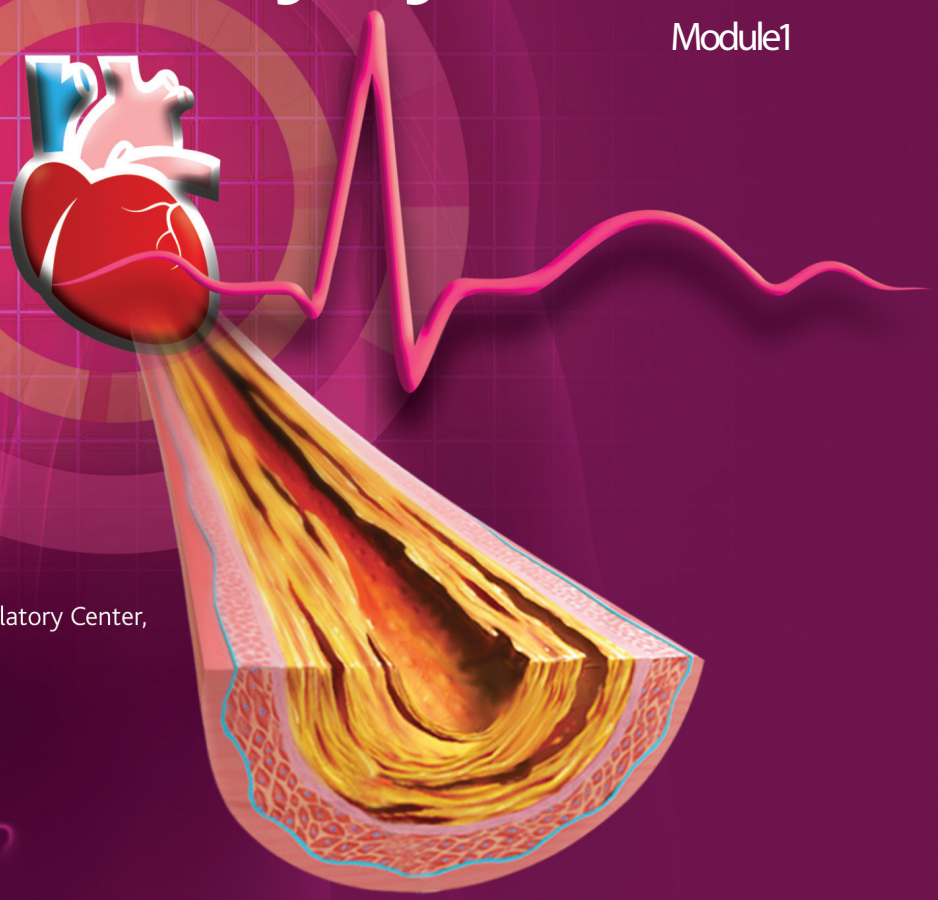
Post Graduate Excellence Program on

Acute coronary syndrome

Module1



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Course code : E.PPOSTGRADACS14P1

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Course Information

Need for the program

Cardiovascular disorders are widely prevalent around the world and are cause of considerable morbidity and mortality. Many disorders among these present as a medical emergency and require aggressive management. Untreated, some of them culminate in sudden cardiac death. Acute coronary syndrome (ACS) is a spectrum of such life-threatening cardiovascular disorders which includes unstable angina and myocardial infarction (MI), both with and without ST segment elevation. All of these high-risk manifestations of coronary atherosclerosis portend high mortality rates and should be satisfactorily managed. It is imperative for physicians and cardiologists dealing with ACS to remain updated with their risk stratification paradigms, diagnostic procedures and management options, both interventional and non-interventional, for these disorders. This Post Graduate Excellence Program is an attempt to address these issues, and in particular, update the participants on management approach in patients with ST-elevation MI (STEMI) and those with non ST-elevation MI (NSTEMI).

Program objectives

After completing this program, the participants will be able to understand:

1: Worldwide rising prevalence of ACS, and its clinical spectrum and presentation

2: Its risk factors and pathophysiology, and mechanistic association between ACS and sudden cardiac death

3. Diagnostic approach and risk stratification paradigms for patients with NSTEMI and STEMI

4. Management approaches for NSTEMI and STEMI.

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Method of participation in the diploma program

- Register for the program where prompted
- Study all parts of the educational activity available in a print format
- The complete program, including two course modules and two webinars, will be followed by an evaluation. Successful candidates (those who score more than 70% in the evaluation) will be issued a diploma certificate of participation.

Diploma program

Release Date : 1st April 2014
Expiration Date : 31st March 2015

Course code : E.PPOSTGRADACS14P1

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ACUTE CORONARY SYNDROME

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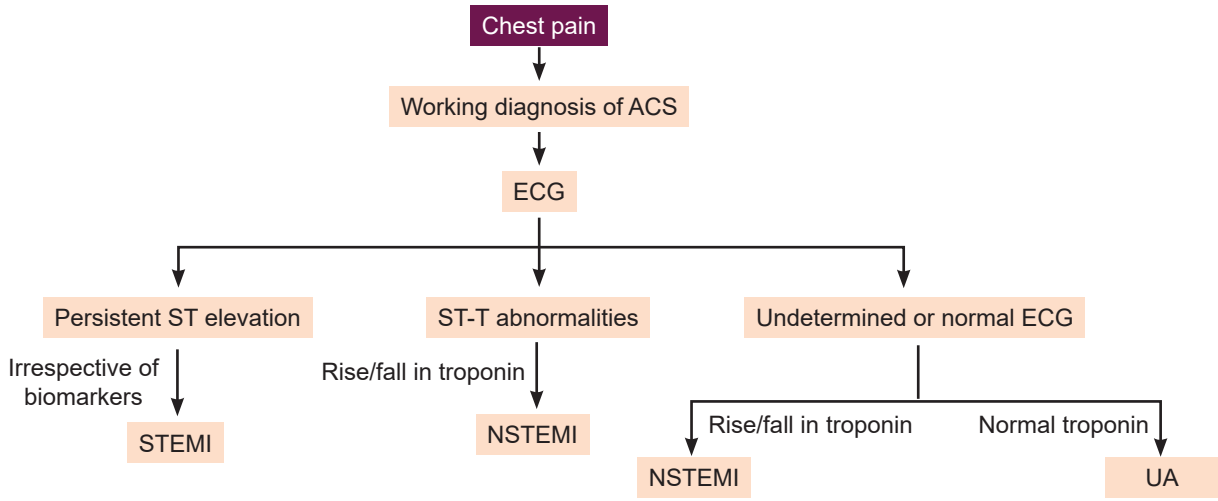
OBJECTIVES

- **To understand worldwide rising prevalence of ACS, and its clinical spectrum and presentation**
- **To provide an update on its risk factors and pathophysiology and decipher mechanistic association between ACS and sudden cardiac death.**

INTRODUCTION

Acute coronary syndrome (ACS) is a life-threatening manifestation of coronary artery disease (CAD) which encompasses a spectrum of clinical conditions ranging from unstable angina (UA) to acute myocardial infarction (AMI); the latter is further subdivided based on findings on 12-lead surface ECG into ST-elevation MI (STEMI) and non ST-elevation MI (NSTEMI). ACS is a significant contributor to global morbidity and mortality. Atherosclerosis is the basic underlying pathology, with partial or complete coronary occlusion due to thrombus overlying a ruptured atheromatous plaque being the immediate precipitating cause. According to currently available data, approximately 70-80% of ACS occur as a result of plaque rupture while remaining cases are usually due to superficial endothelial erosions. In both scenarios, exposure of subendothelial collagen triggers coagulation cascade, which along with impaired fibrinolysis, favors thrombus formation. The developing thrombus obstructs coronary lumen, either partially or completely, culminating in manifestations of ACS. Since myocardial necrosis – which is oftentimes the end result of ACS – is an irreversible process, risk stratification followed by prevention is more covetable than management of this frequently fatal CV event. However, current diagnostic strategies, despite having evolved over time, are inept in predicting precise timing of ACS occurrence, and therefore risk factor modification

Figure 1 **Clinical spectrum of ACS**



Based on information from: Hamm CW, Bassand JP, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2011 Dec;32(23):2999-3054.

using both non-pharmacological and pharmacological modalities is the best preventive approach for ACS.[1,2]

ACS is a symptom manifestation of CAD. Traditionally, both ACS and CAD have been seen to be significant contributors to the disease burden in the developed countries. Despite decline in prevalence, CAD continues to be a major health problem in these regions accounting for 20% deaths in them. The developing countries, on the other hand, have been witnessing rapid health transition over the past few decades owing to growing industrialization and urbanization. Several non-communicable diseases, including CAD, which were of relative rare occurrence in the past have rapidly grown in prevalence in these regions. The current high burden of CAD in developing countries can be highlighted by global mortality estimates of 2002 which showed that 80% of worldwide CV deaths occurred in the developing countries, and CAD alone accounted for 50% of this burden.[3,4]

The following treatise comprehensively evaluates the rising prevalence of CAD in the developing countries, factors responsible for this uptrend, and the risk factors for ACS development. Additionally, clinical presentation and mortality rates associated with ACS, its pathogenesis and mechanisms of sudden cardiac death (SCD) in these patients are also extensively addressed.

THE CLINICAL SPECTRUM OF ACS: AN OVERVIEW

Acute coronary syndrome, which can manifest as either UA or AMI (NSTEMI or STEMI) is an undiscounted major contributor to CV disease-related morbidity and mortality worldwide. It is one of the most common causes for acute medical hospitalization. However, timely diagnosis and intervention with appropriate therapy may incur considerable protection against these adversities. To secure a correct diagnosis of ACS, a quick history along with meticulous physical and cardiac examination is warranted; diagnosis can be substantiated by findings of a 12-lead surface ECG and concentration of cardiac biomarkers. Radiological imaging may also be required in a subset of these patients to authenticate the diagnosis. Invariably, ischemic symptoms, persistent ST elevation on surface ECG along with elevation in concentration of cardiac biomarkers is strongly suggestive of STEMI. However, findings of ST-T abnormalities on ECG along with rise/fall in concentration of cardiac biomarkers are more reflective of NSTEMI. When ischemic symptoms are associated with indeterminate/normal ECG findings without change in concentration of cardiac biomarkers, diagnosis of UA is more plausible. Figure 1 depicts clinical spectrum of ACS. Management

Table 1 **Revised Third Universal definition of AMI by The Joint ESC/ACCF/AHA/WHF Task Force, 2012**

Acute myocardial ischemia with evidence of myocardial necrosis defines acute myocardial infarction. The Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction agrees to its diagnosis if any of the following criterias is present:
• Rise/fall in cardiac biomarkers (preferably cardiac troponin), with at least one value above the 99th percentile upper reference limit (URL) with any of the following features: » Ischemic symptoms » New/presumed new significant ST-T wave changes or new left bundle branch block (LBBB) » Genesis of pathological Q waves » Evidence of new loss of viable myocardium or new regional wall motion abnormalities on imaging studies » Angiographic or autopsy detection of intracoronary thrombus.
• Death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes/new LBBB, even if death occurred before cardiac biomarkers were obtained or before cardiac biomarker values increased.
• Myocardial infarction after percutaneous coronary intervention (PCI) is defined as elevation in cardiac troponin values greater than five times the 99th percentile URL in patients with normal baseline values OR greater than 20% elevation in cardiac troponin values if baseline values are elevated and are stable or falling. Additionally, any of the following features must be present: » Symptoms of myocardial ischemia » New ischemic ECG changes » Angiographic findings indicative of procedural complication » Evidence of new loss of viable myocardium or new regional wall motion abnormalities on imaging studies.
• Coronary angiography or autopsy findings showing stent thrombosis associated with MI in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values, with at least one value above the 99th percentile URL.
• Myocardial infarction after coronary artery bypass grafting may be defined as elevation of cardiac biomarker values greater than ten times the 99th percentile URL in patients with normal baseline cardiac troponin values along with the presence of any of the following features: » New pathological Q waves or new LBBB » Angiographic evidence of new graft or new native coronary artery occlusion » New loss of viable myocardium or new regional wall motion abnormalities on imaging studies.

Based on information from: Thygesen K, Alpert JS, Jaffe AS, et al. Expert Consensus Document. Third universal definition of myocardial infarction. *Journal of the American College of Cardiology.* 2012;60(10).

of ACS differs across its clinical spectrum. Irrespective of the clinical presentation, general management principle of ACS is to provide adequate oxygenation, pain relief and improvement of ischemia. While UA/NSTEMI can be managed with aggressive medical management, STEMI usually warrants emergency reperfusion to reestablish normal coronary blood flow.[1,5,6]

Currently accepted definition of AMI

Most patients with diagnosed ACS present with AMI. The traditional definition of AMI, which was primarily based on the levels of cardiac biomarkers and ECG findings, has undergone periodic revision from time-to-time with gradual evolution and improvement in diagnostic techniques, most of which are currently sensitive enough to accurately detect even minor extent of cardiac injury/necrosis. Table 1 describes currently accepted third universal definition of AMI which is endorsed by the European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the World Heart Federation (WHF). Detection of a rise and/or fall of cardiac biomarker values, with at least one of them being elevated (> 99th percentile upper reference limit) is central to the new definition. Additionally, at least one of the five following diagnostic criteria need to be met to secure MI diagnosis: symptoms of ischemia; new (or presumably new) significant ST/T wave changes or left bundle-branch block (LBBB); development of pathological

Q waves on ECG; imaging evidence of new loss of viable myocardium or regional wall motion abnormality; and identification of intracoronary thrombus by angiography or autopsy.[6]

EPIDEMIOLOGY OF CAD/ACS AND ITS RISING PREVALENCE IN THE DEVELOPING COUNTRIES

Despite rapid advancements in CV medicine, ACS and CAD remain frequently fatal medical disorders which are a source of considerable morbidity and mortality. Available statistics show that 30% of global deaths are attributable to CV diseases. Among these, approximately 50% are due to CAD alone.[7] Rapidly growing prevalence of CAD appears to have reached pandemic proportions worldwide. CAD also significantly impacts personal, societal, and financial health.[8] Both developed and developing countries are known to have significant burden of CAD. However, over the last few years growing inconsistency in the burden of CAD and its age-adjusted mortality rates between developed and developing countries is being recognized. In developed countries, CAD was, and remains, the leading cause of deaths while in developing countries CAD-related mortality rates are rapidly increasing. Even among the developing countries wide inter-regional variation in CAD-related mortality rates has been observed. These variations appear to be closely linked to epidemiologic transition, genetic predisposition, socioeconomic progress, predominant risk factors, and availability of and accessibility to preventive and therapeutic interventions.[7,9] Hence, while in Eastern Europe – a region with developing economy – CV-related deaths account for 58% of all-cause mortality, in the sub-Saharan region – another region with growing economy – CV diseases contribute to only 10% of overall deaths.[7] Burden of CAD, particularly premature CAD, and its associated mortality rates in the Indian subcontinent are comparatively higher than those in many other developing countries. More distressing is the fact that these rates are relentlessly increasing with time at an alarming rate. According to available data, by the year 2015, 2.9 millions deaths in India will be attributable to CAD, of which 40% will occur in younger population (< 45 years of age). These mortality rates due to premature CAD in Indians < 45 years of age are much higher than mortality rates of 1% and 4% in American Caucasian and African-American population < 45 years of age, respectively.[10] This data underscores significant disparity in the peak age of CAD occurrence between developed and developing countries. While in developed countries, CAD is increasingly encountered in the elderly, in the developing countries it usually affects the younger population which negatively impacts their productivity and economic growth.[7]

Gender-related differences in CAD occurrence have also been noted. Traditionally, CAD has been known to occur more frequently in men than in women of comparable age; lifetime risk of CAD at the age of 40 years has been estimated to be 50% in men compared to 33% in women.[11] However, a considerable body of evidence currently supports rising prevalence of CV diseases, including CAD in women, especially during their middle age. Data available from National Health and Nutrition Examination Surveys demonstrated MI prevalence between 1988 -1994 in men and women aged 35-54 years to be 2.5% and 0.7%, respectively. Over the ensuing 5 years spanning from 1999-2004, MI prevalence rates in women rose from 0.7% (in 1988 -1994) to 1% (in 1999 -2004) while those in men showed a marginal decline from 2.5% (in 1988 -1994) to 2.2% (in 1999 -2004).[12,13,14] Growing prevalence of CAD in these middle-aged women may be related, at least in part, to declining estrogen levels – which have been traditionally known to impart cardioprotection.[15,16]

Within the spectrum of ACS, relative prevalence of STEMI, NSTEMI and UA has been shown to vary, as seen from results of many registry studies. There is considerable evidence to suggest that two-third of patients with ACS manifest either as UA or NSTEMI while only one-third of these patients have evidence of STEMI. Data provided by the Global Registry of Acute Coronary Events (GRACE) study,[17] which evaluated ACS patients from 14 countries in North and South America, Europe and the United Kingdom, and Australia and New Zealand, revealed diagnosis of UA in 38%, NSTEMI in 25% and STEMI in 30% patients. Similar were findings of the Euro Heart Survey of Acute Coronary Syndromes (EHSACS),[18] which recruited patients with diagnosed ACS from several countries across Europe and the Mediterranean basin, and showed initial diagnosis of NSTEMI in 51.2% patients, STEMI in 42.3% and undetermined ECG in 6.5% patients. Final discharge diagnosis in this survey was Q wave MI in 32.8% patients, non-Q wave MI in 25.3% patients, and UA in 41.9% patients. Another large registry[19] involving patients with confirmed ACS from the developing countries of Africa, Latin America and Middle East region showed prevalence rates of STEMI and NSTEMI to be 46% and 54%, respectively, thereby attesting higher occurrence of NSTEMI compared to STEMI in these regions as well.

There, however, have been some conflicting reports

related to comparative prevalence of UA/NSTEMI and STEMI as seen in a recent Thai registry[20] which noted equivalent prevalence of composite UA/NSTEMI and STEMI; 33% patients with NSTEMI, 12% with UA and 55% with STEMI. In an evaluation of young Sub-Saharan population, higher prevalence of STEMI compared to NSTEMI was documented. These changing prevalence trends of different manifestations of ACS probably reflect rising prevalence of STEMI in the younger population as opposed to the elderly population in whom predominant ACS manifestation remains either NSTEMI or UA.[21,22]

ACS-RELATED MORTALITY RATES

As alluded to above, CAD is recognized today as a major global health problem. While CAD occurs in both developed and developing countries, CAD-related mortality rates in the developed countries are lower compared to those in the developing countries. Mortality rates secondary to CAD in the developed countries such as Australia, Japan, France, and the United States range between 100-200 per 100,000 population; in the developing countries these rates have been reported to be comparatively higher, 300 per 100,000 population in Brazil and China, 400-450 in South Africa, India and Saudi Arabia; and > 500 in Egypt.[23] Timely implementation of preventive and therapeutic interventions in the developed countries has facilitated decline in mortality rates due to CAD in younger and middle-aged population (< 60 years of age), although in patients > 60 years of age, CAD-related mortality rates continue to remain high. In contrast, in developing countries with limited health resources available, significantly high CAD-related deaths are recorded in the younger and middle-aged population (< 60 years of age), which may in part be due to high prevalence of premature CAD in these regions. This loss in younger workforce has a considerable adverse impact on economic productivity and incurs financial burden on health sector in these regions.[9,24]

Variability in short-term and long-term mortality rates of different manifestations of ACS has also been demonstrated. There is compelling evidence of higher short-term mortality in STEMI compared to NSTEMI (6%-7% vs 2-6%, respectively).[17,25] However, long-term mortality rates are higher with NSTEMI compared to STEMI (documented 1-year and 10-year mortality rates of NSTEMI vs STEMI have been 31% vs 21% and 62% vs 44%, respectively).[26,27] These higher long-term mortality rates of NSTEMI compared to STEMI are attributed to specific patient and clinical characteristics, with patients having NSTEMI more likely to be older, associated with a comorbid condition, such as prior history of angina, MI, heart failure, and diabetes, and less likely to receive life-saving reperfusion therapy.[27,28]

Significant gender-related differences in mortality rates of ACS have also been demonstrated. Women – especially those of younger age group – are at a higher risk of detrimental outcomes compared to men, despite the fact that STEMI is less common in young women compared to young men. An important cause of higher mortality rates in women compared to men is the frequent nature of atypical clinical presentation of CAD. CAD therefore frequently remains unidentified and undertreated in women. Additionally, higher prevalence of CV risk factors in women potentially accounts for higher mortality risk.[1,15,16,29] In accordance with these observations, recent large-scale studies which included men and women with ACS noted approximately two fold higher short-term and long-term mortality rates in women compared to their male counterparts.[30,31]

CLINICAL FEATURES OF ACS

Acute coronary syndrome is a medical emergency that warrants immediate medical attention, failing which there is a looming risk of overwhelming complications and even death. Myocardial ischemic symptoms, although not diagnostic, raise the suspicion for ACS. Typically, angina is a symptom of myocardial ischemia that may appear at rest or manifest during the situations of increased oxygen demand, such as physical exertion, emotional stress, and extreme cold weather. The characteristic presentation of ACS is severe substernal pain, discomfort or pressure sensation >20 minutes in duration that radiates to the left arm, shoulder or neck and is unrelieved by rest or nitroglycerin. Of special note, pain perception on the right side of the body does not exclude ischemic etiology. This diffuse pain that is poorly localized and unaffected by movement of the region or inspiration helps exclude other possible non-cardiac pathologies as the cause of acute chest pain; box 1 depicts the differential diagnoses of acute chest pain presentation. Apart from ischemic pain, these patient may have accompanying complaints of nausea, vomiting and fatigue as well. Canadian Cardiovascular Society Angina (CCSA) grades angina symptoms according to the level of physical activity from class I to IV, and it has been noted that the more severe ischemic symptoms (class III-IV) predict poor long-term outcomes; table 2. However, despite the central role of myocardial ischemia in CAD pathology,

Box 1 **Differential diagnosis of acute chest pain**

- Cardiovascular disorder (ACS)
- Gastrointestinal disorder
- Pulmonary disorder
- Neurological disorder
- Musculoskeletal disorder

Based on information from: Kumar A, Cannon CP. Acute Coronary Syndromes: Diagnosis and Management, Part I. *Mayo Clin Proc*. 2009;84(10):917-938.

not all patients with ACS experience ischemic pain and as many as 6-10% may present with painless ischemia. Moreover, their atypical clinical presentation e.g. dyspnea, nausea, vomiting, diaphoresis, palpitations, and unexplained fatigue in the absence of acute chest pain further perplexes the diagnostic utility of clinical symptoms. Elderly patients; female patients; patients with diabetes, chronic renal disease, dementia; patients with co-existing CV diseases; postoperative patients and critically-ill patients are more likely to experience atypical symptoms.[1,5,6,32-35]

Patients with UA may present with any of the following presentations:[1]

- Rest angina lasting >20 minutes
- New-onset severe angina (<2 months previously)
- Previous stable angina in a crescendo pattern of occurrence (increasing in intensity, duration, severity, or any combination of these factors).

It has been noted that ischemic symptoms of STEMI are more persistent and severe than NSTEMI. An event of STEMI is more likely to occur between 6 am and noon due to high cortisol and catecholamine levels and hypercoagulability status during this time period; these factors are causally associated with STEMI.[36] Nevertheless, diagnosing the spectrum of ACS exclusively on the basis of clinical presentation is a medical conundrum and therefore demands facilitation by other diagnostic modalities, including surface ECG and cardiac biomarkers.[1]

RISK FACTORS FOR ACS

The last few decades have witnessed a decline in ACS-related mortality. Improvement in treating modifiable risk factors has contributed immensely to this reduction and in lowering the global burden of ACS.[37] Traditionally, old age, male sex, hypertension, hypercholesterolemia, cigarette smoking, and diabetes mellitus have been associated with the increased risk of ACS. Moreover, changing epidemiologic trends and increasing prevalence of ACS in the younger population, especially in individuals of South Asian ethnicity, has surfaced the role of genetic and environmental factors and other novel risk factors, such as hyperhomocysteinemia and clotting and fibrinolytic factors, which may engender ACS risk.[8,37] Figure 2 provides an overview of differential risk factors for ACS.

Positive family history and genetic factors

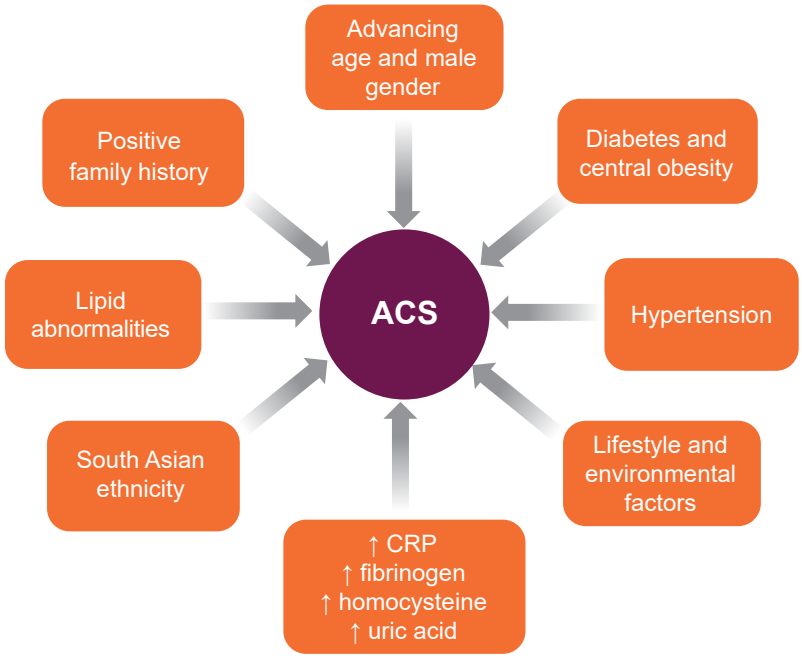
Since positive family history of a medical disorder is reflective of its genetic transmission, familial prevalence of premature CAD underpins its genetic basis. According to The American Journal of Cardiology, 72% of patients with premature CAD (men <55 years of age and women <65 years of age) have a positive family history.[38] Although genetic factors that increase an individual's propensity to develop ACS are far from being completely unveiled, till

Table 2 **Canadian Cardiovascular Society Angina (CCSA) classification of angina depending upon physical activity**

CCSA classification	
Class 1	Angina with strenuous/exertional activity. No limitation of ordinary activity (e.g. walking and climbing stairs)
Class II	Slight limitation of ordinary activity. Rapid walking or climbing stairs; or walking or climbing stairs post meal, or in windy chilly weather, or under emotional stress, or within few hours of awakening. Walking > 2 blocks on level ground or climbing > 1 floor of stairs at a normal pace and in normal conditions
Class III	Marked limitation of physical activity; walking 1-2 blocks on level ground or climbing one floor of stairs at a normal pace and in normal conditions
Class IV	Angina at rest and inability to carry out any physical activity with ease

Based on information from: Kaul P, Naylor CD, Armstrong PW, et al. Assessment of activity status and survival according to the Canadian Cardiovascular Society angina classification. *Can J Cardiol*. 2009;25(7):e225-e231.

Figure 2 **Risk factors for ACS**



Based on information from:

1. Sharma M, Ganguly NK. Premature coronary artery disease in Indians and its associated risk factors. *Vascular Health and Risk Management*. 2005;1(3):217–225.
2. Perk J, Backer GD, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *European Heart Journal*. 2012.

now 33 such variants have been identified.[39] Additionally, certain CV risk factors (hypertension, type 2 diabetes and dyslipidemia) evidence heritable transmission, thereby further asserting genetic predisposition of CAD and ACS.[40] A recent meta-analysis by Lieb and colleagues noted that individuals carrying most systolic and diastolic BP-related risk alleles had 70% and 59% higher risk of CAD, respectively.[41] Similarly, polymorphisms of apolipoprotein E (E4 allele in particular) which presages development of dyslipidemia has been noted as an independent risk predictor for atherosclerosis.[42] Some other genetic polymorphisms which have been linked with increased risk of CAD and ACS include ACE gene polymorphism and apolipoprotein A-I polymorphisms.[43,44] In nutshell, positive family history of CAD which explains its genetic predisposition is a major and independent risk factor for its development.[37]

Advancing age and male gender

Advancing age is an independent and probably the most significant risk predictor for ACS.[37] In addition, gender disparity in the risk of ACS has also been demonstrated. Males are more prone to develop ACS compared to their female counterparts, though this disparity diminishes as females reach their menopausal period. The greater propensity of males to develop ACS, particularly in the younger age group, can be highlighted by the fact that initial ACS presentation in them is about 8-10 years earlier than females.[45] Although risk of ACS progressively increases in postmenopausal females with advancing age (due to declining levels of protective estrogens), it is still lower than their age-matched male counterparts.[46] Greater risk of ACS in males than females is seen despite higher prevalence of certain CV risk factors including obesity, hypertension and diabetes in the latter, irrespective of their age.[45] Notwithstanding high prevalence of these risk factors, the strong estrogenic milieu in women imparts CV protection.[11,45] Moreover, smoking, which is a major risk factor for CAD, is less prevalent in females which may also be a significant contributor to their relative protection against development of CV diseases. Higher levels of high density lipoprotein cholesterol (HDL-C) in females also afford reduced risk of CAD in them.[11,47] Keeping these gender

differences in place, it has been suggested that men >45 years of age and women >55 years of age have increased risk of CAD.[48]

Diabetes and central obesity

The irrefutable association between diabetes and ACS is emphasized by the fact that diabetes increases the risk of ACS by 2 to 3 folds. The causal mechanisms that increase the risk of ACS in diabetes include insulin resistance, microvascular disease, inflammatory milieu, and prothrombotic state.[49] Besides, diabetes has also been linked with the adverse outcomes related to ACS. Hyperglycemia (irrespective of diabetic status) which induces proinflammatory and prothrombotic environment is a significant predictor of worse outcomes in patients with ACS. Moreover, concurrent presence of comorbid conditions with diabetes, such as hypertension and renal disease, presage poor prognosis for ACS. Additionally, insulin-resistance in diabetes promotes glycosylation of proteins and upregulates expression of platelet membrane proteins, such as the P2Y12 receptors, resulting in suboptimal response to platelet inhibitors, such as clopidogrel, in patients with ACS. On the whole, diabetes is not only the risk promoter for ACS development but a negative modulator of its prognosis as well.[50,51]

Obesity is yet another major risk factor for ACS. Moreover, abdominal obesity is an integral part of metabolic syndrome (MS) which is a multiplex risk factor for CV diseases.[48,52] Therefore, mechanistic association between obesity and MS, and ACS can be comprehended. To this effect, low-grade inflammation and oxidative stress have been identified as the common mediators of their pathogenesis. Additionally, low levels of adiponectin in obese individuals (adiponectin offers atheroprotective effects) further underpin the causal association between obesity and MS, and ACS.[53,54] Apart from obesity, the individual components of MS (hypertriglyceridemia, low HDL-C levels, hypertension, increased fasting glucose level) also increase the risk of ACS.[55]

Notwithstanding the mechanistic association between obesity and ACS, more contemporary studies have drawn attention to the hypothesis of "obesity paradox." According to this posit, adipocytes counterintuitively protect against the adverse outcomes of ACS by upscaling the release of adipokines (the antiinflammatory cytokine) and progenitor endothelial cells. Adipocytes have been found to reduce production of pentraxin 3 - a marker of vascular damage and inflammation- and exert some antiarrhythmic effects as well.[56,57] These so called "protective effects of obesity" might offer possible explanation for lower all-cause mortality and CAD-related mortality in elderly overweight and obese patients with CAD.[58]

Hypertension

Hypertension is an established independent risk factor for development and progression of coronary atherosclerosis. It is present in 31%-59% of patients with ACS. Since both conditions share common risk factors, including genetic predisposition, insulin resistance, vasoactive amines (angiotensin II) and sympathetic overactivity, a causal association between them can be deduced. Angiotensin II released during hypertension increases vascular oxidative stress, consequent to which there is endothelial dysfunction, inflammation, and reduced nitric oxide (NO) production. These negative effects foster development of coronary atherosclerosis and ACS. Angiotensin II also engenders a prothrombotic environment by up-regulating plasminogen activator inhibitor-1 (PAI-1) expression, which depletes the body's natural fibrinolytic mechanisms and promotes atherothrombosis. Moreover, it is possible that increased mechanical tension due to high blood pressure may rupture the atherosclerotic plaque and initiate the ACS pathology. Sympathetic hyperactivity in hypertensive patients is also a promoter of coronary atherosclerosis and thrombosis. Furthermore, it should also be remembered that, prolonged and unrelieved hypertension causes left ventricular hypertrophy which is an independent risk factor for AMI.[48,59,60]

Apart from these pathophysiologic mechanisms which portend the risk of ACS in hypertensive patients, emerging data suggests that hypertension has prognostic implications on ACS outcomes as well. In fact, high blood pressure has been confirmed as an independent risk factor for adverse outcomes associated with ACS. However, in elderly populations who often have other comorbid conditions as well (for example diabetes and renal disease), overzealous treatment of hypertension should be avoided so as to prevent hypotension-associated complications, such as renal hypoperfusion.[59,61]

Lipid abnormalities

Hyperlipidemia or dyslipidemia is a major risk factor for ACS. It not only plays a mechanistic role in the development of atherosclerosis and ACS, it is a predictor of its prognosis

as well. Since different components of cholesterol have differential effects on pathomechanics and progression of ACS, it would be highly yielding to measure individual components as opposed to only total cholesterol levels to determine atherogenic burden and the related ACS risk. To this effect, low-density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), and triglycerides (TG) are highly atherogenic whereas HDL-C offers atheroprotection.[10,62]

It has been determined that elevated total cholesterol and LDL-C are major risk factors for ACS in both men and women; LDL-C is an independent risk factor for ACS. However, elevated TG levels, while not independent risk predictors, have been found to confer greater risk of ACS in women compared to men. On the other hand, relatively higher levels of HDL-C (a negative independent risk predictor for CAD) in young adult women than men offer the possible explanation for lower risk of ACS in them. Their declining levels with hormonal transition in middle-aged women possibly account for increasing risk of ACS compared to their younger counterparts. In particular, dyslipidemic profile expressed as low HDL-C and elevated TG levels is associated with high ACS risk.[11,48]

Another component of lipid profile which is pivotal for assessing ACS risk is non-HDL-C levels; measured as total cholesterol exclusive of HDL-C. This highly atherogenic apolipoprotein B (apo B) containing lipoprotein in concert with elevated TG levels, has been appraised as a significant predictor of ACS severity.[10] However, there is a caveat in correlating the atherogenic cholesterol burden with simple measurement of LDL-C and non-HDL-C levels. The variable content of cholesterol in LDL-C particles makes their composition highly heterogeneous. Since they invariably contain one apo-B particle, assessing LDL-C number as opposed to levels would linearly correlate with their atherogenic burden. Overall, experts believe both number and size of LDL-C particles to be more robust predictors of ACS risk than their levels alone.[11,48]

Further proof of adverse impact of dyslipidemia on ACS can be derived from the fact that improvement in deranged lipid profile clinically correlates with reduction in ACS risk and improvement in its outcomes.[62,63]

Ethnicity

Epidemiological transition and ethnic differences are chief contributors to global variations in CAD prevalence. High prevalence of AMI in the South Asians compared to the Caucasians validates the role of heritable genetic and acquired factors in influencing CAD risk. South Asians, similar to the Caucasians, are exposed to traditional CV risk factors. In addition, they are known to have a "peculiar CV risk profile" which is characterized by insulin resistance, glucose intolerance, central obesity, and diabetes; this along with frequently noted increased levels of PAI-1, homocysteine, and lipoprotein(a) increases their CV risk profile. More frequent atypical clinical presentations in them frequently result in late presentation of CV diseases in the emergency department, which makes them all the more vulnerable to CAD-related mortality.[64,65]

The role of ethnicity in influencing CAD prevalence is further attested by lower risk of CAD in individuals of African-American descent compared to the Caucasians. This is notwithstanding the fact that blacks have higher incidence of hypertension and diabetes, which should translate into greater risk for CAD development and progression. The only possible explanation for this counterintuitive fact appears to be existence of certain protective genetic factors and healthy protective habits in individuals of African-American ethnicity.[64]

Ethnicity, by influencing the predominant pathogenic mechanism of ACS, also modulates its prevalence. It is posited that the predominant pathogenic mechanism of ACS in one ethnic group may not be its chief contributor in another ethnic group. A case in point appears to be a retrospective study done in Japanese patients with AMI in whom coronary spasm, rather than a thromboembolic episode, was noted to be the primary underlying pathogenic mechanism of ACS. In this study which compared Japanese and Italian patients with AMI, inducible vasospasm in both infarct and non-infarct coronary arteries was evident in a higher percentage of Japanese patients compared to their Italian counterparts (67% vs 23% and 39% vs 11%, respectively).[66]

Lifestyle and environmental factors

Lifestyle and environmental factors that greatly influence development of ACS include cigarette smoking, low level of physical activity, high fat diet and heavy alcohol consumption.[48] High prevalence of smoking in males compared to females has been traditionally paralleled with their increased risk of ACS.[45] It has been noted that long-term smoking produces systemic and vascular inflammation which is both initiator and promoter of coronary atherosclerosis. Additionally, by inducing sympathetic

overtone, oxidation of LDL-C particles, reduction in NO production and HDL-C levels, and fostering a prothrombotic environment, smoking stimulates pathogenesis of ACS.[45,48,67,68]

Accruing evidence also supports the preventive and therapeutic role of physical activity on ACS. Physical activity lowers the CV risk by 20-30%. Additionally, by increasing nitric oxide production and promoting atheroprotective lipid profiles (elevates HDL-C levels and reduces apo-B and TG levels), it offers therapeutic benefits to patients with ACS. Therefore, physical activity should not only be viewed as a preventive measure against ACS but as a therapeutic modality as well which will lower all cause and CV disease–related mortality in these patients.[69-72]

With respect to dietary modulations of ACS risk, a diet rich in trans-fatty acids increasingly predisposes to this pathology. Unsaturated fats (e.g. clarified ghee) raise LDL-C levels and lower HDL-C levels, producing a dyslipidemic state which accelerates coronary atherosclerosis process, culminating it in an ACS event. Accordingly, American Association of Clinical Endocrinologists (AACE), 2012 recommends reduction in total calorie consumption along with low-fat diet to lower the risk of CAD and ACS.[48,64]

A relatively complex association exists between alcohol consumption and risk of ACS. Alcohol abuse has well-documented adverse health effects, and conceivably abstinence would protect against health adversities. However, in contrast to this credence, it has been noted that alcohol abstinence may serve as a risk factor for ACS development whereas moderate alcohol consumption may lower this risk by inducing favorable lipid profile (increases HDL-C levels), lowering fibrinogen levels and improving glycemic control. These protective effects of moderate alcohol consumption, however, abate with excessive drinking which significantly elevates both systolic and diastolic blood pressure and therefore increases the risk of ACS. It is likely that moderate alcohol consumption would impart vasculoprotective effects, whereas both abstinence and heavy drinking would increase the risk of ACS.[48,73,74]

Cardiac risk biomarkers

In the last century, unprecedented advancements have been made in unraveling pathomechanics of CV diseases, in particular CAD and ACS. The role of inflammation and thrombosis in initiation and acceleration of ACS pathology has led to emergence of some novel risk factors including C-reactive protein (CRP), homocysteine, fibrinogen, uric acid and lipoprotein-associated phospholipase A2 (Lp-PLA2).[37]

While moderate elevation in CRP levels in patients without manifest CV disease predicts increased long-term risk for ACS, high CRP levels following MI episode foretell adverse CV outcomes.[75] The American Heart Association (AHA) recommends consideration of hs-CRP estimation in high-risk CV patients without any overt CV disease.[76] Another inflammatory marker that has attracted tremendous attention in the recent years as a risk predictor for ACS events is Lp-PLA2. Designated as an independent risk factor for plaque rupture and atherothrombotic events, the high cost of running this test serves as a deterrent to its employment as a first-line ACS risk biomarker.[37,77] Elevated serum uric acid level, another marker of inflammation, has also been linked with the presence and severity of ACS in both men and women.[78] Similarly, raised plasma fibrinogen levels correlate with the severity of CAD and may be used as second-line biomarker for ACS risk estimation.[37,79] Hyperhomocysteinemia, a thrombotic biomarker, has also been evaluated as an independent risk predictor for ACS and it has been found that every 5 micromol/L rise in homocysteine level translates into approximately 20% increased risk for ACS which is independent of traditional CV risk factors.[80]

PATHOPHYSIOLOGY OF ACS

Rupture of a coronary atherosclerotic plaque with subsequent formation of thrombus over it that occludes myocardial blood supply either partially or completely is the predominant pathophysiology involved with ACS development. Additionally, endothelial erosion of the atherosclerotic plaque and coronary vasospasm may also engender ACS development.[81,82] Although not a significant contributor to ACS pathology, coronary spasm of a normal artery or artery with stable plaque may engender its development.[81]

Formation of atherosclerotic plaque

Evidence of fatty streaks in the coronary arteries can be traced as early as during the second decade of life. While some lesions regress others follow a progressive course, ultimately culminating in plaque rupture with subsequent thrombus formation.[83]

The process of atherosclerosis invariably begins with endothelial injury. A normal healthy endothelium exerts vasoprotective effects and maintains vascular tone and prevents platelet adhesion, vascular smooth muscle

cell (VSMC) proliferation and vascular inflammation. Endothelial NO production is the key mediator of these protective effects – it mitigates vasoconstriction induced by endothelin and angiotensin II and maintains barrier and protective functions of endothelium.[84,85] However, dysfunctional endothelium with reduced NO production fails to provide these protective effects and allows adherence and transmigration of leukocytes (monocytes and T lymphocytes). The ingressed monocytes differentiate into macrophages which secrete matrix metalloproteinase (MMP) and various cytokines. Simultaneously, the increased permeability of injured endothelial cells allows leakage of LDL-C particles into subendothelial space where they get oxidized and engulfed by the modified macrophages. These macrophages, inundated with lipid assume foam shape and are known as foam cells. The T-lymphocytes which were ingressed alongside the monocytes elaborate a wide variety of chemoattractants and inflammatory cytokines (TNF-α and interleukins), and therefore incite further recruitment of leukocytes in a vicious pattern. The inflammatory milieu generated by transmigrated leukocytes portends alterations in VSMC phenotype, produces MMP and stimulates proliferation and migration of VSMC from tunica media into intimal layer. These phenotypically altered VSMCs in the intimal layer secrete extracellular matrix that forms a fibrous cap over the developing lesion. In the unabated presence of CV risk factors which cause persistent endothelial dysfunction and provide an inflammatory microenvironment, the atherosclerotic plaque continues to grow at its base.[84] A mature atherosclerotic plaque consists of a necrotic core of dead foam cells and extracellular lipid crystals, covered by a fibrous cap of modified VSMC and connective tissues.[86]

Plaque remodeling and mechanisms of coronary thrombosis

Matrix metalloproteinases secreted by macrophages and T-lymphocytes in the atherosclerotic lesion continually degrade the matrix component of the fibrous cap and make it vulnerable to rupture at the shoulder region where these proteolytic enzymes are abundant. Additionally, the cytokines secreted by the macrophages also negatively impact the plaque health by inhibiting VSMC proliferation, migration and fibrous matrix production, and causing senescence of VSMCs as well, making the plaque weak and vulnerable to rupture.[84] Therefore, inflammatory status of the atherosclerotic plaque critically determines its stability and susceptibility to rupture. Frequent intraplaque hemorrhage of microvessels, which had developed to provide nutrition to rapidly growing plaque, also portend to plaque rupture. Overall, an atheromatous plaque with the following characteristics may be classified as high risk plaque that is vulnerable to rupture: Large lipid core, abundant macrophages and T lymphocytes, few VSMCs, thin fibrous cap, and increased plaque neovascularity and intraplaque hemorrhage. Experts suggest that at this stage of increased plaque vulnerability, certain factors may trigger plaque rupture and initiate coronary thrombosis. Apropos to this, acute and diffuse coronary endothelial inflammation portends rupture of the vulnerable plaque and exposes the highly thrombogenic lipid core which results in formation of coronary thrombus. Besides, physical, emotional and environmental stressors may also precipitate plaque rupture. These triggers cause vasoconstriction at the site of vulnerable plaque and foster plaque rupture. Moreover, sympathetic overtone due to these triggers also promotes procoagulant and prothrombotic state that engenders thrombus formation over the ruptured plaque. Additionally sudden perturbations in the physical-chemical characteristics of the plaque which crystallize their cholesterol crystals and afford them needle shape may perforate the fibrous cap and initiate coronary thrombosis in the absence of enhanced inflammatory milieu.[1,82,84,87,88] Box 2 and 3 enumerate various factors that determine plaque stability and vulnerability to rupture, and various triggers of this rupture, respectively.

Box 2 **Factors that determine stability of atherosclerotic plaque and its susceptibility to rupture**

- Large lipid core
- Abundance of macrophages and T lymphocytes
- Scarcity of VSMCs
- Thin fibrous cap
- Intraplaque hemorrhage

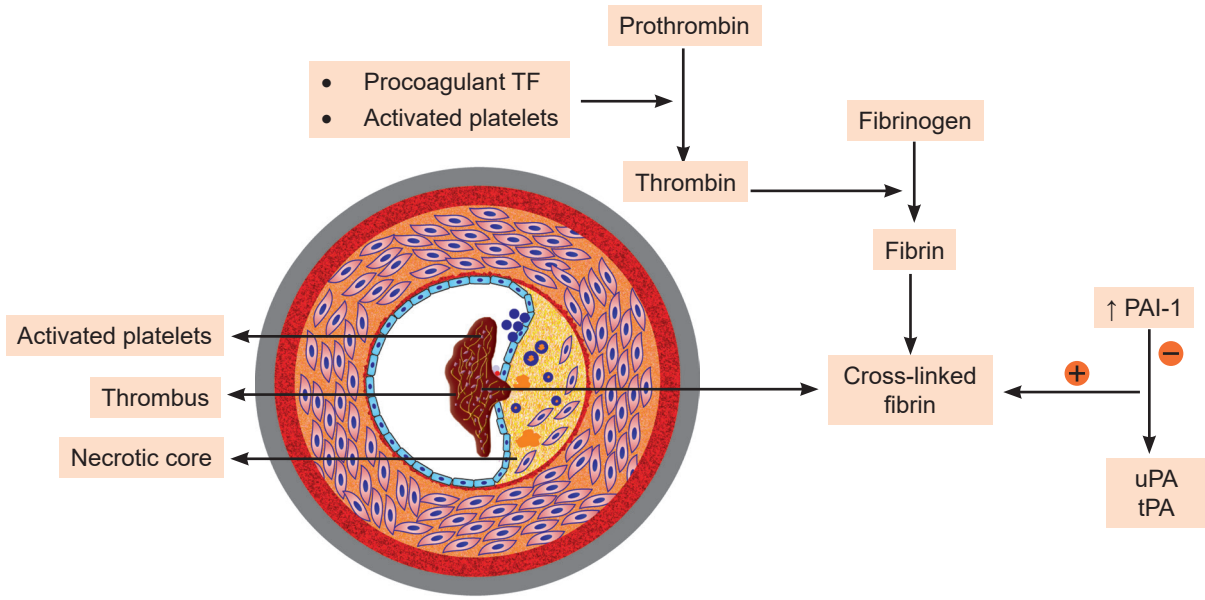
Based on information from: References 84,87

Box 3 **Triggers of plaque rupture and thrombus formation**

- Accentuated inflammatory response
- Physical stressors
- Emotional stressors
- ↑ cholesterol crystallization

Based on information from: References 82,88

Figure 3 **Pathophysiology of ACS**



TF = tissue factors; PAI-1 = plasminogen activator inhibitor 1; uPA = urokinase-type plasminogen activator; tPA = tissue-type plasminogen activator

Based on information from: Libby P, Theroux P. Pathophysiology of Coronary Artery Disease. *Circulation*. 2005;111:3481-3488.

Apart from plaque rupture, which is the major trigger for coronary thrombosis, endothelial erosion, albeit minor, of both fragile and stable advanced plaques also portends thrombus formation and ACS event. Its minor contribution to ACS pathology can be estimated from the fact that for every 4 cases of coronary thrombosis, plaque rupture accounts for 3 cases and endothelial erosion accounts for only 1 case. However, its increasing contribution to ACS pathology has been appreciated in young patients and women patients who often have stable plaque morphology which is not susceptible to rupture. Endothelial erosion not only exposes thrombogenic core, the protective effects afforded by the endothelial cells against platelet aggregation and procoagulant factors get blunted. Together these factors ensue formation of coronary thrombosis.[82]

Formation of coronary thrombus

Systemic and local inflammatory response not only regulates plaque stability and vulnerability to rupture, it is the prime causal mechanism for atherothrombosis as well. It has been noted that size of the thrombus formation is determined by size and thrombogenicity of the exposed core – both linearly correlated with inflammatory plaque burden – as well as local inflammatory response. The local inflammatory cells release cytokines and procoagulant tissue factors (TF) that initiate and perpetuate coronary thrombosis; the role of IL-6 in activation of coagulation cascade and TNF-α and IL-1 in regulation of anticoagulation pathways is well established. Additionally, systemic inflammation also activates the clotting cascade.[82,88]

Exposure of core collagen to the luminal blood activates the circulating platelets. Simultaneously, the procoagulant TFs produced by the macrophages and VSMCs activate the coagulation cascade and convert prothrombin into thrombin. The resultant thrombin promotes degradation of fibrinogen into fibrin and activates platelets. This activation and enhanced recruitment of platelets along with activation of coagulation cascade collectively yields a three-dimensional white-colored network consisting of platelets and fibrin, and is known as white arterial thrombus. Moreover, depletion of body's natural fibrinolytic mechanisms by TFs released by the inflammatory cells – PAI-1 being one such factor – further

potentiate clot formation.[60] Figure 3 comprehensively depicts pathogenesis of coronary atherosclerosis, plaque rupture and the ensuing thrombus formation that results in ACS event.

In contrast to the predominant "white clot" observed in majority of ACS patients, red clot may form in minority of the cases. Slow blood flow due to unrelieved obstruction by white clot facilitates deposition of red blood cells over it and gives it red color appearance and hence the name "red clot." It consists of red blood cells entangled within fibrin strands. Since red thrombus formation implies chronic obstruction and therefore long ischemic time, the risk of fatality is higher with it compared to the white thrombus.[82,89,90]

ACS AND SUDDEN CARDIAC DEATH

Sudden cardiac death (SCD) is an unexpected death due to cardiac causes in a person with or without pre-existing cardiac disease. As defined by the World Health Organization, it is an unexpected death within 1 hour of symptom onset if witnessed or within 24 hours of an individual being symptom free and observed alive, if unwitnessed; exclusion of non-cardiac causes of death is vital for this diagnosis.[91]

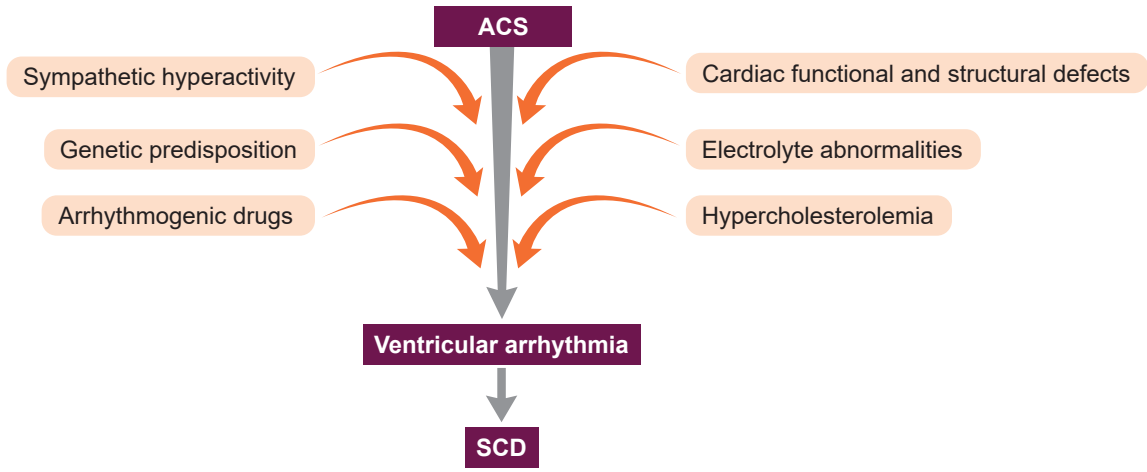
Sudden cardiac death is the predominant cause of death in individuals who are <65 years of age.[92] Coronary artery disease and ACS are undoubtedly its most common cause, accounting for 80% of these cases.[91] In fact, half of the patients with AMI present with SCD due to fatal ventricular arrhythmias as their initial presentation.[93]

Mechanisms of SCD in ACS

The mechanisms by which ACS culminates in catastrophic arrhythmias and SCD have been extensively investigated. The ischemic changes during acute phase of MI produce electrophysiological abnormalities in the myocardial tissues that precipitate ventricular arrhythmias.[91] Sympathetic excitation caused by left ventricular dysfunction in patients with AMI along with ischemia-induced dispersion of repolarization also facilitate development of fatal ventricular arrhythmias. Scars of previous MI may trigger development of re-entry circuits and lead to fatal ventricular arrhythmias. However, mechanical complications of MI, such as ventricular/papillary muscle rupture and pericardial tamponade, may cause SCD that is not due to ventricular arrhythmia but a direct consequence of hemodynamic derangements.[94]

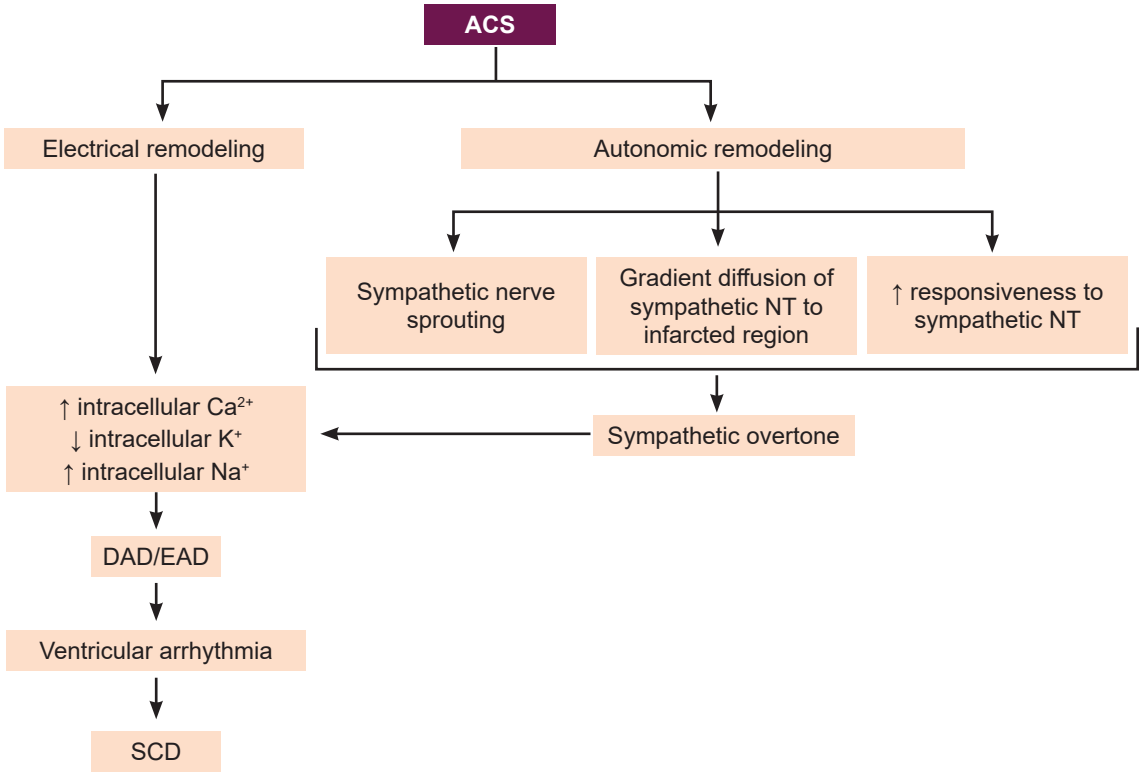
The most common cause of SCD after ACS is development of ventricular tachycardia and degeneration into ventricular fibrillation. However, not all patients of ACS experience these grave but unpredictable events. This inconsistency may be explained by varied presence of arrhythmogenic substrates in these patients –cardiac functional and structural defects, electrolyte abnormalities, sympathetic overtone, hypercholesterolemia, genetic predisposition, and arrhythmogenic drugs - which act as triggers for electrophysiological events that portend fatal arrhythmias; figure 4.[95]

Figure 4 **Arrhythmogenic substrates that portend ACS-related SCD**



Based on information from: Rubart M, Zipes DP. Mechanisms of sudden cardiac death. *J. Clin. Invest*. 2005;115:2305–2315.

Figure 5 **Mechanisms of SCD after ACS**



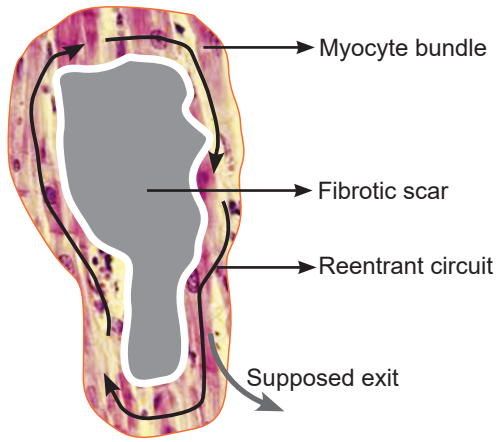
NT = neurotransmitter; DAD = delayed after depolarization; EAD = early after depolarization; SCD = sudden cardiac death

Based on information from: References 94-97

Acute myocardial infarction results in electrophysiological abnormalities due to electrical and autonomic remodeling in the infarcted area. Electrical remodeling induces potassium efflux (extracellular accumulation) and sodium influx, which facilitate intracellular calcium accumulation. These ionic alterations initiate arrhythmogenesis by generating both delayed after depolarization (DAD) and early after depolarization (EAD) that may precipitate into ventricular arrhythmia. Of note, the arrhythmic risk after reperfusion therapy can be similarly explained as it increases intracellular sodium and calcium levels which produce DAD and stunning of myocytes.[95]

Acute myocardial infarction also produces autonomic remodeling and sympathetic excitation. This process begins with sympathetic and parasympathetic nerve damage which follows myocardial infarction. While several mechanisms compensate for the lost sympathetic activity, the parasympathetic activity continues to remain suppressed. Denervation hypersensitivity – increase in regional responsiveness to the available sympathetic neurotransmitters – is one such compensatory mechanism for the lost sympathetic activity. Gradient diffusion of sympathetic neurotransmitters from the normal myocardium to the surrounding infarcted region also results in regional sympathetic hyperexcitation. Additionally, spatially heterogeneous sprouting of sympathetic nerves following their ischemic damage contributes to sympathetic excitation as well. Overall, sympathetic hyperexcitability secondary to these multiple mechanisms results in persistent refractoriness of the infarcted region in contrast to excitability of the surrounding myocardium. This favors initiation of tachyarrhythmias. It has also been noted that regional increases in sympathetic neurotransmitters cause arterial vasoconstriction which may further compromise myocardial blood supply and precipitate ischemia and further susceptibility to arrhythmogenesis. At the molecular level, sympathetic excitation of β adrenergic receptors alters the expression of L-type Ca^{2+} channels and K^{+} channels and leads

Figure 6 **Generation of reentrant ventricular fibrillation**



Based on information from: Stevenson WG. Ventricular scars and ventricular tachycardia. *Transactions Of The American Clinical And Climatological Association.* 2009;120:403-412.

to intracellular Ca^{2+} overload. These ionic alterations prolong action potential duration and increase regional susceptibility to EAD and/or DAD-triggered ventricular arrhythmias.[94-97]

Together, heterogeneous autonomic remodeling and electrical remodeling in the infarcted region act in tandem to create inhomogeneous excitability and refractoriness patterns that favor occurrence of fatal ventricular arrhythmias; figure 5.[94-97]

Apart from the acute phase of ACS that may culminate in SCD, old myocardial scars may trigger arrhythmogenic events by promoting reentry circuits. Ischemic scar is made of two components; dense fibrosis which is electrically unexcitable and surviving myocytes which inherently slowly conduct electrical excitatory waves and set the platform for reentry circuits. Since the fibrotic scar does not conduct electrical waves, the slow waves travel along its periphery, creating a circuit, such that by the time they reach their site of origin they get reactivated and the vicious pattern continues, yielding reentrant ventricular fibrillation. Figure 6 depicts the mechanisms of reentrant ventricular fibrillations.[98]

Risk factors for ACS-related SCD

Sudden cardiac death from CV diseases is a major clinical and public health problem. Therefore, preventive measures may be highly effective in bringing down its incidence. However, identifying patients at increased risk for SCD and offering them timely preventive therapy with implantable cardioverter defibrillator (ICD) is a challenge.[99] Experts suggest that in patients with CAD and ACS, factors that serve as arrhythmogenic substrates may be good predictors of the risk of SCD. Left ventricular ejection fraction is the gold-standard for risk stratification of SCD after ACS, and patients with ejection fraction in the range of 35-40% may be suitable candidates for ICD implantation. Similarly, prolonged corrected QT interval (QTc, ≥450 ms in men and ≥470 ms in women) and impaired creatinine clearance have also emerged as a strong risk predictors for SCD.[100,101] Other factors that may also be used as risk predictors of SCD include T-wave alternans, heart rate variability, and persistently elevated troponin levels.[94]

CONCLUSION

Acute coronary syndrome (ACS) is a life-threatening manifestation of CAD which incurs considerable morbidity and mortality worldwide. Rupture of coronary atherosclerotic plaque with subsequent formation of thrombus over it that occludes myocardial blood supply either partially or completely is its predominant pathophysiology. It is the leading cause of death in the developed nations whereas in the developing nations it is rapidly emerging as a significant contributor to overall mortality. Although generally considered a disease of advancing age, its increasing affliction of younger population (premature ACS) in developing nations accounts for its negative impact on productivity and economic growth of these regions. Diagnosing ACS solely on the basis of clinical presentation is a medical conundrum. Severe substernal pain, discomfort or pressure sensation >20 minutes in duration that radiates to the left arm, shoulder or neck and is unrelieved by rest or nitroglycerin is its characteristic presentation. Since myocardial necrosis is an irreversible process, timely identification and modification of risk factors that engender ACS development is the best preventive approach. These risk factors include positive family history, advancing age and male gender, diabetes and central obesity, hypertension, lipid abnormalities, South Asian ethnicity, lifestyle and environmental factors, and elevated levels of CRP, fibrinogen, uric acid and homocysteine. Sudden cardiac death is a fatal complication of ACS. Ischemic changes during acute phase of MI produce electrophysiological abnormalities in the myocardial tissues that precipitate fatal ventricular arrhythmias.

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