozakova M, et al. Alpha-adrenergic blockade improves recovery of myocardial perfusion and function after coronary stenting in patients with acute myocardial infarction. *Circulation* 1999; 99:482-490.
- 333- S Osula, G M Bell, R S Hornung ,Acute myocardial infarction in young adults: causes and management, *Postgrad Med J* 2002;78:27–30.
- 334- Office of National Statistics. (Key health statistics from General Office, 2000.[http://www.statistics.gov.uk/health and care](http://www.statistics.gov.uk/health%20and%20care)) infarction in young adults: causes and management, *Postgrad Med J* 2002;78:27–30.
- 335- Manzar KJ, Padder FA, Conrad AR, et al. Acute myocardial infarction with normal coronary artery: a case report and review of literature. *Am J Med Sci* 1997; 314:342–5.
- 336- Vaarala O, Puurunen M, Manttari M, et al. Antibodies to prothrombin imply a risk of myocardial infarction in middle-aged men. *Thromb Haemost* 1996; 75:456–9.
- 337- Espanola-Zavaleta N, Vargas-Barron J, Colmenares-Galvis T, et al. Echocardiographic evaluation of patients with primary antiphospholipid syndrome. *Am Heart J* 1999; 137:973–8.

- 338- Reverter JC, Tassies D, Font J, et al. Effects of human monoclonal anticardiolipin antibodies on platelet function and on tissue factor expression on monocytes. *Arthritis Rheum* 1998; 41:1420–7.
- 339- Vaaral O. Antibodies to oxidized LDL. *Lupus* 2000; 9:202–5.
- 340- Castro VJ, Nacht R. Cocaine-induced bradyarrhythmia: an unsuspected cause of syncope. *Chest* 2000;117:275–7
- 341- Pitts WR, Lange RA, Cigarroa JE, et al. Cocaine-induced myocardial ischemia and infarction. *Prog Cardiovasc Dis* 1997; 40:65–76.
- 342- Appleby MA, Michaels AD, Chen M, et al. The importance of the TIMI frame count: implications for future trials. *Curr Control Trials Cardiovasc Med* 2000; 1:31-34.
- 343- The TIMI Study Group; The thrombolysis in myocardial infarction (TIMI) trial, *N Engl J Med* 1985; 31:932-936.
- 344- ACC/AHA Guidelines for the Management of Patients with Myocardial Ischemia; *Circulation Journal* 2011;110;82-292
- 345- ACS Guidelines for the Management of Patients with Myocardial Ischemia: 2011: 77- 112
- 346- JNC VII: classification of hypertension: 2011
- 347- IDF consensus definition of metabolic syndrome: 2011:11-21

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