Introduction

Acute Coronary Syndrome (ACS) is a devastating disease precisely because an otherwise healthy person in the prime of life may die or become disabled without warning. When the afflicted individual is young age, the tragic consequences for family, friends, and occupation are particularly catastrophic and unexpected [1].

Although mortality from acute coronary syndrome (ACS) has declined significantly in the developed world over the past several decades, this disease remains the leading killer of adults in the United States. Although most prevalent in elderly individuals, ACS also affects younger adults. In fact, sudden cardiac death, most often due to ACS, is the most common cause of sudden death in young adults [2]. However, because ACS in this young population is less common, comparatively little information exists on the disease in this age group [3].

Two key elements must be defined to understand ACS in young adults. First, we must explain what is meant by “young” patients, a definition that varies significantly from study to study, ranging from under 35 years of age to under 55 years of age. However various studies had considered the age limit varying from 35 years to 45 years in the spectrum of young CAD [2-10] (Table 1). This arena of cardiology has gained importance very recently due to increased prevalence in this age group over a last few decades, with varying risk factor profiles and difference in prognosis as well as longevity after an acute coronary episode. Recently, apart from the established biomarkers of CAD, many new markers, specifically associated with young CAD are discovered.

Table 1: Spectrum of terminology for young coronary artery disease

No	Terminology	Age group studied	Ref
1	Young CAD	Less than 45 yr	Ericsson et al[2]
2	Young CAD	Less than 40 yr	Konishi et al[3]
3	Young CAD	15-39 yr	Gupta et al[4]
4	Very young CAD	≤ 35 yr	Christus et al[5]
5	Premature CAD	Men ≤ 45 yr Female ≤ 55 yr	Van Loon et al [6]
6	Premature CAD	Less than 60 yr	Genest et al[7]
7	Premature CAD	Less than 45 yr	Pineda et al[8]
8	Precocious CAD	2 case reports of familial CAD of 29 & 31 yr	Norum et al[9]
9	Early onset CAD	Less than 45 yr	Iribarren et al[10]

CAD: Coronary artery disease.

Second, we must define what is meant by "Acute Coronary Syndrome" and "Coronary Heart Disease". They may include only manifestations of atherosclerosis, such as an acute myocardial infarction (AMI), unstable angina (UA), coronary revascularization, or sudden cardiac death. Alternatively, the disease can be defined more broadly as detection of subclinical atherosclerosis.

Acute Coronary Syndrome in young females:

Young women with ACS comprise an especially interesting group, given the protective effect of estrogen; however, which clinical factors are predictive of ACS and related mortality in this uncommon cohort is still poorly understood. Indeed, there is a paucity of studies on ACS in the young adults defined as previously described [11-16], and the records of these analyses are often dated. The most known of these studies is based on the Get with the Guidelines-Coronary Artery Disease registry data [1].

However, it is still unknown whether there is sex-age interplay among the clinical presentation of coronary artery disease (CAD) (STEMI versus non–ST-segment–

elevation ACS) and associated outcomes. Furthermore, almost entirely unexplored is the role of the underlying coronary anatomical features. Women typically have less extensive CAD and, often, non-obstructive CAD [17]. The extent of significant CAD and prognosis may vary between populations of younger patients with different types of ACS.

Young women with acute coronary syndrome have a higher 30-day mortality compared with young men, despite similar quality-of-care and in-hospital procedures. Young age is an independent predictor of lower 30-day mortality in men, but not in women. These findings suggest a sex-specific influence on acute coronary syndrome and provide a possible explanation for sex differences in outcomes.

The young women's risk paradox in patients with acute coronary syndrome cannot be explained by a lower quality of care. There are multiple potential factors that may contribute to high risk in younger women, including psychological and social stressors. Future investigations are warranted to explore potential mechanisms for acute coronary syndrome in young women [17].

Prevalence of ACS in the Young Patients:

Studies that attempt to estimate the prevalence of CHD in young men and women typically rely on data from patients that experience an acute coronary event, often AMI or sudden death. Many studies have demonstrated that young CAD contributes to 2% to 10% of all acute coronary events [18].

Approximately 10% of patients with ST-segment–elevation myocardial infarction (STEMI) were young patients, and 2% of these patients were women. Women were more likely to have lower quality of care and experienced less favorable short-term outcomes than men.

The ISACS-TC (International Survey of Acute Coronary Syndromes in Transitional Countries) registry showed that ≈8% of all patients hospitalized with ACS were aged ≤45 years. In the GRACE (Global Registry of Acute Coronary Events) study, the frequency of young patients with ACS was 6.3% [7]; in the Thai ACS Registry and the ACS Spain Registry, the proportion of young people with ACS was 5.8% and 7%, respectively[12]. As regard to the sex distribution there was a lower percentage of women in the young-age group [11,12].

Young ACS cases were more prevalent among the Malays (49.8%), followed by Indians (24.4%), Chinese (21.8%), and other races (4.1%) [19].

Studies have shown an increased prevalence of CAD in the subjects with family history of premature CAD, than in general population (35% *vs* 14%) [20]. The original as well as offspring cohort data of Framingham study, by National heart lung and blood institute (NHLBI's), from 1880 to 2003 revealed an annual incidence of cardiovascular disease of 3 per 1000 men between 35 to 44 years of age [21].

Centre of disease control prevalence data for the year 2010 revealed that prevalence of CAD in the age group of 18 to 44 years, 45 to 64 years and more than 65 years was 1.2%, 7.1% and 19.8% respectively [22]. Epidemiological data

of United Kingdom published in the year 2000, reported a prevalence of 0.5% and 0.18% in men and women between 35 to 44 years respectively [1].

The mean age of onset of CAD in Southeast Asians seems to be 53 years as compared to European figure of 63 years [23]. South Asians especially Indians are at greater risk of developing CAD at a young age (5% to 10%) when compared to other ethnic groups (approximately 1% to 2%) [24].

The median age of presentation of CAD in young women is higher when compared to men. Singapore myocardial infarction registry of CAD in group less than 65 years showed that men have 4 times greater risk of CAD than women [25]. In Asians 9.7% males and 4.4% females develop first episode of MI under 40 years of age [24].

Risk factors for ACS in young patients:

Atherosclerosis is a disease in which plaque builds up inside the arteries. Plaque is made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, plaque hardens and narrows the arteries. This limits the flow of oxygen-rich blood to heart, organs and other parts of the body. Atherosclerosis can lead to serious problems, including heart attack, stroke, or even death [22].

Most young patients with MI, up to 80%, have typical atherosclerotic coronary artery disease. However, approximately 20% of young patients with MI do not have atherosclerosis, such as cocaine use or anomalous coronary arteries [24].

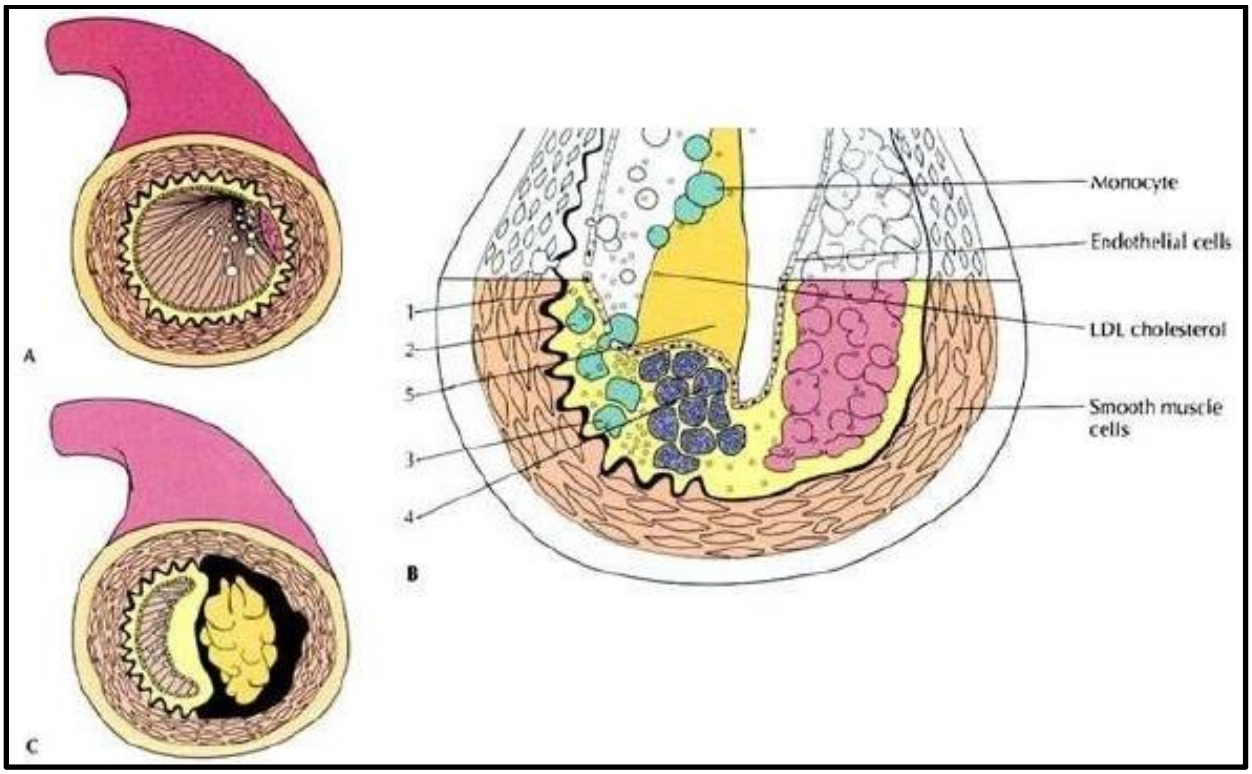

Figure 1: The atherosclerotic process: **A.** Artery depiciting early fatty streaks development. **B.1,** LDL becomes oxidized within the arterial subendothelial space. **2,** Circulating monocytes are recruited to the subendothelial space by chemattractants including oxidized LDL. **3,** These monocytes undergo differentiation, becoming macrophages, which are scavenger cells that recognize and accumulate oxidized LDL. **4,** The lipid-laden macrophages then become foam cells, which cluster under the endothelial lining to form a bulge into the artery. **5,** This bulge is called a fatty streak and is the first overt sign of atherosclerotic change. **C.** Cross-section of an artery with an atherosclerotic lesion with a narrowed lumen.

Table 2 List of conventional and newer risk factors in young coronary artery disease

Conventional risk factors	**Non conventional risk factors**
Age	Cocaine use
Sex	Hypercoagulable states
Hypertension	Spontaneous coronary artery dissection
Diabetes mellitus	Coronary artery anomalies
Dyslipidaemia	Vasculitis
Obesity	*Apo A1, B and E* gene
Smoking	C-reactive protein gene
Family history of premature CAD	Lipoprotein lipase gene
	Factor 5 leiden
Modifiable risk factors:	*MTHFR* gene
By life style: Smoking and obesity	Methionine synthase gene
By pharmacotherapy and or lifestyle:	Polymorphisms in *CETP* gene
Hypertension, DM and dyslipidaemia	Lipoprotein-a, Fibrinogen and D-dimer
Unmodifiable risk factors:	Hepatic lipase gene
Age, sex and genetics	Increased gamma glutamyl transferase
	Raised vitamin D2 and D3
	Decreased osteocalcin

CETP: Cholesterol ester transfer protein; *MTHFR*: Methylene tetrahydrofolate reductase.

Conventional risk factors:

Prevalence of conventional risk factors like diabetes, hypertension, smoking, dyslipidemia and obesity accounts for about 85% to 90% of premature CAD patients [26]. Often young CAD patients have multiple coexisting risk factors contributing to the disease [27]. The most common risk factor associated with young CAD seems to be smoking.

Regarding the influence of sex on acute coronary disease, we know there is a higher prevalence of acute myocardial infarction in men than in women [28]. This association may be related to other risk factors such as alcohol consumption, dyslipidemia or cigarette smoking that are more common in the male population [29]. It is also related to certain hormonal factors such as low levels of androgens and an increased activity of stress-associated hormones such as cortisol, adrenaline, and noradrenaline [30].

The prevalence of conventional risk factors like hypertension (67%), dyslipidemia (67%), obesity (53%), smoking (42%), and diabetes (33%) is higher in women with a family history of CAD [31].

Smoking:

Previous studies have demonstrated that smoking is the most important risk factor associated with the severity of coronary artery disease and is significantly linked with increased risk of coronary plaque vulnerability, myocardial infarction, and cardiovascular death [32]. Previous report showed that the prevalence of smoking in younger coronary artery disease individuals (<45 years of age) ranged from 60% to 90% as compared to 24% to 56% in subjects aged 45 years and over [33]. In addition, smoking served as the most important modifiable risk factor for young adult patients with ACS [34].

Repeated exposure to cigarettes and the resulting frequent catecholamine surges damage endothelial cells, leading to dysfunction and injury of the vascular intima. Smoking produces endothelial dysfunction and can precipitate coronary spasm. Smoking in presence of additional risk factors like diabetes, hypertension and obesity predispose a young individual to increased risk of future acute coronary events [35].

Diabetes and Hypertension:

The prevalence of diabetes and hypertension seems to be higher in young patients with CAD than without CAD. The prevalence of hypertension is 25% in young CAD as compared to 13% without CAD. Similarly, the incidence of diabetes and pre diabetes is 14.3% and 7.6% in young CAD as compared to only 5.4% and 4.3% in patients without CAD respectively [36]. However, prevalence of these risk factors is much higher in older individuals with CAD as compared to young CAD [37-39]. Various studies have demonstrated a recent increase in the prevalence of hypertension [8.86% (2001-2002) to 27.7% (2009-2010)] and dysglycemia [7.6% (2001-2002) to 36.15% (2009-2010)] in young CAD [40].

A major feature of elevated cardiovascular risk in patients with type 2 diabetes probably relates to the abnormal lipoprotein profile associated with insulin resistance known as diabetic dyslipidemia. The LDL particles tend to be smaller, denser, thus more atherogenic. DM is less likely to be associated with MI in young patients than in older patients. Less than 10% of young patients have DM [38].

Obesity:

Obesity is a well-established risk factor for CAD. There is little difference in the prevalence of obesity in young CAD when compared with older CAD patients

[38]. Obesity, particularly the male pattern of centripetal or visceral fat accumulation, can promote an atherogenic dyslipidemia characterized by elevated TG, a low HDL level, and glucose intolerance. Approximately 30% to 58% of young patients with coronary artery disease are obese, a significantly greater proportion than in older patients. Sagittal abdominal diameter to skin fold ratio seems to be a good indicator in predicting premature CAD, even better than body mass index (BMI) and waist circumference [41].

Family history of premature CAD:

Family history of premature CAD is an important risk factor for young CAD. It stresses the role of genes in the etiology of young CAD. Studies have shown that person with a positive family history of premature CAD tend to have severe coronary atherosclerosis and is a very strong predictor of future acute coronary event [42]. Increase of the risk in young patients with family history may be due to inherited disorders of lipid metabolism, blood coagulation, or other genetic factors. The atherosclerosis in coronary vessels, as revealed by increased plaque content is seen in individuals with a positive family history of premature CAD and increases the incidence of severe obstructive CAD [42]. One study revealed around 64% of young CAD patients had a positive family history [18].

Dyslipidaemia:

Hyperlipidemia is a potent risk factor for atherosclerosis and coronary heart disease (CHD) and is present in a substantial proportion of young adults. Hyperlipidemia may be caused by genetic factors, as in certain familial diseases. It may also be caused by secondary factors like certain dietary influences, especially in acquired hyperlipidemia.

Although, dyslipidemia is an important risk factor for young CAD, there seems to be a little difference in prevalence of lipid abnormalities in younger and older patients. One study demonstrated a significantly increased level of LDL and total cholesterol in persons of CAD more than 55 years of age when compared with less than 55 years of age [37]. Conversely in another study there is high prevalence of lipid abnormalities in young CAD when compared to older CAD group. These differences in lipid parameters may due effect of dietary, genetic and environmental factors on lipid metabolism [38].

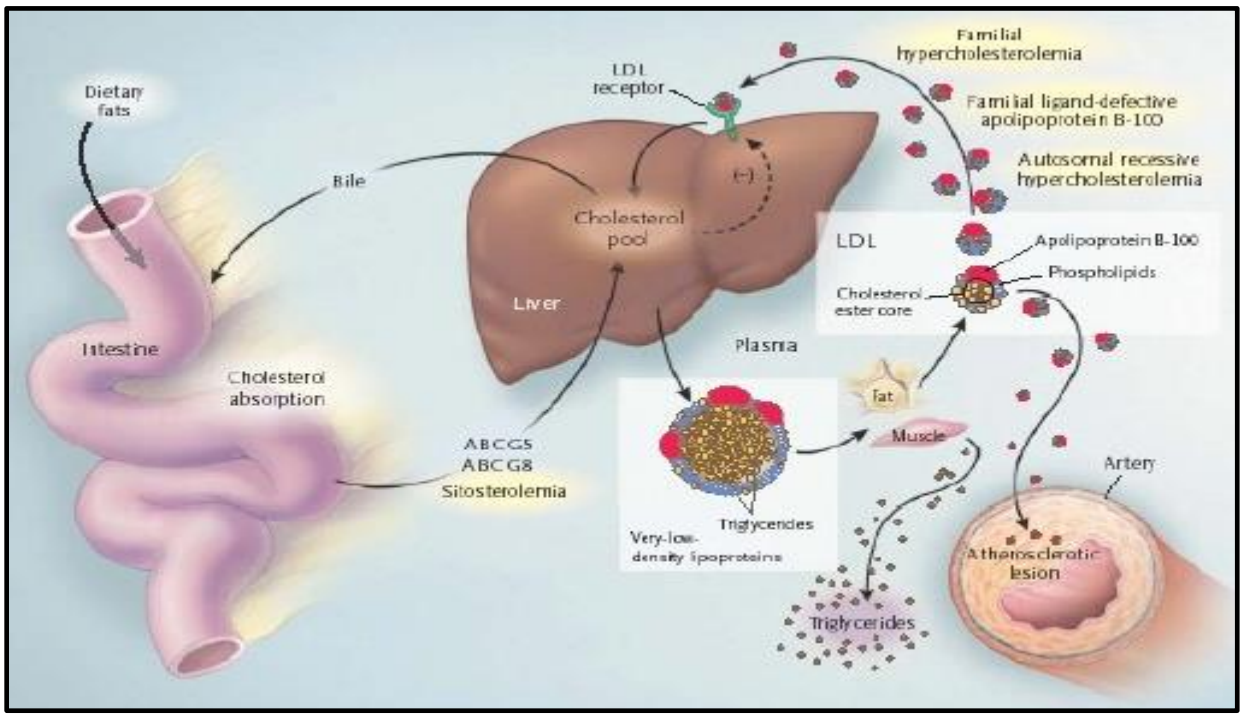

Figure (2): The basic components of cholesterol synthesis and excretion.
Low-density lipoprotein (LDL) molecules are composed of a cholesteryl ester core surrounded by a coat made up of phospholipid and apo-lipoprotein B-100. The liver secretes LDL as larger precursor particles called very-low-density lipoproteins, which contain triglycerides and cholesterol esters. Capillaries in muscle and adipose tissue remove the triglycerides and the lipid particles is modified into an LDL with its cholesteryl ester core and apolipoprotein B-100 coat. LDLs circulate in the plasma and the apolipoprotein B-100 component binds to LDL receptors on the surface of hepatocytes. Through receptor mediated endocytosis, receptor bound LDLs enter hepatocytes and undergo degradation in lysosomes, and the cholesterol remnants enter a cellular cholesterol pool. A negative feedback loop regulates number of LDL receptors. A rise in the hepatocyte cholesterol level suppresses the transcription of LDL-receptor genes and LDL is retained in the plasma. Conversely, a decrease in hepatic cholesterol stimulates the transcription of LDL-receptor genes, removing LDL from the plasma. This mechanism accounts for the LDL lowering action of the statins, which inhibit an enzymatic step in hepatic cholesterol synthesis. Four monogenetic diseases that elevate plasma LDL are highlighted in yellow. ABC denotes ATP-binding cassette.

Familial hypercholesterolemia:

- (Abbreviated FH) is a genetic disorder characterized by high cholesterol levels, specifically very high levels of low-density lipoprotein (LDL, "bad cholesterol"), in the blood and early cardiovascular disease.
- Many people have mutations in the *LDLR* gene that encodes the LDL receptor protein, which normally removes LDL from the circulation, or apolipoprotein B (ApoB), which is the part of LDL that binds with the receptor; mutations in other genes e.g. PCSK9, and ApoE genes are rare.
- People who have one abnormal copy of the *LDLR* gene (are heterozygous) may develop cardiovascular disease prematurely at the age of 30 to 40.
- Having two abnormal copies (being homozygous) may cause severe cardiovascular disease in childhood.
- Heterozygous FH is a common genetic disorder, inherited in an autosomal dominant pattern, occurring in 1:500 people in most countries; homozygous FH is much rarer, occurring in 1 in a million births.
- Heterozygous FH is normally treated with statins, bile acid sequestrants, or other lipid lowering agents that lower cholesterol levels. New cases are generally offered genetic counseling.
- Homozygous FH often does not respond to medical therapy and may require other treatments, including LDL apheresis (removal of LDL in a method similar to dialysis) and occasionally liver transplantation.
- Yellow deposits of cholesterol-rich fat may be seen in various places on the body such as around the eyelids (known as xanthelasma palpebrarum), the outer margin of the iris (known as arcus senilis corneae), in the tendons of the hands, elbows, knees and feet, particularly the Achilles tendon (known as a tendon xanthoma).

- Accelerated deposition of cholesterol in the walls of arteries leads to atherosclerosis, the underlying cause of cardiovascular disease.
- The most common problem in FH is the development of coronary artery disease (atherosclerosis of the coronary arteries that supply the heart) at a much younger age than would be expected in the general population. This may lead to angina pectoris (chest pain or tightness on exertion) or heart attacks.
- Less commonly, arteries of the brain are affected; this may lead to transient ischemic attacks (brief episodes of weakness on one side of the body or inability to talk) or occasionally stroke.
- Peripheral artery occlusive disease (obstruction of the arteries of the legs) occurs mainly in people with FH who smoke; this can cause pain in the calf muscles during walking that resolves with rest (intermittent claudication) and problems due to a decreased blood supply to the feet (such as gangrene).
- Atherosclerosis risk is increased further with age and in those who smoke, have diabetes, high blood pressure and a family history of cardiovascular disease
- Approximately 85% of individuals with this disorder have not been diagnosed and consequently are not receiving lipid-lowering treatments.
- Physical examination findings can help a physician make the diagnosis of FH.
- Tendon xanthomas are seen in 20-40% of individuals with FH and are pathognomonic for the condition [43].

Lipid measurements:

- Cholesterol levels may be determined as part of health screening for health insurance or occupational health, when the external physical signs such as xanthelasma, xanthoma, arcus are noticed, symptoms of cardiovascular disease develop, or a family member has been found to have FH.

- Total cholesterol levels of 350–550 mg/dL are typical of heterozygous FH while total cholesterol levels of 650–1000 mg/dL are typical of homozygous FH.

Table (3): Monogenic Diseases that elevate plasma levels of LDL cholesterol.

Disease	Mutant Gene	Molecular Mechanism	Approximte Plasma Cholesterol Level mg/dl
Familial hypercholesterolemia Homozygous Heterozygous	LDLR	Nonfunctional receptor fails to take up plasma cholesterol	 300 650
Familial ligand-defective apoliporotein B-100 Homozygous Heterozygous	APOB-100	Apolipoprotein B-100 fails to bind LDL receptor	 275 325
Autosomal recessive hypercholesterolemia	ARH	LDL-receptor activity is disrupted	450
Sitosterolemia	ABCG5 & ABCG8	Transcription factors (liver X receptor and sterol regulatory element binding protein) that regulate liver cholesterol synthesis and clearance are suppressed	150-650

The information is adapted from Goldstein and Brown with the permission of the publisher
Am J MED. 1999; 107; 254-261 Myc

Junhua Ge, found that hypertension and smoking are the major risk factors of young male ACS patients, while hyperlipidemia and family history of coronary artery disease played only a negligible role in young male ACS patients.

At present, there are only scanty reports on the prevalence and risk factors as well as outcome of MVD in young ACS patients [44].

Table (4): Summary for the effect of conventional risk factors.

	Young	Old
Smoking	++++	++
Lipid Abnormalities	+++	++
Family History	+++	+
Obesity	+++	+
Hypertension	+	+++
DM	+	+++

Non conventional risk factors:

Cocaine and amphetamine use is considered a risk factor for CAD, it is associated with a number of cardiovascular diseases, including myocardial infarction, heart failure, cardiomyopathies, arrhythmias, aortic dissection, and endocarditis [45].

From a physiopathological approach, this consumption, is related to an excessive release of neurotransmitters such as noradrenaline and dopamine, causing an alteration in the supply-demand relation of oxygen in the myocardial cell secondary to an increase of heart rate and systemic arterial pressure [28,46]. Other effects related to the consumption of these drugs are: an increased platelet aggregation, increased endothelial reactivity, and decreased coronary flow [28,46].

The antiphospholipid syndrome and the hypercoagulability states constitute less than 5% of the causes of acute myocardial infarction in young people. Deficiencies of the natural anticoagulant proteins, such as protein C, protein S and antithrombin III and high levels of factor VII activity or fibrinogen are usually associated with CAD and increased risk of coronary events among young men. However, it has been predicted that as many as 21% of patients with antiphospholipid syndrome could debut with an acute myocardial infarction [46,47]. These patients have been characterized by an increase in the platelet activity due to a higher sensitivity of the platelets in the presence of adenosine diphosphate, by the increase of the activity of the plasminogen inhibitor factor, the increase of the lipoprotein A expression and high levels of oxidized LDL antibodies [46].

Congenital coronary artery anomalies account for approximately 4% of MIs in young patients. Several such anomalies, including a deep intramyocardial course,

an origin from the wrong coronary sinus, or ostial obstruction, have been associated with MI and sudden death in young patients [48].

Spontaneous dissection is a less common cause of ACS in young people (0.07% to 0.1%), the mean age of presentation of spontaneous coronary artery dissection is 35-40 years, and is more common in females. The patients are divided into three groups: peripartum, atherosclerotic and idiopathic group. Dissection occurs in tunica intima of coronary arteries, the blood penetrates and results in intramural hematoma in tunica media, resulting in restriction in the size of lumen, reduction of blood flow and myocardial infarction [49].

Vasculitis is one of the non-conventional risk factors for ACS in young adults. It refers to a heterogeneous group of diseases characterized by inflammation and fibrinoid necrosis of the vascular wall. Vasculitis affects persons of both sexes and all ages. It may be primary in origin, without any identifiable cause, or it may be secondary due to infection, malignancy, or autoimmune disease. There is evidence that the presence of vasculitis can accelerate atherosclerosis in various autoimmune diseases including connective tissue diseases (CTDs), such as rheumatoid arthritis (RA), systemic sclerosis (SSc), sarcoidosis, and systemic lupus erythematosus (SLE). They can involve the aorta and its major branches, as in giant cell arteritis and Takayasu's arteritis (TA), medium-sized vessels, as in polyarteritis nodosa (PAN) and Kawasaki disease (KD), and small vessels (arterioles, capillaries, and venules), as in Wegener granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and mixed cryoglobulinemic vasculitis (MCV).

Cardiac manifestations can occur with varying frequency in these diseases, depending on the type of vasculitis; although they are rarely predominant, they can

be life threatening. Each cardiac tissue can be affected during the course of vasculidites [50].

The inflammation of the coronary arteries is expressed in the form of coronary arteritis and manifested clinically as aneurysms, thrombosis, dissections, and stenosis. All these coronary lesions may lead to myocardial infarction and possibly contribute to HF. Coronary involvement was documented by autopsy in 50% of patients with polyarteritis nodosa (PAN). 16 However, Kawasaki D is the vasculitis with the highest frequency of coronary arteritis, with 20% to 25% of patients developing aneurysms [50].

There are other numerous risk factors found to be associated with CAD in younger people. Polymorphisms in cholesterol ester transfer protein (*CETP*) gene, hepatic lipase gene, lipoprotein lipase gene, C-reactive protein gene, *apo A1* gene, *apo E* gene, *apo B*, hypoxia inducible factor 1 alpha gene, factor 5 leiden, Methylene tetrahydrofolate reductase (*MTHFR*) gene and methionine synthase gene have been associated with premature CAD [51].

The ApoE4 allele has been associated with CAD in several populations. ApoE2/E2 homozygous individuals are at risk for type III hyperlipoproteinemia, which is associated with an increased risk for atherosclerosis [52,53].

Homozygosity for the *MTHFR C677T* mutation has been associated with elevated levels of homocysteine, and homocysteine levels have been associated with CAD risk [54].

Hepatic lipase (HL) is both a phospholipase and a triglyceride lipase and plays an important role in HDL metabolism and in the conversion of VLDL to LDL. Single

nucleotide polymorphisms in the *HL* gene have been shown to associate with plasma lipid concentrations and increased CHD risk [55].

Young CAD patient shows an increased serum levels of lipoprotein-a, fibrinogen and D-dimer as compared to age matched controls [8]. Increased gamma glutamyl transferase, raised vitamin D2 and D3 and decreased levels of osteocalcin are found to be associated with premature CAD [56]. This association of CAD in young with high levels of vitamin D is in contradiction to the studies done in general population where deficiency of vitamin D is associated with adverse cardiovascular outcomes [57].

Diseases such as hypothyroidism, systemic lupus erythematosis, rheumatoid arthritis, HIV patients on highly active anti retroviral therapy (HAART) (especially with protease inhibitors), homocysteinaemia, kawasaki disease in childhood, patent foramen ovale (causing paradoxical embolism) and various other conditions are found to associated with accelerated atherosclerosis [58].

Lesion criteria in Young Patients:

Unlike in older people, lesions are usually less complex (40% to 60% of cases occurs in only one arteria), mainly located in the anterior descending and right coronary arteries. Only 10% to 15% of cases may present angiographically with significant obstructive lesions (obstruction> 50% of vessel lumen diameter) [28,59]. In recent study from Nepal of young CAD less than 45 years angiography revealed 7.6% had normal or non critical disease, 6.1% had triple vessel disease, 36.9% had double vessel disease and 53.8% had single vessel disease [60].

Single vessel disease involving left anterior descending artery is much more common in young women when compared with young men with CAD [61]. The prevalence of normal coronary arteries in patients with young CAD is about 8% to 22% as reported in various studies [62] compared to 3% to 4% in general CAD population [63]. The cause of this high prevalence of normal angiography in young CAD patients is still unclear. The probable reason could be the natural extra luminal progression of disease in the initial stages, as the vessel wall compensates to maintain unrestricted luminal blood flow [64]. An occlusive thrombus produced by the rupture of an angiographically "invisible" vulnerable plaque totally lysed after few hours or a long-lasting vasospasm leading to complete occlusion of a normal coronary artery or a combination of these two are the most likely mechanism of CAD in patient with normal coronaries [65].

Previous studies demonstrated that MVD was less common and associated with worse prognosis compared to SVD patients [66].

The association between hypertension and MVD in young ACS patients remains controversial. Sukhija et al. observed higher prevalence of MVD in hypertensive patients compared to nonhypertensives [67]. However, Zand Parsa et al. did not find any relationship between hypertension and MVD [68]. Junhua Ge, et al. indicated a strong association between hypertension and MVD in young male ACS patients, in that the prevalence of hypertension is as high as 72.1% in MVD group compared to 38.6% in SVD group ($p<0.001$). Moreover, results of the ordinal logistic regression model for MVD revealed that hypertension was a significant independent risk factor for MVD after adjustment for smoking, BMI, family history of premature CAD, BNP, LVEF, and hyperlipidemia in young male ACS patients. In addition, our results suggested that SBP >150mmHg and/or DBP

>90mmHg as the cut-off value could fairly predict the presence of MVD (sensitivity of 72% and specificity of 58%) in young male ACS patients [44].

Pathophysiology of ACS in young patients:

Conventional ACS accounts for about 80% of ACS in young adults. About 4% of heart attacks in young adults are due to congenital abnormalities of the coronary artery anatomy, about 5% due to blood clots that originate elsewhere and are carried to otherwise normal coronary arteries, and block the artery, in another 5%, various disorders of the blood clotting system increase the risk of clot formation. The remaining 6% of ACS in young adults is due to spasm or inflammation of the coronary arteries, radiation therapy for chest tumors, chest trauma, and abuse of cocaine, amphetamines, and other drugs. Coronary segments, with non-significant stenosis and non-calcified plaque, shows positive remodeling that might be the cause of ACS in young individuals with normal coronary artery. Positive remodeling is related to plaque instability, suggesting it is more prone to rupture and erosion with subsequent coronary events. Lipid core plaques, in contrast to the severely calcified plaques, showed positive vascular remodeling, thus early plaques are more prone for ACS [69].

Prognosis of ACS in young patients:

Obesity and current smoking are the two important conventional risk factors associated with adverse outcomes in the form of increased mortality and future acute coronary events [3]. Mortality of CAD in people of China, less than 40 years of age, was 13.81/100000 in 2006 which increased to 19.07/100000 in 2009 [70]. There is a widespread decrease in mortality due to CAD in older age group in the

recent years but it not seen in CAD in younger age group [71]. The possible explanation that is proposed is increase in prevalence of risk factors such as diabetes, obesity and hypertension in younger age groups [71]. Mortality after an acute coronary event is two times higher in women than in men under 50 years of age [72]. The cause of increased incidence of adverse event in women with premature CAD is still unknown.

In patient with acute coronary event both per-cutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are associated with excellent immediate survival (mortality of 0.8% *vs* 1.4% for PCI and CABG respectively at 30 d) as well as long term survival outcomes at end of 5 years [73]. But PCI seems to associated with lower rate of repeated acute coronary events and revascularisation procedures when compared to CABG at the end of 5 years (repeat myocardial infarction 89.9% *vs* 96.6% for PCI *vs* CABG) [74]. Mortality outcomes at 30 d and 3 years after an ST segment elevation myocardial infarction in 3601 patients with and without family history of premature CAD were compared in Harmonizing outcomes with revascularization and stents in acute myocardial infarction (HORIZONS-AMI) trial, which did not show any significant association of family history of premature CAD with mortality outcomes [75]. In patients with young CAD high C-reactive protein have been associated recurrence of future acute coronary event and raised fibrinogen levels seems to be associated with increased mortality [6]. Persons with positive family history of premature CAD and coronary artery calcium scores greater than 80th percentiles benefit from treatment with statins for primary prevention of acute coronary events [76].

Young CAD patients have higher rates of normal coronary vessels on angiography, mild luminal irregularities and increased prevalence of single vessel disease than older CAD patients [77].

The morbidity reported in young patients who have suffered an acute myocardial infarction is 1.5% and in-hospital mortality during the 30 days after the event is 8.3% [29,59,78].

Likewise, in relation to gender, no relevant differences in mortality were reported. However, there are some characteristics in women that could worsen the prognosis, such as the presentation of atypical symptoms, less alteration of cardiac biomarkers at the time of diagnosis, later access to reperfusion therapy and are more likely to not receiving adequate doses of beta-blockers and antiplatelet agents [30,79,80,81].

In the "Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO)" study, made in a cohort of 3,572 patients (1,175 men and 2,397 women), the percentage of patients with atypical chest pain was higher in women than in men (16% vs 10%, $p < 0.001$). There was a higher elevation of troponin values in males (9.6 ng / mL) compared to females (5.8 ng / mL) ($p < 0.001$), and there was a higher risk of death in women that do not receive coronary reperfusion treatment (RR = 2.31; 95% CI: 1.32 - 4.06) [80].

Other studies as those carried out by Dreyer *et al.* showed that women have a higher risk of not being treated with primary angioplasty when compared to men (HR = 1.65; 95% CI: 1.55 - 1.75) [81]. Davis *et al.* showed that within the group of female patients, those who were younger were more likely to not receive optimized medical treatment after discharge compared to older women [79].

In the case of patients with acute myocardial infarction, but without injury in the coronary arteries, long-term mortality can reach up to 18% [82].

Management of ACS in young patients:

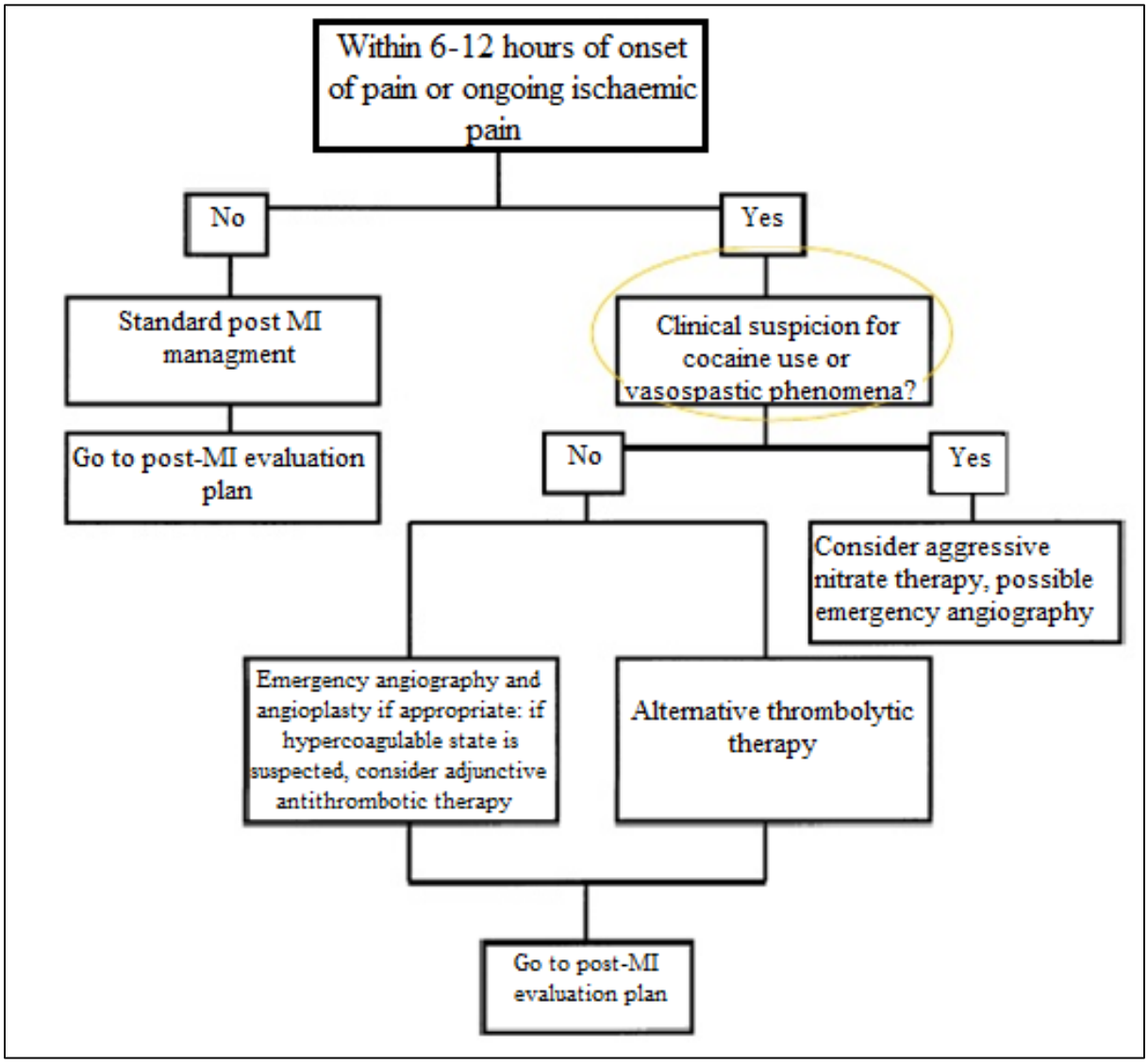

Figure 3: Algorithm for management of acute myocardial infarction (MI) in young patients.

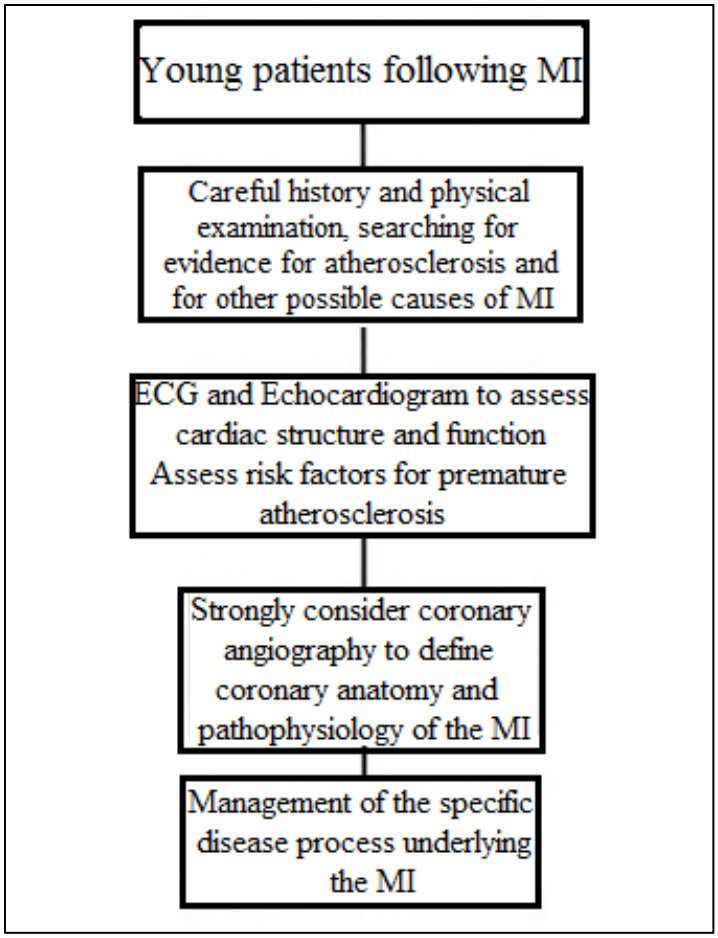

Figure 4: Plan for evaluation of young patients after myocardial infarction (MI).

Conclusion:

The overall prevalence of CAD including the subset of young CAD is on decreasing trend but mortality of CAD doesn't seems to be decreasing when comparing to older CAD patients.

Unlike older adults, young people with acute coronary events have a different risk profile, characterized by a higher prevalence of obesity, smoking and dyslipidemia; and a lower influence of hypertension and diabetes [83].

In addition to conventional risk factors numerous other risk factors and genes play an important role in the causation of the disease.

The prognosis of CAD in younger people is better than older people. Current smoking and obesity have major impact in long term mortality and morbidity. Young CAD patients with an acute coronary event undergoing PCI and CABG have an excellent immediate and long term survival rates.

ACS at a young age is characterized by less severe coronary disease and high prevalence of ST-segment-elevation myocardial infarction. Women have higher mortality than men. Young age is an independent predictor of lower 30-day mortality in men, but not in women.

The presence of thrombus in the absence of underlying coronary disease suggests a thromboembolic event or de novo thrombotic occlusion, which may reflect primary hemostatic dysfunction in a considerable number of these patients [84].

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