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Review Article

Young-Onset Coronary Artery Disease: Clinical Insights, Epidemiology, And Evolving Management Strategies

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Abstract:

Despite remarkable advancements in cardiovascular medicine, coronary heart disease (CHD) continues to exert a devastating global impact. Atherosclerotic Coronary Artery Disease (ACAD) often begins silently at a young age and progresses unnoticed until manifesting as acute events- myocardial infarction (MI) or sudden cardiac death (SCD). Traditional ischemia-centric approaches to CHD diagnosis and management intervene too late. Therefore, a paradigm shift is urgently needed- reframing CHD as ACAD, a lifelong, progressive condition. SCD remains a major concern in this population. Early identification through advanced imaging modalities (invasive and non-invasive) and novel biomarkers is key to implementing timely, personalized interventions. This review emphasizes the need for global health systems to adopt prevention-focused, equity-driven strategies and calls for increased research investment in early-stage atherosclerosis, especially in diverse and underserved populations. We explore the epidemiology, pathophysiology, risk factors diagnostic advancements, and preventive treatments and management strategies aimed at reducing CHD burden among young adults.

Key words: coronary artery disease; myocardial infarction; acute coronary syndrome; heart failure

Introduction:

Cardiovascular disease (CVD) in young adults is an emerging public health concern, comprising both congenital and acquired conditions. The incidence has risen globally, particularly in Asian populations. Coronary artery disease (CAD), a major subset of CVD, now contributes significantly to morbidity and economic burden in younger individuals, often presenting with severe outcomes [1]. Histological evidence shows subclinical atheromatous plaques developing early in life, indicating that atherosclerosis begins much earlier than previously thought [2].

In 2022, there were an estimated 315 million global CAD cases, with a prevalence of 3,605 (2,892–4,454) per 100,000. Among young individuals, CAD accounts for 1-16% of cases, with acute coronary syndrome (ACS) being the predominant presentation [3]. Urbanization influences CAD rates, with urban prevalence ranging from 6.5% to 13.2%, versus 1.6% to 7.4% in rural areas. Non-atherosclerotic causes, including autoimmune and connective tissue disorders, account for nearly 20% of cases.

Modifiable risk factors such as smoking, hypertension, dyslipidemia, and obesity, alongside genetic predisposition, play central roles [4]. Advances in imaging- coronary computed tomography angiography (CCTA), cardiovascular magnetic resonance, single-photon emission computed tomography— now allow early detection of subclinical CAD. This review discusses epidemiology, risk factors, and evolving diagnostic tools in young-onset CAD to support proactive, personalized care.

Key points:

- Current focus on identification and treatment of CAD based on acute events like myocardial infarction (MI) and ischemia is flawed as it in the disease progression it intervenes too late, limiting effectiveness of therapeutic strategy.
- Atherosclerotic coronary artery disease (ACAD) should be considered as a continuous lifelong disease starting early and

progressing silently, often diagnosed until MI is induced by late-stage complications like plaque erosion or plaque rupture.

- Clinical significance should be provided to proactive strategies of early prevention, management and diagnosis of atherosclerosis across all phases of disease in comparison to reactive management of clinical events of ACAD.
- Mortality rate of 82% due to ACAD could be reduced by targeted screening for early signs of atherosclerosis combined with aggressive strategies for prevention of modifiable risk factors (smoking, hypertension, cholesterol, diabetes, poor diet).
- Considering the high mortality rate of ACAD due to delayed diagnosis, inappropriate treatment access, and limiting prevention in low- and middle-income countries (LMIC), healthcare system should be reformed globally.
- Instead of focusing only on advanced-stage treatment, healthcare delivery must be evolved to integrate risk assessment, screening and lifestyle interventions at primary care and community levels.
- To reduce ACAD global burden, specifically for early-stage disease, LMIC specific challenges, current cardiovascular research funding is insufficient.
- With the aim to prevent reverse or eliminate the progression of atherosclerosis early in its course, investment is needed in designing the new drugs, advances imaging modalities or vaccines [5].
- Effective and adaptable prevention strategies, research, treatment models should be implemented across various cultural, economic and healthcare settings- moving beyond high-income country data dominance.
- Multi-directional efforts involving healthcare societies, government researchers, and international societies must be implemented to achieve reversal, stabilization, and eventual elimination of ACAD as a major reason behind global mortality.

Epidemiology Of Coronary Heart Disease (Chd)

Defining "young" patients varies across studies, typically ranging from 35 to 55 years. For this review, young adults are considered those under 40 years of age [6]. Although CAD is more prevalent in individuals over 40, approximately 3% of cases occur in patients younger than 40. This may be an underestimate, as asymptomatic young adults rarely undergo diagnostic evaluation.

CVDs have become leading causes of global mortality [7] and disability-adjusted life years (DALYs), accounting for 7 million deaths and 129 million DALYs annually in LMIC. In 2015, CAD contributed to 164 million DALYs and 8.9 million deaths worldwide [8]. Regions like Latin America and the Middle East have seen sharp increases in cardiac events, primarily due to lifestyle-related risk factors like smoking and obesity.

In India, CVD often manifests a decade earlier than in Western populations, affecting individuals during their most productive years. Notably, 52% of CVD deaths in Indians occur before age 70, compared to 23% in Western countries [9]. This disparity is attributed to both social and biological determinants.

South Asia—especially India, Pakistan, Bangladesh, Sri Lanka, and Nepal—bears a disproportionate CVD burden. Even in the absence of classic risk factors, South Asian migrants experience higher CHD mortality at younger ages.

Meanwhile, high-income nations have witnessed a decline in CVD mortality due to improved acute care and preventive strategies. Major contributors to early CAD include smoking, dyslipidemia, obesity, dysglycemia, and family history. Early identification and intervention are critical to reducing the burden in young adults.

Pathogenesis And Risk Factors of Cad in Young Adults

Although traditionally viewed as a disease of older adults, CAD is increasingly seen in younger populations, with significant clinical and socioeconomic implications. ACAD, the primary mechanism underlying CAD, begins early in life and progresses silently over decades [10]. This slow progression, paired with the rising prevalence of risk factors like obesity, smoking, diabetes, and dyslipidemia, highlights the urgent need to understand early atherogenesis.

1. Pathogenesis of Early CAD: From Endothelial Dysfunction to Plaque Rupture

The process starts with endothelial dysfunction, impairing vasodilation and promoting leukocyte migration into the sub-endothelial space. Monocytes differentiate into macrophages and engulf oxidized low-density lipoprotein (LDL), forming foam cells— early markers of fatty streaks. Persistent risk factor exposure leads to fibrous plaque development with a necrotic lipid core and fibromuscular cap. Inflammatory cytokines and proteolytic enzymes destabilize plaques, predisposing them to rupture. Plaque rupture or erosion exposes thrombogenic material, triggering thrombus formation and acute coronary events— often the first presentation of CAD in young adults [11].

2. Histopathological Evidence of Early Atherosclerosis

Autopsy and electron microscopy studies in young individuals show fatty streaks, foam cells, extracellular lipid, and early fibrous caps in coronary arteries [12]. These features closely resemble early-stage plaques in symptomatic adults and are more common in individuals with modifiable risk factors. Such findings stress the need for early risk assessment and preventive interventions to halt disease progression before clinical onset.

Mechanisms of Acad

• Development of ACAD occur through multiple steps:

1. Endothelial wall dysfunctioning.
2. Formation of fatty streaks with foam cells.
3. Proliferation of vascular smooth muscle cell.
4. Inflammation and necrosis within plaque core.
5. Plaque growth, thrombus formation, rupture/erosion and vessel obstruction.

• Expression of adhesion molecules, increased permeability and impaired vasodilation attract leukocytes and initiate formation of plaque [13].

• Inflammation, recruitment of macrophages and development of foam cells is triggered by the retention of ApoB-containing lipoproteins (LDL, VLDL) in the vessel wall [14].

• Oxidized LDL forming foam cells are engulfed by macrophages → cell death → necrotic debris → amplification of inflammation within plaques.

• Extracellular matrix (collagen, proteoglycans), is produced by migration of vascular smooth muscle cells which further produce the fibrous cap over the lipid-rich necrotic core.

• Various factors such as huge concentration of inflammatory cells (specifically at plaque region), large lipid core potentiate the risk of thrombus and plaque rupture [15].

• Positive remodeling (vessel expansion) can preserve lumen despite plaque growth, delaying identification but modulating risk.

• Traditional risk factors: hypertension, smoking, obesity, dyslipidemia.

• Emerging risk factors: Pregnancy hypertensive disorders, air pollution, sleep problems, changes in gut microbiome, social determinants, stress.

• Rupturing of plaque can occur irrespective of severity; even acute event may be triggered by mild lesions; symptoms do not always associate with disease severity.

• Clinical focus must be provided to early assessment of lipid deposition, inflammation and endothelial-wall dysfunctioning instead of treatment of

late-stage ischemia-enabling regression, prevention and potential treatment of ACAD in early stage.

Risk Factors Of ACAD

Atherosclerosis begins early, even in childhood, highlighting the need for timely prevention. ACAD arises from metabolic (hypertension, diabetes), behavioral (smoking, diet), genetic (family history), and environmental (pollution, stress) factors. Novel risks include microbiome imbalance, sleep disorders, and hypertensive pregnancy complications. Age-related cellular senescence increases vulnerability [16].

By 2070, ≥65-year-olds will outnumber children globally, emphasizing preventive needs in aging societies [16]. Although ACAD manifests later in females, risk rises post-menopause due to estrogen decline; testosterone extremes raise risk in males [17,18]. Female-specific factors include gestational diabetes, PCOS, and pregnancy hypertension [17].

Family history, including polygenic and monogenic patterns, raises risk. Ethnic and regional genetic variations necessitate inclusive risk tools [19]. Rising hypertension rates in youth (e.g., 32% in Zimbabwe, age 18–24) reflect urgent needs in LMICs. Major atherosclerotic and non-atherosclerotic risk factors responsible for CAD in young adults are summarized in table 1.

Atherosclerotic Risk Factors	Non-Atherosclerotic Risk Factors
Family history of premature CHD.	Congenital coronary artery anomalies.
Dyslipidemia (elevated LDL, reduced HDL, hypertriglyceridemia).	Myocardial bridging.
Obesity and central adiposity.	Connective tissue disorders (e.g., Marfan syndrome, Takayasu's arteritis, giant cell arteritis).
Hypertension.	SCAD, especially in pregnancy.
Type-2 diabetes mellitus or insulin resistance.	Drug abuse (cocaine, amphetamines).
Cigarette smoking/tobacco use.	Use of oral contraceptives.
Sedentary lifestyle/lack of physical activity.	Inflammatory or autoimmune diseases (e.g., lupus, vasculitis).
Psychosocial stress/depression.	Coagulation disorders (e.g., antiphospholipid syndrome, Factor V Leiden mutation).
Metabolic syndrome.	Infectious agents (e.g., Mycoplasma pneumoniae, Helicobacter pylori, HIV).
Male sex.	Radiation-induced coronary injury (post-chemotherapy/radiotherapy).

Table 1: Invasive and Non-Invasive Risk Factors Responsible for CAD in Young Adults [19-23].

†CHD: Coronary Heart Disease; CAD: Coronary Artery Disease; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; SCAD: Spontaneous Coronary Artery Dissection; HIV: Human Immunodeficiency Virus.

Key Modifiable Risk Factors

1. Smoking promotes ACAD via inflammation and endothelial damage. MI risk normalizes 5–15 years after cessation. Despite declining trends, smoking remains high in Africa and the Eastern Mediterranean, with growing e-cigarette use [20].
2. Obesity—especially visceral fat—drives inflammation, hypertension, and insulin resistance. Global obesity has doubled in 30 years.
3. Hypertension is a leading modifiable risk. A 10 mmHg BP reduction lowers ACAD risk by 17% [21]. Yet, control remains poor in LMICs.
4. Diabetes/Insulin Resistance increases ACAD risk through metabolic and vascular damage, even below diagnostic thresholds. Global diabetes cases may reach 1.3 billion by 2050 [22].
5. Dyslipidemia, particularly high LDL and lipoprotein(a), is central to plaque formation [23].
6. CKD increases risk via inflammation, oxidative stress, and mineral imbalance. ACAD and CKD share a bidirectional relationship.
7. Sex Differences: Women are more vulnerable post-menopause; pregnancy-related disorders heighten risk [17].
8. Genetic Factors: Polygenic/familial risks are significant, though predictive tools need broader validation [19].
9. Global Disparities: Youth in LMICs face rising ACAD risk due to shifting disease patterns and limited healthcare access.

NOVEL RISK FACTORS FOR ACAD

1.Inflammation

- Major key contributor to ACAD development is chronic low-grade inflammation.
- Elevated biomarkers like tumor necrosis factor (TNF), IL-6, and high-sensitivity c-reactive protein (hs-CRP) are associated to increased risk of ACAD.
- ACAD risk is further modulated by autoimmune diseases and immune dysregulation [23].
- Perivascular fat imaging is an emerging non-invasive imaging tool to identify vascular inflammation.

2.Hyperhomocysteinaemia

- Elevated level of homocysteine induces dysfunctioning in endothelial wall and increases oxidative stress [24].
- While reduction in the level of homocysteine hasn't produce any positive clinical outcomes in European populations, its role in African and Asian populations may be more significant, needing further studies to validate it.

3.Gut Microbiome

- Atherogenic metabolites like trimethylamine N-oxide, can be produced by Gut dysbiosis which can further potentiate formation of plaque and inflammation.
- Modulating the probiotics with microbiome could provide positive clinical outcomes, though microbiome measurement reproducibility is quite challenging [25].

4.Physical inactivity

- Risk of ACAD rise due to lack of physical activity through hypertension, insulin resistance, weight gain and lipid abnormalities.
- Improvement in Endothelial function and reduction in risk of inflammation occur due to regular exercise [26].

5.Diet

- Quality of diet significantly affects risk of ACAD.
- Beneficial established dietary patterns for cardiovascular health include plant-based diets, DASH and Mediterranean.
- Reduction in consumption of sodium in diet remains a proven option for reducing vascular mortality and blood pressure.

6. Stress & Psychosocial Factors

- Excessive stress potentiates the risk of ACAD in patients [27], as stress leads to a rise in the level of cortisol and triggers harmful psychological patterns like poor diet, physical inactivity and smoking.
- Chronic stress also leads to dysfunctioning in endothelial wall and hypertension.

7.Sleep Disorders & Obstructive Sleep Apnea (OSA)

- ACAD risk increases in patients due to both short and long sleep durations [28].
- Another marked independent risk factor development of ACAD is OSA as it leads to systemic inflammation, intermittent hypoxia and over-activation of the sympathetic nervous system.

8. Cancer Survivors

- Risk of ACAD in high in long-term cancer survivors, specifically those managed with cardiotoxic therapies (like chest radiations) [29].
- Major possible pathogenic pathways associated between ACAD and cancer are proliferation of abnormal cell, suggesting common therapeutic and preventive targets.

9.Emerging risk factors

- The ACAD risk landscape is evolving with huge rise in the relevance of various factors like sleep disorders, health social determinants, hypertensive disorders in pregnancy and air pollution.
- Personalized preventive strategies and more inclusive research across populations Is needed to reduce these emerging risks.

10.Opportunity for Integrated Prevention

- Significance of holistic ACAD prevention strategies is highlighted by various novel risk factors, which include integrating gut stress, management of stress, control of inflammation, lifestyle modifications and high-risk populations screening.
- Research gap exists in assessment of these novel risk factors in diverse setting and populations.

Diagnosis Of Atherosclerosis By Non-Invasive Imaging Methods

It is clear that in patients present with autoimmune or coagulation disorders, as well as with cocaine consumers and cigarette smokers are at very high risk of developing CHD as young adults. Subclinical disease assessment in such patients could provide insights about early therapeutic intervention to prevent the risk of acute coronary events [30].

Incorporation of various traditional CHD risk factors is carried out in various population-based screening algorithms, which are quite helpful in the prediction of adverse cardiovascular event risk even in young adults [31]. However, the absence of arteriosclerosis is not guaranteed by the absence of these conventional risk factors, and several adverse cardiovascular events are reported in patients who are at their LDL cholesterol goals [32]. Considering this, study of various additional cerebrovascular screening biomarkers is carried out to assess for their residual risk.

From various years, diagnosis and risk stratification in CHD patients have been carried out by various exercise stress testing modalities, including stress echocardiography and stress electrocardiography [33]. However, findings of the various studies in young adults demonstrated that stress assessment generates a huge number of false-negative results, due to which its clinical use is specifically limited in screening young asymptomatic populations [34].

Further, for the early assessment of asymptomatic SCA in patients, various non-invasive imaging modalities like computed tomography angiography (CTA) computed tomography coronary artery calcium (CAC), and CCTA have extensively been studied [35]. These methods facilitate vital diagnostic insights into ACS, cardiovascular outcomes, ischemia and risk stratification in CAD. Progression of atherosclerotic lesions may occur from non-atherosclerotic intimal lesions to high-risk, thin cap fibroatheromas (TCFA) susceptible to rupture or vulnerable plaques. CCTA play quite significant role in the assessment of these plaques and the overall coronary artery state. CCTA used for combined illustration of SCA by groups is demonstrated in figure 1.

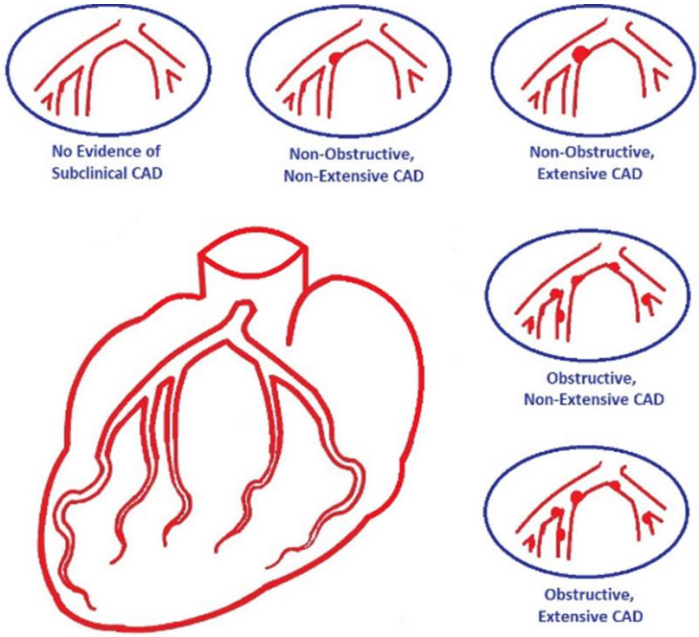


Figure 1: CCTA used for illustration of combined subclinical coronary atherosclerosis by groups. Major two categories were Obstructive (<50% stenosis or non-obstructive stenosis (>50% stenosis) in which classification of coronary luminal diameter stenosis was done. Patients were categorized as absence of atherosclerosis, non-obstructive stenosis, obstructive extensive, and non-obstructive non-extensive.

†CCTA: Coronary Computed Tomography Angiography.

A strong association exists between CAC and atherosclerotic plaque burden. Findings of the CARDIA study suggested that elevated levels of CAC lead to a marked rise in the risk of CVD and CHD events, even a minimal rise in CAC increases the risk [36]. However, only non-calcified plaques have been observed in a huge proportion of young patients present with CHD, CAC may under-diagnose CHD in young adults to a great extent in comparison to older individuals.

Carotid plaque burden and Carotid intima-media thickness (CIMT) are characterized as predictors of cardiovascular risk. Ultrasound assessment of CIMT is a well-developed biomarker to detect atherosclerotic load in CAD and cardiovascular therapeutic interventions effectiveness [37]. Findings of a recent study demonstrate the 75% specificity and 78% diagnostic sensitivity of CIMT however its precision increase if it is coupled with other inflammatory biomarkers like hs-CRP [38].

CCTA has evolved into a mature non-invasive imaging modality that facilitate precise imaging of coronary arteries, ensuring accurate assessment of obstructive CAD. It is also associated with the significant potential to assess components of atherosclerotic plaque and to detect high-risk plaque features. IVUS and CCTA used to demonstrate characteristics of coronary artery plaque is demonstrated in figure 2. CCTA derived imaging methods are demonstrated in figure 3.

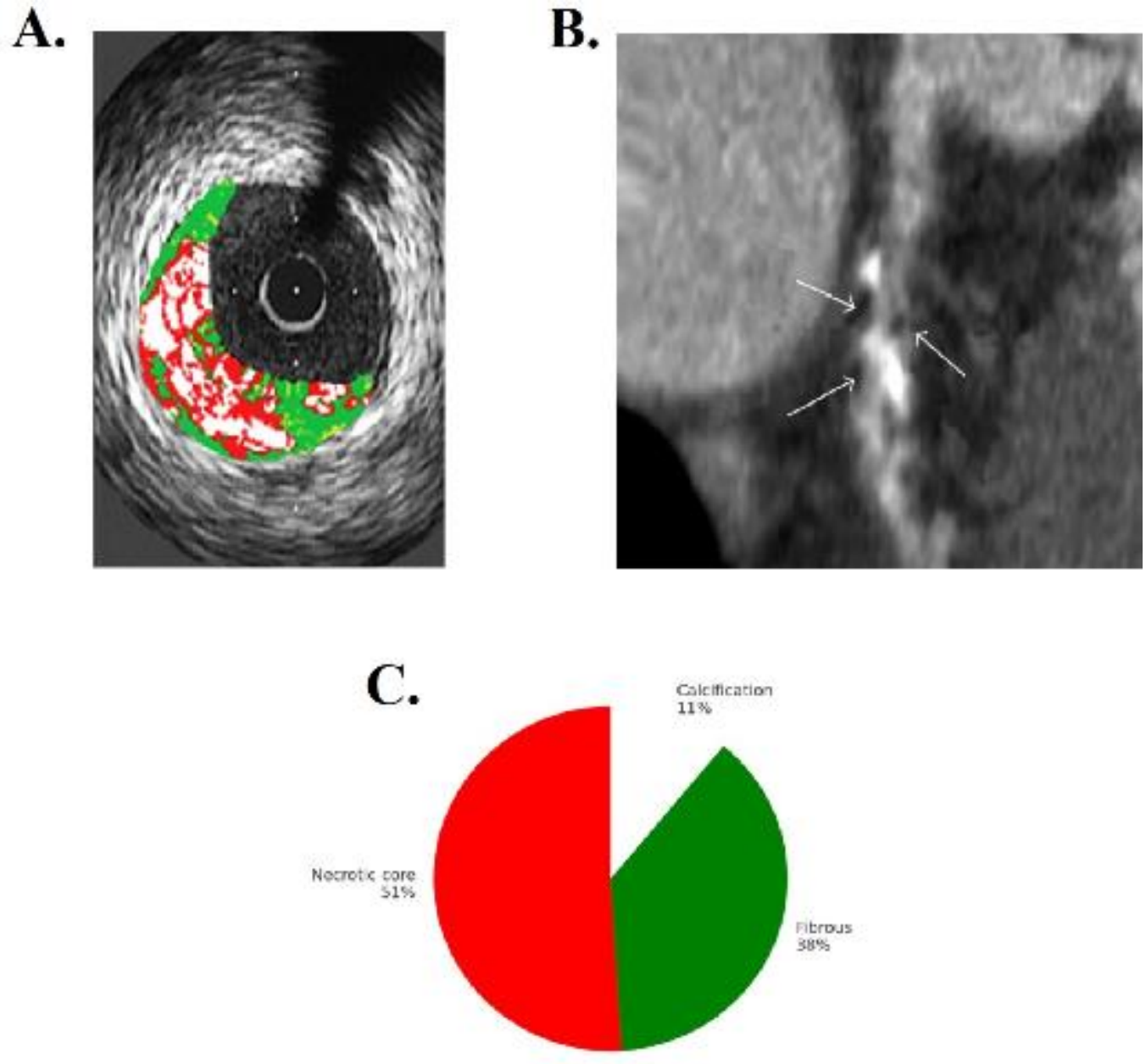


Figure 2: IVUS and CCTA utilized to investigate the features of coronary artery plaque. On CCTA, a high clinical risk of vulnerability was seen in various morphological features of coronary plaque, including (A) positive remodeling (B) low-attenuation plaque (C) spotty calcification.

†IVUS: Intravascular Ultrasound; CCTA: Coronary Computed Tomography Angiography.

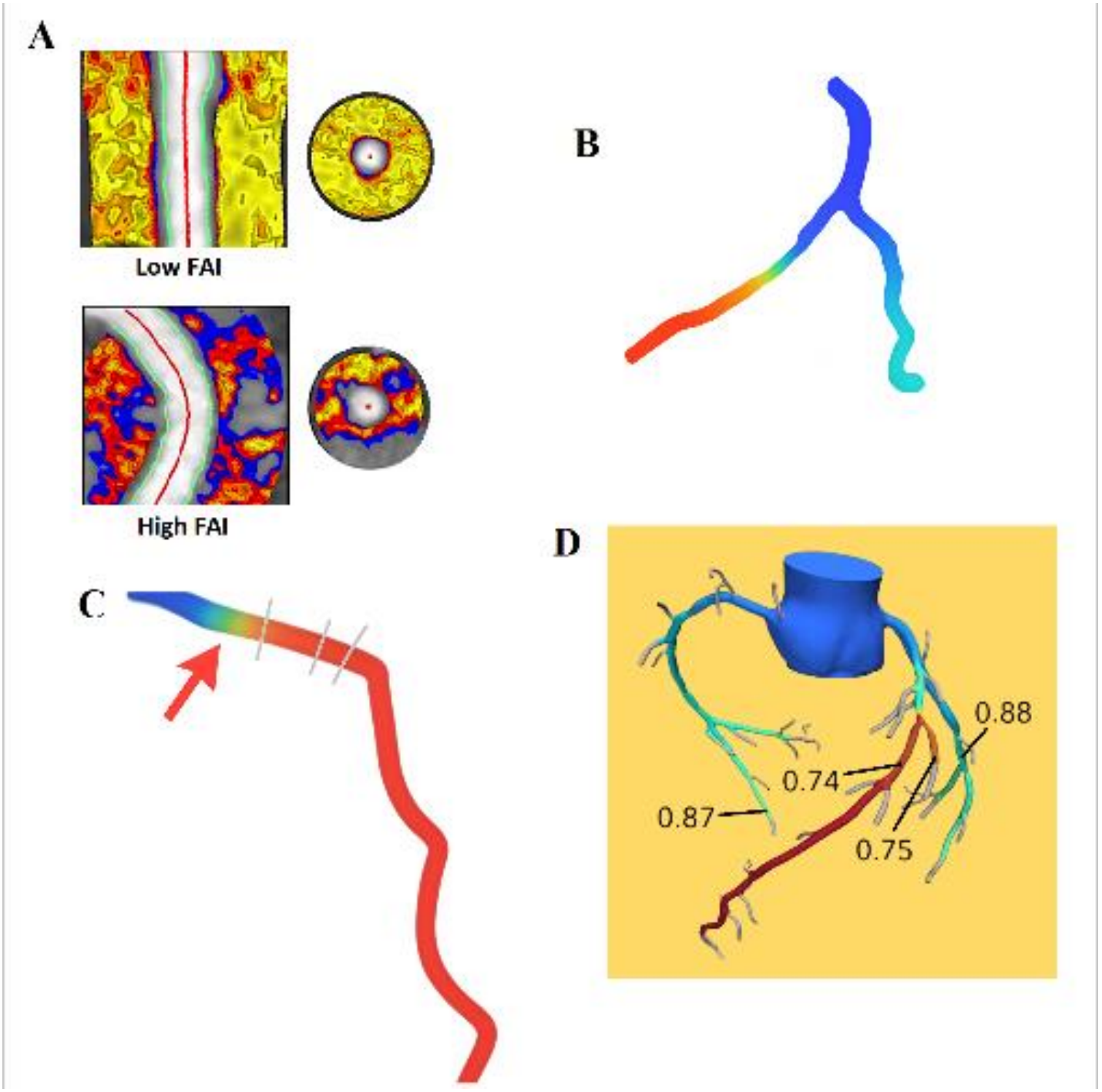


Figure 3: CCTA derived emerging technologies. (A) CCTA was utilized for investigation of two patients present with high and low perivascular fat attenuation index (B) Right and left coronary arteries three-dimensional view is demonstrated using vascuCAP (Elucid Bioimaging, Boston, Massachusetts, USA) from CCTA utilized for the plaque quantification and characterization. (C) Example of CCTA utilized for demonstration of superimposed profile of wall shear stress on a coronary artery tree (D) CCTA utilized for fractional flow reserve-computed tomography calculations extractions.

†CCTA: Coronary Computed Tomography Angiography.

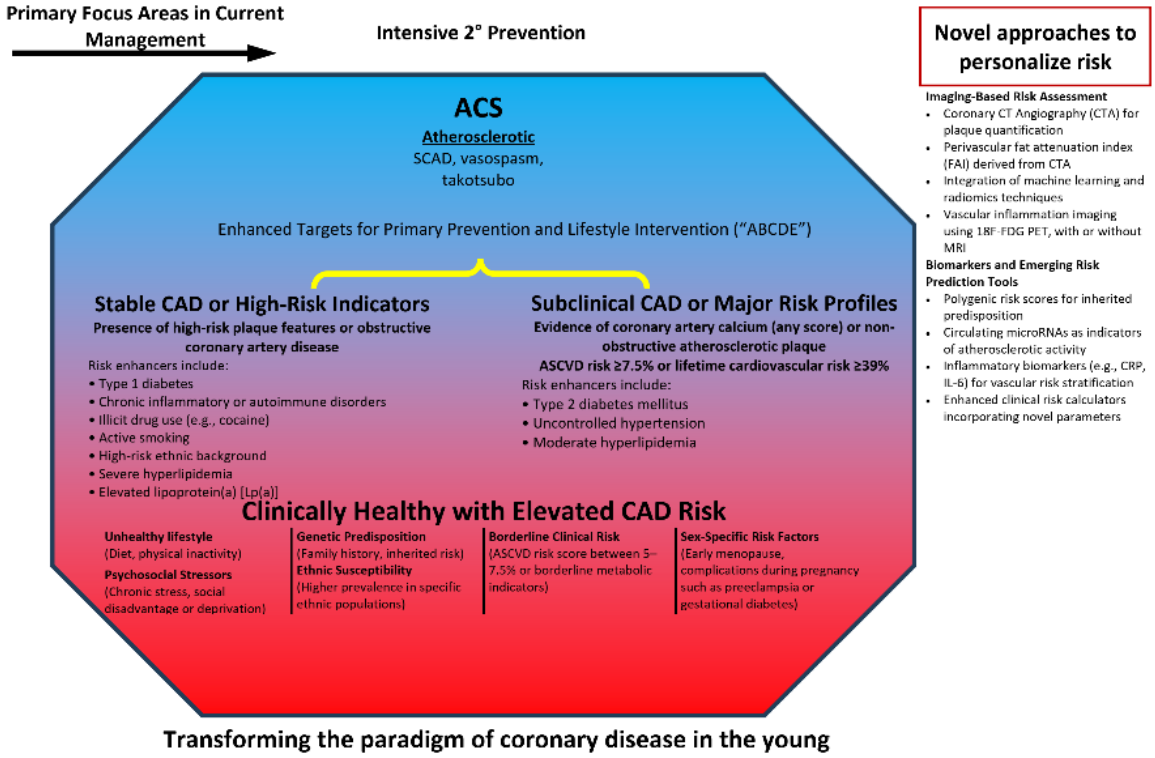


Figure 4: Multipronged approach utilized to break the coronary artery disease cycle in young adults. A multipronged strategy is needed to break the CAD cycle in young adults present at high risk of acute coronary syndrome. Patients screening for risk of conventional atherosclerotic cardiovascular disease should be carried out and patients should be managed by using "ABCDE" approach, Various novel biomarkers, various scoring methods can be utilized to assess the personalized risk assessment.

†ACS: acute coronary syndrome; SCAD: spontaneous coronary artery dissection; CAD: coronary artery disease; Lp(a): lipoprotein (a); ASCVD: atherosclerotic cardiovascular disease; CTA: computed tomography angiography; FDG: fluorodeoxyglucose; PET: positron emission tomography; MRI: magnetic resonance imaging.

Findings of a study conducted by Hoffmann et al [39] and Motoyama et al [40] suggested that distinct features including low-attenuation components (typically spotty calcification, napkin-ring sign and positive remodeling are observed in coronary plaques in patients present with the ACS.

A useful clinical insight about the development of CAD is provided by various proteins and biomarkers associated with inflammation, metabolic syndrome and oxidation. Combining these with conventional risk factors potentiates the accuracy of the prediction of CAD risk. The risk of CAD in young adults is highlighted by various emerging biomarkers like lipoprotein-associated phospholipase-A2 [41].

Polygenic risk score (PRS) quantitative metrics which has emerged as useful diagnostic tools for genetic risk stratification of CAD specifically for those with a familial history of CAD. The role of PRS in prediction of risk of CAD in young adults is emphasized by Khera et al [42]. Furthermore, deep clinical insights into the progression of atherosclerotic plaque and stable CAD is provided by quantitative plaque imaging. Quantification of CTA plaque, by CCTA, predicts the severity of coronary artery plaque, and assessment of traditional risk in the prediction of adverse cardiovascular events [43].

Fat attenuation index (FAI) is another novel imaging metrics, which was validated against 18-F fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging. CT attenuation of perivascular tissues around the arterial wall and pericoronary inflammation in CAD patients is quantified by FAI. Magnetic Resonance Imaging (MRI) has emerged as an ideal imaging technique for the repeated assessment of the progression of atherosclerotic plaque. MRI not only provides accurate detection of plaque thickness and size but it also facilitates differentiation between vessel wall and vessel lumen [44].

Coronary microvascular dysfunction, an advanced imaging biomarker, facilitates the microvascular impairment early assessment, a key factor in understanding the pathological mechanism of CAD behind the epicardial coronary arteries. A quite significant role is played by MV in the development of CAD and its assessment through various non-invasive imaging methods provide useful information for the identification of patients who are at huge risk for adverse cardiovascular outcomes.

Personalized risk profiling, which includes assessment of advanced risk tools and genetic testing, has gained significant importance in an era of precision medicine in the management of CAD. Understanding genetic variants that potentiate the risk of CAD facilitates tailored therapeutic options that cater to the needs of individual patients. Moreover, various risk prediction methods that integrate lifestyle, genetic and clinical factors have played a potential role in the identification of patients present with a huge risk of CAD, thereby facilitating the implementation of timely preventive and therapeutics strategies.

In recent era, developments in artificial intelligence (AI) and (ML) technologies not only improve diagnostic accuracy but also provide useful diagnostic insights that are difficult to predict. Deep learning system are utilized in ML which are associated with the strong potential to accurately detect plaque stenosis and severity from CCTA scans. 5-year Machine learning all-cause mortality was detected better with CCTA data and ML combining data in comparison to existing clinical or CCTA metrics alone [45]. Emerging imaging modalities and biomarker-based tools that may personalize risk prediction in young individuals are summarized in table 2.

Advanced Imaging Modalities	Novel Biomarkers / Risk Prediction Tools
CCTA with plaque morphology analysis.	HS-CRP.
CTA-based perivascular FAI.	PRS.
CAC scoring.	MicroRNAs (e.g., miR-126, miR-155).
Machine learning-based radiomics and predictive modeling.	Circulating inflammatory cytokines (e.g., IL-6, TNF-alpha).
18F-FDG PET/CT or PET/MRI for vascular inflammation imaging.	Genetic markers for familial hypercholesterolemia.
IVUS and OCT.	Lipoprotein(a) levels.
MRI-based plaque characterization.	Advanced clinical risk calculators integrating lifestyle and genomic data.
AI-enabled multimodal risk scoring platforms.	Epigenetic markers (e.g., DNA methylation signatures).

Table 2: Emerging Imaging and Biomarker-Based Strategies to Personalize Risk Prediction in Young Individuals [36, 37, 39, 40, 42, 45].

†CCTA: Coronary Computed Tomography Angiography; HS-CRP: High-Sensitivity C-Reactive Protein; FAI: Fat Attenuation Index; PRS: Polygenic Risk Score; CAC: Coronary Artery Calcium; FDG: Fluorodeoxyglucose; PET: Positron Emission Tomography; IVUS: Intravascular Ultrasound; OCT: Optical Coherence Tomography; MRI: Magnetic Resonance Imaging; AI: Artificial Intelligence.

Instead of these recent advancements, challenges are still associated with promoting the adoption of these imaging modalities. The requirement of operating expertise, associated costs and access to advanced imaging methods, are certain issues that must be addressed. Further studies assessing the clinical application of these imaging techniques, and cost-effectiveness in the routine management of CAD is the need of hour.

Preventive Strategies in Acad: A Comprehensive Framework

I. Primary Prevention and Risk Prediction in ACAD

Primary prevention aims to halt disease before clinical onset, particularly in high-risk but asymptomatic individuals. Despite strong evidence supporting interventions like smoking cessation, BP/glucose/lipid control, and statins (effective at ≥2.5% 10-year risk) [49][52], real-world implementation remains suboptimal.

- Lifestyle & Diet: The Mediterranean diet shows strong ACAD prevention efficacy [46]. Salt reduction and healthy diet promotion remain under-researched.
- Smoking Cessation: Population-level strategies (e.g., bans, taxation) are more effective than pharmacotherapy alone.
- Obesity: Obesity has risen globally. New drugs (e.g., GLP-1 agonists, tirzepatide) show promise, though lifestyle intervention remains essential.
- Hypertension & Diabetes: Tight BP control reduces ACAD risk by 17%; diabetes management with SGLT2 inhibitors and GLP-1 receptor agonists is beneficial [47].
- FH and Emerging Lipid Targets: FH is underdiagnosed. New therapies (PCSK9 inhibitors, antisense oligonucleotides) target high-risk lipoprotein(a).
- Gene Editing: CRISPR therapies (e.g., PCSK9 editing) may offer one-time LDL reduction; trials are ongoing [48].
- AI-Driven Risk Prediction: AI tools integrating genetic, lifestyle, and socioeconomic factors improve prediction accuracy. Smartphone-based calculators may aid resource-limited areas.
- Limitations of Traditional Risk Scores: Tools like Framingham and SCORE underperform in women, youth, and diverse ethnicities [49].
- Emerging Risk Factors: Inflammation, inactivity, sleep, and psychosocial/environmental stressors are poorly captured in current models.
- Polygenic Risk Scores (PRS): PRS can identify high-risk individuals before traditional markers appear. Integration with clinical scores and EHRs (including social and biological variables) is needed.
- Future Research Priorities: Include early-life (primordial) interventions, large-scale RCTs on lifestyle strategies, and equitable, tech-enabled global policies.

II. Secondary Prevention Strategies IN ACAD

Secondary prevention reduces recurrence of MI, stroke, and mortality in patients with established ACAD [50]. Future care models may shift to view ACS as preventable "never events."

- Proven Interventions: Include lifestyle modification, smoking cessation, risk factor control (BP, glucose, lipids), and antiplatelet therapy [51]. Despite equal efficacy, women and minorities are often under-treated.
- Gender & Ethnic Disparities: Women (esp. Indigenous and minority) face doubles the mortality; transgender and gender-diverse populations also remain underserved.
- Adherence Barriers: Only ~60–65% adhere to prevention protocols; 9% of European ACAD events stem from poor adherence [52]. Solutions include long-acting therapies and polypills.
- Digital Support Tools: Text reminders, wearables, and mobile apps have shown mixed success and require broader validation [53,54].
- Cardiac Rehabilitation: Comprehensive programs (exercise, counseling, nutrition) reduce ACAD events [46]. Utilization remains low due to access, referrals, and dropout—especially in women and LMICs.
- Mobile Rehab: Smartphone-based models are comparably effective and better suited for remote or low-income settings.
- Polypills: Simplify regimens and improve adherence; highly useful in resource-limited areas.
- Atherosclerosis Vaccines: Novel vaccines targeting inflammation/lipid metabolism may revolutionize secondary prevention [55].
- Equity & Access: Prevention must prioritize inclusivity—addressing ethnic diversity, gender, low-resource settings, and overcoming logistic barriers.

Surgical And Device Interventions In Acad – Current Evidence And Future Directions

1.Revascularization in Stable ACAD: Prognostic Benefit Debated

- Findings of recent randomized trial suggested that mortality or major adverse events are not reduced by PCI in stable ACAD ((without left main or severe LV dysfunction) [56].
- In patients present with left main disease, LV dysfunctioning or multivessel disease [57], CABG exhibit survival benefits as suggested by older trials but contemporary benefits remain uncertain.

2.Revascularization in ACS: Undisputed Role

- In NSTE-ACS, ischemia, reinfarction and death incidence are reduced by invasive therapeutic strategy [58].

- Primary PCI has emerged as gold standard therapy in patients present with STEMI, reducing the incidence of complications and mortality.

3.PCI vs CABG: Context-Specific Choices

- CABG is recommended for management of patients present with mutlivessel disease, diabetes or poor function of LV.
- PCI is suggested for patients where risk of CABG outweigh clinical benefits [59].
- Global variations in clinical practice pattern occur due to patient factors, expertise and expertise.

4.Future Research Gaps in Revascularization

- Needs for trials demonstrating:

a. PCI optimal timing in cardiac arrest, cardiogenic shock and bleeding scenarios [60].
b. Revascularization physiological vs anatomical completeness.
c. A key role played by proteomics, genomics and imaging in guiding therapeutic interventions.
d. Symptom Relief: Primary Role of PCI in Stable Disease

- In angina relied in symptom is provided by PCI, but clinical benefits are modest in placebo-controlled trials (e.g., ORBITA-2) [61].
- Unblinded and limited data is reported for CABG on relief of angina.
- In patients present with stable ACAD, revascularization primarily provide symptom control instead of mortality benefit.

1.Post-PCI Angina: Unmet Need for Research

- Instead of clinical use of multiple antianginal drugs, many patients still have angina post PCI.
- Assessment of clinical predictors of relief in symptoms with PCI is essential.
- On the basis of symptoms features, selection of patients in the better way for PCI is required [60]

2.Limitations of Current Symptom Assessment Tools

- Variability and biasness are reported in patients reported outcome measures (PROMs).
- Culture environment, socioeconomic status, language and culture affect symptoms.
- Future research studies should refine diagnostic tools for reproducible symptoms identification.

3. Alternative Devices and Therapies for Angina

- Investigational therapies include:

1. Shockwave therapy.
2. Cell-based therapies.
3. Enhanced external counterpulsation.
4. Coronary sinus reducer devices.
5. Transmyocardial laser revascularization.
6. Before widespread clinical use, placebo-controlled trials to be conducted with most of the devices.

4.New Technologies in PCI

- Evolving devices like:
- Bioresorbable scaffolds.
- Next-generation drug-eluting stents.
- Drug-coated balloons [62].

Must balance innovation with clinical evidence of cost-effectiveness and durable clinical benefit.

5.Future Focus of ACAD revascularization Strategy

- Treatment strategy should be shifted from revascularization to patients-specific selective approach:

a. Burden of symptoms.
b. Biology of plaque.
c. Finding of imaging studies.
d. Patients-reported clinical outcomes.

Greater focus should be provided to lifestyle therapeutic interventions, pharmacotherapy and prevention to reduce the revascularization need.

I. Future Directions In Acad Management

The evolving understanding of ACAD highlights the need to move beyond traditional ischemia-based strategies. The focus now shifts to early detection, plaque biology, and system-level changes supported by precision medicine and technology integration.

1. Beyond Ischemia-Centric Models

Traditional revascularization for stable CAD offers limited prognostic benefit. Most acute coronary events stem from vulnerable, non-obstructive plaques missed by stress testing.

2. Imaging Plaque Burden and Risk

Advanced tools like CCTA, IVUS, OCT, and NIRS detect high-risk features (e.g., necrotic cores, thin-cap fibroatheroma). Trials like PROSPECT [5], CLIMA [63], and PROSPECT II [64] support imaging-guided risk stratification. A hybrid model integrating imaging, genetics, and biomarkers is likely the future.

3. Precision Therapeutics

Next-gen care includes PRS, pharmacogenetics (e.g., SLCO1B1, CYP2C19), and endotyping. Emerging therapies—colchicine, IL-1β inhibitors, RNA-based lipid-lowering agents, PCSK9 vaccines—and regenerative options like CRISPR and stem cell therapy [65] show promise.

4. AI and Digital Health

AI enables risk prediction, plaque assessment, and remote monitoring. Digital tools and wearables improve adherence and surveillance, especially in underserved regions. Rigorous validation across populations remains essential.

5. Implementation Science

Despite available therapies, adherence and access remain poor. Implementation strategies include polypills, long-acting drugs, behavioral nudges, and digital interventions.

6. Inclusive Research

Underrepresentation of women, elderly, LMIC populations limits generalizability. Future trials must be pragmatic, diverse, and enriched by surrogate endpoints like inflammation and plaque regression.

7. Cost-Effective and Scalable Solutions

New therapies must prove value with substantial risk reduction and cost-effectiveness. Basic interventions like BP control, statins, and smoking cessation remain vital in low-resource settings.

8. Toward ACAD Eradication

The ultimate goal is not control but eradication. This requires:

- Early-life prevention,
- Genomic tailoring,
- Digital support,
- calable healthcare models,

Future Research

1.Future ACAD Research Must Be Interdisciplinary

- Genetics, epigenetics, environmental science and social science factors integration is important.
- With the objective to understand the risk factors long-term interaction, multi-centre, diverse and longitudinal population studies are needed.

2.ACAD is Largely Preventable and Acquired

- 70-80% of acute coronary events are attributable to a few modifiable risk factors [66].
- Strategies to prevent the risk of ACAD should span from early life to older age, majorly working to delay the onset of disease and halting development of disease.

3.Move Beyond Primary & Secondary Prevention to Primordial Prevention

- Risk factors elimination is the major target of primordial prevention strategies before they progress, ideally starting from childhood and conception [67].
- Extremely low lifetime risk of ACAD have been observed in individuals reaching midlife without risk factors (≤8%).

4.Genomics and Epigenetics to Revolutionize ACAD Prevention

- ACAD risk prediction and implementation of personalized therapies is possible with advancements in future genomics.
- Reversible changes influenced by stress, toxins and lifestyle modifications could be uncovered by epigenetic research.

5.Prenatal and Early Life Exposures Are Critical

- During pregnancy, hypertension, smoking, maternal dyslipidaemia and gestational diabetes potentiate the offspring future risk of ACAD [68].
- Childhood and fatal exposure to adverse environments potentiate the progression of early atherosclerosis.

6.Early Life Risk Factor Control Needed

- Globally, huge rise in dyslipidaemia, type-2 diabetes, childhood obesity and hypertension have been observed.
- Long-term health benefits are offered by therapeutic interventions during pregnancy and childhood, but need better implementation options and research.

7.Health Behaviours Must Be Targeted Early

- It is quite crucial to implement healthy habits (non-smoking, physical activity and diet) from a young age.
- High priority should be provided to effective prevention strategies for family environment, public policies and schools.

8.Upstream Prevention Has Cumulative Lifelong Benefits

- Prevention of progression of risk factor early reduce the need for implementation for more aggressive therapeutic options later in life.
- In comparison to late-life risk management, at younger age, prevention strategies facilitate higher return over time.

9.Implementation Science is Crucial

- Research studies should focus on real-world application, sustainability and scalability of prevention strategies.
- Hybrid trial designs combining efficacy with implementation research are essential.

10.Public Health Policies and Hybrid Research Models Are the Future

- Obesity, hypertension, diabetes and tobacco are major targets of large-scale public health intervention policies.
- ACAD burden across diverse settings can be reduce by Collaborative research which must guide global strategies and policy formation.
- Coordinated global research and policy.

II. Therapeutic Reform, Precision Medicine & Implementation Strategies

1. Ischemia-Guided Strategy: Limitations

Revascularization doesn't improve outcomes in stable CAD [69]. Vulnerable plaques evade detection via stress tests, and total atheroma burden better predicts events [70,71].

2. High-Risk Plaque Detection

CCTA, OCT, IVUS, and NIRS identify dangerous plaque characteristics. Validated by PROSPECT [5], CLIMA [72], and PROSPECT II [73], these methods support preemptive intervention. Various invasive and non-imaging methods to assess sub-clinical atherosclerosis in young adults is demonstrated in Central Illustration.

3. Limits of Plaque-Centric PCI

Local interventions ignore systemic disease. Imaging finds only 4–25% of high-risk plaques. Whole-vessel imaging is costly and impractical.

4. Future Therapeutics

Stabilization of vulnerable plaques via anti-inflammatories, PCSK9 inhibitors, and high-dose statins is under study [74].

5. Addressing Implementation Gaps

Therapy underuse remains a major challenge. Adherence, affordability, and equitable application of proven drugs must be prioritized.

6. Inequity in Access

LMICs lack infrastructure and access to guideline-based care. Global inequities limit the reach of emerging treatments.

7. Clinical Trial Inclusion

White males dominate trials, marginalizing women, elderly, and low-income populations [75]. Broader inclusion is essential.

8. Precision Therapy Approach

Future care will tailor treatment based on:

- Disease endotypes,
- AI-enhanced risk profiling,
- Proteomics and imaging.

9. New Technologies

Wearables and AI tools will enhance early detection, monitor disease progression, and personalize therapy.

Research And Implementation Strategies

1.Early-Stage Focus: Shift from late-stage treatment to early prevention.

2.Long-Term Studies: Needed in young adults (18–39), with emphasis on diversity and protocol adherence.

3.Standardized Data: Global registries (e.g., Scandinavian models) will support comparative analysis [75].

4.Imaging & Biomarker Trials: Serial imaging, inflammation markers, and guided interventions.

5.New Endpoints: Beyond death and MI—include adherence, safety, and surrogate markers.

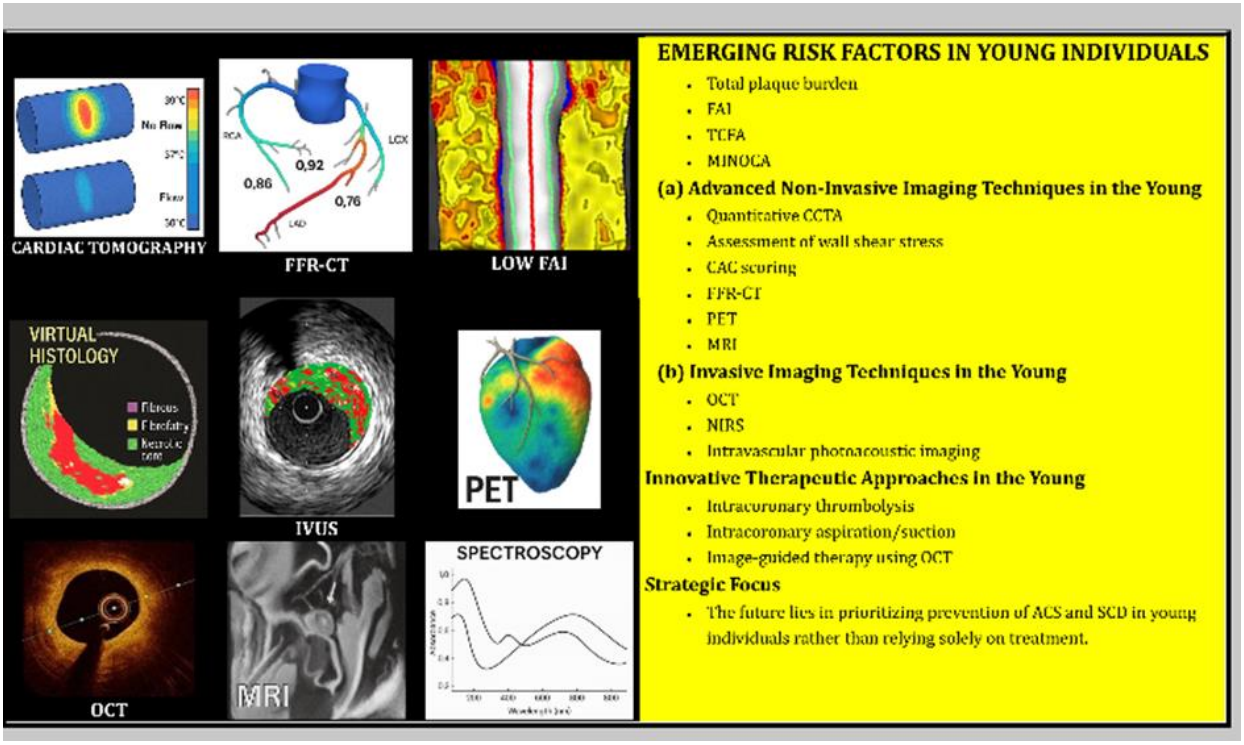
6.Improving Adherence: Leverage digital tools, depot drugs, polypills, and behavioral approaches [76].

7.Inclusive Participation: Focus on women, disadvantaged, and biomarker-enriched populations.

8.Locally Relevant Research: Align studies with regional needs and healthcare realities.

9.Safety Monitoring: Long-term data systems for adverse event tracking in new therapies.

10.Policy Integration: Embed research into health policy via coordination among governments, global health bodies, and academia.



Central Illustration: Various non-invasive and invasive imaging modalities to investigate sub-clinical atherosclerosis in young patients present with coronary artery disease**.**

†FFR-CT: fractional flow reserve-computed tomography; FAI: Fat-Attenuation Index; TCFA: Thin-Cap Fibroatheroma; IVUS: intravascular ultrasound; PET: Positron Emission Tomography; OCT: optical coherence tomography; MRI: Magnetic Resonance Imaging; MINOCA: Myocardial Infarction with Non-Obstructive Coronary Arteries; NIRS: Near-Infrared Spectroscopy; CCTA: Coronary Computed Tomography Angiography; CAC: Coronary Artery Calcium; FFR-CT: Fraction Flow Reserve-Computed Tomography; ACS: Acute Coronary Syndrome; SCD: Sudden Cardiac Death.

Conclusion

1.Young CAD is a Distinct Clinical Subset: Young adults with CAD differ significantly in etiology, presentation, and prognosis from older patients, necessitating tailored diagnostic and therapeutic approaches.

2.Rising Concern Despite Declining Incidence: Although overall incidence of CAD in young adults may be stabilizing or decreasing, mortality rates remain concerningly stagnant, often due to delayed diagnosis or missed risk recognition.

3.Genetics and Modifiable Risks Play a Dual Role: Both genetic predisposition and modifiable risk factors—particularly smoking and obesity—play a critical role in the pathogenesis of CAD in younger populations.

4.Early Detection Is Critical but Underutilized: Early screening in asymptomatic young individuals may reveal subclinical atheroma, offering an opportunity to intervene before symptomatic or catastrophic events like MI or sudden cardiac death.

5.Procedural Outcomes Are Excellent in the Young: Young CAD patients undergoing PCI or CABG for ACS typically show excellent immediate and long-term survival, reinforcing the value of timely invasive therapy when indicated.

6.Reframe Young CAD Within the ACAD Continuum: CAD in youth must be viewed as part of a broader, lifelong atherosclerotic process—beginning early and progressing silently—underscoring the need for a life-course prevention model.

7.From Reactive to Proactive Care Models: The healthcare focus must shift from treating acute events to preventing their occurrence through early risk factor modification, lifestyle change, and public health interventions.

8.Research Must Include the Young: More studies are needed to define normative ranges for imaging, biomarkers, and risk scores in the young, ensuring that prevention and treatment guidelines are inclusive and evidence-based.

9.Empowerment Through Awareness and Education: Raising awareness among clinicians and young populations about the seriousness of early-onset CAD is vital for promoting lifestyle change and adherence to preventive measures.

10.A Vision for Elimination of Premature CAD: With the integration of genetics, imaging, digital health, and preventive policy, the stabilization, reversal, and potential elimination of young-onset CAD become an achievable global health objective.

Future Directions

Future trials should be conducted to demonstrate the significance of novel risk factors, like FAI, TCFA, plaque burden and MINOCA clinical significance in the prevention of CAD. A potential role in understanding plaque features and tools to prevent or treat these plaques in young patients is played by various invasive methods, like OCT, NIRS and intravascular photoacoustic and CCTA derived characteristics, FFR-CT, PET and MRI. Role of intracoronary suction, intracoronary lytic agents or management with OCT facilitate assessment and management of plaque in performing primary PCI. Most significantly, the future lies in prevention of SCAD and ACS for young patients rather than management.

Author Contributions

The lead author of the review article is Dr Rohit Mody. Dr Harpreet Singh, Dr Debabrata Dash, Dr Bhavya Mody, Dr Umanshi Dash and Dr Rajeev Gupta had equal and substantial contributions in the formation of this review article. They were involved in conceptualization, data curation, formal analysis, resources, software, validation, visualization, writing - original draft, Writing, review & editing.

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Availability Of Data And Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval And Consent To Participate

Ethical approval was not required since it is an accepted procedure

Consent For Publication

Written consent has been obtained to publish the review article from the guardian. The consent copy is available with the authors and ready to be submitted if required.

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References

1. Andersson C, Vasan RS.(2018), Epidemiology of cardiovascular disease in young individuals. Nat Rev Cardiol. Apr;15(4):230-240.
2. Khoury, S.; Soleman, M.; Margolis, G.; et al. (2020),Incidence, characteristics and outcomes in very young patients with ST segment elevation myocardial infarction. Coron. Artery Dis. 31, 103–108.
3. Trzeciak, P.; Gierlotka, M.; Polonski, L.; et al. (2017),Treatment and outcomes of patients under 40 years of age with acute myocardial infarction in Poland in 2009–2013: An analysis from the PL-ACS registry. Polish Arch. Intern. Med., 127, 666–673.
4. Gimbrone MA Jr, García-Cardeña G. (2016),Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circ Res 2118: 620–636
5. Stone GW, Maehara A, Lansky AJ, et al.(2011), A prospective naturalhistory study of coronary atherosclerosis. N Engl J Med; 364: 226–235.
6. Rubin JB, Borden WB. Coronary heart disease in young adults. Curr Atheroscler Rep. 2012;14(2):140-149.
7. Vaduganathan M, Mensah GA, Turco JV, et al. (2022),The global burden of cardiovascular diseases and risk: a compass for future health. J Am Coll Cardiol; 80: 2361–2371.
8. Zhang G, Yu C, Zhou M, et al. (2015), Burden of ischaemic heart disease and attributable risk factors in China from 1990 to: findings from the global burden of disease 2015 study. BMC Cardiovasc Disord. 2018;18:18
9. Prabhakaran D, Jeemon P, Roy A. (2016;),Cardiovascular diseases in India: current epidemiology and future directions. Circulation. 133(16):1605-1620.
10. Herrington W, Lacey B, Sherliker P, et al. (2016),Epidemiology of atherosclerosis and the potential to reduce the global burden of atherothrombotic disease. Circ Res.;118(4):535-546.
11. Nayor M, Brown KJ, Vasan RS. (2021),The molecular basis of predicting atherosclerotic cardiovascular disease risk. Circ Res; 128: 287–303.
12. Chew NWS, Chong B, Kuo SM, et al.(2023), Trends and predictions of metabolic risk factors for acute myocardial infarction: findings from a multiethnic nationwide cohort. Lancet Reg Health West Pac; 37: 100803.
13. Xu S, Ilyas I, Little PJ, et al. (2021),Endothelial dysfunction in atherosclerotic cardiovascular diseases and beyond: from mechanism to pharmacotherapies. Pharmacol Rev; 73: 924–967.
14. Borén J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020; 41: 2313–2330.
15. Verhagen SN, Visseren FL. (2011),Perivascular adipose tissue as a cause of atherosclerosis. Atherosclerosis; 214: 3–10.
16. López-Otín C, Blasco MA, Partridge L, et al. The hallmarks of aging. Cell 2013; 153: 1194–217.
17. Vogel B, Acevedo M, Appelman Y, et al. (2021),The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. Lancet; 397: 2385–2438.
18. Ke W, Rand KA, Conti DV, et al. (2018),Evaluation of 71 coronary artery disease risk variants in a multiethnic cohort. Front Cardiovasc Med; 5: 19.
19. Ke W, Rand KA, Conti DV, et al. Evaluation of 71 coronary artery disease risk variants in a multiethnic cohort. Front Cardiovasc Med 2018; 5: 19.
20. WHO. WHO global report on trends in prevalence of tobacco use 2000–2025, fourth edition. 2021.
21. Ettehad D, Emdin CA, Kiran A, et al. (2016),Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet; 387: 957–967.
22. Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. Cell Metab 2011; 14: 575–585.
23. Libby P. (2021),The changing landscape of atherosclerosis. Nature; 592: 524–33.
24. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 2002; 288:–22.
25. Liu H, Chen X, Hu X, et al. (2019),Alterations in the gut microbiome and metabolism with coronary artery disease severity. Microbiome; 7: 68.
26. Winzer EB, Woitek F, Linke A. (2018).Physical activity in the prevention and treatment of coronary artery disease. J Am Heart Assoc; 7: e007725.
27. Santosa A, Rosengren A, Ramasundarahettige C, et al. (2021),Psychosocial risk factors and cardiovascular disease and death in a population based cohort from 21 low-, middle-, and high-income countries. JAMA Netw Open; 4: e2138920.

28. Han H, Wang Y, Li T, et al. (2023),Sleep duration and risks of incident cardiovascular disease and mortality among people with type 2 diabetes. Diabetes Care; 46: 101–110.
29. Dixon SB, Liu Q, Chow EJ, et al. (2023),Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. Lancet; 401: 1447–1457.
30. Nayor M, Brown KJ, Vasan RS.(2021), The molecular basis of predicting atherosclerotic cardiovascular disease risk. Circ Res; 128: 287–303.
31. Robertson WB, Geer JC, Strong JP, McGill HC Jr.(1963), The fate of the fatty streak. Exp Mol Pathol;2(suppl):28–39.
32. Krittanawong C, Kumar A, Wang Z, et al. (2020),Coronary artery disease in the young in the US population-based cohort. Am J Cardiovasc Dis. Aug 15;10(3):189-19
33. Hammond EC, Horn D. Smoking and death rates: report on forty-four months of follow-up of 187 783 men. 2. Death rates by cause. J Am Med Assoc 1958; 166: 1294–1308.
34. Steinberg D, Lewis A.(1997), Conner Memorial Lecture: oxidative modification of LDL and atherogenesis. Circulation;95:1062–1067.
35. Willett WC, Green A, Stampfer MJ, et al.(1987), Relative and absolute excess risks of coronary heart disease among women who smoke cigarettes. N Engl J Med; 317: 1303–1309.
36. Marios Sagris, Alexios S Antonopoulos, Panagiotis Theofilis, et al, (2022),Risk factors profile of young and older patients with myocardial infarction, Cardiovascular Research, Volume 118, Issue 10, June, Pages 2281–2292
37. X, Raposeiras-Roubin S, Oliva B, et al. (2021),Glycated hemoglobin and subclinical atherosclerosis in people without diabetes. J Am Coll Cardiol; 77: 2777–2791.
38. Manoharan MP, Raja R, Jamil A, et al. (2022),Obesity and Coronary Artery Disease: An Updated Systematic Review 2022. Cureus. Sep 23;14(9):e29480.
39. Hoffmann Udo, et al. (2006),Noninvasive assessment of plaque morphology and composition in culprit and stable lesions in acute coronary syn- drome and stable lesions in stable angina by multidetector computed tomography. J Am Coll Cardiol.;47(8):1655–1662
40. Motoyama Sadako, et al. (2007),Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. J Am Coll Cardiol.;50(4):319–326
41. Khera AV, Kathiresan S.(2017), Genetics of coronary artery disease: discovery, biology and clinical translation. Nat Rev Genet. ;18(6):331-344.
42. AV, Emdin CA, Drake I, et al. (2016),Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med.;375(24):2349-2358.
43. Joana Guimarães, José de Almeida, Paulo Lázaro Mendes, et al. (2024),Advancements in non-invasive imaging of atherosclerosis: Future perspectives. Journal of Clinical Lipidology. Volume 18, Issue 2., Pages e142-e152.
44. Bansal A, Hiwale K.(2023), Updates in the Management of Coronary Artery Disease: A Review Article. Cureus. Dec 16;15(12):e50644.
45. Motwani M, et al. (2017;),Machine learning for prediction of all-cause mortality in patients with suspected coronary artery disease: a 5-year multicentre prospective registry analysis. Eur Heart J. 38(7):500–507.
46. Visseren FLJ, Mach F, Smulders YM, et al. (2021), ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J 2021; 42: 3227–337.
47. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. (2023),Semaglutide and cardiovascular outcomes in obesity without diabetes. N Engl J Med; 389: 2221–2232.
48. Cohen JC, Boerwinkle E, Mosley TH Jr, Hobbs HH. (2006),Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. N Engl J Med; 354: 1264–1272.
49. Rana JS, Tabada GH, Solomon MD, et al. Accuracy of the atherosclerotic cardiovascular risk equation in a large contemporary, multiethnic population. J Am Coll Cardiol 2016; 67: 2118–30.
50. Virani SS, Newby LK, Arnold SV, et al. (2023), AHA/ACC/ACCP/ ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on clinical practice guidelines. Circulation 2023; 148: e9–119.
51. Byrne RA, Rossello X, Coughlan JJ, et al. (2023), ESC Guidelines for the management of acute coronary syndromes. Eur Heart J; 44: 3720–826.
52. Chowdhury R, Khan H, Heydon E, et al. (2013),Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J; 34: 2940–2948.
53. Chow CK, Klimis H, Thiagalingam A, et al.(2022), Text messages to improve medication adherence and secondary prevention after acute coronary syndrome: the TEXTMEDS randomized clinical trial. Circulation; 145: 1443–1455.
54. Palmer MJ, Barnard S, Perel P, Free C. (2018),Mobile phone-based interventions for improving adherence to medication prescribed for the primary prevention of cardiovascular disease in adults. Cochrane Database Syst Rev; 6: CD012675.
55. Ma Z, Mao C, Chen X, et al. (2023),Peptide vaccine against ADAMTS-7 ameliorates atherosclerosis and postinjury neointima hyperplasia. Circulation; 147: 728–42.
56. Maron DJ, Hochman JS, Reynolds HR, et al.(2020), Initial invasive or conservative strategy for stable coronary disease. N Engl J Med; 382: 1395–1407.
57. Marui A, Kimura T, Nishiwaki N, et al. (2014),Comparison of five-year outcomes of coronary artery bypass grafting versus percutaneous coronary intervention in patients with left ventricular ejection fractions≤50% versus >50% (from the CREDO-Kyoto PCI/CABG Registry Cohort-2). Am J Cardiol; 114: 988–996.
58. Mehta SR, Cannon CP, Fox KA, et al.(2005), Routine vs selective invasive strategies in patients with acute coronary syndromes: a collaborative meta-analysis of randomized trials. JAMA; 293: 2908–2917.
59. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. (2019), ESC/EACTS guidelines on myocardial revascularization. Eur Heart J; 40: 87–165.
60. Rajkumar CA, Foley MJ, Ahmed-Jushuf F, et al. (2024),N-of-1 trial of angina verification before percutaneous coronary intervention. J Am Coll Cardiol; 84: 1–12.
61. Rajkumar CA, Foley MJ, Ahmed-Jushuf F, et al. (2023),A placebo controlled trial of percutaneous coronary intervention for stable angina. N Engl J Med; 389: 2319–30.
62. Korjian S, McCarthy KJ, Larnard EA, et al. (2024),Drug-coated balloons in the management of coronary artery disease. Circ Cardiovasc Interv; 17: e013302.
63. Prati F, Romagnoli E, Gatto L, et al. (2020).Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: the CLIMA study. Eur Heart J; 41: 383–391.
64. Erlinge D, Maehara A, Ben-Yehuda O, et al.(2021),Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. Lancet; 397: 985–995.

65. Henry TD, Bairey Merz CN, Wei J, et al. (2022),Autologous CD34+ stem cell therapy increases coronary flow reserve and reduces angina in patients with coronary microvascular dysfunction. Circ Cardiovasc Interv; 15: e010802.
66. Yusuf S, Hawken S, Ounpuu S, et al.(2004), Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet; 364: 937–952.
67. Lloyd-Jones DM, Albert MA, Elkind M. (2021),The American Heart Association's focus on primordial prevention. Circulation; 144: e233–235.
68. Wang Y, Gao E, Wu J, et al. (2009),Fetal macrosomia and adolescence obesity: results from a longitudinal cohort study. Int J Obes; 33: 923–928
69. Xing L, Yamamoto E, Sugiyama T, et al. (2017),EROSION study (effective anti-thrombotic therapy without stenting: intravascular optical coherence tomography-based management in plaque erosion): a 1-year follow-up report. Circ Cardiovasc Interv; 10: e005860.
70. Reynolds HR, Shaw LJ, Min JK, et al.(2021), Outcomes in the ISCHEMIA trial based on coronary artery disease and ischemia severity. Circulation; 144: 1024–1038.
71. Kedhi E, Berta B, Roleder T, et al. (2021),Thin-cap fibroatheroma predicts clinical events in diabetic patients with normal fractional flow reserve: the COMBINE OCT-FFR trial. Eur Heart J; 42: 4671–4679.
72. Erlinge D, Maehara A, Ben-Yehuda O, et al.(2021), Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study. Lancet; 397: 985–995.
73. Ahn JM, Kang DY, Lee PH, et al. (2023),Preventive PCI or medical therapy alone for vulnerable atherosclerotic coronary plaque: rationale and design of the randomized, controlled PREVENT trial. Am Heart J; 264: 83–96.
74. Mas-Llado C, Gonzalez-Del-Hoyo M, Siquier-Padilla J, et al.(2023), Representativeness in randomised clinical trials supporting acute coronary syndrome guidelines. Eur Heart J Qual Care Clin Outcomes; 9: 796–805.
75. Figtree GA, Vernon ST, Hadziosmanovic N, et al. (2021),Mortality in STEMI patients without standard modifiable risk factors: a sex disaggregated analysis of SWEDEHEART registry data. Lancet; 397: 1085–1094.
76. Salzwedel A, Jensen K, Rauch B, et al.(2020), Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: update of the Cardiac Rehabilitation Outcome Study (CROS-II). Eur J Prev Cardiol; 27: 1756–1774.

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