Review Article

Young hearts at risk: Unveiling novel factors in myocardial infarction susceptibility and prevention

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Abstract

The increasing incidence of acute myocardial infarction (AMI) among the young population represents a significant and emerging health concern, contributing substantially to both mortality and morbidity. Unlike myocardial infarctions occurring in older individuals, traditional risk factors such as diabetes and hypertension exhibit a weaker association in the younger demographic. Consequently, there is a pressing need for a deeper understanding of novel risk factors that contribute to AMI in young patients. In this review, we explore distinct risk factor profiles associated with young-onset AMI in comparison to older patients. Special attention is given to novel risk factors, examining their susceptibility factors and exploring preventive measures. The comprehensive risk profile of extremely young South Asians who develop early coronary arterial disease is not yet fully understood. There are many novel evolving risk factors associated with young AMI which need intervention to reduce morbidity and mortality. It has been seen that established inflammatory markers like lipoprotein (a), dyslipidaemia, long COVID, and new emerging risk factors like air pollution (micro- and nanoplastics), periodontitis, acute stress, energy drinks, misuse of recreational drugs may increase risk and influence treatment, and outcomes of AMI in this young population. Screening of emerging novel risk markers and their optimization is important in preventing young patients with AMI. The role of conventional risk factors should not be overlooked and should be treated aggressively. Sex and geographic-specific base approaches are required to reduce risk factors and prevent AMI in young. More prospective studies are needed to evaluate the increasing incidence of young AMI and its associated novel risk factors.

Keywords: Acute myocardial infarction in young, conventional risk factors, novel risk markers

Introduction

The rise in acute myocardial infarction (AMI) in young is a major emerging health problem and an important cause of mortality and morbidity. This issue is also important because it puts at risk later, more productive years of life.[1] It was probably due to the underappreciation of important differences that exist between "young" myocardial infarction (MI) patients versus older patients. With emerging evidence, it is now clear that there is geographical, pathophysiological, clinical, and prognostic differences between both cohort groups.[2] There are traditional differences in the risk factor profiles of young MI compared to older patients. In contrast to MI in older age, conventional risk factors like diabetes, and hypertension are less associated in young, and they require more insight into emerging novel risk factors which trigger AMI in young patients. Recognizing and avoiding these risk factors can prevent MI in these people since they are frequently avoidable.[3]

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Here we review different risk factor profiles associated with young AMI compared to older patients with special emphasis on novel risk factors and their susceptibility and preventive aspects.

Geographic variation can be seen in the epidemiology of young coronary artery disease (CAD), with reported prevalence rates ranging from 4.4 to 33% in various studies.[2] Patients from South Asia seem to be more likely to develop CAD and AMI at a younger age.

There is not yet a standard age at which someone is considered "young" in the context of an AMI. For men, the age ranges from 40 to 55 years and for women, from 55 to 65 years,[3] and the majority of studies recommend a cut-off age of 45 years for both males and females.[4] The pathophysiology of "young" patients with AMI is unclear. The proportion of "young" MI patients who arrive with ST-elevation MI is rising, while non-ST elevation MI still accounts for the majority of these individuals. In "young" MI patients, coronary angiography typically indicates less severe disease, which has therapeutic implications. Although "young" MI patients have a better short-term prognosis than older patients, recent research raises questions about long-term results, particularly in individuals with decreased left ventricular systolic function.[5]

Risk profile: Geographical and gender differences

The full risk profile of extremely young South Asians developing early CAD is still unclear. According to a study of 877 CAD patients in India, one-third of them were diagnosed at age 45.[5] Ninety percent of this young population had MIs associated with low consumption of fibres and an increase in smoking, diabetes, hypertension, dyslipidaemia, alcohol, sedentary lifestyle, psychosocial factors, and abdominal obesity.[6]

In a recent study, it was found that the relationship between young individuals and risk variables for AMI varies significantly by gender. Women show a higher incidence of hypertension, diabetes, smoking, depression, and a history of congestive heart failure, while physical inactivity and high cholesterol are more significantly related to men than women According to recent data from the VIRGO and GENESIS-Praxy study, young women who present with AMI may acquire coronary disease by different less-known processes, often recover more slowly, and are more likely to experience morbidity, death, and readmission than men of a comparable age.[7]

Conventional cardiovascular (CV) risk factors associated with young AMI

Traditional risk factors for AMI, such as smoking, high cholesterol, high blood pressure, family history of atherosclerosis, obesity, and diabetes mellitus (DM), are becoming more common in younger people. Traditional risk factor profile is different for old and young coronary patients. Younger AMI patients have more chances of smoking, dyslipidaemia, and a family history of early CAD.[8]

Smoking is the biggest and most common risk factor for young AMI. In a study by Singh *et al.*,[9] smoking (37.6%) was shown to be the most common risk factor, followed by DM (16.8%) and hypertension (16%) for young STEMI subjects (under 45 years old). Smoking is also known to be a very powerful indicator of future acute coronary syndrome (ACS) in young people. Hypertension is the most important cause of recurrent CV insults in the younger group. Hypertension is also associated with multivessel CAD with a dismal prognosis.[8] A few studies revealed that type 2 DM had the highest crude hazard ratio) of 2.36 (95% CI, 1.07–5.28, $P = 0.036$) among established risk factors.[10] Obesity in the young as a risk factor has increased by 98% (greatest increase in frequency) from 2005 to 2015 according to Yandrapalli *et al.*[11] Obesity, hyperlipidaemia, smoking, and family history of CAD were linked to a greater risk of developing AMI in young patients in a population-based analysis across the country. Lower good cholesterol (HDL-C) levels in young had a higher risk of MI, more severe coronary artery lesions, and a worse prognosis.[11] Numerous investigations have revealed that a family history of CAD is mostly associated with young AMIs.[12] Loneliness has the same mortality impact as heavy smoking.[13] Early healthcare intervention in young populations with a family history of CAD is required to reduce these established traditional risk factors and reduce overall ACS morbidity and mortality.

Novel cardiovascular risk factors in young AMI

There are many new emerging novel risk factors associated with young AMI which need intervention to reduce morbidity and mortality. A few of them are discussed here.

1. Lipoprotein (a), or Lp (a): Lp (a) is the most discussed novel risk factor which increases inflammation, thrombosis, and fibrin formation in blood vessels, although its involvement in atherosclerosis is not entirely known. An elevated level of Lp (a) is associated with clinical presentation as AMI rather than stable angina. It is more associated with the formation of complicated atherosclerotic plaque.[5] Asians and Latin Americans having AMI had high (>50 mg/dL) Lp (a) levels. Regardless of race, women have Lp (a) levels that are 5–10% higher than men. The Lipoprotein (a) level (>180 mg/dL) patient has the same atherosclerotic cardiovascular disease (ASCVD) risk as that of untreated heterozygous familial hypercholesterolemia patients. Thus, according to European Society of Cardiology recommendations, adults should have their Lp (a) concentrations evaluated at least once.[14] For patients with verified or suspected familial hypercholesterolaemia, ischemic stroke, or young ASCVD with no other risk factors, Lp (a) estimation is recommended even in less than 20 years of age. Elevated Lp (a) levels have been linked to an increased risk of developing CAD or ischaemic stroke in younger people. There are currently no approved medications for reducing Lp (a) concentrations. Lipoprotein aphaeresis may be an option for individuals with very high Lp (a).

   Several studies that focus on Lp (a) lowering treatments are currently being conducted. Inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9) enzyme have been demonstrated to reduce Lp (a) and LDL-C. ODYSSEY

Outcomes trial showed that PCSK9 inhibitor reduces Lp (a) and major adverse cardiovascular events (MACE) independently in patients with ACS.[15] Antisense oligonucleotides [AKCEA-APO(a)-LRx] are one of these prospective treatments because they prevent the synthesis of apo (a) mRNA in the liver.[16]

The new drug olpasiran decreases Lp (a) by interacting with RNA that blocks hepatocyte Lp (a) assembly. In one study, olpasiran led to a considerable and durable decrease in the Lp (a) in patients with established atherosclerotic CV disease and an Lp (a) concentration of more than 150 nmol per litre.[17]

Therefore, it is believed that standardizing measurement of Lp (a) and developing new Lp (a)-lowering agents offer considerable promise in future for improving young AMI outcomes.

2. Periodontitis: A recent study revealed periodontitis (inflammation of tooth and surrounding tissue) as an emerging novel risk factor accounting for a 9% increased risk of ACVD.[18] P. gingival bacteria are associated with damage to periodontal tissue either directly or by inflammatory mediator-like cytokines. Therefore, the role of treating periodontitis to decrease the risk of ACVD should be considered. Proper oral care to prevent periodontitis can lower the risk of this cardiometabolic disease. Counselling on quitting smoking, a balanced diet, and avoiding chewable tobacco products can improve not only dental caries or periodontitis but also overall health.[18]
3. Long COVID: 2019 coronavirus disease (COVID-19) infection and its sequel cause an inflammatory state that is accompanied by an increased immune response and atherosclerotic plaque instability, which can result in acute coronary syndromes. Additionally, a substantial incidence of coagulation disorders and coronary thrombosis is linked to SARS-CoV2 infection.[19] The majority of COVID-19 patients with increased cardiac enzymes do not have any clinical signs of a cardiac pathology or an underlying epicardial coronary artery blockage (essentially ruling out type 1 MI). Myocardial injury caused by COVID-19 is caused by a combination of direct viral invasion and indirect (hypercoagulability and immune-mediated) cellular injuries.[20] There is still no direct evidence between myocarditis and cardiotoxicity following COVID-19 vaccination. Therefore, patients with substantial acute myocardial injury associated with COVID-19 necessitate routine follow-up with clinical examination, arrhythmia monitoring, serial imaging tests, and prompt supportive treatment.
4. Micro- and Nanoplastics (MNPs) and other environmental factors: Air pollution is recognized as a major global public health risk factor. The Air Pollution and Health Training Toolkit designed by the World Health Organization is for health workers, in both the clinical and public health fields, to understand the health risks of air pollution and identify risk reduction measures.[21] Air pollutants like MNPs are ubiquitous in the environment, making exposure to them inevitable. Animal and human cell models showed that MNPs act as direct cardiotoxic agents leading to impairment of cardiac function and myocardial fibrosis. MNPs caused vascular endothelial injury, haemolysis, thrombosis, and blood coagulation on (micro) vascular sites. The primary pathways were interactions between MNPs and other cellular components, oxidative stress, inflammation, apoptosis, and inflammatory response. Furthermore, to enable more accurate health risk assessment, future paths of CV research on MNPs are advised.[22] Recently, it has been shown that sodium-glucose co-transporter 2 (SGLT2) is associated with premature endothelial dysfunction. New SGLT2 inhibitors class drugs may target this potential target to help in preventing and/or treating CV disorders caused by environmental pollutants.[23]
5. Obstructive sleep apnoea (OSA)
   Prior research has shown that severe OSA goes undetected in up to 42% of STEMI-admitted patients.[24] It is believed to be due to reactive oxygen species-induced oxidative stress and endothelial and coronary microvascular injury. According to one study, OSA is a novel risk factor independent of classic atherosclerotic risk factors, and according to another, OSA is a reliable indicator of the likelihood of having another MI in the future. Patients with OSA who tolerated continuous positive airway pressure had a decreased risk of recurrent MI and revascularization.[25]
6. Systemic lupus erythematosus (SLE)
   SLE is a diverse autoimmune illness and is associated with endothelial and systemic inflammation in numerous organs including coronary arteries with the acceleration of atherosclerosis. Up to 16% of SLE patients may experience MI, one of the common comorbidities associated with the disease. Several studies have revealed that SLE patients had a greater adjusted risk of MI than non-SLE controls. SLE patients were nearly 50 times more likely to experience an MI in the 35- to 44-year age range in the Framingham Offspring compared to healthy controls.[26]
7. Non-Mediterranean Diet: A high intake of vegetables and legumes was negatively correlated with the risk of nonfatal AMI. With the increasing non-Mediterranean diet in our society, there is a low consumption of vegetables, legumes, fruit and nuts, cereals, fish, and seafood and dairy products and high consumption of saturated lipids. This led to an increase in nonfatal AMI in the Southern Asian and European populations.
8. Energy Drinks (EDs) and Myocardial Ischaemia: MI has been linked to excessive energy drink use in a few case reports. This association can be supported by a few reasonable explanations. ED leads to an increase in inotropic effect with an increase in cardiac output, heart rate, and systolic blood pressure. It also leads to endothelial dysfunction with platelet aggregation and hyperglycaemia. Even though a direct link between excessive ED intake and myocardial ischemia cannot be demonstrated at present, worries about the CV risk of this behaviour seem to be warranted.[27]
9. Hypertriglyceridaemia: More than 20% of people in Europe and South Asia have hypertriglyceridaemia, a significant novel risk factor for developing ASCVD before age 65.

Hypertriglyceridaemia has been shown to increase vascular inflammation and lead to subclinical atherosclerosis even in middle-aged people who appear healthy and have no history of CV risk. The United States Food and Drug Administration (FDA) approved high dose icosapent ethyl (IPE) (4g/d), to treat severe hypertriglyceridemia after a landmark trial Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial. Later, the FDA expanded the drug's approved uses to include lowering the risk of cardiovascular events in adults taking statins. In 2021, the European Medicine Agency found 12.5% to 23.3% benefit from IPE treatment in high-risk populations (known CV illness, or diabetes and at least one other CV risk factor) with high triglyceride levels [>150 mg/dL]). These patients included those with young AMI, CAD, and those undergoing cardiac rehabilitation.[28]

10. Misuse of androgenic–anabolic steroids (AAS) and recreational drugs (RDs): Teenagers, bodybuilders, and sportsmen are particularly fond of using AAS these days. Although it is often believed that MI is an old-age illness, young patients with MI who have no risk factors call attention to the potential role of substances like cocaine, AAS usage, and amphetamine. When a young athlete experiences AMI, doctors should always take the likelihood of AAS misuse into account. Through the acceleration of coronary atherosclerosis, AASs can increase the risk of AMI. Additionally, likely, thrombosis in AAS users who do not have underlying atherosclerosis or vasospasm will result in AMI. AAS users may experience complications following AMI more frequently. Nearly 25% of all young ACS patients who had been tested for drug use had RD use, compared to nonusers. This use was associated with worse left ventricular performance and a larger MI. Additionally, RD users were more likely to smoke and were younger than nonusers. Recently, a study by Tersalvi *et al.*[29] has established a link between ACS and alcohol consumption. This study showed 40% higher rate of in-hospital mortality in heavy drinkers (>2 drinks/day) than light drinkers. One study by Kajanoja *et al.* showed earlier occurrence (about 8.7 years) of ACS in patients with a history of alcohol consumption than their nonalcoholic counterparts.[30]
11. Acute stress disorder (ASD): In patients with AMI, higher levels of ASD symptoms brought on by MI are independently associated with a higher inflammatory response. The results point to a connection between ASD symptoms brought on by MI and an intensified acute phase response, which may affect the prognosis of cardiovascular illness.[31]
12. Physical inactivity: The increasing influence of social media and poor sedentary life has led to a 23 and 17% increase in cardiovascular mortality and morbidity, respectively, to those who get the recommended per week 150 min of moderate physical activity. Sudden AMI has been linked to a family history of early CAD, DM, and physical inactivity.[32]

Discussion and Implications: Previously, there was an underestimation of the importance of CAD in young patients, but with new studies, it is clear that it has different pathophysiological and clinical features and has an important impact on the patient's psychology, socioeconomic, and professional burden, family, as well as long-term morbidity and mortality. It is crucial to examine important risk factors that affect the increasing incidence of AMI in the South Asian young population including India. Conventional risk factors in young AMI patients are less appreciated and differ from old patients. Compared with older patients, patients <45 years were more likely to be male, current smokers, obese, and have a family history of premature AMI, and their low-density lipoprotein-cholesterol levels were higher. A diet rich in refined carbohydrates, sodium, and saturated lipids and a sedentary lifestyle may lead to an increase in hypertension, dyslipidaemia and abdominal obesity in these populations. New novel risk factors are emerging that correlate well in explaining the pathophysiology of young AMI particularly where conventional risk factors are absent. Examining newly discovered cardiovascular risk factors according to particular geographical, gender, and ethnic groups is also crucial. It has been seen that novel markers like air pollution and acute stress, OSA, misuse of RDs as well as inflammatory markers like lipoprotein (a), periodontitis, and long COVID may increase risk, treatment, and outcomes of AMI in this young population. Women need extra care as they have aggressive diseases and poor prognoses and risk factors like hypertension, diabetes, smoking, and depression should be treated aggressively. Males should be encouraged to have a more active smoking-free lifestyle.

Recommendations and Future Research

The role of conventional risk factors should not be overlooked and should be treated aggressively. It is important to provide an integrated approach to screen, treat, and prevent conventional and novel cardiovascular risk factors.

In South Asian regions, public health policies to promote good cardiovascular health (CVH) by fruit, fibre-rich, whole grain diet, less sugar consumption and aggressive control of diabetes, hypertension, and dyslipidaemia can be game changers in decreasing the incidence of Young AMI. Regular updating knowledge about emerging novel risk factors should be encouraged through more prospective studies. Social media awareness about good CVH is also crucial.

Conclusion

Screening of emerging novel markers and their optimization is important in preventing young patients with AMI particularly where conventional risk factors are absent. The role of conventional risk factors should not be overlooked and should be treated aggressively. Sex and geographic-specific base approaches are required to reduce risk factors and prevent AMI in young women. Expanding national health efforts is also necessary to raise awareness for good CVH. More prospective studies are needed to evaluate the increasing incidence of these patients and its associated novel risk markers.

List of abbreviation

AAS Androgenic–anabolic steroids
ACS Acute coronary syndrome,
ASCVD Atherosclerotic cardiovascular disease,
CPAP Continuous positive airway pressure
Lp(a) Lipoprotein (a)
PCSK9 Proprotein convertase subtilisin/kexin type 9
MACE Major adverse cardiovascular events
MNPs Micro- and nanoplastics
SGLT2 Sodium-glucose co-transporter 2.

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Conflicts of interest

There are no conflicts of interest.

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