Publisher Name: ZenToks Publication
Editorial Book: Current Trends in Cardiovascular
ISBN: 978-81-986895-2-8

Chapter 2

Coronary Artery Disease in the Young

Dr. Sandeepan Saha[1*] and Dr. Bhayolina Bora[2]

[1]*Assistant Professor, Department of Cardiology, AIIMS, Guwahati, Assam - 781101, India.*
[2]*Consultant Nephrologist, GNRC Hospital, North Guwahati, Assam, india.*
[*]*Corresponding Author.*

Abstract

Coronary artery disease (CAD) in individuals under 45 years represents a clinically distinct entity with escalating epidemiological burden, unique aetiological characteristics, and profound socioeconomic consequences. Although traditional atherosclerotic risk factors—smoking, hypertension, dyslipidaemia, and diabetes—account for approximately 85–90% of cases, younger patients present a distinct pathophysiological substrate characterised by positive vascular remodelling, lipid-rich vulnerable plaques, and a higher propensity for plaque rupture despite angiographically mild disease. Beyond conventional risk factors, genetic polymorphisms in lipoprotein metabolism genes, elevated lipoprotein(a), and an array of non-traditional factors including autoimmune disorders, infectious disease sequelae, and spontaneous coronary artery dissection contribute meaningfully to premature CAD. Approximately 5–15% of young myocardial infarction presentations occur without significant obstructive atherosclerosis, attributable instead to vasospasm, thromboembolism, or coronary dissection. Young MI survivors face substantially elevated recurrence risk and carry a higher burden of psychosocial morbidity than older cohorts, yet demonstrate significantly lower adherence to secondary prevention therapies. This chapter synthesises current epidemiological data, delineates the heterogeneous pathophysiological mechanisms underlying premature CAD, provides a systematic framework for comprehensive aetiological investigation, and outlines evidence-based management strategies encompassing acute intervention, long-term secondary prevention, and psychosocial support. Given that mortality from young CAD is not declining at rates observed in older populations, addressing the epidemic of premature atherosclerosis demands upstream public health intervention targeting modifiable risk factors whilst simultaneously ensuring rigorous individual-level clinical assessment and lifelong preventive therapy in young MI survivors.

Keywords: Coronary artery disease, Premature atherosclerosis, Young myocardial infarction, Lipoproteina, Vulnerable plaque, MINOCA, Spontaneous coronary artery dissection, Secondary prevention.

Introduction

Coronary artery disease (CAD) has long been regarded as a condition of the elderly, yet a substantial and growing burden falls on individuals under the age of 45. This demographic shift has attracted increasing attention, not only because premature atherosclerosis carries a longer lifetime risk than its late-onset counterpart, but because the underlying mechanisms, risk factor profiles, and long-term consequences differ in meaningful ways from CAD in older adults. The management of a 35-year-old with an acute myocardial infarction (MI) demands an entirely different clinical framework than that of a 70-year-old presenting with the same event: different questions must be asked, different investigations pursued, and different conversations held about the rest of a life still largely unlived.

Various studies have demonstrated that young CAD contributes to approximately 2% to 6% of all acute coronary events globally [1], though specific registry data place the proportion of MI in patients younger than 45 years at between 4% and 10% in some series [2]. In absolute numbers, this represents tens of thousands of patients annually in most large countries. Although traditionally considered a disease of older adults, ischaemic heart disease imposes a substantial burden on younger populations. Global Burden of Disease 2019 data estimated nearly 28.7 million DALYs and approximately 597,000 deaths attributable to IHD among adults aged 25–49 years worldwide, highlighting the growing importance of premature CAD as a public health challenge [3]. Data from the National Cardiovascular Data Registry in the United States have shown a steady rise in the proportion of young adults particularly young women presenting with acute MI between

How To Cite: S. Saha and B. Bora. *Coronary Artery Disease in the Young.* F.R.B. Marquez (Ed). Current Trends in Cardiovascular. Pages 4-12, 2026. ZenToks Publication, India. ISBN: 978-81-986895-2-8

1995 and 2014 [4]. The reasons for this trend are multifactorial, reflecting deteriorating metabolic health in younger populations alongside increasing rates of obesity, diabetes, and hypertension beginning in early adulthood.

Defining Young in the Context of CAD

There is no universally accepted age cutoff for what constitutes ”young” CAD, and the literature reflects this heterogeneity considerably. Some authors use 40 years, others 45 or 50, and a few extend the definition to 55 in women to account for the protective effect of pre-menopausal hormonal status. The terminology itself varies: ”premature CAD,” ”early-onset CAD,” ”precocious CAD,” and ”very young CAD” (used for patients aged 35 or below) all appear in the literature referring to broadly overlapping but not identical populations [2]. Most contemporary series use 45 years as the upper boundary, and this threshold will be used throughout this chapter unless otherwise stated.

Atherosclerosis is a lifelong process beginning as early as the first decade of life, with fatty streaks identified in the aortas of children and adolescents in autopsy series [5]. What distinguishes premature presentation is not a fundamentally different disease process, but rather the presence of risk factors of unusual severity, an underlying genetic predisposition, or non-atherosclerotic mechanisms that would not otherwise cause clinical events for decades. Conventional atherosclerotic CAD accounts for approximately 80% of CAD in young adults; the remaining 20% encompasses congenital coronary anomalies, embolic occlusion, haematological disorders, vasospasm, and spontaneous dissection [2].

Epidemiology and Trends

Although the overall burden of coronary heart disease has declined in many high-income countries, premature coronary artery disease continues to represent a major public health challenge, accounting for substantial mortality, disability, and loss of productive life-years among young adults worldwide [3][6]. Within this burden, the epidemiology of young CAD is evolving in a concerning direction. The Framingham Heart Study, reporting in the early 1980s, documented a 10-year CAD incidence of 12.9 per 1000 in men aged 30–34 years and 5.2 per 1000 in women aged 35–44 years [7]. Centre for Disease Control prevalence data for 2010 recorded CAD prevalence of 1.2%, 7.1%, and 19.8% in the age groups 18–44, 45–64, and above 65 years respectively [8], illustrating just how sharply risk escalates with age but also confirming that young CAD is far from rare in absolute terms.

Young women with MI are more likely than their male peers to have had a prior diagnosis of autoimmune disease, depression, substance use disorder, or chronic kidney disease [9]. In the Singapore Myocardial Infarction Registry, men had approximately four times the risk of CAD compared to women in the under-65 age group [10], and in Asian populations 9.7% of males and 4.4% of females develop their first MI under 40 years of age [11].

The ethnic dimension of young CAD is striking and clinically important. The mean age of onset of CAD in Southeast Asians is approximately 53 years compared to 63 years in European populations [12]. South Asians particularly Indians face a risk of young CAD estimated at 5% to 10%, compared to approximately 1% to 2% in other ethnic groups [11]. This vulnerability likely reflects a convergence of lifestyle, environmental, and genetic factors, including higher rates of insulin resistance, more adverse lipid profiles, and possibly unfavourable genetic variants in lipoprotein metabolism [11]. Studies have also shown that persons with a positive family history of premature CAD have a prevalence of CAD of approximately 35%, compared to 14% in the general population [13], underscoring the heritable dimension of this risk.

Risk Factors

Classical Risk Factors

Conventional risk factors viz. smoking, hypertension, diabetes mellitus, dyslipidaemia, obesity, and family history account for approximately 85% to 90% of premature CAD patients [14], and young CAD patients frequently carry multiple coexisting risk factors [15]. What differs from older CAD is not the identity of these risk factors but their relative contributions and the severity with which they manifest in a younger person.

Smoking stands apart as the single most commonly associated risk factor in young CAD. Its prevalence in individuals under 45 years with CAD has been reported at 60% to 90%, compared to 24% to 56% in those older than 45 [1][16]. The effect of smoking is amplified considerably when additional risk factors are present: the combination of smoking with diabetes, hypertension, or obesity confers a risk of future acute coronary events far exceeding the sum of its parts [17]. The mechanism involves endothelial dysfunction, accelerated platelet activation, and promotion of plaque rupture, including in vessels with relatively modest atherosclerotic burden, which explains the well-documented occurrence of MI in angiographically near-normal coronary arteries in young smokers [18].

Hypertension is present in approximately 25% of young CAD patients compared to 13% in age-matched controls without CAD [19]. Diabetes and pre-diabetes occur in 14.3% and 7.6% of young CAD patients respectively, compared to only 5.4% and 4.3% in those without CAD [19]. Importantly, there has been a dramatic increase in the prevalence of both conditions in young CAD populations over the past decade, hypertension rising from 8.86% (2001–2002) to 27.7% (2009–2010), and dysglycaemia from 7.6% to 36.15% over the same period [20], a trend that almost certainly underlies part of the rising incidence of young MI.

Family history of premature CAD defined as a first-degree male relative affected before age 55 or female before age 65 is one of the strongest predictors of young MI. One series found that approximately 64% of young CAD patients had a positive family history [1]. The mechanism is partly mediated through plaque biology: individuals with a positive family history demonstrate increased coronary plaque content and a higher incidence of severe obstructive CAD, suggesting that heritable factors accelerate not just atherogenesis but plaque instability [21]. In women with a family history of CAD, the prevalence of conventional risk factors is particularly high hypertension and dyslipidaemia each at 67%, obesity at 53%, smoking at 42%, and diabetes at 33% [22].

Dyslipidaemia remains one of the most important modifiable risk factors for premature CAD. Elevated low-density lipoprotein cholesterol (LDL-C), reduced high-density lipoprotein cholesterol (HDL-C), and hypertriglyceridaemia are consistently associated with an increased risk of early-onset atherosclerotic cardiovascular disease, particularly in South Asian populations [23]. Among lipid abnormalities,

elevated lipoprotein(a) [Lp(a)] has emerged as a particularly important genetically determined risk factor, contributing to both accelerated atherosclerosis and thrombosis independent of traditional lipid parameters [24]. Familial hypercholesterolaemia deserves special attention in young patients presenting with CAD, as untreated individuals may develop clinically significant coronary atherosclerosis decades earlier than the general population, making early diagnosis and cascade screening of family members essential [25].

Genetic Risk Factors

Genetic influences on young CAD extend beyond family history to specific polymorphisms and mutations in genes involved in lipid transport and metabolism. Variants in the cholesterol ester transfer protein (CETP) gene, hepatic lipase gene, lipoprotein lipase gene, apolipoprotein A1 (ApoA1) gene, ApoE gene, ApoB gene, hypoxia-inducible factor 1-alpha (HIF1A) gene, Factor V Leiden, methylene tetrahydrofolate reductase (MTHFR) gene, and methionine synthase gene have all been identified in association with premature CAD [26-30].

The CETP locus has been found to have a significant association with angiographic progression of coronary atherosclerosis in men with coronary heart disease [31]. The ApoE4 allele is associated with CAD in several populations, while ApoE2/E2 homozygosity predisposes to type III hyperlipoproteinaemia and accelerated atherosclerosis [32, 33]. Homozygosity for the MTHFR C677T mutation leads to elevated homocysteine levels, which in turn are associated with increased CAD risk [34, 35]. Hepatic lipase, acting as both a phospholipase and a triglyceride lipase, plays a key role in HDL metabolism and the conversion of VLDL to LDL; single nucleotide polymorphisms in its gene have been shown to associate with plasma lipid concentrations and increased coronary risk [36].

Inherited disorders of lipid metabolism, particularly those associated with markedly elevated LDL-cholesterol and lipoprotein(a) concentrations, are strongly associated with accelerated atherosclerosis and markedly increased risk of premature coronary artery disease, often manifesting clinically decades earlier than in the general population [37]. It remains underdiagnosed in the majority of those affected, and cascade screening of first-degree relatives following a young MI should be considered standard practice.

Non-Traditional and Emerging Risk Factors

Beyond the classical framework, young CAD is associated with a set of risk factors that receive less systematic attention in clinical practice yet carry substantial pathobiological significance.

Lipoprotein(a) and Haemostatic Markers

Young CAD patients demonstrate increased serum levels of lipoprotein(a) [Lp(a)], fibrinogen, and D-dimer compared to age-matched controls [38]. Lp(a) is a genetically determined lipoprotein with both pro-atherogenic and pro-thrombotic properties; its plasma concentration is approximately 80–90% heritable and largely unresponsive to lifestyle modification or conventional lipid-lowering therapy [1]. High C-reactive protein has been associated with recurrence of future acute coronary events in young CAD, while raised fibrinogen levels are associated with increased mortality in this population [39].

Cocaine and Sympathomimetic Drug Use

Cocaine use is a well-documented though often under-recognised cause of MI in young adults. It is associated with a broad spectrum of cardiovascular complications including myocardial infarction, heart failure, cardiomyopathy, arrhythmias, aortic dissection, and endocarditis [40]. Cocaine induces coronary vasospasm, accelerates atherogenesis, and promotes thrombus formation through platelet activation. Management of cocaine-related MI deviates from standard atherothrombotic protocols, beta-blockers are relatively contraindicated acutely due to the risk of unopposed alpha-adrenergic stimulation and paradoxical vasoconstriction [13]. A history of recreational drug use should be actively sought in every young MI patient.

Novel Biomarkers

Several novel biomarkers have emerged in recent years as potential markers of premature CAD. Decreased serum Wnt-1, increased gamma-glutamyl transferase (GGT), raised vitamin D2 and D3, and decreased osteocalcin levels have all been found to be associated with premature MI in younger cohorts [41-43]. The association with elevated vitamin D levels in young CAD is intriguing and apparently paradoxical, it stands in contradiction to findings in general populations, where vitamin D deficiency is associated with adverse cardiovascular outcomes [44-46], suggesting that the relationship between vitamin D metabolism and atherogenesis may be more complex in young individuals.

Physical markers of premature ageing have also been associated with young CAD. The prevalence of premature arcus senilis (16.1%), premature greying (34.9%), and premature balding (22.3%) are all significantly elevated in young CAD patients compared to non-CAD controls [47-49]. Premature arcus senilis in this context may serve as a marker of familial hypercholesterolaemia. These cutaneous findings, taken together, suggest that young CAD may be accompanied by accelerated biological ageing beyond the coronary vasculature itself.

Autoimmune, Infectious, and Systemic Conditions

Systemic lupus erythematosus (SLE), rheumatoid arthritis, and antiphospholipid syndrome are increasingly recognised as independent CAD risk factors, particularly in younger women. The mechanisms involve chronic systemic inflammation, accelerated atherosclerosis, corticosteroid use, and direct pro-thrombotic effects in antiphospholipid syndrome. Additionally, HIV-positive patients on highly active antiretroviral therapy (HAART), especially those receiving protease inhibitors, are at significantly elevated risk of premature atherosclerosis [50]. Kawasaki disease in childhood through its propensity to cause coronary artery aneurysms may manifest as premature MI in young adulthood. Patent foramen ovale, through paradoxical embolism, is another recognised contributor to MI in young patients with otherwise normal coronary arteries [51]. Homocysteinaemia and hypothyroidism round out the list of systemic contributors to premature coronary disease [51].

Premature Menopause and Hormonal Factors

Natural menopause before age 40 is associated with a roughly twofold increase in CAD risk, and bilateral oophorectomy at a young age carries even greater risk [52]. Oral contraceptive use, particularly high-dose oestrogen formulations in the context of smoking, significantly elevates the risk of arterial thrombosis [52]. Polycystic ovary syndrome (PCOS), affecting approximately 10% of women of reproductive age, is associated with insulin resistance, dyslipidaemia, and adverse cardiovascular risk profiles that may accelerate subclinical atherosclerosis [53].

Pathophysiology of CAD in the Young

The pathophysiological substrate of young CAD is heterogeneous. Conventional atherosclerotic disease accounts for approximately 80% of CAD in young adults. The remaining cases are attributable to a heterogeneous group of non-atherosclerotic mechanisms including congenital coronary anomalies, coronary embolism, hypercoagulable states, vasospasm, spontaneous coronary artery dissection, inflammatory vasculopathies, and substance abuse [2].

A particularly important pathophysiological concept in young CAD is positive vascular remodelling. Coronary segments with non-significant stenosis and non-calcified plaques undergo outward remodelling, maintaining apparently unrestricted luminal blood flow while concealing a growing, unstable plaque beneath. Such plaques, lipid-rich, non-calcified, and positively remodelled are substantially more prone to rupture and erosion than the heavily calcified, negatively remodelled plaques of older patients [48, 49]. This explains why young MI patients not infrequently present with angiographically normal or near-normal coronary arteries: an occlusive thrombus formed by rupture of an angiographically invisible vulnerable plaque may lyse spontaneously within hours, or prolonged vasospasm may cause complete, transient occlusion of a structurally normal vessel [54, 55].

Non-Atherosclerotic Mechanisms

A subset of young MI estimated at 5–15% of cases depending on the thoroughness of investigation occurs in the absence of significant obstructive atherosclerosis. These cases require a different diagnostic algorithm and carry distinct management and prognostic implications.

Spontaneous Coronary Artery Dissection (SCAD)

The mean age of presentation of spontaneous coronary artery dissection (SCAD) is 35–40 years, and the condition is substantially more common in females [56]. Patients are broadly categorised into peripartum, atherosclerotic, and idiopathic groups. The mechanism involves a tear in the tunica intima allowing blood to penetrate and form an intramural haematoma within the tunica media, compressing the true lumen and precipitating ischaemia or infarction [57]. SCAD is now recognised as an important cause of MI in women younger than 50 years and may account for up to one-third of cases in selected registry populations [14]. Distinctive associations include fibromuscular dysplasia, extreme physical or emotional stress, the peripartum period, and connective tissue disorders such as Marfan syndrome and Ehlers-Danlos syndrome [15].

Optical coherence tomography (OCT) significantly improves diagnostic accuracy by directly visualising the intimal tear or intramural haematoma where angiography may be equivocal [16]. Percutaneous coronary intervention in SCAD carries higher complication rates than in atherothrombotic disease, and conservative management is preferred in haemodynamically stable patients without ongoing ischaemia [14]. Long-term management should include evaluation for systemic arteriopathy and psychological support, given high rates of post-SCAD anxiety, recurrence, and post-traumatic stress.

Coronary Artery Spasm

Vasospastic angina characterised by episodic, reversible coronary constriction usually occurring at rest can precipitate MI and sudden cardiac death even in the absence of fixed stenosis. It is more prevalent in younger patients, in smokers, and in East Asian populations [17]. The pathophysiology involves vascular smooth muscle hyperreactivity, possibly related to endothelial nitric oxide deficiency and enhanced Rho-kinase signalling [19]. Calcium channel blockers and nitrates are the mainstay of treatment, with strict avoidance of cocaine and tobacco, both of which are potent vasospastic triggers.

Coronary Thromboembolism

Embolic occlusion of a coronary artery from atrial fibrillation, infective endocarditis, paradoxical embolism through a patent foramen ovale, or left atrial myxoma accounts for a small but diagnostically important subset of young MI [23]. The index of suspicion should be elevated in young patients with no conventional risk factors, particularly those with a history of paroxysmal palpitations, a recent febrile illness, or simultaneous evidence of systemic embolism. Transoesophageal echocardiography and prolonged cardiac monitoring for occult arrhythmia are essential components of the diagnostic workup.

Thrombophilia and Hypercoagulable States

Inherited thrombophilias viz. Factor V Leiden, prothrombin gene mutations, and protein C and S deficiency are occasionally implicated in arterial thrombosis in young patients, though their association is weaker for arterial than venous events [24]. Antiphospholipid syndrome is a more consistently demonstrated cause of premature coronary thrombosis. Homocysteinaemia, whether heritable (via MTHFR polymorphisms) or acquired (through vitamin B12 or folate deficiency), is another recognised contributor [34-35]. Testing for these conditions should be deferred at least 12 weeks after an acute event to avoid false-positive results related to acute phase reactivity.

Clinical Presentation

Young patients with acute MI do not always present in the textbook fashion. While chest pain remains the dominant symptom, younger individuals particularly women are more likely to present with atypical features including dyspnoea, fatigue, nausea, jaw pain, or arm discomfort without a prominent chest pain component [58]. There is a well-documented tendency for clinicians to underestimate the probability of MI in young patients, and multiple studies have shown that young women experience longer door-to-balloon times than either young men or older women, a disparity that has persisted over decades [4]. Mortality after an acute coronary event is approximately twice as high in women as in men under 50 years of age [59, 60], a striking sex disparity whose mechanistic explanation remains incompletely understood.

The psychological dimension of young MI is clinically significant and frequently under-addressed. A young person facing MI must simultaneously contend with the acute physiological threat, profound disruption to self-image, concerns about employment and financial security, the impact on family relationships, and an abrupt encounter with their own mortality. Rates of post-MI depression, anxiety, and post-traumatic stress disorder are higher in young patients than in older ones, and untreated psychological distress is an independent predictor of adverse cardiac outcomes [25].

Diagnostic Evaluation

The standard diagnostic evaluation for acute MI including electrocardiography, high-sensitivity troponin measurement, echocardiography, and coronary angiography applies equally in young patients. What distinguishes the workup in this population is the aetiological investigation that must follow. In an elderly patient with multiple traditional risk factors, atherothrombotic disease can be assumed with reasonable confidence. In a young patient, this assumption is far more dangerous.

Angiographic findings in young CAD differ importantly from those in older patients. Young CAD patients have higher rates of normal coronary vessels or mild luminal irregularities on angiography [16]. Data from a Nepalese series of young CAD patients (under 45 years) found that 53.8% had single vessel disease, 36.9% had double vessel disease, 6.1% had triple vessel disease, and 7.6% had normal or non-critical disease [61]. The prevalence of entirely normal coronary arteries in young MI patients is reported at 8% to 22% across various series [62-64], compared to 3% to 4% in general subjects of the same age [19]. Single vessel disease involving the left anterior descending artery is disproportionately common in young women compared to young men [65, 66].

The minimum aetiological investigation in a young MI patient should include a fasting lipid profile with Lp(a), HbA1c, thrombophilia screen (deferred 12 weeks if possible), antiphospholipid antibodies, inflammatory markers, autoimmune screen (ANA, dsDNA, ANCA, complement), urine toxicology, and intravascular imaging at the time of angiography if the coronary anatomy appears non-obstructive or SCAD is suspected. Genetic testing for FH should be pursued where the clinical profile is consistent. Intravascular OCT should be considered whenever angiography reveals normal or near-normal vessels in the context of a definite acute MI, as it may reveal SCAD, plaque erosion, or spontaneous thrombus that would otherwise be missed.

Management

Acute Management

The immediate management of STEMI and NSTEMI in young patients follows established evidence-based protocols — primary PCI for STEMI, antiplatelet and anticoagulant therapy, and early invasive strategy for high-risk NSTEMI. In young CAD patients undergoing revascularisation, both PCI and coronary artery bypass grafting (CABG) are associated with excellent immediate and long-term survival outcomes, with 30-day mortality of 0.8% and 1.4% for PCI and CABG respectively [67]. PCI appears associated with lower rates of repeated acute coronary events and revascularisation at five years, with repeat MI rates of 89.9% versus 96.6% freedom from re-MI for PCI versus CABG [68]. Family history of premature CAD did not significantly affect mortality outcomes in the large HORIZONS-AMI trial [69].

In cocaine-associated MI, benzodiazepines and calcium channel blockers are preferred for managing vasospasm; beta-blockers should be avoided acutely [13]. In SCAD, conservative management is recommended unless haemodynamic compromise or refractory ischaemia necessitates intervention, given the higher procedural complication rates [14].

Long-Term Secondary Prevention

Secondary prevention in young MI survivors carries particular weight given their long expected lifespan. High-intensity statin therapy targeting an LDL-cholesterol below 1.4 mmol/L (55 mg/dL) is recommended in line with ESC/EAS guidelines for very high cardiovascular risk [26]. Asymptomatic individuals with a positive family history of premature CAD and elevated coronary artery calcium scores (above the 80th percentile) benefit from primary prevention statin therapy, as demonstrated in the St. Francis Heart Study [70].

Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is typically maintained for 12 months following acute MI, with extended therapy considered in high-ischaemic-risk patients. Cardiac rehabilitation has robust evidence for reducing mortality and improving quality of life across all age groups, yet remains substantially underutilised in young patients. Work and family commitments, a perception that rehabilitation programmes are not designed for their age group, and an underestimation of their own ongoing risk all contribute to non-attendance. Home-based and digitally delivered rehabilitation programmes represent important alternatives for this demographic.

Fertility and Pregnancy Counselling

Young women who have experienced MI require individualised counselling regarding future pregnancies. Women with a history of myocardial infarction should undergo preconception counselling and specialist cardiovascular evaluation before pregnancy, as underlying coronary artery disease may increase the risk of adverse maternal and fetal outcomes, particularly in those with residual ventricular dysfunction or persistent myocardial ischaemia [71]. Statins, ACE inhibitors, and ARBs are contraindicated in pregnancy and must be substituted with appropriate

alternatives ahead of any planned conception.

Prognosis

In general, CAD in the young carries a better prognosis than CAD in older subjects, largely reflecting lower rates of comorbidity, less extensive coronary disease, and better baseline ventricular function. However, this relative optimism must be tempered by several important observations. Mortality due to CAD in younger populations does not appear to be declining at the same rate as in older populations, an important divergence from the epidemiological trends seen over the past three decades [72]. In China, mortality from CAD in individuals under 40 years rose from 13.81 per 100,000 in 2006 to 19.07 per 100,000 in 2009 [73], and similar unfavourable trends have been observed elsewhere, driven by worsening metabolic risk profiles in younger generations.

High C-reactive protein predicts recurrence of coronary events, while elevated fibrinogen is associated with increased mortality in this population [39]. The sex disparity in acute outcomes is notable: mortality after an acute coronary event is approximately twice as high in women as in men under 50 years of age, though the mechanism underlying this excess female mortality remains incompletely characterised [59, 60].

Long-term follow-up data confirm that young MI survivors carry a substantially elevated risk of recurrent events, heart failure, and death compared to age- and sex-matched controls. Rates of guideline-adherent secondary prevention in young MI survivors are disappointing, with statin discontinuation within one year more common in young patients than in older ones likely reflecting a perception that the MI was a singular event rather than the manifestation of a chronic underlying condition. Psychosocial recovery represents an additional dimension of prognosis that is seldom captured in outcomes registries: young MI survivors report significantly higher rates of depression, anxiety, and post-traumatic stress disorder than the general population, and these psychiatric comorbidities impair medication adherence, exercise participation, and overall quality of life .

Conclusion

Coronary artery disease presenting in the young is a clinically distinct entity shaped by a risk factor profile that differs from late-onset disease in both composition and relative weight. In addition to conventional risk factors of which smoking remains overwhelmingly dominant, genetic polymorphisms in lipoprotein metabolism genes, novel biomarkers including Lp(a) and GGT, cutaneous markers of premature ageing, and a range of systemic conditions all contribute meaningfully to the burden of premature CAD. The pathophysiological substrate is heterogeneous: while conventional atherosclerotic disease accounts for the majority of cases, a clinically important minority is attributable to SCAD, vasospasm, thromboembolism, and hypercoagulable states, each demanding a distinct diagnostic and management approach.

The overall prevalence of CAD may be on a decreasing trend in older age groups, but this progress does not extend reliably to young patients, in whom risk factor burdens are worsening and mortality trends are concerning. The growing epidemiological burden of young CAD demands not only improved clinical frameworks at the individual level including more systematic aetiological investigation, cascade genetic screening, and long-term secondary prevention but sustained public health investment in addressing the upstream drivers of premature atherosclerosis: the escalating prevalence of tobacco use, metabolic syndrome, and sedentary lifestyles in younger generations worldwide. Young CAD should no longer be viewed as an uncommon clinical curiosity. Its rising prevalence, unique etiological spectrum, and profound socioeconomic consequences demand earlier preventive strategies, systematic evaluation for inherited and non-atherosclerotic causes, and lifelong adherence to secondary prevention measures.

References

[1] Cole JH, Miller JI, Sperling LS, Weintraub WS. Long-term follow-up of coronary artery disease presenting in young adults. J Am Coll Cardiol. 2003; 41: 521–528.

[2] Egred M, Viswanathan G, Davis GK. Myocardial infarction in young adults. Postgrad Med J. 2005; 81(962): 741–745.

[3] Wu P, Yu S, Wang J, et al. Global burden, trends, and inequalities of ischemic heart disease among young adults from 1990 to 2019: a population-based study. Front Cardiovasc Med. 2023; 10: 1274663.

[4] Arora S, Stouffer GA, Kucharska-Newton AM, et al. Twenty year trends and sex differences in young adults hospitalized with acute myocardial infarction. Circulation. 2019; 139(8): 1047–1056.

[5] Berenson GS, Srinivasan SR, Bao W, et al. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. N Engl J Med. 1998; 338(23): 1650–1656.

[6] Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J. 2014; 35: 2929.

[7] Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction: an update on the Framingham study. N Engl J Med. 1984; 311: 1144–1147.

[8] Centers for Disease Control and Prevention (CDC) Prevalence of coronary heart disease–United States, 2006-2010. MMWR Morb Mortal Wkly Rep. 2011; 60: 1377–1381.

[9] Lichtman JH, Leifheit EC, Safdar B, et al. Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction. Circulation. 2018; 137(8): 781–790.

[10] Kam R, Cutter J, Chew SK, et al. Gender differences in outcome after an acute myocardial infarction in Singapore. Singapore Med J. 2002; 43: 243–248.

[11] Sharma M, Ganguly NK. Premature coronary artery disease in Indians and its associated risk factors. Vasc Health Risk Manag. 2005; 1: 217–225.

[12] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study). Lancet. 2004; 364: 937–952.

[13] McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association. Circulation. 2008; 117(14): 1897–1907.

[14] Hayes SN, Kim ESH, Saw J, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. Circulation. 2018; 137(19): e523–557.

[15] Saw J, Mancini GBJ, Humphries KH. Contemporary review on spontaneous coronary artery dissection. J Am Coll Cardiol. 2016; 68(3): 297–312.

[16] Zimmerman FH, Cameron A, Fisher LD, Ng G. Myocardial infarction in young adults: angiographic characterization, risk factors and prognosis (Coronary Artery Surgery Study Registry). J Am Coll Cardiol. 1995; 26: 654–661.

[17] Aggarwal A, Aggarwal S, Sarkar PG, Sharma V. Predisposing factors to premature coronary artery disease in young (age $\leq$ 45 years) smokers. J Cardiovasc Thorac Res. 2014; 6: 15–19

[18] Gori T, Münzel T. Oxidative stress and endothelial dysfunction: therapeutic implications. Ann Med. 2011; 43(4): 259–272.

[19] Aggarwal A, Aggarwal S, Goel A, Sharma V, Dwivedi S. A retrospective case-control study of modifiable risk factors and cutaneous markers in Indian patients with young coronary artery disease. JRSM Cardiovasc Dis. 2012; 1: pii:cvd.2012.012010.

[20] Aggarwal A, Aggarwal S, Sharma V. Cardiovascular risk factors in young patients of coronary artery disease: differences over a decade. J Cardiovasc Thorac Res. 2014; 6: 169–173.

[21] Otaki Y, Gransar H, Berman DS, et al. Impact of family history of coronary artery disease in young individuals (from the CONFIRM registry). Am J Cardiol. 2013; 111: 1081–1086.

[22] Choi J, Daskalopoulou SS, Thanassoulis G, et al. Sex- and gender-related risk factor burden in patients with premature acute coronary syndrome. Can J Cardiol. 2014; 30: 109–117.

[23] Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study). Lancet. 2004; 364: 937–952.

[24] Pineda J, Marín F, Marco P, et al. Premature coronary artery disease in young (age $<$45) subjects: interactions of lipid profile, thrombophilic and haemostatic markers. Int J Cardiol. 2009; 136: 222–225.

[25] Setia N, Verma IC, Khan B, Arora A. Premature coronary artery disease and familial hypercholesterolaemia: need for early diagnosis and cascade screening in the Indian population. Cardiol Res Pract. 2012; 2012: 658526.

[26] Anderson JL, Horne BD, Camp NJ, et al. Joint effects of common genetic variants from multiple genes and pathways on the risk of premature coronary artery disease. Am Heart J. 2010; 160: 250–256.

[27] Abd El-Aziz TA, Mohamed RH. Human C-reactive protein gene polymorphism and metabolic syndrome are associated with premature coronary artery disease. Gene. 2013; 532: 216–221.

[28] Kay A, März W, Hoffmann MM, et al. Coronary artery disease and dyslipidemia within Europe: genetic variants in lipid transport gene loci in German subjects with premature coronary artery disease. Atheroscler Suppl. 2002; 3: 27–33.

[29] López-Reyes A, Rodríguez-Pérez JM, Fernández-Torres J, et al. The HIF1A rs2057482 polymorphism is associated with risk of developing premature coronary artery disease. Exp Mol Pathol. 2014; 96: 405–410.

[30] Kanth VV, Golla JP, Sastry BK, et al. Genetic interactions between MTHFR (C677T), methionine synthase variants with vitamin B12 and folic acid determine susceptibility to premature coronary artery disease in Indian population. J Cardiovasc Dis Res. 2011; 2: 156–163.

[31] Kuivenhoven JA, Jukema JW, Zwinderman AH, et al. The role of a common variant of the cholesteryl ester transfer protein gene in the progression of coronary atherosclerosis. N Engl J Med. 1998; 338: 86–93.

[32] Nieminen MS, Mattila KJ, Aalto-Setälä K, et al. Lipoproteins and their genetic variation in subjects with and without angiographically verified coronary artery disease. Arterioscler Thromb. 1992; 12: 58–69.

[33] Eto M, Watanabe K, Makino I. Increased frequencies of apolipoprotein epsilon 2 and epsilon 4 alleles in patients with ischemic heart disease. Clin Genet. 1989; 36: 183–188.

[34] Brattström L, Wilcken DE, Ohrvik J, Brudin L. Common methylenetetrahydrofolate reductase gene mutation leads to hyperhomocysteinaemia but not to vascular disease: the result of a meta-analysis. Circulation. 1998; 98: 2520–2526.

[35] Danesh J, Lewington S. Plasma homocysteine and coronary heart disease: systematic review of published epidemiological studies. J Cardiovasc Risk. 1998; 5: 229–232.

[36] Chatterjee C, Sparks DL. Hepatic lipase, high density lipoproteins, and hypertriglyceridaemia. Am J Pathol. 2011; 178: 1429–1433.

[37] Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease. Consensus Statement of the European Atherosclerosis Society. Eur Heart J. 2013; 34(45): 3478–3490.

[38] Pineda J, Marín F, Marco P, et al. Premature coronary artery disease in young (age <45) subjects: interactions of lipid profile, thrombophilic and haemostatic markers. Int J Cardiol. 2009 136: 222–225.

[39] van Loon JE, de Maat MP, Deckers JW, van Domburg RT, Leebeek FW. Prognostic markers in young patients with premature coronary heart disease. Atherosclerosis. 2012; 224: 213–217.

[40] Rezkalla SH, Kloner RA. Cocaine-induced acute myocardial infarction. Clin Med Res. 2007; 5: 172–176.

[41] Shabbir S, Khan DA, Khan FA, et al. Serum gamma glutamyl transferase: a novel biomarker for screening of premature coronary artery disease. Cardiovasc Revasc Med. 2011; 12: 367–374.

[42] Goliasch G, Blessberger H, Azar D, et al. Markers of bone metabolism in premature myocardial infarction ($\leq$ 40 years of age). Bone. 2011; 48: 622–626.

[43] Goliasch G, Wiesbauer F, Kastl SP, et al. Premature myocardial infarction is associated with low serum levels of Wnt-1. Atherosclerosis. 2012; 222: 251–256.

[44] Sood A, Arora R. Vitamin D deficiency and its correlations with increased cardiovascular incidences. Am J Ther. 2010; 17: e105–109.

[45] Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. Curr Opin Clin Nutr Metab Care. 2008; 11: 7–12.

[46] Dobnig H, Pilz S, Scharnagl H, et al. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. Arch Intern Med. 2008; 168: 1340–1349.

[47] Klein LW. Acute coronary syndromes in young patients with angiographically normal coronary arteries. Am Heart J. 2006; 152: 607–610.

[48] Tanaka M, Tomiyasu K, Fukui M, et al. Evaluation of characteristics and degree of remodeling in coronary atherosclerotic lesions by 64-detector MSCT. Atherosclerosis. 2009; 203: 436–441.

[49] Kullo IJ, Edwards WD, Schwartz RS. Vulnerable plaque: pathobiology and clinical implications. Ann Intern Med. 1998; 129: 1050–1060.

[50] de Saint Martin L, Vandhuick O, Guillo P, et al. Premature atherosclerosis in HIV positive patients and cumulated time of exposure to antiretroviral therapy (SHIVA study). Atherosclerosis. 2006; 185: 361–367

[51] Othman KMS, Assaf NY. Early detection of premature subclinical coronary atherosclerosis in systemic lupus erythematosus patients. The Egyptian Heart Journal. 2013; 65: 281–288.

[52] Honigberg MC, Zekavat SM, Aragam K, et al. Association of premature natural and surgical menopause with incident cardiovascular disease. JAMA. 2019; 322(24): 2411–2421.

[53] Dokras A, Bochner M, Hollinrake E, et al. Screening women with polycystic ovary syndrome for metabolic syndrome. Obstet Gynecol. 2005; 106(1): 131–137.

[54] Chandrasekaran B, Kurbaan AS. Myocardial infarction with angiographically normal coronary arteries. J R Soc Med. 2002; 95: 398–400.

[55] Alpert JS. Myocardial infarction with angiographically normal coronary arteries. Arch Intern Med. 1994; 154: 265–269.

[56] DeMaio SJ, Kinsella SH, Silverman ME. Clinical course and long-term prognosis of spontaneous coronary artery dissection. Am J Cardiol. 1989; 64: 471–474.

[57] Dhawan R, Singh G, Fesniak H. Spontaneous coronary artery dissection: the clinical spectrum. Angiology. 1979; 53: 89–93.

[58] Canto JG, Goldberg RJ, Hand MM, et al. Symptom presentation of women with acute coronary syndromes: myth vs reality. Arch Intern Med. 2007; 167(22): 2405–2413.

[59] Sharma K, Gulati M. Coronary artery disease in women: a 2013 update. Glob Heart. 2013; 8: 105–112.

[60] Vaccarino V, Badimon L, Corti R, et al. Presentation, management, and outcomes of ischaemic heart disease in women. Nat Rev Cardiol. 2013; 10: 508–518.

[61] Tamrakar R, Bhatt YD, Kansakar S, et al. Acute myocardial infarction in young adults: study of risk factors, angiographic features and clinical outcome. Nepalese Heart Journal. 2014; 10: 12–16.

[62] Kaul U, Dogra B, Manchanda SC, et al. Myocardial infarction in young Indian patients: risk factors and coronary arteriographic profile. Am Heart J. 1986; 112: 71–75.

[63] Gohlke H, Gohlke-Bärwolf C, Stürzenhofecker P, et al. Myocardial infarction at young age — correlation of angiographic findings with risk factors and history in 619 patients. Circulation. 1980; (Suppl III)62: 39

[64] Lim YT, Ling LH, Tambyah PA, Choo MH. Myocardial infarction in patients aged 40 years and below: an angiographic review. Singapore Med J. 1996; 37: 352–355.

[65] Li Z, Li ZZ, Gao YL, et al. Clinical and coronary angiographic features of young women with acute myocardial infarction. Zhonghua Xinxue Guanbing Zazhi. 2012; 40: 225–230.

[66] Liu W, Mukku VK, Liu YY, et al. Long-term follow up of percutaneous coronary intervention in women $\leq$ 45 years of age. Am J Cardiol. 2013; 112: 918–922.

[67] Fournier JA, Sánchez A, Quero J, et al. Myocardial infarction in men aged 40 years or less: a prospective clinical-angiographic study. Clin Cardiol. 1996; 19: 631–636.

[68] Biancari F, Gudbjartsson T, Heikkinen J, et al. Comparison of 30-day and 5-year outcomes of PCI versus CABG in patients aged $\leq$ 50 years (the CRAGAS Study). Am J Cardiol. 2014; 114: 198–205.

[69] Ertelt K, Généreux P, Mintz GS, et al. Clinical profile and impact of family history of premature CAD in patients undergoing primary PCI for STEMI: analysis from the HORIZONS-AMI Trial. Cardiovasc Revasc Med. 2014; 15: 375–380.

[70] Mulders TA, Sivapalaratnam S, Stroes ES, et al. Asymptomatic individuals with a positive family history for premature CAD and elevated coronary calcium scores benefit from statin treatment: a post hoc analysis from the St. Francis Heart Study. JACC Cardiovasc Imaging. 2012; 5: 252–260.

[71] Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J. 2018; 39: 3165–3241.

[72] Nichols M, Townsend N, Scarborough P, Rayner M. Trends in age-specific coronary heart disease mortality in the European Union over three decades: 1980–2009. Eur Heart J. 2013; 34: 3017–3027.

[73] Yang WX, Yang Z, Wu YJ, et al. Factors associated with coronary artery disease in young population (age $\leq$ 40): analysis with 217 cases. Chin Med Sci J. 2014; 29: 38–42.