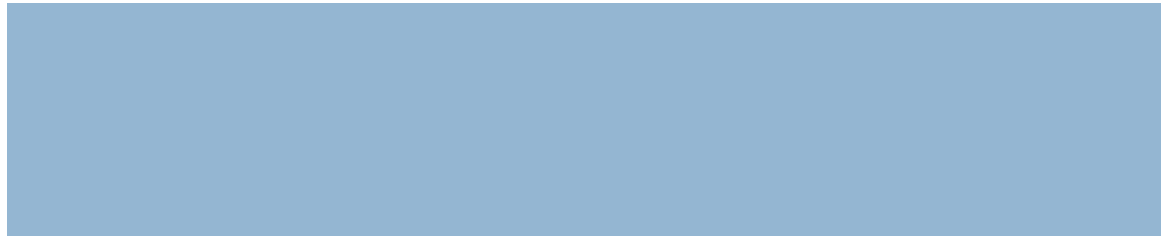# INTRODUCTION

INTRODUCTION

According to World Health Organisation (WHO) approximately 17 million people die of Cardiovascular Diseases (CVDs), particularly heart attacks and strokes, every year. According to report of World Health Organisation 2002, cardiovascular diseases will be the largest cause of death and disability by 2020 in India. In 2020, 2.6 million Indians are predicted to die due to coronary artery diseases which constitute 54.1% of all CVD deaths. Nearly half of the deaths are likely occur in young and middle age individuals. Currently Indians experience CVD deaths atleast a decade earlier than their counterparts in countries with established market economies. The Global burden of disease study estimate that 52% of CVD deaths occur below the age of 70 years in India as compared to 23% established market economies. Recent reports of WHO on CVDs says that approximately 17.3 million people died from CVDs in 2008 and 2030 more than 23 million people will die annually from CVDs throughout the world.

Cardiovascular diseases are a group of disorders of the heart and blood vessels and which includes coronary heart disease, cerebrovascular disease, peripheral artery disease, congenital heart disease (WHO, 2013 and WHO, 2016)

- **Coronary Heart Disease**: Disease of the blood vessels supplying the heart muscle;

- **Cerebrovascular Disease:** Disease of the blood vessels supplying the brain;

- **Peripheral Arterial Disease**: Disease of blood vessels supplying the arms and legs;

- **Rheumatic Heart Disease**: Damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria;

- **Congenital Heart Disease**: Malformations of heart structure existing at birth;

- **Thrombosis and Pulmonary Embolism**: Blood clots in the leg veins, which can dislodge and move to the heart and lungs.

Heart attacks and strokes are usually acute events and are mainly caused by a blockage that prevents blood from flowing to the heart or brain. The most common reason is a build-up of fatty deposits on the inner walls of the blood vessels. Strokes can be caused by bleeding from a blood vessel in the brain or by blood clots (Hulley *et al.* 1980; Robciuc *et al.*, 2016).

Over 80% of CVD deaths take place in low- and middle-income countries. Worldwide, the Global Burden of Disease study estimated that in 2001, 12.45 million of >56 million total worldwide deaths were caused by cardiovascular disease (CVD) and cerebrovascular disease. Ischemic heart disease was the leading cause of global mortality, accounting for 1.4 million deaths in the developed world and 5.7 million deaths in developing regions (Lopes 2006).

Physical inactivity and unhealthy diet are main risk factors which increase individual risks to cardiovascular diseases. A substantial number of these deaths can be attributed to tobacco smoking, which increases the risk of dying from coronary heart disease and cerebrovascular disease 2–3 fold (WHO, 2013).

Coronary Heart Disease

A condition and especially one caused by atherosclerosis that reduces blood flow through the coronary arteries to the heart and typically results in chest pain or heart damage.

Atherosclerosis

Atherosclerosis is accumulation of lipid-rich plaques within the walls of large arteries.And it is caused by abnormalities in lipids and lipoprotein metabolism and

impairment of endothelial function have been implicated as the main contributing factors in atherosclerosis and its progression.

Major contributing risk factors of atherosclerosis (Frohlich and Al-Sarraf, 2013)

- **Age and Gender:** The risk for atherosclerosis increases with age. In men, the risk increases after age 45. In women, the risk increases after age 55. In early menopause, cardiovascular risk increases substantially, mainly because of the loss of the protective effects of estrogens (Nicoll *et al*., 2016).

- **Hypertension**

- **Smoking:** Smoking can damage, tighten blood vessels, raise cholesterol levels, and raise blood pressure. Smoking also does not allow enough oxygen to reach the body's tissues.

- **Diabetes**

- **High levels of LDL and Low levels of HDL**

- **Obesity**

- **Sedentary lifestyle**

- **Genetic Factors:** Often things like hypertension, hyperlipidaemia and diabetes run in families, and are multi-genetic.

Atherosclerosis involves many processes such as hypercholesterolaemia, oxidation and inflammation (Lowenstein and Matsushita, 2004). Hypercholesterolemia is the initiative factor in the process of atherosclerosis. Oxidative modifications of low-density lipoprotein (LDL) play a pivotal role in the development of atherosclerosis. Elevated levels of oxidized LDL have been positively correlated to the severity of acute coronary events and have been considered a biochemical marker for coronary heart disease (Witzum, 1994).
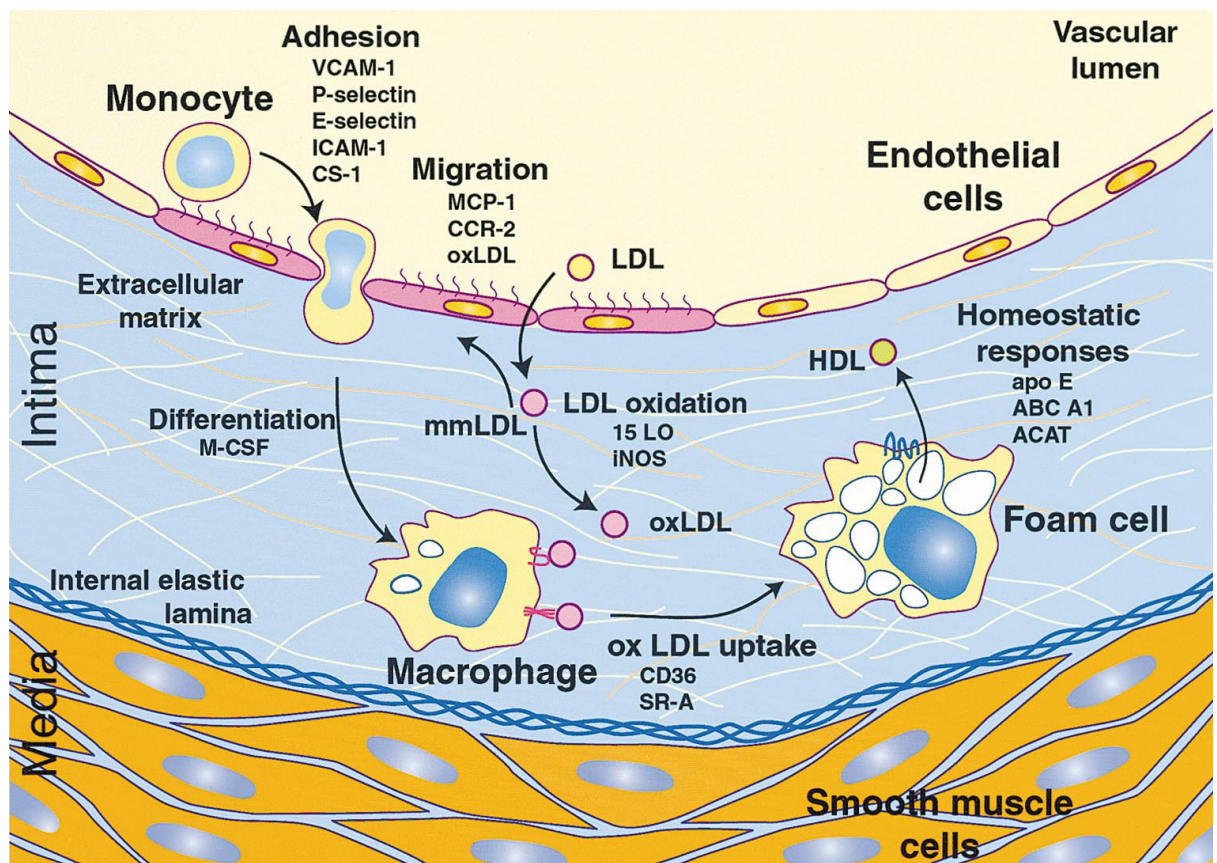
FIGURE 1

LDL is subject to oxidative modifications in the subendothelial space, progressing from minimally modified LDL (mmLDL), to extensively oxidized LDL (oxLDL). Ox-LDL induces chemotaxis through chemokines (MCP-1 and CCR-2) and recruits Monocytes to endothelial cells via expression of cell adhesion molecules (VCAM-1, ICAM-1, P-Selectin, E-selectin).Monocytes migrate through endothelial wall to intimal layer and differentiate into macrophages with the help of M-CSF. Ox-DL is taken up by Macrophages of via scavenger receptors and accumulates into macrophages. Progressive accumulation of macrophages and their uptake of Ox-LDL ultimately lead to development of foam cell formation and it is known as hall mark of both early and late atherosclerotic lesions (https://www.google.co.in/search? q=atherosclerosis+mechanism&safe=strict&biw=1366&bih=667&source=lnms&tbm

=isch&sa=X&sqi=2&ved=0ahUKEwjPi8Ca_ZbPAhUDTo8KHVJJAxsQ_AUIBigB#
safe=strict&tbm=isch&q=+foam+cell+formation+mechanism&imgrc=tH)OrGx7GGJ
QYOM%3A).

Types of Plaque (Otsuka *et al*., 2013**)**

Atherosclerotic plaque rupture – pathologic basis of plaque stability and instability on

the basis of stability Atherosclerotic plaque can be classified into two types.

i. Stable plaque and ii. Unstable plaque

   i.   Stable plaque is composed of solid fibrous or fibrocellular tissue, and only

        small amounts of extracellular lipid or no lipid at all. In coronary arteries

        most of these lesions remain clinically silent, or on the long term, may lead

        to stable angina pectoris.

   ii. Vulnerable plaques or unstable plaques are characterized by large lipid

        pools and have a thin or virtually absent fibrous cap. At autopsy, lipid-rich

        plaques are frequently found underlying coronary thrombosis therefore

        lipid plaques are considered 'rupture prone'.

        The degree of coronary occlusion due to plaque formation determines the

        nature of the clinical state. Patients with incomplete coronary occlusion

        have unstable angina and it may cause myocardial infarction.

        Finally, if the disruption is very deep or ulceration exposes the lipid core,

        collagen, tissue factor and other elements, a thrombotic occlusion that is

        relatively persistent (i.e., 2 to 4 hours or longer) may result in acute

        myocardial infarction. It may cause either sudden death of myocardium

        due to ischemic condition or it may heal with scar formation in to left

        ventricle. Healing and the reparative episodes of plaque eruption cause

        further activation of many inflammatory mechanism of slowly progressive

growth of plaques; it serves to encapsulate the soft atheroma and organizes

episodes of thrombus formation. This may lead to chronic ischemic

condition and results into cardiac failure.

http://php.med.unsw.edu.au/medwiki/index.php?
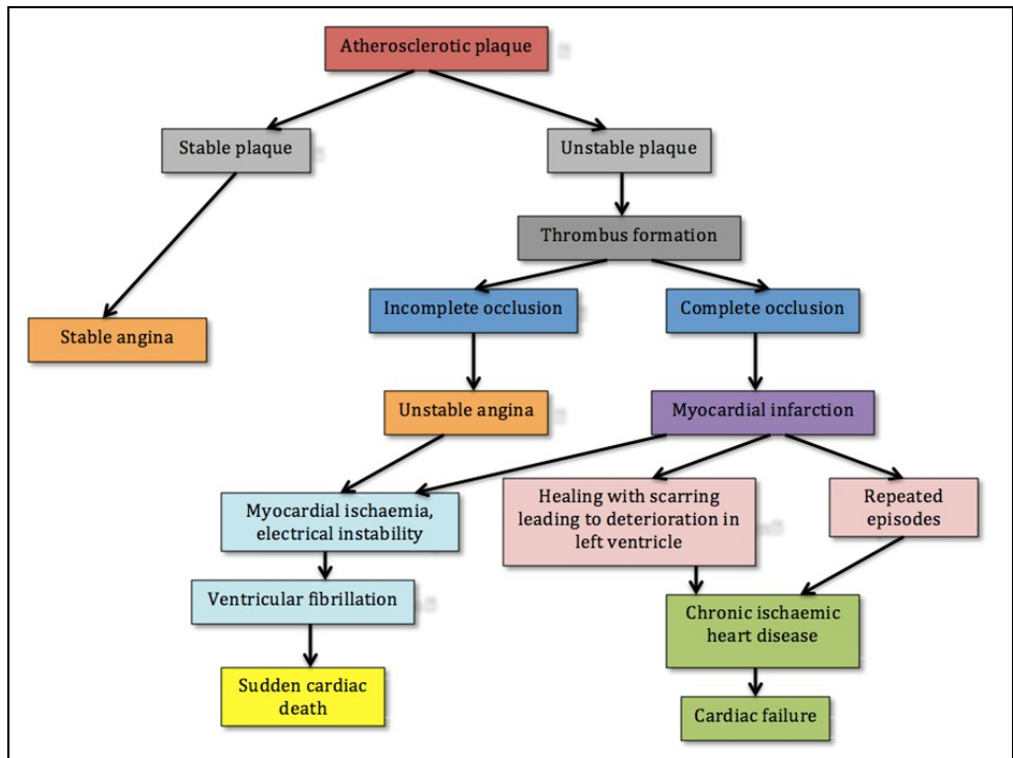title=Pathophysiology_of_syndromes_of_Ischaemic_Heart_Disease#cite_
note-Zhang-31

FIGURE 2

<h1 style="text-align:center">Ischemic Heart Diseases</h1>

Ischemic Heart Disease (IHD) is defined as myocardial impairment due to an imbalance between coronary blood flow and myocardial requirements caused by changes in the coronary circulation. IHD comprises acute and temporary as well as chronic conditions, and may be due to functional changes or organic disease. The term "IHD" is synonymous with the term "coronary heart disease." IHD are categorised into different symptomatic conditions as below (Andrew, *et al.*, 2014).

Primary Cardiac Arrest

Primary cardiac arrest is a sudden event, presumably due to electric instability of the heart, where evidence which allows other diagnosis is lacking. If no resuscitation is applied or if resuscitation is unsuccessful, primary cardiac arrest is referred to as sudden death. Evidence of previous IHD may or may not be present. If death occurred in the absence of witnesses, the diagnosis is presumptive.

Angina Pectoris

Angina of Effort

Effort angina is also known as stable angina and it is characterized by transient episodes of chest pain precipitated by exercise or by other situations resulting in an increased myocardial oxygen demand. The pain usually disappears rapidly with rest or with sublingual nitroglycerin

Spontaneous Angina

Spontaneous angina is characterized by episodes of chest pain that occur without apparent relation to increased oxygen demand of the myocardium. This paint ends to

be more prolonged, more severe, and less readily relieved by nitroglycerin than that of effort angina. No enzyme changes are observed. The ECG often shows some transient ST-segment depression or T-wave changes. Spontaneous angina may occur alone or in conjunction with angina of effort.

Myocardial Infarction

Myocardial infarction is typical in many cases severe and prolonged chest pain is present. Sometimes pain may be mild or even absent, or other symptoms may predominate. In myocardial infarction clinical changes are observed in ECG and serum enzymes.

Heart Failure in IHD

Heart failure may occur for many reasons in IHD. It may occur as a complication of acute or previous myocardial infarction or it may be precipitated by anginal episodes or arrhythmias. For patients presenting with heart failure in the absence of clinical or ECG evidence of previous IHD (other causes being eliminated), the diagnosis of IHD remains presumptive.

Arrhythmias

Arrhythmias may be the only symptom of IHD. In this event, the diagnosis of IHD is presumptive unless coronary arteriography is performed and demonstrates coronary arterial obstructions. The terms "preinfarction angina" and "intermediate coronary syndrome" are not included in this report because, in the committee's opinion, diagnosis of the former is a retrospective diagnosis which is verified only in a minority of cases, and because all cases diagnosed as the latter can be located in one of the categories of IHD described in this report.

Acute Myocardial Infarctionhttps://en.wikipedia.org/wiki/Myocardial_infarction#/media/File:Blausen_0463_HeartAttack.png

Acute myocardial Infarction (AMI) is the ischemic condition that develops due to plaque formation in coronary artery (Atherosclerosis) that reduces blood supply to the myocardium. In scarcity of
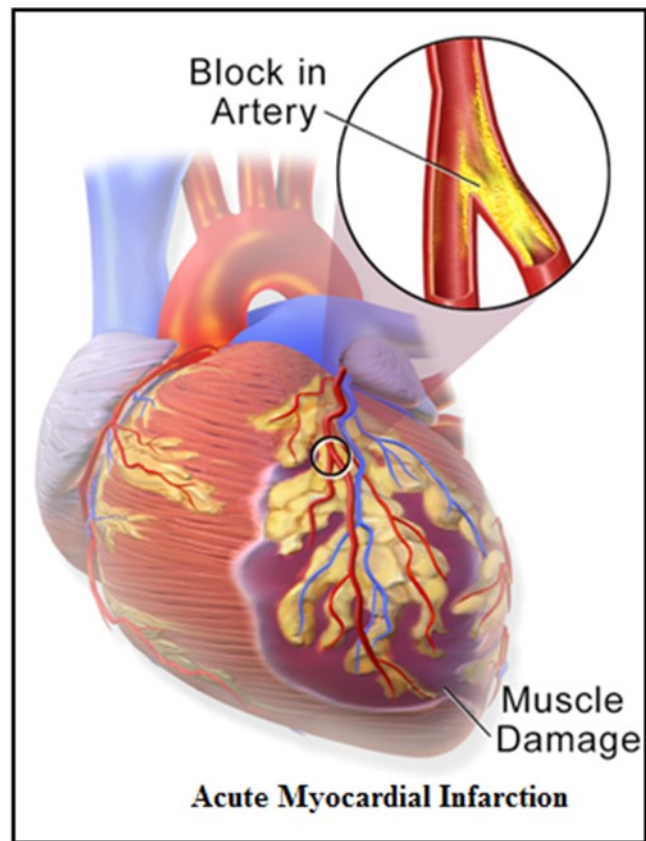

FIGURE 3

oxygen and nutrients supply to cardiac cell causes damage to cardiac tissue and can compromise survival. AMI is commonly known as heart attack.

According to WHO estimates ischemic heart disease also known as (Coronary artery disease) and cerebrovascular disease are the 2 leading cause of mortality worldwide and account for well over 20% death (Kim and Johnston, 2011; Mathers and Loncar, 2006).

Geographic distribution of relative mortality from stroke and ischemic heart disease (World Health Organization Global Burden of Disease Program, 2004) is shown in Figure 3. Age and sex adjusted absolute stroke mortality rates per 100 000, standardized to standard World Health Organization population. The intensity of red shading is proportional to the absolute stroke mortality rates indicating 60-120 death per 100000 mortalities in figure 4A, in figure 4B the intensity of blue shading is

proportional to death due to absolute ischemic heart disease and it is 120-240 deaths per 100000 in India Figure 4C.Mortality from stroke relative to ischemic heart disease. Countries with more intense blue shading have higher relative mortality rates from stroke than from ischemic heart disease, and countries with more intense red shading have higher relative mortality rates from ischemic heart disease than from stroke.

FIGURE 4: Geographic distribution of relative mortality from stroke and ischemic heart disease

(Kim and Claiborne 2011)
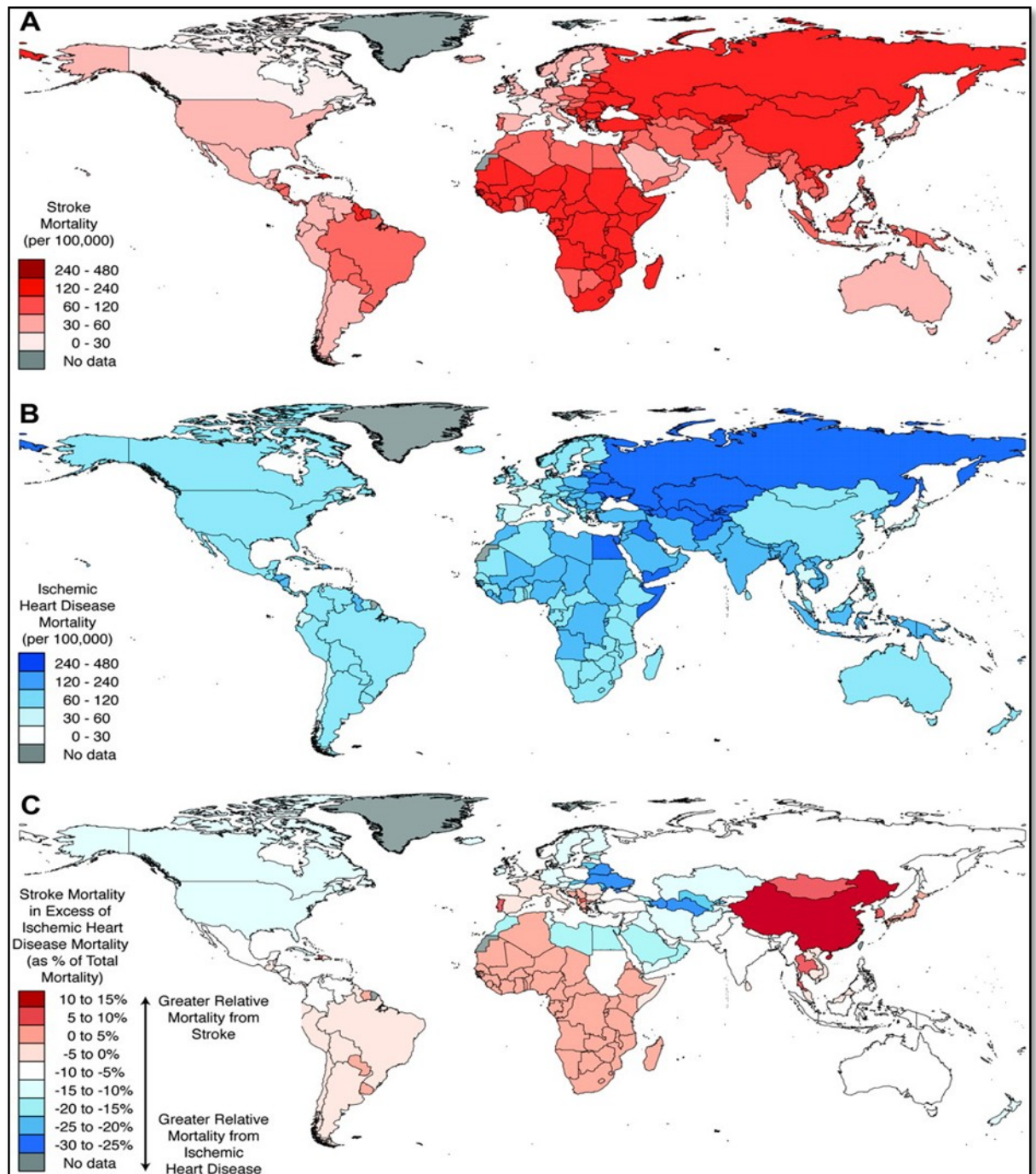
Clinical Classification of Acute Myocardial Infarction

Acute myocardial infarction was classified into 5 different types on the basis of clinical symptoms (Thygesen *et al*, 2007).

Type 1: Spontaneous myocardial infarction related to ischaemia is caused by a primary coronary event, such as plaque fissuring or rupture

Type 2: Myocardial infarction secondary to ischaemia resulting from an imbalance between oxygen demand and supply, such as coronary spasm

Type 3: Sudden death from cardiac disease with symptoms of myocardial ischaemia, accompanied by new ST elevation or left bundle branch block, or verified coronary thrombus by angiography. In this type of myocardial infarction death occurs before blood samples can be obtained

Type 4: Myocardial infarction associated with primary percutaneous coronary intervention

Type 5: Myocardial infarction associated with coronary artery bypass graft

Atherosclerosis

Atherosclerosis does not trigger any signs and symptoms until it severely narrows or totally blocks an artery and hence a medical emergency such as a heart attack or stroke is often a consequence. Elevated plasma levels of cholesterol and glucose are the indicators for the detection of high risk of initiation and progression of atherosclerosis. Angiography test can show whether plaque is blocking the arteries and the extent of blockage will determine future risk (Berliner et. al., 1995)

Blood Test

Elevate plasma levels of cholesterol and glucose are the main indicators for the detection of high risk of initiation and progression atherosclerosis.

Acute Myocardial Infarction

Elevation of plasma titre of Cardiac enzymes are indicative of cardiac damage and they should be interpreted in the context of clinical and ECG findings. Troponin is a contractile protein that normally is not found in serum. It is released only when myocardial necrosis occurs. Cardiac troponins T and I are the preferred markers for myocardial injury as they have the highest sensitivities and specificities for the diagnosis of acute myocardial infarction. Serum levels increase within 3-12 hours from the onset of chest pain, peak at 24-48 hours, and return to baseline over 5-14 days.Myocardial muscle creatine kinase (CK-MB) is found mainly in the heart.CK-MB levels increase within 3-12 hours of onset of chest pain, reach peak values within 24 hours, and return to baseline after 48-72 hours. Myoglobin is found in cardiac and skeletal muscle. It is released more rapidly from infarcted myocardium than troponin and CK-MB and may be detected as early as 2 hours after an acute myocardial infarction. Myoglobin has high sensitivity but poor specificity. It may be useful for the early detection of myocardial infarction.A high sensitivity C-reactive protein (HS-CRP) test measures levels of CRP in the bloodstream. CRP is a protein that is released when inflammation is present in the body. Inflammation of the arteries is a risk factor for cardiovascular disease, and CRP may be a predictor of risk for heart attack, stroke, or other cardiovascular problems. An electrocardiogram, also called an ECG or EKG, is a quick, painless test that measures the heart's electrical activity and records any disturbances in heart rhythm. The heart's electrical activity determines if it keeps a normal rhythm. Echocardiography is effective for detecting enlargement of chambers of the heart and great vessels. In general, the degree of chamber enlargement parallels disease severity (Thygesen et. al. 2007).

Medication Against Atherosclerosis and Myocardial Infarction

(http://www.nhs.uk/Conditions/Atherosclerosis/Pages/Treatment.aspx)

There are several medications available to treat many of the underlying causes of atherosclerosis and myocardial infarction, such as a high cholesterol level and hypertension.

Reducing blood pressure (hypertension)

i. Angiotensin-converting enzyme (ACE) inhibitors

Angiotensin-converting enzyme (ACE) inhibitors work by blocking the actions of some of the hormones that help to regulate blood pressure. By stopping these hormones from working, ACE inhibitors reduce the amount of water in blood, as well as widening your arteries, both of which will lower blood pressure.

ii Calcium channel blockers

Calcium channel blockers work by relaxing the muscles of artery walls, which causes arteries to widen and lowers blood pressure.

ii. Thiazide diuretics

Thiazide diuretics work by reducing the amount of water in blood and widening the walls of arteries.

Lowering High Cholesterol Levels

Statins

Statins are a type of medication used to lower blood cholesterol levels. Statins block the effects of an enzyme in liver called HMG-CoA reductase, which is used to make cholesterol.

Preventing Blood Clots

Heart attack or stroke is associated with blood clots and hence Anticlotting medication is given to reduce the risk of a blood clots.

Antiplatelet

Medications used to prevent blood clots developing are known as antiplatelet. Platelets are tiny particles in the blood that help it to clot. Antiplatelet works by reducing the 'stickiness' of platelets.

Synthetic Drug Side-Effect

Reducing blood pressure (hypertension)

i. **Angiotensin-converting enzyme (ACE) inhibitors**

    ACE inhibitors are not suitable for pregnant or breastfeeding women. The side effects of ACE inhibitors include dizziness, tiredness and headaches.

ii. **Calcium channel blockers**

    Side effects include a flushed face, headaches, swollen ankles and dizziness.

iii. **Thiazide diuretics**

    They are not recommended for pregnant women or people with gout (a type of arthritis where crystals develop inside the joints).Thiazide diuretics have been known to reduce the level of potassium in blood, which can interfere with heart and kidney functions.

Lipid lowering drugs

Statins sometimes have mild side effects including constipation, diarrhoea and headaches. Statins can also cause muscle pain, weakness and tenderness.

Prevention

Life style changes such as regular exercise, loss of excessive body weight, control of high blood pressure, diabetes and chiefly cessation of smoking and limitation of alcohol intake may result in health benefits in terms of minimizing propensity of atherosclerosis. Change in diet such as reduction in total fat and saturated fat intake is recommended. Mostly dietary fat should be polyunsaturated or monounsaturated.

Herbal medication for the treatment of cardiac and cardiovascular disease

About four billion people, (80% of the World population) presently use herbal medicine for primary healthcare, the World Health Organization (WHO) has estimated.

Herbal medicine in management Atherosclerosis

Plant/Herb	Medication	References
Coriandrum sativum	Reduces LDL oxidation and peroxyl radical formation	Patel *et al.*, 2013
Clerodendron glandulosum.Coleb	Reduces LDL oxidation and peroxyl radical formation	Jadeja *et al.*, 2011
Sidarhomboidea. Roxb	Prevents HMDM induced LDL oxidation and Cu^{+2}mediated LDL oxidation and foam cell formation	Thounaujam *et al.*, 2011
Tropaeolum tuberosum	Peroxyl radical scavenger, chelating agent, protects against oxidation of LDL	Chirinos *et al.*, 2008
Terminalia bellerica	Prevents formation of superoxide, nitric oxide and hydroxyl radicals, potential inhibitor of LDL oxidation	Nampoothiri *et al.*, 2011
Zanthoxylumail anthoides	Prevents lipid accumulation in THP--1 cell line, deceases scavenger receptor expression and CD 36, prevents CuSO4 mediated LDL oxidation	Chu *et al.*, 2009
Black soybean seed	Potent DPPH radical scavenger andattenuates LDL oxidation	Astadi *et al.*, 2009

Hibiscus sabdariffa L.	Inhibition of ApoB fragmentation, Potent DPPH radical scavenger, inhibits TBARS formation, inhibits Ox-LDL induced apoptosis	Chang *et al.*, 2006
Pinus morrisonicola Hay	Potent free radical scavenger, inhibits copper induced oxidation, decreases lipid accumulation and foam cell formation, inhibits nitric oxide production and decreases relative electrophoretic mobility	Yen *et al.*, 2008
Wheat bran	Reduces lipid peroxidation in LDL, potent DPPH and ABTS free radical scavenger	Yu *et al.*, 2005
Punica granatum L.	Showed antihyperlipidemic effects with attenuated liver damage due to high fat diet	Sadeghipour *et al.*, 2014
Crataegus species	Prevents cholesterol uptake in liver of rats fed an atherogenic diet.	Rajendran *et al.*, 1996
Allium sativum	Reduces blood pressure and protects the elastic properties of aorta	Steiner *et al.*, 1996
Commiphora mukul	Induces uptake and metabolism of LDL cholesterol by liver	Singh *et al.*, 1994

Anethum greviolens **L.**

Anethum graveolens L. or dill (AG; family Apiaceae or Umbelliferae) is an annual aromatic herb that grows in the Mediterranean region, Europe, central and southern Asia and is widely cultivated in southeastern region of Iran (Yazdanparast and Bahramikia, 2008). In India, it is known as 'sowa' and is grown chiefly in the states of Punjab, Uttar Pradesh, Gujarat, Maharashtra, Assam and West Bengal. *A.graveolens* (Dill) is an annual, erect, 50 - 150 cm tall and glabrous herb with hollow, furrowed and branched stems; alternate, multipinnate and feathery leaves. The yellowish flowers are arranged in compound terminal umbels. The brown coloured fruit is tiny, oval and flat.

A= Flowers, B and C = Seeds

Source: A = http://www.graines.be/photos/Anethum-Graveolens.jpg
B = http://www.torontomastergardeners.ca/wp-content/uploads/2012/05/DillSeeds-AnethumGraveolens.jpg
C = http://pureintentessentials.com/pure/wp-content/uploads/2013/06/Dill-Seeds.jpg

FIGURE 5

Scientific Classification of *Anethum graveolens* L.

Kingdom   : Plantae – Plants

Subkingdom   : Tracheobionta – Vascular plants

Super-division: Spermatophyta – Seed plants

Division   : Magnoliophyta – Flowering plants

Class   : Magnoliopsida – Dicotyledons

Subclass   : Rosidae

Order   : Apiales

Family   : Apiaceae Carrot family

Genus   : Anethum L. – dill

Species   : graveolens L. – dill

It is a popular Indian culinary item and traditionally known as a carminative, antispasmodic, sedative, lactagogue and diuretic agent besides serving as a home remedy against hyperlipidemia (Jana and Shekhawa, 2010). Pharmacological properties such as antibacterial (Singh *et al*., 2001, Lopez *et al*., 2005), antifungal (Stavri and Gibbons, 2005), antioxidant *(*Singh *et al*., 2006, Taher *et al*., 2007), anti-ulcer (Hosseinzadeh *et al*., 2002), anticancer (Zheng *et al*., 1992), anti-diabetic (Panda, 2008), chemopreventive (Zheng *et al*., 1992) and diuretic (Mahran *et al*., 1992) have all been accredited to AG in recent times. AG extract has been reported to be rich in flavonoids, phenolic compounds, alkaloids, tannins, saponins and cardiac glycosides (Kaur and Arora, 2009). Aqueous extract and essential oils present in AG have been reported to possess hypolipidemic and cardioprotective potentials (Hajhashemi and Abbasi, 2008). Studies on a detailed phytochemical analysis have established the presence of flavonoids (rutin, quercetin), hydroxicinnamic acid

derivates (caffeic acid, chlorogenic acid), coumarins (scopoletin), sterols (beta sitosterol/stigmasterol) and mucilages (Ortan *et al.*, 2008).

Previous studies in our lab had shown that various functional foods (Shankari *et al.*, 2010), therapeutic herbs (Jadeja *et al.*, 2012) and spices (Patel *et al.*, 2012) exhibit cardioprotective potentials due to their powerful free radical scavenging properties. Though AG essential oils have been extensively reported for their therapeutic potentials, there is a lacuna in scientific information on AG seed extract. These studies have been restricted to lipid lowering potential only (Sadeghipour *et al.*, 2014) but the studies have not been carried out to investigate their alleviating potential in cardiovascular disease models. Owing to the extensively reported therapeutic potentials, it was pertinent to subject AG seed extract to a detailed scientific scrutiny and to access its cardioprotective and atherosclerotic potential via series of *in vivo* and cell based experimental models through a variety of carefully scripted protocols.