Acute Myocardial Infarction in Young Individuals

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Abstract

Globally, cardiovascular disease remains a major cause of adverse outcomes in young individuals, unlike its decline in other age groups. This group is not well studied and has a unique risk profile with less traditional cardiovascular risk factors compared with older populations. Plaque rupture still remains the most common etiology of myocardial infarction, but unique syndromes such as plaque erosion, coronary microvascular dysfunction, spontaneous coronary artery dissection, and coronary spasm related to drug use are more prevalent in this age group. Such diversity of diagnosis and presentation, along with therapeutic implications, underscore the need to study the profile of myocardial infarction in young persons. We searched PubMed for articles published from 1980 to 218 using the terms acute myocardial infarction, young, plaque rupture, plaque erosion, spontaneous coronary artery dissection (SCAD), coronary vasospasm, variant or Prinzmetal angina, drug-induced myocardial infarction, myocarditis, coronary embolism, microvascular dysfunction, MINOCA, and myocardial infarction in pregnancy and reviewed all the published studies. With the data from this search, we aim to inform readers of the prevalence, risk factors, presentation, and management of acute myocardial infarction in young patients and elaborate on special subgroups with diagnostic and therapeutic challenges. We also outline a parsimonious method designed to simplify management of these complex patients.

Mortality from cardiovascular diseases (CVDs) has declined from 2003 to 2013. However, more than 2000 Americans die of CVD daily, and a significant proportion of them are younger than 65 years of age. Although the incidence of acute coronary syndrome (ACS) has decreased in older populations, younger men and women who present with acute myocardial infarction (MI) have not had similar declines (especially men) in cardiovascular events. Most studies have used an age cutoff of 40 to 45 years to define young patients with CVD. For this review, we will use an arbitrary cutoff of 55 years or younger to define young. This demarcation is important because the risk factor profile of the younger population is unique, women in general are premenopausal or perimenopausal, traditional atherosclerotic cardiovascular risk factors are less common compared with older populations, and, importantly, age-related multimorbidity, frailty, and poor cognition are encountered less frequently. Cardiovascular disease, however, remains a major cause of morbidity and mortality among young individuals globally, even as significant strides are made in improvement in diagnosis and therapeutics. Current challenges include atypical and delayed presentation, nonadherence to treatment, and syndromes unique to this age group. For example, spontaneous coronary artery dissection (SCAD), vasospastic angina, MI with intact fibrous cap, and cocaine/methamphetamine use are more prevalent in the younger age group.

Such diversity of diagnosis and presentation, along with the therapeutic implications, underscore the need to study the profile of MI in young persons. We searched PubMed for
articles published from 1980 to 2018 using the terms acute myocardial infarction, young, plaque rupture, plaque erosion, spontaneous coronary artery dissection (SCAD), coronary vasospasm, variant or Prinzmetal angina, drug-induced myocardial infarction, myocarditis, coronary embolism, microvascular dysfunction, MINOCA, and myocardial infarction in pregnancy and reviewed all the published studies. With the data from this search, this review aims to inform readers of the prevalence, risk factors, presentation, and management of MI in young individuals and also elaborate on special subgroups with diagnostic and therapeutic challenges. Most data are derived from large prospective registries, but readers will find many important studies with small numbers of enrolled patients, especially among the descriptions of uncommon etiologies of MI.

Myocardial infarction in young individuals can be grouped into 5 categories: (1) MI related to traditional cardiovascular risk factors similar to those in older individuals, (2) use of recreational drugs such as cocaine and methamphetamine, (3) MI due to SCAD, myocarditis, or coronary embolism (CE), (4) MI due to atheromatous coronary artery disease (CAD) but without critical coronary stenosis, and (5) coronary vasospasm.

PREVALENCE
Overall, prevalence estimates vary because the clinical profile of atherosclerotic and non-atherosclerotic phenotypes is poorly defined. This lack of definition is especially true for patients who present with MI with nonobstructive coronary arteries (MINOCA) because angiography-based differentiation without routine intracoronary imaging and nonuniform work-up have led to poor identification of nonplaque mechanisms. There are also limited data on the incidence of MI in young patients. The Framingham Heart Study’s 10-year follow-up data revealed that the incidence of MI was 12.9, 38.2, and 71.2 per 1000 in men and 2.2, 5.2, and 13.0 per 1000 in women in the age groups of 30 to 34, 35 to 44, and 45 to 54 years, respectively (Figure 1). Of 708 MIs among 5127 participants, more than 25% were silent, and the proportion of unrecognized MIs was higher in women.

MI Related to Traditional Cardiovascular Risk Factors in Patients With Atherosclerotic CAD
Plaque rupture accounts for approximately 60% to 65% of cases of MI in young individuals, and similar to older individuals, it is the most common cause of MI in this age group (Figure 2). In the United States, each year more than 30,000 women younger than 55 years are hospitalized with a diagnosis of MI. Hospitalization rates, characteristics of patients, and short-term survival were studied in a Nationwide Inpatient Sample of 230,684 hospitalizations from 2001 to 2010. Hospitalization rates for MI did not decline over the study period (Figure 1). Compared with men, younger women (who represented 23% of MIs) had higher comorbidity, stayed longer in the hospital, and had higher inhospital mortality (Figure 3). Similar findings were noted in another study from British Columbia. The authors observed significant declines in both 30-day mortality and hospital admissions for MI; however, younger women had higher mortality and hospital readmissions, underscoring our need to focus on this subgroup. The Framingham coronary risk score and prevalence of MI were assessed in adults between 35 and 54 years who participated in the National Health and Nutrition Examination Survey (NHANES) during 2 periods, 1988-1994 and 1999-2004. For MI, the gap between men and women narrowed.
recently (2.5% vs 0.7% in 1988-1994 and 2.2% vs 1.0% in 1999-2004 [both \( P < .01 \)). The authors also noted an increase in the Framingham coronary risk score in young women (3.0% vs 3.3% in NHANES 1988-1994 and NHANES 1999-2004, respectively \( P = .02 \)).

Recreational Drug Use and Psychosocial Factors

Obtaining a good drug history is paramount in younger patients presenting with MI. In the NHANES-3 survey of 10,085 adults between 18 and 45 years of age, frequent cocaine use accounted for 25% of nonfatal MIs. In the Cocaine Associated Chest Pain (COCHPA) study, MI with cocaine use was seen in 6%. A lower incidence of MI associated with cocaine use was observed with different presenting symptoms and diagnostic criteria for MI. Rates of MI associated with cocaine use range between 0.7% and 6%, and a careful history of cocaine intake must be obtained.

One study reported an average age of 38 years in 130 patients presenting with MI associated with the use of cocaine. Case series or case-control studies have described young patients with MI who used amphetamines, oral contraceptives (especially with smoking), or marijuana. Among 3882 patients with MI studied by Mittleman et al., 124 (3.2%) used marijuana in the preceding year. Its use was associated with an almost 5-times higher risk of MI over baseline, especially within the first hour after use. In the CARDIA (Coronary Artery Risk Development in Young Adults) study, 3617 young adults had a 15-year follow-up. Following adjustment of risk factors, the authors did not find an association between use of marijuana and risk of CVD. However, another study of 1913 adults who had survived acute MI found that during 3.8 years of follow-up, use of marijuana was associated with higher mortality.

The role of psychosocial stress is poorly recognized and underappreciated, and a

![Incidence and Prevalence of MI in Young Individuals](image-url)

**FIGURE 1.** A, Ten-year follow-up data in younger patients enrolled in the Framingham Heart Study demonstrating higher incidence of myocardial infarction (MI) in men, especially beyond age 45 years. The incidence in the corresponding age brackets in women was approximately one-fifth to one-seventh that of men (see text). B, Myocardial infarction trends in men and women 30 to 54 years old from the Nationwide Inpatient Sample (2001-2010). Comorbidity increased in both sexes during the study period. Women had higher in-hospital mortality but also significant decline compared with men. AMI = acute myocardial infarction. Adapted from *J Am Coll Cardiol,* with permission from the American Heart Association, Inc.
higher prevalence of depression, anxiety, and hostility in younger patients likely contributes not only to addiction but to the pathogenesis of acute and chronic CVD.22-25

**MI Due SCAD, Myocarditis, and CE**

SCAD is initiated by intimal disruption or intramural hematoma and is not due to underlying atherosclerosis, iatrogenic causes, or trauma (Table 1).26 It is commonly seen in younger women with a paucity of known cardiac risk factors. Recent series suggest that up to 1% to 4% of all cases presenting with ACS may be caused by SCAD and occur in younger women (<50 years).27-32 SCAD is also an important etiology in MI related to pregnancy. In a Mayo Clinic registry, 54 of 323 women with SCAD were pregnant or were 12 weeks or less postpartum.33 Only 4 occurred during pregnancy, and most events occurred within the first month postpartum.26,28,34,35

The prevalence of myocarditis varies, but a recent meta-analysis reported it in 33% of patients (183 of 556) with MINOCA.36 The prevalence of myocarditis varies from 2% to 42% in autopsy series37,38 and 9% to 16% by endomyocardial biopsy in adults with nonischemic dilated cardiomyopathy.39,40 Coronary embolism is considered the cause of MI in 4% to 13% of cases.41-43 Mechanisms of CE are akin to venous thromboembolism and can be delineated based on the Virchow triad (Figure 4). In a study of de novo ST-segment elevation MI, 53 of 1232 patients (4.3%) had CE. These patients were not young but had no evidence of coronary atherosclerosis.45 In the Young Adult Myocardial Infarction and Ischemic Stroke (YAMIS) Study, major venoarterial shunt was found in 25% of 101 young patients (16-39 years) who survived an MI and stroke.46 Paradoxical embolism as the cause should be considered in young adults in the presence of additional hypercoagulable risk factors (pregnancy, ischemic stroke, factor V Leiden).47-49

**MI Due to Atheromatous CAD Without Critical Coronary Stenosis**

Antemortem characterization of unruptured plaque is now feasible with optical coherence tomography (OCT) and intravascular ultrasound (IVUS).50-54 The classic demographic profile of such patients includes younger women who are smokers but do not have other cardiovascular risk factors such as diabetes mellitus or hyperlipidemia commonly seen in patients with plaque rupture.55-57

The VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients) registry enrolled young (18-55 years) patients with MI between 2008 and 2012.4 Using angiography-based classification, the investigators divided the cohort into those with revascularization or plaque of 50% or greater (88.4%) or MINOCA (obstruction with plaque <50%) or other etiologies (11.1%) (Figure 5). Women had an almost 5 times higher incidence of MINOCA than men. A large majority (224 of 299 patients [75%]) remained undefined, and a minority were categorized as SCAD, coronary spasm, or embolization (Figure 5), underscoring the need for a systematic approach and liberal imaging utilization for better plaque characterization.
**Coronary Vasospasm (Microvascular Dysfunction)**

The true prevalence of microvascular dysfunction in coronary arteries is unknown but depends on the population (higher in Asians), timing (higher with ACS), and use of provocative testing (higher if routinely employed for its detection) (Table 1). In 1089 patients who underwent coronary angiography, coronary spasm was induced with ergonovine in 20% who had recent MI and in 15% who had chest pain. T he prevalence of epicardial and microvascular spasm was 33.4% and 24.2%, respectively, among 921 patients with nonobstructive CAD in whom intracoronary acetylcholine provocation was used. In the CASPER (Coronary Artery Spasm in Patients With Acute Coronary Syndrome) study, among 138 (of 488) patients with ACS who had no demonstrable coronary disease, coronary spasm was seen in approximately half (48.8%) of those tested. Recent American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines acknowledged the importance of coronary microvascular dysfunction as an etiology for sudden cardiac death.

**RISK FACTORS**

**MI Related to Traditional Cardiovascular Risk Factors in Patients With Atherosclerotic CAD**

In a large, multinational cohort study with follow-up of 2 decades, the traditional comorbidities have increased in both sexes and women had a relative reduction in mortality. Adapted from J Am Coll Cardiol, with permission from the American Heart Association, Inc.
cardiovascular risk factors were equally predictive of mortality in young men compared with older men.\textsuperscript{63} Similarly, among 7302 eligible young women without major electrocardiographic abnormalities or prevalent CAD at baseline, the long-term (31-year) risk of development of CAD and mortality was higher in women with major coronary risk factors.\textsuperscript{64} A similar risk factor profile and association with outcomes was found in the Framingham Heart Study and the Nurses’ Health Study.\textsuperscript{65,66} These data underscore the importance of earlier interventions to positively modify the risk factor profile and lifestyle approaches in younger patients presenting with MI.

The INTERHEART investigators provided the most compelling global perspective on the effect of risk factors associated with MI.\textsuperscript{67} Increased apolipoprotein B/apolipoprotein A1 ratio (odds ratio [OR], 3.25 [highest vs lowest quintile]), smoking (OR, 2.87 [current vs never]), abdominal obesity (1.12 [highest vs lowest tertile]), hypertension (OR, 1.91), diabetes mellitus (OR, 2.37), psychosocial issues (OR, 2.67), eating fruits and vegetables daily (OR, 0.70), regular alcohol use (OR, 0.91), and regular physical exercise (OR, 0.86) were factors significantly related to MI (\(P<.0001\) for all risk factors and \(P=.03\) for alcohol). The profile of risk factors in younger patients presenting with MI mirrors those in the older age group. Smoking and hyperlipidemia are 2 major risk factors accounting for almost two-thirds of the population-attributable risk for MI.

Recent national trends underscore the growing epidemic of obesity (body mass index [BMI], \(\geq 30\); calculated as weight in kilograms divided by height in meters squared) in youth and young adults, with current (2015-2016) age-standardized prevalence estimates of 42.8% among adults between 40 and 59 years. These estimates

FIGURE 4. Anatomic and pathophysiologic mechanisms involved in coronary embolism are based on the Virchow triad for venous thromboembolism. Careful attention to anatomic predisposition is required for accurate diagnosis. The criteria for diagnosis of coronary embolism revolve around the absence of atherosclerosis, the presence of coronary thrombus (particularly at multiple locations), and concomitant systemic embolization. ASD = atrial septal defect; DVT = deep venous thrombosis; LV = left ventricular; PFO = patent foramen ovale. From J Am Coll Cardiol Intv,\textsuperscript{75} with permission from Elsevier.
were significantly higher compared with the 36.2% noted in 2007-2008 in the same age group and higher than the overall prevalence of 39.6%. The association of obesity with accelerated atherosclerosis was underscored by the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study in which arteries, blood, and other tissue from 3000 persons (aged 15 to 34 years) was examined and a significant correlation was seen, especially in young men, between obesity and fatty streaks, raised lesions in the right coronary artery, and stenosis in the left anterior descending artery. The Framingham Heart Study's 5209 participants (aged 15 to 34 years) was examined and a significant correlation was seen, especially in young men, between obesity and fatty streaks, raised lesions in the right coronary artery, and stenosis in the left anterior descending artery.

![VIRGO Classification System](image-url)

**FIGURE 5.** The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study developed an angiography-based classification of myocardial infarction in young patients. Importantly, most myocardial infarctions fall into class I or plaque-mediated mechanism, and in only a minority could a clear nonplaque mechanism be identified (class IV). Classes II and III are based on the presence or absence of significant obstructive coronary artery disease (CAD) and further subdivided based on the presence or absence of oxygen (O2) supply-demand mismatch. PCI = percutaneous coronary intervention; SCAD = spontaneous coronary artery dissection. From Spatz ES, Curry LA, Masoudi FA, et al. The Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) Classification System: a taxonomy for young women with acute myocardial infarction. Circulation. 2015;132(18):1710-1718 (www.ahajournals.org/journal/circ), with permission from Wolters Kluwer Health Inc.

Obese patients not only have earlier pathologic evidence and higher RR for CVD but also experience earlier MI. Among 111,847 patients with non–ST-elevation MI included in the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) registry, mean patient age at the time of MI was 58.7 years in the most obese patients (BMI ≥40 kg/m²) compared with the leanest patients (BMI ≤18.5 kg/m²). An excellent recent review...
summarizes the role of metabolically healthy obesity, the obesity paradox, and various lifestyle modifications for weight loss that would be important in the management of young obese individuals who present with an MI.\textsuperscript{72}

**Recreational Drug Use and Psychosocial Factors**
The risk of MI associated with reactional drug use and psychosocial factors is discussed in the Prevalence section.

**MI Due to SCAD, Myocarditis, and CE Spontaneous Coronary Artery Dissection.** The factor most commonly associated with SCAD is fibromuscular dysplasia (FMD), seen in 25\% to 86\% of patients.\textsuperscript{27} Two recent series described FMD in 50\% (diagnostic iliac angiograms) to 72\% of 168 patients with SCAD.\textsuperscript{27,28} Other factors associated with SCAD include pregnancy, connective tissue disorder, hormones, systemic inflammatory disorders (eg, Kawasaki disease, systemic lupus erythematosus), precipitating events (>50\% recall a precipitating factor) akin to that seen in patients with Takotsubo cardiomyopathy (ie, intense exercise or emotional stress, cocaine, retching, vomiting).\textsuperscript{26,73}

**Coronary Embolism.** In the study by Shibata et al,\textsuperscript{42} the most common underlying disease in patients with CE was atrial fibrillation (73\%), followed by cardiomyopathy (25\%) and valvular heart disease (15\%). Less frequent cardiac etiologies of CE included infective endocarditis and tumors. The systemic disorders associated with CE include antiphospholipid antibody syndrome, malignancy, and autoimmune disorders. No clear etiology could be discerned in 26.4\%.\textsuperscript{45}

**Myocarditis.** Viral infections account for most cases of myocarditis in North America and Europe.\textsuperscript{74} Autoimmune myocarditis can occur with sarcoidosis, scleroderma, or systemic lupus erythematosus. Immune-mediated myocarditis can also be seen with drugs (eg, penicillin, furosemide, phenytoin) or heart transplant rejection. Toxic myocarditis is seen with drugs (eg, amphetamine, anthracyclines, cocaine, cyclophosphamide, lithium), heavy metals (copper or iron deposits), or snake bite.

**MI Due to Atheromatous CAD Without Critical Coronary Stenosis**
Plaque rupture could not be demonstrated in autopsy studies in approximately one-third of cases of sudden death from ACS.\textsuperscript{57,75} Plaques with an intact fibrous cap (without plaque rupture) are seen more frequently in younger women (especially smokers) without known cardiac risk factors.\textsuperscript{76}

**Coronary Vasospasm (Microvascular Dysfunction)**
Multivariable predictors of microvascular dysfunction in a study by Nakayama et al\textsuperscript{77} included previous MI (OR, 5.37), baseline elevation of biomarkers (OR, 2.84), age younger than 70 years (OR, 2.19), glomerular filtration rate greater than 60 mL/min per 1.73 m\(^2\) (OR, 1.72), and lack of a traditional cardiovascular risk profile. Such paucity of cardiovascular risk was also noted in the Paris-Sudden Death Expertise Center study, with the exception of smoking and drug abuse.\textsuperscript{78} Smoking, older age, and higher levels of inflammatory markers (high-sensitivity C-reactive protein) have also been noted to be significant risk factors for coronary microvascular dysfunction.\textsuperscript{79}

**CLINICAL PRESENTATION**
Concordant with overall trends, two-thirds of all MIs in young patients present with non–ST-elevation (Table 2).\textsuperscript{80} In general, clinical presentation in young patients with MI is indistinguishable from that of older patients, and most patients present with chest pain due to plaque rupture. However, certain differences are noteworthy. First, a history of angina symptoms before MI is less common, seen in approximately one-fourth of patients.\textsuperscript{81} Second, 69\% of patients younger than 45 years do not report chest pain before MI.\textsuperscript{82,83} Third, the onset of symptoms is within 1 week of MI.\textsuperscript{82,83} In addition, younger women typically have longer delays in reporting symptoms and getting medical attention in the setting of MI; possible reasons could be varying prodromal symptoms, inaccurate
assessment for personal cardiac risk, competing and conflicting priorities affecting their decision making, less consistent response of the health care system to symptoms, and poor access to primary care. In young patients who present with MI in the setting of normal coronary arteries, recent recreational drug use should be recorded and signs of sympathetic overactivity should be noted (sweating, mydriatic pupils, tachycardia).

Clinical and family history of recurrent arterial and/or venous thrombosis should be diligently evaluated. Presenting symptoms of myocarditis vary from dyspnea or chest pain to life-threatening shock or arrhythmias, and therefore, this diagnosis requires a high index of suspicion. Two main presentations of myocarditis are new or worsening congestive heart failure or symptoms of chest pain akin to those of ACS. Preceding viral illness (respiratory or gastrointestinal symptoms), younger age, and inflammatory markers (high C-reactive protein level) can point to a diagnosis of myocarditis (Table 3). Similar to other MIs, patients with SCAD present with chest pain (95.9%) and elevation of cardiac biomarkers (26%-87% with ST-segment elevation MI). Ventricular arrhythmia or sudden cardiac death is the presenting symptom in 3% to 11% of patients.

Vasospastic angina (Prinzmetal) typically presents with ST-elevation MI without provocation, is associated with stress, cold, or hyperventilation, and is characterized by prompt relief with sublingual nitroglycerine. A circadian variation is noted with this syndrome, with most attacks occurring during the morning hours. Vasospastic angina typically affects women smokers.

### DIAGNOSIS OF MI IN YOUNG PATIENTS

#### General Principles

The current classification for MI ignores patients with minimal or no CAD, and using the Universal Definition of Myocardial Infarction, its etiology is still unclear in approximately 12% of women. Furthermore, patients with different etiologies and varying severity of atherosclerosis and left ventricular function are combined, leading to management dilemmas and phenotypic heterogeneity. To address the deficiencies in the current classification, using an inductive approach and grouping patients with similar clinical

#### TABLE 2. Clinical Presentation of Young Patients With Myocardial Infarction

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Diagnostic criteria</th>
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<tbody>
<tr>
<td>Two-thirds present with non–ST-elevation myocardial infarction</td>
<td>Electrocardiographic, Holter monitoring, stress test abnormalities (heart block, ST-T changes, ventricular tachycardia/ventricular fibrillation)</td>
</tr>
<tr>
<td>Chest pain characteristics similar to those in older patients</td>
<td>Elevated troponin level</td>
</tr>
<tr>
<td>Women have 5-times higher odds of having myocardial infarction with nonobstructive coronary artery disease</td>
<td>New regional wall motion abnormality, functional decline, thrombus, increase in wall thickness, or pericardial effusion</td>
</tr>
<tr>
<td>Look for drug use (coca) or source of thromboembolism</td>
<td>Tissue characterization by cardiac magnetic resonance imaging</td>
</tr>
<tr>
<td>Suspect myocarditis in patients with a history of viral illness who present with worsening heart failure or chest pain</td>
<td></td>
</tr>
</tbody>
</table>

#### TABLE 3. Diagnosis of Myocarditis

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute chest pain</td>
<td>Electrocardiographic, Holter monitoring, stress test abnormalities (heart block, ST-T changes, ventricular tachycardia/ventricular fibrillation)</td>
</tr>
<tr>
<td>New-onset (&lt;3 mo) worsening dyspnea</td>
<td>Elevated troponin level</td>
</tr>
<tr>
<td>Subacute/chronic (≥3 mo) worsening dyspnea</td>
<td>New regional wall motion abnormality, functional decline, thrombus, increase in wall thickness, or pericardial effusion</td>
</tr>
<tr>
<td>Arrhythmia, syncope, or sudden death</td>
<td>Tissue characterization by cardiac magnetic resonance imaging</td>
</tr>
<tr>
<td>Unexplained cardiogenic shock</td>
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Data from Eur Heart J.
characteristics, a novel VIRGO taxonomy classified 2802 young women with MI according to the underlying pathophysiologic mechanisms: obstructive CAD (most common) with or without supply-demand ischemia, no obstructive CAD, or patients in whom a clear mechanism is not related to plaque rupture. This classification still is very complex to follow and combines various disease mechanisms that require different management into one class (eg, dissection, vasospasm, embolism). It also does not delineate distinct pathways that help clinicians with their management (Figure 5).58

MI Related to Traditional Cardiovascular Risk Factors
The most common etiology of MI in young individuals is plaque rupture, which is seen in almost 88% to 89% of patients and should be suspected in those who smoke or have hyperlipidemia, diabetes mellitus, or hypertension. We propose a simple diagnostic algorithm that will delineate most causes of MI in young patients, Figure 6.

Recreational Drug Use and Psychosocial Factors
A careful drug history is essential in young patients as it points to the right diagnosis, pathophysiology (coronary vasospasm), and management (psychosocial support, counseling). Depression can interfere with medication compliance, affect self-care, increase ambulatory visits, and negatively impact health status.88 Depressive symptoms can be associated with other mood disturbances (eg, anxiety) or substance abuse, which also are associated with adverse cardiac outcomes.89

MI Due to SCAD, Myocarditis, and CE Spontaneous Coronary Artery Dissection.
SCAD should be suspected in younger patients with MI, and diagnosis is confirmed by coronary angiography. Presently, computed tomographic angiography has insufficient sensitivity for SCAD diagnosis.90-94 A careful search for FMD in coronary and other vascular territories should be done routinely. Intravascular imaging with OCT or IVUS can shed some light on the mechanism of SCAD based on the presence or absence of identifiable intimal tear. This differentiation may have clinical implications as the risk of clinical deterioration in patients with SCAD who are managed conservatively is higher in those with intramural hematoma without identifiable intimal tear and the highest risk of worsening is noted within 6 days of presentation.93,103

Myocarditis. Diagnostic criteria for myocarditis include the presence of one clinical (new-onset/worsening heart failure/ACS) and one diagnostic (electrocardiography, stress test, Holter monitoring, elevated biomarkers, and typical tissue characterization by cardiac magnetic resonance imaging) criterion in the presence of normal coronary arteries (no significant coronary stenosis that exceeds 50% or patients with preexisting CVD) (Table 3). Twelve-lead electrocardiography, echocardiography, and cardiac magnetic resonance imaging are indicated before endomyocardial biopsy in patients suspected to have myocarditis. Among the 374 patients enrolled in the Italian Multicenter Study on Acute Myocarditis, late gadolinium enhancement was a significant predictor (OR, 2.73; 95% CI, 1.2-5.9; P = .01) of adverse events including mortality, hospitalization with heart failure, resuscitated cardiac arrest, or appropriate firing of implantable cardioverter-defibrillator.104

Coronary Embolism. Coronary embolism is diagnosed with coronary angiography demonstrating angiographic thrombus, concomitant CE in multiple locations/vessels, or evidence of systemic embolization (Figure 4). Patients should be screened for the source of embolic material. Echocardiography is needed to identify left ventricular, left atrial, or appendage thrombus, intracardiac shunt, or a patent foramen ovale. Coronary embolism is frequently associated with systemic embolism, and other sites (eg, abdomen, brain) should be screened.

MI Due to Atheromatous CAD Without Critical Coronary Stenosis

Myocardial Infarction With Nonobstructive Coronary Arteries. To diagnose patients
with MI with no obstructive CAD, a good history, physical examination, electrocardiography, measurement of cardiac biomarkers, echocardiography, and coronary angiography with or without left ventricular angiography are needed to identify various causes that fall under the umbrella of MINOCA. Proposed diagnostic criteria for MINOCA include Universal Definition of Myocardial Infarction criteria, nonobstructive CAD on angiography, and no overt cause of similar presentation such as pulmonary embolism or dissection. Many investigators include myocarditis and Takotsubo syndrome in MINOCA. For this review, we have not included Takotsubo cardiomyopathy because it principally affects older, usually postmenopausal, women. Recently, European guidelines to diagnose MINOCA required clinical documentation of MI, the presence of no significant obstruction (<50% stenosis) in coronary arteries, and no specific etiology for their acute presentation necessitating further evaluation (Figure 7).105

Guidelines to diagnose MINOCA required clinical documentation of MI, the presence of no significant obstruction (<50% stenosis) in coronary arteries, and no specific etiology for their acute presentation necessitating further evaluation (Figure 7).105

**Coronary Plaque Disease.** For patients with coronary plaque disease, antemortem imaging of plaque characteristics has allowed cardiologists with tools to base their management decisions on plaque characteristics such as the presence or absence of plaque rupture. With the advent of OCT, antemortem diagnosis of plaque erosion is now feasible. It is based on patient demographic characteristics (young, women, minimal cardiovascular risk factors) and the
presence of thrombus on angiography and is aided by the absence of plaque rupture on intracoronary imaging.\textsuperscript{76,106}

**Coronary Vasospasm/Microvascular Dysfunction**

Coronary microvascular dysfunction reflects an endogenous hyperreactivity and may present de novo, as seen in patients with variant angina, or in the context of exogenous vasospastic stimuli such as the use of stimulants (cocaine, methamphetamine) or can be induced in the cardiac catheterization laboratory with a stepwise increase in the doses of intracoronary acetylcholine or ergonovine (Figure 8).\textsuperscript{107} The test results are considered abnormal if the patient’s symptoms and/or electrocardiographic changes can be reproduced with significant (≥90%) (focal/diffuse) narrowing of epicardial coronary arteries.

**Pregnancy and MI**

The population-based incidence of acute MI in pregnancy was determined in California.\textsuperscript{108} The incidence of MI during pregnancy between 1991 and 2000 was 1 in 35,700 deliveries and increased during the study period. Higher maternal mortality rates (7.3%) were noted in patients who had MI during pregnancy, and multivariate predictors included older maternal age. In a Nationwide Inpatient Sample from 2000-2002, a higher incidence of MI (6.2 in 100,000) was noted in pregnancy,\textsuperscript{109} and most MIs occurred during the third trimester or during the early postpartum period. Atherosclerosis is not very common, and many pregnant women have SCAD (see preceding Spontaneous Coronary Artery Dissection section), microvascular dysfunction, thrombus, or coronary emboli as determined by 2 small studies.\textsuperscript{110,111} Presentation is similar to other young patients, but a higher incidence of ST-segment elevation MI (75%) in the anterior wall (69%) is noted. Treatment should be individualized based on the needs and health of the mother and child and requires a multidisciplinary approach. Optimal care may include bare metal stents and postponing delivery by 2 to
3 weeks after MI. During MI, measures should be instituted to reduce cardiac workload (epidural anesthesia, left lateral position, treatment of hypertension and tachycardia). Aspirin and β-blocker use are safe in pregnancy, but other drugs (statins/angiotensin-converting enzyme inhibitors/fibrinolytic therapy) either have been found to be unsafe or have not been tested during pregnancy. Heparin is the anticoagulant of choice (during stent placement) because it does not cross the placenta. Bleeding may be more problematic during longer-term heparin use. The complication rates of MI are high in pregnant patients, and in one study 38% experienced heart failure/shock, 12% had ventricular arrhythmias, and 20% had recurrent angina.110

TREATMENT

MI Related to Traditional Cardiovascular Risk Factors

The treatment of young patients with MI due to plaque rupture should follow the current guidelines. This process would require guideline-directed medical management and coronary revascularization, similar to treatment for older individuals.

Recreational Drug Use and Psychosocial Factors

Recreational drug use and psychosocial factors are important and need to be considered in every young patient presenting with MI, especially patients who lack traditional cardiovascular factors and those in whom

FIGURE 8. Angiographic protocol for coronary microvascular dysfunction. Typical functional angiography demonstrating coronary flow reserve (CFR) changes in an endothelial-dependent (CFRe) and endothelial-independent (CFRne) manner. The protocol, initiated with diagnostic angiography and moving on to adenosine and acetylcholine (ACh) infusion, is depicted at the top of the figure. The angiogram (far left) shows an example of vasoconstriction after the administration of ACh. Endothelial-independent CFR is assessed using blood flow velocity profiles (average peak velocity [APV]) at rest and after adenosine infusion (bottom middle figure). Assessment of CFRe is depicted on the far right with a normal pre-ACh reading consisting of a predominant diastolic component on the top. The lower right figure shows a marked reduction in APV after the infusion of ACh indicative of poor microvascular recruitment of blood flow seen in patients with microvascular disease. Arrows indicate range of doses that can be used for adenosine and acetylcholine. The dose for acetylcholine is 10⁻⁶ mol/L to 10⁻⁴ mol/L. IC = intracoronary; Microcirc [microcirc] = microcirculation.
coronary vasospasm is detected during coronary angiography. Once detected, these patients should be referred for further counseling and treatment.

**MI Due to SCAD, Myocarditis, and CE Spontaneous Coronary Artery Dissection.**

The management for SCAD remains uncertain because of the lack of randomized studies of treatment outcomes or comparison between surgical or percutaneous revascularization. Observational data have indicated healing of most lesions with spontaneous dissection (70%-97%), with most healing occurring by 35 days. Recurrent MI is observed early (<7 days) in 5% to 10% of patients and calls for extension of inpatient monitoring. Indications for urgent revascularization include left main coronary artery involvement, ongoing chest pain, and ischemia or any hemodynamic instability. However, most patients with SCAD are managed conservatively, especially if coronary blood flow is not compromised. Once the ischemia resolves with conservative management, angiographic resolution and long-term outcomes are excellent. Routine angioplasty and stent placement in patients with SCAD are associated with worse outcomes because guidewires and balloons can track the false lumen, thereby extending the hematoma and dissection. The role of dual antiplatelet therapy, statins, or systemic anticoagulation has not been extensively tested. Recent American Heart Association consensus supports aspirin use for at least 1 year. In a study of 327 patients from Canada, β-blockers were beneficial and reduced dissection recurrence in these patients (hazard ratio, 0.36), underscoring the need for its routine administration.

**Myocarditis.** Patients presenting with decompensated heart failure should be treated at centers with expertise in invasive monitoring, catheterization, and endomyocardial biopsy. These sick patients may require inotropic support, extracorporeal membrane oxygenators, or left ventricular assist devices until recovery of left ventricular function occurs or they require cardiac transplant. If possible, cardiac transplant should be deferred because many patients recover over time. Physical activity should be restricted for 6 months and reassessed at that time, especially to allow athletes to compete. Treatment with acyclovir, ganciclovir, and valacyclovir for herpesvirus and interferon beta for adenoviral or enteroviral infection can be considered. High-dose intravenous immunoglobulins are associated with improvement in heart function, but in the IMAC (Intervention in Myocarditis and Acute Cardiomyopathy) randomized trial of recent-onset dilated cardiomyopathy, immunoglobulins produced no benefit in 62 patients.

Most immunosuppression trials have used corticosteroids with or without cyclosporine or azathioprine. The results were favorable in giant cell or virus-negative myocarditis. Immunosuppression was not helpful in myocarditis of unknown etiology in the Myocarditis Treatment Trial. In this trial, 111 patients with an ejection fraction of less than 45% and histopathologically proven myocarditis were randomized to receive either routine treatment or immunosuppression (24 weeks) with prednisone and either cyclosporine or azathioprine. The change in the ejection fraction at 28 weeks (primary end point) and survival did not differ between the 2 groups. The usefulness of immunosuppression with cyclosporine and corticosteroids was also demonstrated in patients with giant cell myocarditis.

**Coronary Embolism.** The initial treatment of CE is indistinguishable from common garden variety of ACS and includes antiplatelet therapy and anticoagulation with unfractionated heparin. If the diagnosis during coronary angiography is CE, thrombectomy is performed for large thrombus burden, sometimes aided by intracoronary glycoprotein IIB/IIIa inhibitors or thrombolytic therapy. Balloon angioplasty and coronary stents are not required. We favor intravascular ultrasound or OCT for determining the underlying mechanism (e.g., plaque erosion). Oral anticoagulation with warfarin or noval newer anticoagulants need to be started and continued for at least 3 months, longer...
if the risk factor for CE persists (e.g., atrial fibrillation). In patients with atrial fibrillation, oral anticoagulation should be prescribed regardless of the CHADS-VASC score. Systematic search for potential precipitating factors need to be done once the acute phase is over. There is no need for routine thrombophilia screening, unless there is a clinical suspicion.

**MI Due to Atheromatous CAD Without Critical Stenosis**

If an intact fibrous cap of a coronary plaque is detected in a patient presenting with MI, it portends a favorable prognosis. Typically, less severe coronary stenosis is observed in patients presenting without plaque rupture, and patients may benefit from aggressive anticoagulation and antiplatelet therapy with or without catheter-based aspiration of thrombus without routine stent deployment. Prati et al studied 31 patients presenting with ST-elevation MI who underwent OCT following aspiration of thrombus. Of the patients without significant obstructive plaque, 19 were treated with stents, whereas 12 were treated with antiplatelet therapy alone. At 24-month follow-up, no patients treated conservatively and one who received a stent needed repeated revascularization; however, this conservative approach needs further investigation.

**Coronary Vasospasm/Microvascular Dysfunction**

Coronary artery microvascular dysfunction should be suspected in young patients with MI who have normal findings on coronary angiography or have minimal CAD (<50% stenosis). There are no protocols that are routinely followed in such patients to detect or induce microvascular dysfunction, leading to underdiagnosis of microvascular dysfunction. Radico et al used fractional flow reserve for indeterminate lesions and intracoronary acetylcholine to uncover coronary microvascular dysfunction if an obvious etiology of ACS remained undetected. Exclusion of other causes of MI in young patients is important (myocarditis, Takosubo cardiomyopathy, or paroxysmal atrial fibrillation–related MI) before invasive investigations for the presence of coronary microvascular dysfunction.
are undertaken. The approach and its safety in 80 patients was demonstrated by Montone et al.\textsuperscript{129}

The treatment of patients with coronary microvascular dysfunction should be guided by the outcomes and the results of the invasive testing. Once detected, most patients need basic CVD prevention (diet, exercise, and weight loss) and long-term nitrates with or without nondihydropyridine calcium-channel blockers. Their doses in isolation or in combination can be gradually increased to the maximum tolerated dose. β-Blockers (especially nonselective), in general, are avoided because they can exacerbate and prolong vasospasm. Nicorandil (a nitrate and potassium channel activator), magnesium, antioxidants, rho kinase inhibitor, and statins have been tried with some success in these patients.\textsuperscript{130-132}

**FOLLOW-UP AND PROGNOSIS**

The prognosis for young patients with MI is not benign. The adverse cardiovascular events are similar in patients presenting with or without significant obstruction in coronary arteries. Mortality is higher compared with age- and sex-matched controls.

Patients with SCAD typically have recurrent MI rates of 10% to 30% at 2 to 3 years. The event rate at 5 years is between 15% and 37% and at 10 years is approximately 50%.\textsuperscript{28,117,133} In a report from Mayo Clinic, recurrence of SCAD was noted in 17% (15 of 87 patients) and 10-year recurrence was estimated to be 29.4%.\textsuperscript{27}

The detection of microvascular dysfunction can lead to significant adverse cardiac events on follow-up. In one study, patients with severe endothelial dysfunction had a higher incidence of cardiac mortality, MI, or revascularization.\textsuperscript{134} In another study, patients presenting with MI who had testing-confirmed microvascular dysfunction had significantly higher all-cause (32.4% vs 4.7%; \(P=.002\)) and cardiac (18.9% vs 0.0%; \(P=.005\)) mortality compared with patients who had negative test results. In addition, higher rates of hospital readmissions with ACS and worse anginal symptoms were reported at 1 year in patients with microvascular dysfunction.\textsuperscript{129}

In 50% of patients with resolution of myocarditis over the ensuing 2 to 4 weeks, 12% to 25% may experience deterioration and development of worsening congestive heart failure that may further progress to requiring cardiac transplant.\textsuperscript{74} Patients with biopsy-proven giant cell myocarditis have a poor prognosis.\textsuperscript{135}

**RECOMMENDATIONS**

We recommend a systematic approach to arriving at a correct diagnosis. Any young patient with confirmed MI should undergo coronary angiography to identify the atherothrombotic culprit (Table 4 and Figure 6). If risk factors (smoking, diabetes mellitus, hyperlipidemia, hypertension, peripheral arterial disease) and angiographic features (thrombus, presence of atherosclerotic disease elsewhere in the coronary vascular bed) favor atherothrombotic disease, then we recommend following the American Heart Association/American College of Cardiology guidelines for medical management and/or coronary revascularization with either percutaneous coronary intervention or surgery.

If thrombus is detected on angiography in patients without traditional cardiovascular risk factors and significant CAD, we recommend work-up for a hypercoagulable state (deficiency in protein C and S factors, factor V Leiden, oral contraceptives) and/or

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**TABLE 6. When the Initial Work-up for MINOCA is Negative**

<table>
<thead>
<tr>
<th>Precipitating causes:</th>
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<tr>
<td>*Drug history (cocaïne, methamphetamine, marijuana) *Preceding viral illness favors myocarditis</td>
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<tr>
<td>*Type II myocardial infarction due to supply/demand mismatch Cardiac MRI (late gadolinium enhancement): *Subepicardial (myocarditis) *Subendocardial (ischemia, dissection, thromboembolism)</td>
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MINOCA = myocardial infarction with nonobstructive coronary arteries; MRI = magnetic resonance imaging.
looking for a source of embolism (atrial fibrillation, valvular [native or prosthetic], left ventricular) and considering evaluation for supportive evidence of thromboembolic infarction in other end organs, such as cerebral or abdominal imaging. If thrombus is present without risk factors (with the exception of smoking), a diagnosis of plaque erosion should be considered (see subsequent discussion).

If no obvious thrombus is seen on coronary angiography, one should carefully look for SCAD or coronary microvascular dysfunction, especially in premenopausal women (Table 5). If SCAD is recognized, conservative management suffices in most patients (see the section on SCAD). The medical management of these patients includes β-blockers and baby aspirin.

In young patients with MI, spontaneous coronary microvascular dysfunction should be investigated thoroughly and the diameter of the coronary vasculature with and without intracoronary nitroglycerine should be routinely measured, especially if coronary angiographic findings are normal. If coronary microvascular dysfunction is identified, these patients can be treated effectively with oral nitrates and/or nondihydropyridine calcium-channel blockers.

If coronary angiographic findings are inconclusive and no culprit is visible angiographically, we recommend ruling out any precipitating cause such as drugs (cocaine, methamphetamine, marijuana for coronary spasm), hypercoagulable state (CE), preceding viral illness (myocarditis), or supply-demand mismatch (type II MI) (anemia, thyrotoxicosis). Cardiac magnetic resonance imaging is an important investigation because the late gadolinium enhancement in the subendocardium suggests ischemic injury, whereas subepicardial localization favors myocarditis or an infiltrative disorder. Ischemic injury characteristics should prompt a closer reexamination of the initial diagnostic coronary angiogram for SCAD or small missing branches and allows clinicians to reevaluate and recalibrate their diagnosis (Table 6).

If the diagnosis is still elusive, 2 procedures should be considered: (1) invasive provocation of microvascular dysfunction and evaluation of endothelial function at 6 to 8 weeks of follow-up and (2) utilization of IVUS/OCT to rule out plaque erosion, especially in cases of coronary lesions with angiographic thrombus. For better plaque characterization, we favor OCT, which can differentiate a ruptured from an intact fibrous cap and a red from a platelet-rich thrombus and can help guide conservative or invasive management in these patients.2,36,137

CONCLUSION
This review focuses on the prevalence, risk factors, unique syndromes, and overall profile of young patients presenting with MI. We also discuss the management of important syndromes that are more prevalent in the younger population. Lastly, we propose a unique method that will help clinicians stratify young patients with MI into different diagnostic categories. This approach will be of immense help in arriving at the right diagnosis and individualizing the treatment of MI in young patients.

Abbreviations and Acronyms: ACS = acute coronary syndrome; BMI = body mass index; CAD = coronary artery disease; CE = coronary embolism; CVD = cardiovascular disease; FMD = fibromuscular dysplasia; IVUS = intravascular ultrasound; MI = myocardial infarction; MINOCA = MI with nonobstructive coronary arteries; NHANES = National Health and Nutrition Examination Survey; OCT = optical coherence tomography; OR = odds ratio; RR = relative risk; SCAD = spontaneous coronary artery dissection

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REFERENCES
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