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Premature Myocardial Infarction: A Rising Threat

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Myocardial infarction mostly presents with atypical signs and symptoms and has different risk factors in young individuals compared to older individuals. These risk factors are often preventable, therefore recognizing them and taking precautions can save these patients from suffering myocardial infarction. Scarcity of studies and lack of guidelines for assessment and management of young MI patients, make it more challenging for these individuals to get accurate medical care, even though MI in this age group is on the rise. Traditional risk factors, such as smoking, hyperlipidemia, hypertension, male sex, obesity, and family history of premature cardiovascular disease, contribute to the risk of myocardial infarction at a young age, but additional non-traditional risk factors, such as substance abuse, thrombophilia, coronary anomalies, immune disease, allergic reactions, and psychological stressors, uniquely contribute to the risk profile of young individuals. This review is aimed to discuss and guide the risk factor assessment for the development of myocardial infarction in young individuals based on current evidence and our >20-year of experience in Young Myocardial Infarction Clinic.

The risk of a cardiovascular event increases with age. Myocardial infarction (MI) is rarely expected at younger ages and is accepted as a disease of older ages. However, premature MI is on the rise and is a leading cause of premature death worldwide. A possible reason of this rise may be the increased prevalence of traditional atherosclerotic cardiovascular disease (ASCVD) risk factors, such as hypertension, dyslipidemia, diabetes mellitus (DM), and smoking, among younger age groups.[1,2] Additional risk factors, such as drug abuse and acquired or inherited causes of hemostatic dysfunction, should not be overlooked. Currently, the coronavirus disease-2019 (COVID-19) pandemic has accelerated the increased numbers of young individuals suffering from MI.[3]

The proportion of MIs in young individuals varies according to the age limit used to define young MI in studies and is generally reported as 5%–13%.[1,4-7] The MI incidence for a 10-year follow-up was 12.9, 38.2, and 71.2 per 1000 in males and 2.2, 5.2, and 13.0 per 1000 in females in the age groups of 30–34, 35–44, and 45–54 years, respectively, in the Framingham Heart Study.[8] Young MI prevalence in some countries like Turkey and MENA region is unexpectedly high and constitutes a major health problem.[9-14] MI prevalence before the age of 50 years is 12% in Europe in the EUROASPIRE IV study, whereas 19% in the Turkish arm of the study.[11] In the same study, the mean age of patients with an acute coronary syndrome (ACS) for the European countries was 62.5 ± 9.6 years, whereas 58.6 ± 10.3 years for Turkey.

The clinical course, risk factors, and coronary anatomy of MIs that develop at a young age differ from those at older ages.[15] Young patients with MI usually have a better short-term prognosis than middle-aged and elderly patients.[16,17] In the TUMAR study in the early 2000s, in-hospital mortality of acute MI was significantly lower in patients aged <50 years than in other age groups.[10,11,18,19] Long-term survival is also considered better in younger patients compared to older patients presenting with MI. However, the 10-year survival of a person with MI at the age of 40 will be considerably shorter than that of those aged 60 years.[16] Therefore, attending physicians should be aware of the differential characteristics of premature MIs and the need for a more comprehensive approach to these patients. All available evidence highlights the importance of earlier interventions to modify the risk factor profile and lifestyle approaches in those with premature MI.[20] Moreover, the decrease afforded in the incidence of ACS in the last decades is valid in older populations, not in younger males and females who present with MI. This review is aimed to discuss and assess the risk factors that account for MI development in young individuals based on current evidence and our >20-year of experince in young MI Clinic.[17]

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DEFINITION AND CUT-OFF AGE FOR MYOCARDIAL INFARCTION IN YOUNG INDIVIDUALS

A universal definition or diagnostic criteria of premature MI is unavailable. Moreover, due to the lack of a consensus for a universally accepted age cut-off for defining young MI, there is a disparity in the literature; some studies vary from ≤40 to ≤55 years of age and others define young MI as <45 years of age.[21-25] Most registries and studies have preferred to use a cut-off age of 40–45 years to define "young" patients with coronary artery disease (CAD) or acute MI. However, a stratification approach of these patients by different factors seems more appropriate based on our experience.[17] These patients can be divided into two groups, as also proposed by the recent literature,[1] based on the age of the first MI. The classification of patients who had their first heart attack earlier than 40 years of age as 'very young' MI patients, and those who had the first MI between ages 40 and 50 as 'young' MI patients may appear to be rational. This approach may also oversee the important differences with sex, race, and genetics. It's obvious that either very young or young, both age groups require aggressive secondary prevention.[1,26,27]

Generally, type 1 MI, which is caused by atherosclerotic damage and rupture or erosion of a preexisting plaque, is considered when mentioning premature MI. However, understanding that young individuals could suffer from all types of MI is important. Additionally, even with the recent more comprehensive MI definition, it still underestimates other causes of troponin elevation that are unique to younger patients such as autonomic neurocardiogenic syndrome.[28]

RISK FACTORS

The distribution of etiological risk factors differs in MIs in young individuals than the older ones. The traditional risk factors account for almost 80%–85% of premature MIs, whereas 15%–20% of are due to other factors that trigger thrombosis and/or inflammation, so-called non-atherosclerotic risk factors,[20,29] which constitute only the 5% of MIs at older ages.[30-32] Yang et al. highlighted that patients with very young MI aged <40 years are more likely to use both marijuana and cocaine compared to older patients, and patients with young MI between the ages 40 to 50 years are more likely to have traditional risk factors including hypertension, peripheral vascular disease, and higher ASCVD scores.[1,4] Patients with young MI usually have multiple risk factors, and a cumulative number of these factors significantly increase morbidity and mortality.[15] Factors that are involved in the etiology should be carefully examined to effectively prevent the re-infarction or further cardiovascular events in patients with young MI. Table 1 and Figure 1 depict the factors that play a role in the development of young MI.

Traditional Atherosclerotic Cardiovascular Disease Risk Factors

Atherosclerosis is well-known to generate at early ages. The fatty streaks, which could be attributed as the precursors of atheroma, are the cholesterol deposits in the arterial intima and appear in very early childhood. A postmortem study revealed that 20% of males and 8% of females have atherosclerotic CAD at the mean age of 30–34 years.[33] Whereas, the prevalence of CAD was 50% in cardiac donors with a mean age of 30–33 years as detected by intravascular ultrasound.[34] In the same study, coronary atherosclerotic lesions were observed in one in six teenage patients. Consequently, the immense presence of atherosclerotic risk factors since early childhood may expose to premature atherosclerosis, thereby leading to early MIs. Therefore, early detection and effective treatment of high-risk young individuals are extremely important for the prevention of early MIs and premature mortality.

One of the earliest studies regarding ASCVD risk factors in patients with young MI, published in 1987 by Weinberger et al,[35] presented the most common risk factor for these individuals as smoking with a prevalence of 66%. Among these patients (≤30 years of age), 56% reported a smoking history of 20 or more cigarettes per day and only 10% were smoking <10 cigarettes per day. There is no doubt that smoking is the most common and modifiable risk factor in young MIs.[27] Smoking is reported in 65%–92% of young patients with MI and 24%–56% in older patients with MI.[6,15]

Cardiometabolic factors, including obesity, DM, and dyslipidemias, could trigger or promote the development of MI at early ages. Hypertension and DM are less common in young patients with MI than those at older ages, in whom the most common risk factor for MI is hypertension by far.[36,37] DM has been present in only 3%–5% of patients with MI aged <45 years.[38] However, patients with MI at younger ages frequently have subtle problems of glucose metabolism. A study of 108 patients without overt DM who had young MI before the age of 45 years revealed that impaired glucose response to oral glucose challenge was present in 65%.[39]

Being overweight or obese is significantly more common in younger patients with ASCVD than in older patients. The Framingham experience has denoted that obesity in middle-aged individuals could account for 15% of CAD cases in females and

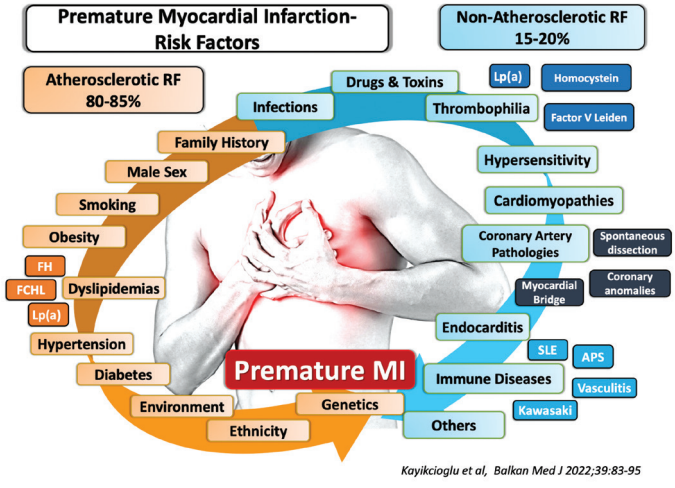

FIG. 1. Risk factors associated with premature myocardial infarction

APS, antiphospholipid antibody syndrome; FCHL, familial combined hyperlipidemia; FH, familial hypercholesterolemia; Lp(a), lipoprotein (a); MI, myocardial infarction; RF, risk factor; SLE; systemic lupus erythematosus

TABLE 1. Etiological Factors for the Development of Young Myocardial Infarction

A. Atherosclerotic factors (frequency 80%–85%)	B. Non-Atherosclerotic factors (frequency 15%–20%)
Family history of premature ASCVD	**Drugs and toxins** • Substance abuse (amphetamines, cocaine, marijuana, etc.) • Oral contraceptives • Anabolic steroids • Binge drinking • Antiretrovirals
Smoking Male Sex Obesity Diabetes Mellitus Hypertension	**Coronary artery pathologies** • Anomalous coronary arteries, coronary fistulas • Myocardial bridge • Spontaneous dissection (Pregnancy, inflammatory diseases, hyperhomocysteinemia, etc.)
Dyslipidemias Familial Hypercholesterolemia,Familial Combined Hyperlipidemia, Elevated Lipoprotein (a) Other ultra-rare genetic dyslipidemias - Tangier disease (*ABCA1 mutations)* - Loss of expression of the scavenger receptor B1 (SR-B1) - LRP8/ApoER2 variants including single nucleotide polymorphism R952Q	**Immune-mediated inflammatory disease** • Connective tissue disorders (SLE, etc) • Vasculitis (Behçet's disease, Takayasu arteritis, Kawasaki disease, Giant cell arteritis, etc.) • Antiphospholipid antibodies
Ethnicity, Founder effect, Consanguinity	**Allergic reactions and hypersensitivity** (Kounis syndrome, Eosinophilic coronary periarteritis, Eosinophilic granulomatosis with polyangitis, etc.)
Environmental factors (air pollution, socioeconomic status, etc.)	**Infections** (SARS-CoV-2, HIV, Chlamydia, Helicobacter pylori, etc.)
	Thrombophilia Factor V Leiden, Factor II G20210A, MTHFR mutations, Hyperhomocysteinemia, Protein C, Protein S, and Antithrombin-III deficiency; Protein Z A-13G, G-103A, and G79A Polymorphisms; Platelet glycoprotein VI 13254C alleles, PAI-1 4G allele, Thrombomodulin G-33A polymorphism, Factor VII Arg/Gln(353), Factor V (G1691A)
	Others • Patent foramen ovale (paradoxical embolism) • Radiotherapy, • Tumors • Endocarditis • Cardiomyopathies
	Other genetic factors
	• Hutchinson-Gilford progeria syndrome (*LMNA* mutations) • Fragile arteries (*NOTCH1* mutations) • Generalized arterial calcification of infancy (*ENPP1* and *ABCC6* mutations) • Pseudoxanthoma elasticum (*ABCC6* mutations) • Kabuki Syndrome (*KMT2D* and *KDM6A mutations)* • *ACE*-DD genotype • *MEF2A* mutations including 21-bp and 6-bp deletions, and N263S, P279L, and G283D polymorphisms • *SIRT1* polymorphisms • eNOS polymorphisms including G894T Glu298ASP, and T786C • *ELA2* deletions • *TNFRSF1A* polymorphism R92Q • *NTN1* variant Arg590Leu

ASCVD: Atherosclerotic Cardiovascular Disease; CAD: Coronary artery disease; HIV: Human immunodeficiency virus; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; MI: myocardial infarction; SLE: Systemic lupus erythematosus; MTHFR: Methylenetetrahydrofolate Reductase; PAI-1: plasminogen activator inhibitor-1; *LRP8/ApoER2*: LDL receptor Related Protein 8/ Apolipoprotein E receptor 2; *SIRT1*: sirtuin 1 ; eNOS: endothelial nitric oxide synthase; *ELA2*: Elastase 2; *TNFRSF1A*: TNF Receptor Superfamily Member 1A; *ABCA1:* ATP-Binding Cassette transporter A1*; NTN1:* Netrin 1; *LMNA: Lamin A: ENPP1:* ectonucleotide pyrophosphatase/phosphodiesterase 1; *ABCC6:* ATP-Binding Cassette Subfamily C Member 6; *KMT2D:* Lysine Methyltransferase 2D; *KDM6A:* Lysine Demethylase 6A; *MEF2A*: Myocyte Enhancer Factor 2A; *ACE-DD*: Angiotensin-I converting enzyme genotype deletion; *NOTCH1:* Notch homolog 1; translocation-associated

23% in males.[37] Moreover, obesity is suggested to increase the risk of MI by two to threefold in subjects aged <45 years.[40] However, the current exponential increase of obesity prevalence has been identified as a particular concern for the further increased incidence of young MIs.[15,41]

Primary and secondary dyslipidemias are commonly reported in young patients with CAD.[20] Increased low-density lipoprotein (LDL) and decreased high-density lipoprotein (HDL) levels have been more frequently detected in individuals with CAD before the age of 40 years compared with those who develop the disease after the age of 60 years.[42,43] Additionally, independent of LDL or HDL levels, elevated triglycerides are consistently identified in patients with early-onset ASCVD.[43] Patients with young MI have also higher levels of non-HDL-cholesterol.[44] Goliasch et al. revealed an association of non-HDL-cholesterol with MI in patients aged 40 years depicting an adjusted odds ratio (OR) of 5.02 (95% confidence interval [CI]: 2.75–9.15) compared to controls adjusted for age, sex and other traditional ASCVD risk factors.[44]

More than half of young patients experiencing MI are reported to have hyperlipidemia.[1,2,20,45] Inherited hyperlipidemias are also highly prevalent among patients with young MI. Especially familial hypercholesterolemia (FH) and familial combined hyperlipidemia (FCHL) account for an important proportion of premature ASCVD.[2,20] Wiesbauer et al. reported that approximately 50% of patients with young MI before the age of 40 years had FH or FCHL. In their young MI population, FCHL alone was associated with a 24-fold increased adjusted risk (95% CI: 7.5–81; $P < 0.001$) for MI.[45] FH is an inherited disease of special interest for preventive cardiology within the scope of premature ASCVD, including young MI, as these patients are exposed to high LDL-cholesterol levels since their birth unless being started on the lipid-lowering therapy at early ages.[46] FH has been clinically detected in almost 10% of patients who suffer from MI before the age of 50 years.[47] Patients with premature CAD have a >15-fold higher prevalence of FH mutations compared with the healthy controls.[48] Premature atherosclerosis is extremely common, particularly in patients with homozygous FH.[49] Specific mutation-positive FH patients are more susceptible to premature MI due to more severe coronary lesions compared to mutation-negative individuals. Additionally, polygenic forms of FH are more common, which might be associated with smaller risk of MI, compared with the monogenic FH.[48] It's also important to be aware that Dutch Lipid Network Criteria (DLNC) has the highest OR to detect FH in families with premature MI.[50]

Lipoprotein(a) (Lp[a]) is an apolipoprotein (apo)-B containing lipoprotein that is structurally similar to LDL but with an additional plasminogen-like domain that interferes with fibrinolysis.[51,52] High Lp(a) is an established independent risk factor for early ASCVD and aortic sclerosis. Singh et al. reported that one in three patients aged <50 years with MI had an Lp(a) level that exceeds the 80th percentile in the YOUNG-MI cohort.[47] Patients with premature atherosclerosis and their first-degree relatives have higher levels of Lp(a).[53] Moreover, children aged <18 years, who have premature atherosclerosis in their families, have two to three times higher Lp(a) levels.[54] More than 90% of the levels of Lp(a) are genetically determined, and the impact of high Lp(a) levels vary based on the race, with the highest rate in Asian Indians.[55]

Another factor to consider is the family history of premature ASCVD. Family history is reported in a wide range of 14% to 69% in patients with young MI in different series.[37] For example, 40% of the young patients with CAD have first-degree relatives with premature atherosclerosis.[42] However, in Weinberg's cohort, the family history of the ischemic disease was positive in only 4%.[35] This discrepancy is probably based on the different criteria used to define the family history of premature ASCVD (usually defined as documented ASCVD in a first-degree relative before 55–60 years of age) and the reliability of questioning (recall defect) the family history.[16] Nevertheless, younger patients with CAD more often have a family history of premature ASCVD compared to those with MI at older ages (41% compared to 28% in middle-aged or 12% elderly).[56] Additionally, the offspring of patients with premature CAD are more likely to have traditional ASCVD risk factors than those without such a family history.[57] These include cardiometabolic risk factors, including obesity, higher lipid levels, insulin resistance, and endothelial dysfunction.[58] Furthermore, the association between family history and premature atherosclerosis is not only due to genetic factors but also the shared environmental factors.[59] Environmental factors include lifestyle, air pollution, socioeconomic status, etc. Low socioeconomic status appears to be associated with an increased risk of MI, which may be even more profoundly exhibited in young individuals.[60]

Certain populations due to genetic and environmental factors may have an increased risk of young MI. A very large cohort of patients aged <40 years (n = approximately 12 million) of databases in the United States revealed that males were predominant, of which a greater portion of individuals was either African American or Hispanic.[61] Further, the Ashkenazi Jewish population revealed that a Lithuanian mutation, which has been known for >2 decades, leads to FH due to *LDL receptor* changes, thereby premature CAD.[62] Additionally, despite the lower prevalence of premature ASCVD in the developed Western World, the increase in South Asia and the MENA region cannot be hindered.[63,64] Noticeably, the high prevalence of consanguineous marriages in the MENA region, India, and Turkey constitute an important underlying cause of MI in young individuals through the increased prevalence of inherited rare dyslipidemias such as FH, FCHL, etc.

There is a large gender bias with most early MIs occurring in males. Male gender is particularly a strong risk factor for ASCVD in young individuals. Therefore, some researchers prefer to define *young age* as 5–10 years older for females than they define for males in ASCVD. Chan et al. reported that 90% of patients who suffer from MI aged <45 years were males compared to 68.4% (OR: 3.59; 95% CI: 2.37–5.44) of older patients.[65] Females constitute only 5%–15% of young patients with CAD compared with 40%–50% in older populations and overall, this proportion among the young MI is suggested to be growing with the increasing proportion of cardiometabolic risk factors and smoking in young females.[35,66] Several hormonal conditions, such as pregnancy and polycystic

ovary disease, increase the risk of young MI in females. Other hormonal pathologies, including congenital adrenal hyperplasia, Cushing's syndrome, and other androgen synthesizing tumors, may predispose to young MI in both males and females via elevated endogenous dehydroepiandrosterone sulfate (DHEA-S) levels. Excessive DHEA-S is an independent risk factor for premature MI but not for MI in individuals of ≥50 years of age.[67]

Non-Traditional Modifiable Risk Factors

A variety of non-atherosclerotic risk factors have been identified as promoters and/or contributors in young patients with MI (Table 1, Figure 1). These factors should be evaluated in all patients with MI under the age of 40 years. The younger the age of a patient with premature MI, the higher the possibility of the contribution of non-atherosclerotic risk factors.

Drugs and toxins: Obtaining a detailed drug history is paramount in younger patients with MI. Illicit drug use, particularly cocaine abuse, should be kept in mind in patients with young MI. Amphetamines trigger acute MI through increased sympathetic activity leading to coronary vasospasm and hypercoagulability. Cocaine induces these effects by blocking the presynaptic noradrenaline receptor uptake.[2] Moreover, long-term cocaine use accelerates atherosclerosis by interrupting the endothelial functions and increasing the cholesterol penetration to the intima.[68] Smoking marijuana may rarely trigger MI. A study of substance abuse in the YOUNG MI registry cohort revealed a 10.7% cocaine or marijuana use, which was significantly associated with long-term ASCVD and all-cause mortality.[68] Binge drinking may also be associated with MI and arrhythmias.

Physically active individuals, without an underlying medical condition, who use anabolic steroids or protein supplements may also have early MI.[69] Additionally, the use of oral contraceptives, even in low doses, may cause early MI, in females without other predisposing factors.[70]

Coronary Artery Pathologies: Coronary artery pathologies, including coronary congenital anomalies, aberrant anatomy of coronary arteries including fistulas, myocardial bridge, and spontaneous coronary artery dissection (SCAD), constitute important causes of MIs in the young population. Congenital CAD has been suggested to cause sudden cardiac death (5%–35%) in young individuals.[71] Abnormal coronary origin is an example of congenital CAD as a possible cause of young MI.[71] Aberrant course of a coronary artery between the aorta and pulmonary artery may lead to severe ischemia by narrowing the luminal diameter. An enlarged pulmonary artery in patients with severe pulmonary hypertension may also be a cause of young MI. Thrombophilia, either inherited or acquired, and hormone therapy could increase the risk of MI even in non-significant coronary abnormalities.

SCAD is a rare cause of MI in young individuals, particularly in females aged ≤40–50 years without other predisposing factors. One-third of all cases of pregnancy-associated MIs are related to SCAD.[72] However, SCAD is not a phenomenon reserved for pregnant women, which may be the cause of MI even in unexpected individuals such as professional athletes at a young age. Moreover, connective tissue disorders (i.e., Ehlers-Danlos syndrome and Marfan syndrome),[72] hormones, and systemic inflammatory diseases, such as Kawasaki disease and systemic lupus erythematosus (SLE) could be associated with SCAD. Of note, in more than half of the cases with SCAD leading to a MI, there are precipitating factors or events, i.e., intense exercise, emotional stress, cocaine, and vomiting etc. SCAD leads to a hematoma in the outer layers of the coronary arteries, creating a false lumen, which causes ischemia by compressing the true lumen. Mild atherosclerosis is also suggested to cause SCAD. Furthermore, SCAD is associated with fibromuscular dysplasia in >50% of cases.[6]

Myocardial bridging (MB) is a developmental anomaly of the coronary artery, usually the left anterior descending, anatomically passing through the myocardium, and mostly detected incidentally. Coronary compression during each systolic contraction may result in delayed opening during diastole leading to ischemia.[73] MB may be associated with coronary vasospasm. Moreover, systolic compression may trigger coronary atherosclerosis by causing endothelial injury.[73] MB is a rare cause of MI in general; however, its prevalence is relatively high in patients with young MI. A study that included 884 patients between the ages of 18 and 30 years with chest pain revealed that the most common coronary artery anomaly was MB with 17.3% compared with CAD, which was only detected in 4.3%.[74,38] Detecting MB in patients with chest pain is important as it may cause life-threatening arrhythmias even in the lack of apparent thrombo-embolism or atherosclerotic plaques

Immune-mediated Inflammatory Disease: Immune-mediated inflammatory diseases including connective tissue disorders and vasculitis can cause non-atherosclerotic MI in young individuals. Connective tissue disorders cause myocardial damage by several mechanisms such as a coronary artery or aortic dissection, coronary artery aneurysm formation, and thrombus formation. Granulomatous vasculitis, such as Takayasu's disease or Giant cell arteritis (Temporal arteritis), can affect the coronaries and result in MI. Takayasu's arteritis involves the major branches of the aorta and pulmonary arteries and rarely coronary arteries. Takayasu's disease usually affects the coronary ostia[75] and may present as an isolated coronary lesion in <5% of patients. Giant cell arteritis mainly affects large- and medium-sized vessels, most commonly temporal and vertebral arteries. Atherosclerosis may coexist with Giant cell arteritis and usually favors the anterior component of the polygon of Willis and the carotid system. Coronary involvement is rare but may ensue MI. Behçet's Disease may rarely affect the coronary arteries but should be questioned in all patients with young MI, particularly in males. Patients with immune-mediated inflammatory diseases are also prone to accelerated atherosclerosis.

Kawasaki Disease, which is a disease of children aged <5 years, can affect the coronaries leading to coronary aneurysm formation and/or dissection in children and young adults.[76] Post-Kawasaki disease patients are known to have triggered early atherosclerosis and have a higher MI risk probably due to vascular sequela.[20]

The autoimmune disorders, particularly the presence of antiphospholipid antibodies (APLA), can cause ACSs via increased coagulability. APLA can develop either alone or in conjunction with other immune disorders, such as SLE. Patients with SLE should always be considered as potential premature MI candidates, not only because they have the most common predominating rheumatic condition among the premature MI cohorts,[77] but because premature MI can be the first sign of SLE. Patients with SLE harbor a fivefold increased risk of ASCVD, even without APLA.[78] Immune complexes and complement activation in SLE enhance atherosclerosis initiated by endothelial injury and dysfunction.[2]

Allergic Reactions and Hypersensitivity: Kounis syndrome is a rare cause of coronary artery spasms due to hypersensitivity reaction, which may eventually result in type 2 MI. Drugs and contrast media, such as gadolinium, can result in Kounis syndrome.[79]

Eosinophilic coronary periarteritis (ECPA) is a rare cause of SCAD, which should raise the suspicion in atopic individuals for the risk of premature MI, as the results may be catastrophic. Young patients with ECPA tend to have a history of intermittent vasospastic angina with usually no other accompanying comorbidities. Another cause of eosinophilic tissue infiltration is eosinophilic granulomatosis with polyangitis (EGPA) (formerly known as Churg-Strauss Syndrome) has also the ability to invade the coronary arteries, resulting in granulomatous inflammation, mimicking CAD. The coronary lesions in these patients are usually responsive to immunosuppressive treatment, without a need for revascularization. The known history of EGPA or a previous history of airway hypersensitivity should hinder the recognition of this rare phenomenon.[80]

Infections: Acute and chronic infections increase the risk of MI and atherosclerosis. Acute infections by fever, tachycardia, hypoxia, etc. could lead to a mismatch between the oxygen supply and demand of the heart, leading to myocardial ischemia and acute coronary events. Additionally, chronic infections may account for low-grade chronic inflammation that triggers atherosclerosis. *Chlamydia*, *Mycoplasma*, and *Helicobacter pylori*, which can cause chronic systemic inflammation, are well-documented infectious agents associated with atherosclerosis. Septic vegetations on the aortic or mitral valves may cause MI in case of endocarditis.

Moreover, viral infections may trigger both innate and chronic immune responses and lead to ischemia and MI. Human immunodeficiency virus (HIV), hepatitis C virus, coronaviruses, etc. are important examples of viral infectious agents that are associated with ischemic syndromes. HIV requires special attention since the metabolic effects of the antiretroviral therapy in terms of dyslipidemia can easily be missed and may contribute to the etiology of premature MI.[81]

Currently, the COVID-19 pandemic has also accelerated the increased numbers of young individuals suffering from MI. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) encompasses a variety of cardiovascular syndromes, including pericardial effusion, tamponade, myocarditis, and coronary events. Significant uncertainty remains on the prevalence of acute myocardial injury in patients with COVID-19, which has been reported to cause obstructive or nonobstructive CAD and SCAD. Myocarditis, cytokine storm, and stress cardiomyopathy are the leading considerations, whereas additional potential causes include hypoxemia and microvascular dysfunction from small vessel thrombosis. In cases with COVID-19, fever and tachycardia increase the myocardial oxygen demand, whereas hypoxia decreases oxygen delivery to the heart, leading to myocardial ischemia. A severe form of coagulopathy may also develop during COVID-19 due to the following possible mechanisms: 1) hyperimmune response resulting from cytokine storm, 2) direct endothelial damage, 3) deep hypoxia, and/or 4) continuous prone position. However, the major pathology includes the uncontrolled hyperimmune reaction. There are too many cases of young COVID-19 patients presenting with MI and even further chronic damage to the cardiovascular system by SARS-CoV-2 is highly suspected as the infection presents itself with endothelial dysfunction and is known to lead to thromboses.[82] We still do not know whether the history of contracting COVID-19 will be a predictor of ASCVD in the future. Moreover, we still don't know if the children who developed multisystem inflammatory syndrome (MIS) due to COVID-19 would be prone to ASCVD in early adulthood.

Thrombophilia: Thrombophilia either acquired or inherited, approximately accounts for 5% of all MIs in young patients.[20] The lower the age of patients with young MI, the higher the possibility of an underlying thrombophilia. Several genetic mutations that disrupt the balance between coagulation and fibrinolysis are well-known associates of MI in young individuals.[29,30,32,52] Thrombophilias also harbor the risk of ventricular thrombi in the course of young MI. Thrombophilia predispose to increased risk of thromboembolic events, particularly in the coexistence of acquired or inherited disorders of the hemostatic system/triggering factors, such as pregnancy,[32] arthropod bite,[30] and heavy smoking. Prothrombotic mutations in combination with cigarette smoking increase the risk of MI by 12-fold in young females. Similarly, oral contraceptive agents have been associated with increased risk of MI, especially in smoking females; however, the risk appears low with newer agents.

Factor V Leiden and Factor II G20210A allelic variants are known to cause early MI, especially in young individuals aged <35 years. Resistance to activated protein C (APCR) or acquired deficiency of protein C are also among the well-known causes of young MI.[83] Polymorphisms of other coagulation factors may also have important roles in the prognosis and etiology of premature MI. Moreover, fibrinogen and homocysteine (Hcy) levels are accepted as intermediate risk factors that potentiate the effect of the underlying genetic causes.[29,30,32,52,84]

Factor V Leiden is inactivated ten times slower than the normal factor V, leading to a hypercoagulable state (APCR).[31] The risk of venous thrombosis is increased 3–5 times in heterozygotes and 50–80 times in homozygotes. Factor V Leiden mutation is the

most common inherited thrombophilia in certain populations with a prevalence of 5%–10% in Caucasians, which is significantly higher than African and Asian.[85] It's suggested that this mutation has arisen from Anatolia with a prevalence of 7%–8% in the Turkish population.[86] APCR could be acquired in pregnancy or with hormone therapy and APLA syndrome.

Prothrombin G20210A gene mutation, which leads to increased prothrombin activity, is present in 1%–6% of Caucasians and was demonstrated to be more common in patients with premature CAD (2.7%–5.1%).[30] The prevalence of this mutation in Turkish subjects is 2.2%–2.7%.[86] With other inherited or acquired risk factors, venous thrombosis is 2–3 times more frequent.

Antithrombin-III deficiency, which is a rare cause of MI, can be inherited or acquired due to a variety of diseases including disseminated intravascular coagulation, nephrotic syndrome, or renal failure.[2] Antithrombin-III deficiency mainly increases the risk of venous thrombosis with a relative risk of 8 but may increase up to 20-fold when other acquired risk factors are co-existing.

Inherited protein C and S deficiency can cause severe thrombotic events at early ages. Both could be acquired due to hepatic diseases, warfarin use, inflammatory conditions, pregnancy, and hormone therapy.[2] Venous thrombosis is increased by approximately 10-fold in the heterozygote individuals. Arterial thrombosis is rare but significant thrombotic events usually develop in early ages in inherited forms.

Hyperhomocysteinemia is an independent risk factor for ASCVD. Up to 40% of patients with premature CAD, peripheral vascular disease, or recurrent venous thrombosis are detected to have elevated Hcy levels.[2] High Hcy levels cause premature atherosclerosis mainly via endothelial dysfunction and apoptosis of the endothelial and smooth muscle cells. Apoptosis of the smooth muscle cells disturbs the collagen synthesis, which causes plaque instability and increased thrombosis.[87] Hyperhomocysteinemia impairs the endothelial nitric oxide (eNO)-dependent vasodilation leading to decreased bioavailability of NO but preserving the expression of endothelium-derived nitric oxide synthase (eNOS).[2] The mutations in the genes that encode the four enzymes involved in Hcy catabolism, including cystathionin ß-synthase, methionine synthase, 5,10-methylenetetrahydrofolate reductase (*MTHFR*), and betaine-homocysteine methyltransferase and the deficiencies of their cofactors (vitamin B6, B12, and folic acid) lead to hyperhomocysteinemia. A meta-analysis depicted a relative risk of 1.05 (95% CI, 0.86-1.27) for MI and 1.46 (95% CI, 1.19-1.79) for ischemic cerebrovascular accident when there was a mutation in the *MTHFR* gene.[88] C-to-T substitution at nucleotide 677 within the *MTHFR* gene, is a relatively frequent missense mutation that is associated with a thermolabile variant and reduced enzyme activity leading to an increased risk of venous thrombosis.[30,33,89] Patients who are homozygous for the T allele are more likely to have thermolabile MTHFR and elevated Hcy levels compared with other genotypes, and this polymorphism is accepted as a possible genetic risk factor for premature MI.[89]

Other Genetic Causes of Premature Myocardial Infarction: Several gene mutations in lipoprotein metabolism, inflammation, and oxidation may also be associated with young MI (Table 1). Apolipoproteins do not only contribute to the pathophysiology of familial hyperlipidemia syndromes but also have an important association with premature MI. ApoE4/E4 genotype suggests a strong association with premature MI. Mice with lacking ApoE lose the expression of the scavenger receptor B1 (SR-B1), leading to early CAD.[90] On the contrary, ApoD has shown cardioprotective properties in experimental atherosclerosis models.[91] Low levels of ApoCII have been detected in normotriglyceridemic patients with young MI.[92] These studies are of utmost importance since some severe forms of these mutations (i.e., frameshift mutations) may result in extreme hyperlipidemias in some families, putting the whole family at risk for premature MI, as seen in FH.[93]

A variant of *LDL receptor-related protein 8 (LRP8),* which encodes the receptor for Reelin and ApoE-containing ligands, is associated with premature and familial MI. *LRP8* variant R952Q results in an increased p38 MAPK stimulation, which leads to increased leukocyte migration and accumulation in the endothelium.[94] Additionally, *LRP8* acts as an LDL receptor. Some haplotypes of the *LRP8* gene may be protective against familial premature MI.[95]

Tangier disease is a rare but severe inherited condition, resulting in HDL and ApoAI deficiency. Mutations in ATP-Binding Cassette transporter A1 (*ABCA1*) gene lead to cholesterol ester accumulations in tissues resulting in hepatomegaly, splenomegaly, neuropathy, and premature MI. These patients mostly present with yellow-orange tonsils.[96] In young male patients, *ABCA1* polymorphisms can predict the prognosis following MI.[97]

Oxidative stress-related molecules, including eNOS and sirtuin 1 (SIRT1), can also contribute to the pathophysiology of premature MI. In high-risk patients aged <45 years, elevated SIRT1 and decreased eNOS levels were associated with premature MI, wherein certain SIRT1 polymorphisms might result in >2-fold increased risk.[5,98]

Neutrophil elastase (*ELA2)* gene deletions, *TNFRSF1A* gene R92Q polymorphism, which encodes tumor necrosis factor receptor 1, and the Arg590Leu variant of the netrin-1 (*NTN1)* gene, which functions in immune cell migration, were depicted as possible inherited causes of premature MI.[99] Additionally, some molecular deviations result in generalized arterial dysfunction as seen by *NOTCH1, ENPP1,* or *ABCC6* genes. *NOTCH1* gene is responsible for transmembrane protein encoding, therefore affording regulatory signals for cell differentiation. Its mutations may result in fragile arteries. The literature already presents a pregnant woman with *NOTCH1* mutation, who suffered from premature MI-associated SCAD.[100] Alterations in genes *ENFP1* and *ABCC6* cause generalized arterial calcification of infancy and pseudoxanthoma elasticum, respectively. These recessively inherited mutations are characterized by excessive tissue calcifications leading to premature atherosclerosis and severe hypertension.[101] *MEF2A* variations can result in autosomal dominant early coronary artery syndromes.[102] The *ACE-DD* genotype is associated with premature

TABLE 2. Baseline Risk Factor Assessment and Diagnostic Algorithm in Patients with Myocardial Infarction at a Young Age (for Females <50 Years and Males <45 Years)*

	Assessment components	Description and details
Detailed Physical Examination	Additional findings of predisposing factors of coronary events	- Lipid depositions that could be a clue for FH (arcus cornea, xanthoma, xanthelasma, etc.) - Any bruits on renal and carotid arteries - Varicose lower limb veins
	Anthropometric measures (weight, height, waist, and hip measurement)	- BMI of >25 kg/m^2 should be an alert for overweight and obesity to be associated with obstructive sleep apnea
Screening for cardiovascular risk factors	- Hypertension - Obesity - Diabetes mellitus	- Systolic BP of ≥140 mmHg, diastolic BP of ≥90 mmHg, or a documented diagnosis and/or treatment of hypertension - BMI of ≥30 kg/m^2 or a documented diagnosis of obesity - FBG of >126 mg/dl or random blood glucose of >200 mg/dl or previous diagnoses or treatment of antidiabetic medications
	Dyslipidemia	Total cholesterol of ≥200 mg/dl, LDL-cholesterol of >130 mg/dl, serum triglycerides of ≥150 mg/dL, HDL-cholesterol of <40 mg/dL in males or <50 mg/dl in females, or a documented diagnosis and/or treatment of dyslipidemia
	Smoking	(Ex/passive, etc.) Daily amount, duration
	Alcohol use	Duration, amount
History of ASCVD and concomitant disease	Any ASCVD	- Previous MI, stroke, revascularization, SCD, restenosis, heart failure, cardiac devices, and arrhythmias - Claudication and peripheral vascular disease - Transient or permanent vision loss denoting retinal vein or arterial thrombosis - Erectile dysfunction
	Other Heart diseases	- Atrial fibrillation - Valvular heart disease - Infective endocarditis - LV hypertrophy, cardiomyopathies, etc.
	Infectious disease (Chronic or acute)	- HIV, chlamydia, tuberculosis, COVID-19, etc. - Endocarditis, myocarditis (viral illness preceding chest pain and heart failure symptoms) - Any history of infection during the last few weeks to 3 months
	Immune-mediated inflammatory diseases	- Any connective disease (Ehlers-Danlos syndrome and Marfan syndrome, and fibromuscular dysplasia) - Systemic inflammatory diseases or vasculitis (especially SLE, APAS, and Bechet's disease) - Morning stiffness, arthritis, oral or genital aphthous lesions might be alerting - Kawasaki disease or similar clinical findings in childhood or adolescence
	Malignancy, chemotherapy, irradiation, etc.	Previous or active tumors and related treatments
	Thrombophilia	- Any acquired or inherited hypercoagulable state including hyperhomocysteinemia, high Lp(a) levels, anticardiolipin or antiphospholipid antibodies, inherited thrombogenic mutations, malignancies, oral contraceptive use, thrombocytosis, erythrocytosis, etc. (see below for laboratory analysis) - Hypercoagulable states should be assessed in case of normal coronaries, history of VTE, history of stillbirth, and missed abortion - Thrombophilia factors generally coexist and potentialize each other
	Others	- Thyroid diseases - Renal disease and failure - Hepatic disorders - Gastrointestinal hemorrhage - Bleeding diathesis
Predisposing/ triggering factors related to the index MI	Illicit drug use (cocaine, marijuana, etc.) Binge drinking	- Patients may be hesitant to report the use of amphetamines or illicit drugs during the initial visits. Thefore, evaluations for such drugs should be repeated after a few visits - During the index hospitalization, unexpected tachycardia could be a sign of drug abstinence - Sweating, dilated pupils, and tachycardia should be an alert for illicit drug use
	Concomitant medication	- Anabolic steroids or protein supplements - Oral contraceptives might increase the risk of premature MI
	Heavy sports or activity (football match, heavy lifting, etc.)	- Heavy sports activity preceding the index event might be a clue for coronary or aortic dissection
	Takotsubo Syndrome	- Extraordinary happiness or sadness (broken heart) might be denoting Takotsubo Syndrome

TABLE 2. Continued

	Assessment components	Description and details
Predisposing/ triggering factors related to the index MI	Venous thromboembolism	- Long-distance flying, lower extremity stasis, etc. could be associated with VTE and patent foramen ovale
	Allergy or hypersensitivity	- Kounis syndrome
	Any acute or subacute infection during the last few weeks to 3 months	- Infective endocarditis and myocarditis
	Information about women cycles, menstruation Menopause (age) Use of Hormones or oral contraseptives for women	- History of stillbirth and missed abortion might be a clue for thrombophilia - History of macrosomia may denote diabetes - Low birth weight children might be associated with placental insufficiency (atherosclerosis) or fetal hypoxia - Preeclampsia, hypertension, or diabetes associated with pregnancy - Polycystic ovarian syndrome (hirsutism and unregular cycles)
Family history	Premature ASCVD events	- MI, revascularization (stent and bypass operation), SCD, heart failure, etc. in first-degree relatives before the age of 55–60 years - How to define family history? First-degree relative: parents, children, and siblings Second-degree relative: aunt, uncle, grandpa, grandma, and nephew Third-degree relative: cousins and grandparents' siblings - If possible, at least three generations should be questioned
	Dyslipidemia	- A detailed family history and lipid profile of all family members should be obtained as possible, and family screening should be conducted. - The presence of arcus cornea, xanthoma, and/or xanthelasma should be attributed to FH.
	Thromboembolic events	- Thromboembolic events in the family may denote inherited hypercoagulable states
	Immune disease including vasculitis	- Bechet's disease, SLE, etc.
	Other information	- Diabetes mellitus, hypertension, consanguinity
Lifestyle assessment	Information about healthy lifestyle, Dietary habits (daily dietary consumption of fats, carbs, etc) Environmental factors	- Several questionnaires might be used to obtain data on dietary habits, physical activity, etc. Dietary Habits and Daily Dietary Consumption Frequency Diagnosis Form International Physical Activity Questionnaire - Depression, anxiety, and psychotic disorders are defined as having a documented diagnosis and/or treatment for these conditions - Environmental factors include lifestyle, air pollution, socioeconomic status, etc.
Psychosocial evaluation	Psychosocial factors	- Social status, marital status, psychosocial issues, etc.
Laboratory analysis	Lipid profile	- Total Cholesterol, LDL-cholesterol, HDL-cholesterol, non-HDL-cholesterol, triglycerides, and Lipoprotein (a) - LDL levels of >155 mg/dL in patients with young MI are defined as possible FH according to DLNC
	Routine biochemistry	- Analyses include transaminases, creatinine, albumin, uric acid, FBG, HbA1c, electrolytes, TSH, hemoglobin, and platelet counts.
	Thrombophilia assessment	- Blood levels of fibrinogen, homocysteine, B12 vitamin, folic acid, Lp(a), Protein C, S, and ATIII - Genetic thrombosis panel including Factor V Leiden, Factor V R2, Prothrombin mutation, MTHFR mutations, and Apo E polymorphism
	Immune markers	- CRP, Anti-Nuclear Antibodies, Anti-phospholipid antibodies, Anti-cardiolipin antibodies - Additional history of morning stiffness, aphthous lesions, arthritis, etc. that might be a clue for vasculitis or connective tissue disorders

AT-III: Anti-thrombine III, Apo: Apoprotein; ASCVD: Atherosclerotic cardiovascular disease; APAS: Antiphospholipid syndrome; BMI: Body mass index; BP: Blood pressure; CRP: C-reactive protein; Ca+2: Calcium; CT: Computed tomography; DLNC: Dutch lipid network criteria; EF: Ejection fraction; FBG: Fasting Blood Glucose; FCHL: Familial combined hypercholesterolemia; FH: Familial hypercholesterolemia; HDL-C: High-density lipoprotein cholesterol; LDL-C; low-density lipoprotein cholesterol; LV: Left ventricular; MI: myocardial infarction; MR: Magnetic resonance; MTHFR: methylenetetrahydrofolate reductase; SCD: Sudden cardiac death; SLE: systemic lupus erythematosus; USG: Ultrasonography; TSH: Thyroid-stimulating hormone; VTE: Venous thromboembolism

*The presented information is based on the algorithm established by the Young MI Clinic of Ege University Cardiology Department.

MI due to the deletion of both *ACE* gene alleles, with a 2-fold risk in males compared to females.[103]

Hutchinson-Gilford progeria syndrome is an ultra-rare disease with the autosomal dominant inheritance of *LMNA* mutations leading to defective lamin A, which is an intermediate filament that normally provides structural support to the cells, leading to structural deformities that mostly affect the smooth muscle cells. These patients mostly die in early decades due to either premature stroke or MI.[104] Kabuki syndrome, which is associated with intellectual disability and visceral and skeletal abnormalities due to *KMT2D* and *KDM6A* mutations, may cause premature atherosclerosis and MI.[105]

Other Causes of Premature Myocardial Infarction: Other possible causes of MI in young adults should be considered upon initial presentation, as well as irradiation for the treatment of malignant mediastinal disorders, which can lead to intimal damage, medial hypertrophy, and scar formation. Permanent complications rarely develop with a cumulative dose of <40 Gy.

Coronary embolism and in the presence of patent foramen ovale paradoxical embolism could generate young MI. Paradoxical embolism should be considered in the presence of additional hypercoagulable states (pregnancy, hormone replacement therapy, thrombophilia, etc.) in younger adults with MI. Very rarely, endocarditis, tumors, and immune disorders may cause coronary embolus. Trabeculae of the noncompaction cardiomyopathy may also serve as a source of coronary embolism.

DIAGNOSTIC WORKUP TO IDENTIFY THE UNDERLYING RISK FACTORS

Table 2 displays our standardized approach to uncover the underlying risk factors in young patients presenting with MI in the Premature MI Clinic of the Ege University Cardiology Department. All patients presenting with MI aged <45 years should be carefully evaluated for underlying risk factors for premature atherosclerosis and early MI. For females, the age range might be <50 years. The assessment of risk factors for premature MI should be initiated with the diagnosis of MI. Lipid depositions in the physical examination are clues for FH (arcus cornea, xanthoma, xanthelasma, etc.), whereas bruits on renal and/or carotid arteries may denote severe and extensive atherosclerosis, which might be associated with FH or FCHL.

We use a standard questionnaire covering 6 sections for the evaluation of young patients presenting with MI. We initially focus on the traditional cardiovascular risk factors, i.e., dyslipidemia, hypertension, and DM. If any of these 3 risk factors are present then we ask for the age at diagnosis of each risk factor, the drugs used, efficacy of the treatment (response to treatment), and patients' adherence to therapy.

Secondly, a detailed history of ASCVD and concomitant diseases is collected. History of MI, stroke, revascularization, restenosis, heart failure, cardiac devices, arrhythmias, and claudication are obtained in detail, as well as transient or permanent vision loss denoting retinal vein or arterial thrombosis. Erectile dysfunction should also be questioned in males. Chronic infectious diseases (HIV, chlamydia, and tuberculosis) or acute infections (COVID-19, etc.) might be associated with atherosclerosis or thrombosis. Viral illness preceding chest pain should not be missed in anamnesis. Immune-mediated inflammatory diseases including connective tissue diseases and vasculitis are important in young MI. Symptoms, such as morning stiffness, arthritis, oral or genital aphthous lesions, etc. could be a sign of an underlying immun-mediated disease. The history of Kawasaki disease in childhood should also be considered. Previous or active tumors and related treatments (chemotherapy or irradiation) could be associated with young MI. Thrombophilia evaluation is paramount in those presenting with young MI. Inherited or acquired thrombophilia should be considered in young patients with MI with normal coronaries in the angiogram or history of VTE, history of stillbirth, missed abortions, etc. Furthermore, the presence of permanent or paroxysmal atrial fibrillation, valvular heart disease, and/or infective endocarditis should be kept in mind as rare but possible causes of young MI. Cardiomyopathies, especially those characterized by hypertrophy or metabolic storage diseases may cause young MI either by embolic events or myocardial demand-perfusion mismatch.

Thirdly, we explore the possible predisposing or triggering factors of the index event. Obtaining a careful history of illicit drug use (especially cocaine, rarely marijuana, etc.) is extremely important in patients with young MI. However, patients may be hesitant to report the use of these drugs at initial visits. Therefore, such drug evaluation should be repeated after a few visits. During the index hospitalization, unexpected tachycardia could be a sign of drug abstinence. Heavy sports activity preceding the index event might be a clue for coronary or aortic dissection, meanwhile, extraordinary happiness or sadness (broken heart) might denote Takotsubo Syndrome. Long-distance flying could be associated with venous thromboembolism and patent foramen ovale in patients with young MI. Presence of early menopause, regularity of menstrual cycles, and use of birth control pills or hormone replacement therapy should be evaluated in females. Investigating previous pregnancy-related problems in females is also necessary. Additionally, physical examination findings, such as hirsutism, which may be clues to hormonal disorders, such as polycystic ovary, should be evaluated. Lifestyle assessment and psychosocial evaluation with specific surveys are also important components of the evaluation of young MI patients that will serve for their management (Table 2).

Next, we focus on obtaining a good family history detailed for premature ASCVD events, DM, hypertension, thromboembolic events, immune disease, and dyslipidemia. ASCVD in family history is generally defined as any cardiovascular event in a first-degree relative before the age of 55–60 years. Meanwhile, we prefer not to limit the family evaluation to the first-degree relatives (i.e., parents, children, or siblings) but also to the second-degree (i.e., aunt, uncle, grandpa, grandma, or nephew) and third-degree relatives (i.e., cousins and grandparents' siblings). If possible, we explore at least three generations for family history. Family history of dyslipidemia is extremely important as FH, FCHL, and high Lp(a) are frequently inherited contributors of premature atherosclerosis and young MI. Additionally, family members should be assessed for abnormal lipid profiles.

Our laboratory evaluation includes lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, non-HDL-cholesterol, triglycerides, Apo A1 and B, and Lp[a]), laboratory analysis (transaminases, creatinine, urea, uric acid, albumin, fasting blood glucose, electrolytes, thyroid-stimulating hormone, hemoglobin, and platelet counts), thrombosis panel for genetic analysis and immune panel (Table 2). For imaging echocardiography, carotid and vertebral ultrasonography and retinal examination are among the routine workup of patients with young MI. Patients presenting with either acute or subacute MI should undergo

coronary angiography as early as possible. Any coronary anomaly, plaque erosion, myocardial bridge, SCAD, coronary vasospasm (microvascular dysfunction) and embolism, ectasia, slow flow, and fistulas could be associated with young MI. Younger patients frequently present with single-vessel coronary disease. Multivessel diseases should raise the suspicion of FH, FCHL, HIV, etc. in patients with young MI. Further, Ca^{+2} scoring is unnecessary in patients presenting with MI. However, healthy relatives may need screening with coronary Ca^{+2} scoring. Computerized tomographic (CT) angiography could be used in follow-up or especially in females when coronary angiography observes normal or near-normal coronaries. Coronary CT easily captures the coronary plaques with eccentric remodeling and provides information about plaque characterizations either soft or calcified. Plaque morphology also differs between young and advanced age groups. A Chinese optical coherence tomography study revealed that the culprit lesions in patients with acute MI aged ≤50 years had more plaque erosion (32.0% vs. 21.1%, $P < 0.001$) and larger minimal lumen area (2.3 ± 1.7 mm^2 vs. 1.9 ± 1.1 mm^2, $P < 0.001$) than in those aged >50 years.[106] Plaque vulnerability has inclined from age ≤50 years to 50–70 years to >70 years. Lipid-rich plaque, thin cap fibroatheroma, calcification, spotty calcification, and cholesterol crystals were less frequently observed in young patients. Likewise, multivariate regression analysis depicted that age of ≤50 years was independently associated with less plaque rupture frequency and less vulnerable plaque features.

A recent study further analyzed patients with ACS caused by plaque erosion,[107] of whom advanced age was associated with higher coronary risk factor prevalence, greater plaque burden, and more vulnerability features. However, predisposing factors, such as FH and other genetic dyslipidemias, may significantly change the plaque morphology. Therefore, an individualized approach would be more appropriate for the treatment of patients with young MI.

In conclusion, the number of younger individuals presenting with MI is steeply increasing and the decrease afforded in the prevalence of ASCVD does not account for young MIs. Individuals with MI at a young age constitute a special patient population with different clinical features compared to patients with older MI. In addition to the traditional risk factors, non-traditional risk factors, such as substance abuse, thrombophilia, coronary anomalies, immune disease, allergic reactions, and psychological stressors, uniquely contribute to the risk profile of young MI. Therefore, patients with young MI should be carefully examined for both traditional and non-atherosclerotic risk factors for effective cardiovascular prevention. However, current guidelines still overlook the cardiovascular risk among patients with young MI, but all available evidence highlights the importance of earlier interventions to modify the unique risk factor profile in premature MI. Therefore, the awareness of the cardiologists on the need for a more comprehensive approach to the distinctive characteristics of premature MIs should be increased. Consensus documents for the management of patients with premature MI are needed.

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