ESC European Society of Cardiology

Cardiovascular Research (2022) **118**, 2281–2292
https://doi.org/10.1093/cvr/cvab264

REVIEW

Risk factors profile of young and older patients with myocardial infarction

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Received 18 December 2020; editorial decision 2 August 2021; accepted 3 August 2021; online publish-ahead-of-print 6 August 2021

Abstract

Myocardial infarction (MI) among young adults (<45 years) represents a considerable proportion of the total heart attack incidents. The underlying pathophysiologic characteristics, atherosclerotic plaque features, and risk factors profile differ between young and older patients with MI. This review article discusses the main differences between the younger and elderly MI patients as well as the different pathogenic mechanisms underlying the development of MI in the younger. Young patients with MI often have eccentric atherosclerotic plaques with inflammatory features but fewer lesions, and are more likely to be smokers, obese, and have poor lifestyle, such as inactivity and alcohol intake. Compared to older MI patients, younger are more likely to be men, have familial-combined hyperlipidaemia and increased levels of lipoprotein-a. In addition, MI in younger patients may be related to use of cannabis, cocaine use, and androgenic anabolic steroids. Genomic differences especially in the pathways of coagulation and lipid metabolism have also been identified between young and older patients with MI. Better understanding of the risk factors and the anatomic and pathophysiologic processes in young adults can improve MI prevention and treatment strategies in this patient group. Awareness could help identify young subjects at increased risk and guide primary prevention strategies. Additional studies focusing on gene pathways related to lipid metabolism, inflammation, and coagulation are needed.

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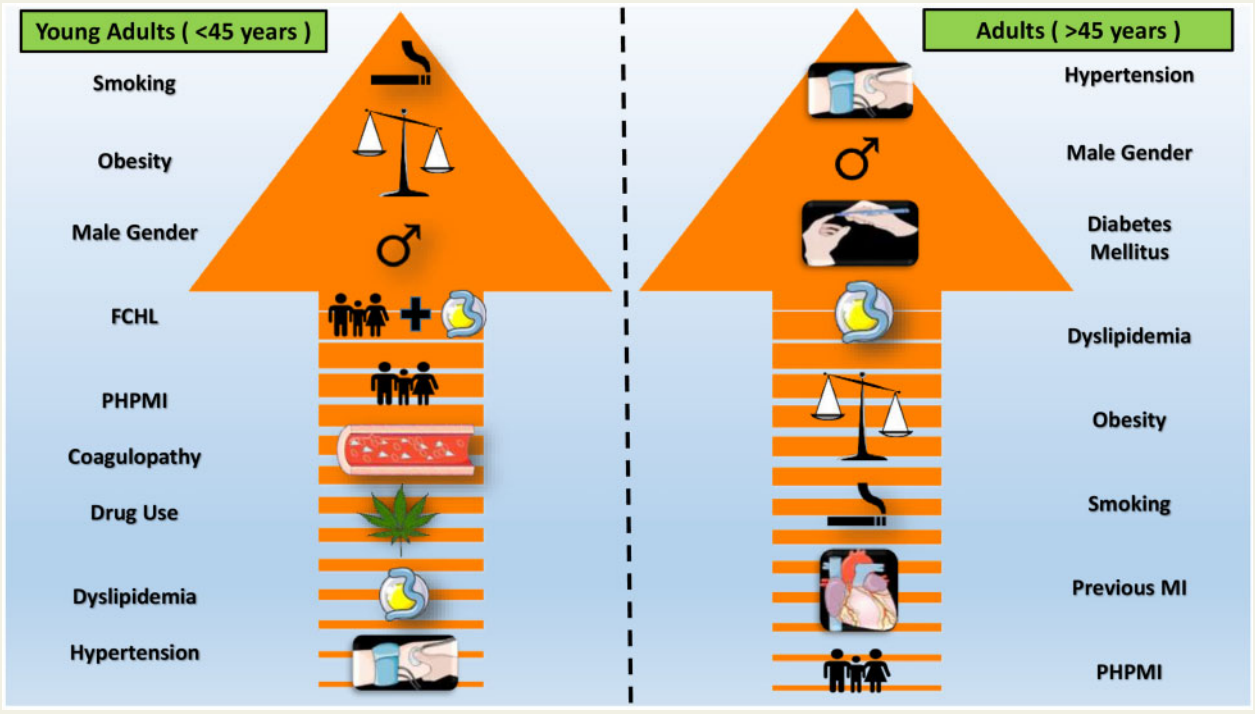
†This paper was handled by consulting editor Henning Morawietz.

Graphical Abstract



Keywords • Myocardial infarction • Risk factors • Young patients • Atherosclerotic plaque features • Genetic factors •

1. Introduction

Coronary artery disease (CAD) and its complications remain the most common cause of death worldwide.[1] Evidence of elevated cardiac troponin (cTn) values with at least one value above the 99th percentile upper reference limit is characterized as myocardial injury.[2] In the 4th Universal Definition of Myocardial Infarction (MI), myocardial injury differs from the term of MI. More specifically, the term MI should be used for myocardial injury with clinical evidence of acute myocardial ischaemia, plus the detection of a rise and/or fall in cTn values.[3] Additionally, one of the following features has to be present: (i) symptoms of myocardial ischaemia; (ii) new ischaemic electrocardiogram changes; (iii) development of pathological Q waves; (iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; and (v) identification of a coronary thrombus by angiography or autopsy.[2,3]

Five MI types have been recognized. Type 1 MI is presented with acute atherothrombosis in an artery, which irrigates a certain part of myocardium. Criteria for Type 2 MI are met when an imbalance of myocardial demanded oxygen occurs.[4] Type 3 MI is described by cardiac death from suspected myocardial ischaemia based on electrocardiogram changes in symptomatic patients, with no notification of elevated cTn levels until then. Finally, Type 4 procedural MI is directly related to percutaneous coronary intervention and Type 5 with coronary artery bypass grafting.[4,5]

CAD mainly affects older individuals as shown in the landmark Framingham heart study, demonstrating an eight-fold increase in the MI incidence in the older age group compared to participants younger than 55 years of age.[6] The incidence of MI among young adults has increased in the past decade as reported recently in the analysis of the Atherosclerosis Risks in Communities study. Overall, data regarding MI incidence in younger patients are sparse, but increasing numbers of studies are being conducted in this important subgroup (*Table 1*). Another documented difficulty is the lack of a universally established age cut-off across the published studies, making comparisons virtually impossible. For the purpose of this review, an age cut-off of 45 years was used as the incidence of aggravating cardiovascular risk factors, such as arterial hypertension, dyslipidaemia, and diabetes mellitus (DM) exponentially increases past that point,[7,8] accounting for excess risk factor-related mortality. These results highlight how challenging it is to identify risk and genetic factors in young individuals and suggest that future research is needed to identify and treat cardiovascular risk in young adults, particularly those under the age of 45 who are only rarely candidates for statin therapy.[9,10] Additional studies are needed to evaluate the impact of gender on clinical presentation, treatment patterns, and outcomes of MI in young patients.[9] The mechanisms of MI in young individuals seem to differ significantly from those affecting older patients and could be grouped into three main categories: (i) atherosclerotic CAD; (ii) non-atherosclerotic ischaemic heart disease; and (iii) hypercoagulable state. The individual's genetic profile contributes, together with other

Table 1 Comparative incidence of MI in young and old patients according to completed studies

Study	Country	Time interval	Young age cut-off	Young MI, %	Old MI, %
ARIC[45]	USA	1995–99	<55 years	27	73
		2000–04		30	70
		2005–09		32	68
		2010–14		32	68
Qureshi *et al.*[109]	USA	2005–14	<55 years	30	70
Odoi *et al.*[110]	USA	2005–14	<45 years	4.3	95.7
Wittlinger *et al.*[111]	Germany	2005–14	<40 years	2	98
Wang *et al.*[112]	New Zealand	2006	<45 years	3.3	96.7
		2016		2.9	97.1
Jortveit *et al.*[113]	Norway	2013–16	<45 years	4.4	95.6
Schmidt *et al.*[114]	Denmark	1989–98	<50 years	7.5	92.5
		1999–2008		8	92
Seo *et al.*[115]	Korea	2006–10	<50 years	15.6	84.4
		2011–15		14	86
Alkhouli *et al.*[50]	USA	2003–15	<45 years	10.5	89.5

MI, myocardial infarction; USA, United States of America.

predisposing factors, to create a favourable milieu for the development of atherosclerosis and MI at a younger age[11] (*Figure 1*).

This review article discusses the main differences that exist between the younger and elderly MI patients in the four different categories mentioned above. The article also addresses the different pathogenic mechanisms underlying the development of MI in the younger.

2. Coronary plaque features—differences between elderly and younger MI patients

Angiographic as well as pathologoanatomical coronary findings are different in younger patients with CAD compared with the elderly (*Table 2* and *Figure 2*). The left anterior descending (LAD) is the most commonly affected artery in both patient groups. Younger patients frequently present with single-vessel CAD,[12,13] fewer coronary lesions,[12] and lower lesion complexity, as estimated by the Gensini score,[11] which is a strong predictor of successful restoration of myocardial perfusion[14] as well as short- and long-term adverse cardiovascular events.[15,16] Moreover, Gensini score was an independent predictor of long-term mortality in elderly individuals.[17]

With regards to histological findings, younger patients were more likely to have eccentric lesions, as well as lymphocytic infiltration of large- and medium-sized coronary arteries and thrombosis compared with older MI patients.[12] Specifically, 82% of the young patients had eccentric atherosclerosis with an inflammatory response being observed in all of them. On the contrary, an eccentric atherosclerotic pattern was detected in 39% of the elderly, while the presence of inflammation declined with ageing.[12] Plaque haemorrhage was less common in young subjects (32% vs. 61% among older patients).[12] Pultaceous debris, the principal component in atherosclerotic plaques of both groups of patients, was more common in the elderly, whereas foam cells and fibrous tissue were common in both patient groups.[12]

These findings suggest that young MI patients frequently have eroded plaques,[18] characterized by eccentricity and infiltration by lymphocytes.[19] Inflammation and intraplaque haemorrhage are among the main mechanisms of vulnerable thin-cap fibroatheromas formation in the elderly, leading to plaque rupture and MI.[20] Interestingly, those alterations in plaque morphology lead to distinct clinical phenotypes. An MI event in young patients is more frequently caused by plaque erosion whereas plaque rupture is more often detected in older patients.[21,22] Moreover, plaque erosions have been associated with a less complex, LAD-localized atherosclerotic pattern[23] as in the case of young MI patients and a better prognosis compared to ruptured plaques, which are more frequently found in elderly subjects.[24] Last but not least, the presence of plaque erosions, as in young MI patients, has important therapeutic implications since a stentless, intensive anti-thrombotic approach in a small clinical study of acute MI patients with evidence of plaque erosion led to significant or complete thrombus resolution[25] and freedom from adverse cardiac events after 4 years of follow-up.[26] The discovery of biomarkers of plaque erosion may ultimately result in a non-invasive management of patients with non-ST-elevation MI may guide treatment decisions towards an individually tailored treatment of intense anti-thrombotic regimens.[27]

3. Traditional risk factors for MI Type-1 in young patients

The role of traditional risk factors for MI in young patients is summarized in *Table 3* and discussed in details below.

3.1 Tobacco

Younger MI patients are more likely to be current smokers (80% vs. 57%) compared with the elderly.[28] Smoking is highly prevalent in ST-segment elevation MI in young patients.[29] A dose–effect between smoking and MI is present with patients who smoked >25 cigarettes/day having eight-fold higher odds of MI compared to never smokers.[30] Both cigarette and waterpipe smokers were more common among younger first-time MI patients than older first-time MI patients.[31] Smokeless tobacco has been associated with lower high-density lipoprotein (HDL) and higher total cholesterol levels and can potentiate coronary vasoconstriction, therefore possessing atherogenic and thrombogenic properties.[32] The detailed mechanism through which cigarette smoking is associated with cardiovascular disease has not yet been clarified. It is strongly suggested that smoking has two effects on platelets: (i) a significant acute potentiation of platelet activation occurring shortly after smoking a cigarette and (ii) a chronic desensitization of the cell to activating agents occurring during the period between cigarettes leading to Type 1 MI.[33,34]

3.2 Dyslipidaemia

Dyslipidaemia is an established MI risk factor among all age groups. Hovingh *et al.*[35] reported a high prevalence (10%) of familial-combined hyperlipidaemia (FCHL) in survivors of premature MI, while the levels of low-density lipoprotein (LDL-C) remained >70 mg/dL irrespective of statin use. More specifically, FCHL was associated with a 24-fold increased adjusted risk for MI with very low-density lipoproteins and non-HDL constituting aggravating factors for MI incidence.[36] FCHL is often present in patients with a family history of premature CAD (20% prevalence in young MIs) and/or high levels of LDL-C (60% prevalence 'young' MIs).[36] Dyslipidaemia has a stronger correlation with Type 1 MI incidence in the elderly compared with younger individuals (43% vs. 36%). However, cross-sectional studies found that triglyceride, LDL-C, and

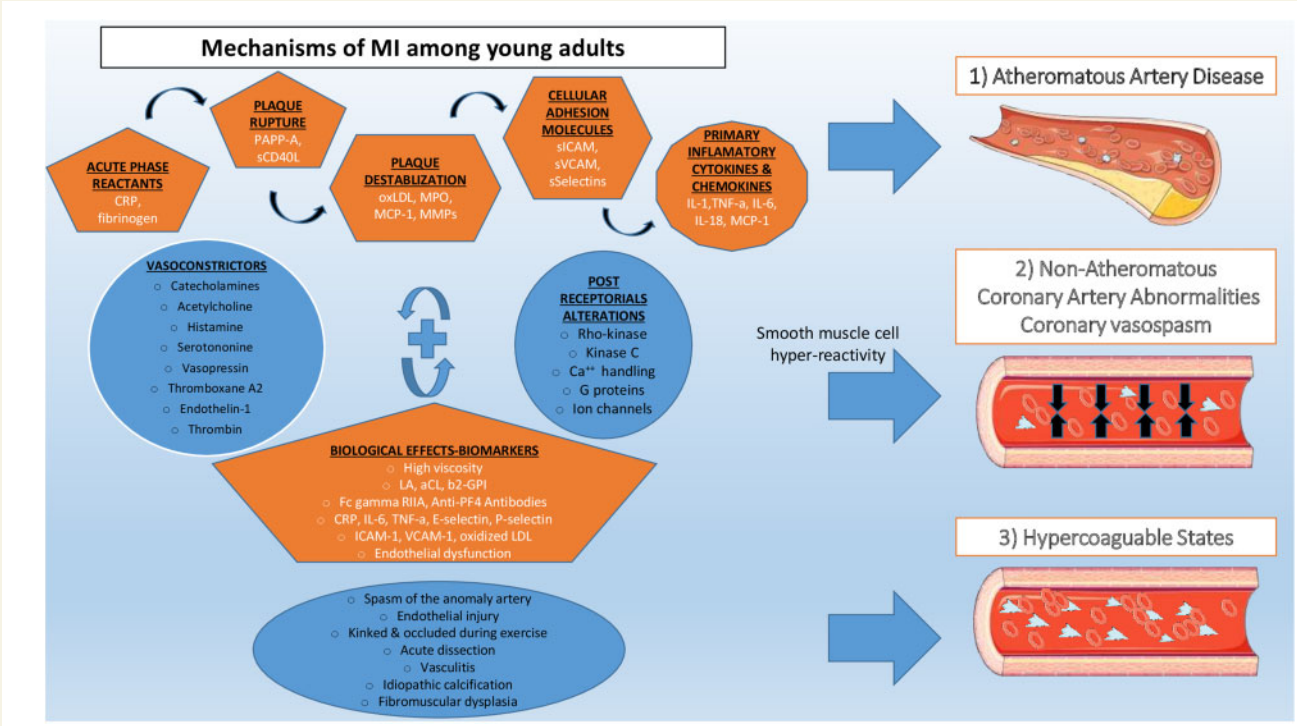


Figure 1 Pathophysiology of MI among young adults. MI, myocardial infarction; CRP, C-reactive protein; PAPP-A, pregnancy associated plasma protein-A; sCD40L, soluble CD40 ligand; oxLDL, oxidized low density lipoprotein; MPO, myeloperoxidase; MCP-1, monocyte chemoattractant protein-1; MMPs, matrix metalloproteinases; sICAM, circulating soluble intercellular adhesion molecule; sVCAM, circulating soluble vascular cell adhesion molecule; IL-1/IL-6/IL-18, interleukin-1/-6/-18; TNF-a, tumour necrosis factor-a; LA, lupus anti-coagulant; aCL, anticardiolipin antibodies; Anti-b2–GPI, anti-beta2-glycoprotein I; Fc gamma RIIA, Fc gamma RIIA/CD32a recombinant protein antigen; Anti-PF4, anti-platelet factor 4.

Table 2 Coronary plaque features of young and older MI patients

	Plaque feature	<45 years	>45 years	Clinical implications
ANGIOGRAPHIC FINDINGS	Number of infarcted arteries	No disease or single vessel[13]	Two or more vessels[13]	Angiographic complexity and severity of coronary artery disease is associated with increased in-hospital, short- and long-term MACE[15,116–118].
	Number of lesions	2 or less[12]	3 or more[12]	
	Gensini score	7.69 ± 5.23[11]	16.08 ± 7.81[11]	
PLAQUE CHARACTERISTICS	Plaque eccentricity	82%[12]	39%[12]	Young MI patients frequently present with plaque erosions (eccentric with lymphocytic inflammatory infiltrate), which are met with a favourable prognosis and an opportunity for conservative management with intense anti-thrombotic treatment.
	Inflammatory response	100%[12]	61%[12]	
	Thrombosis	47%[12]	11%[12]	
	Plaque haemorrhage	32%[12]	61%[12]	
	Principal component	39% pultaceous debris 25% foam cells[12]	64% pultaceous debris 18% dense fibrous tissue[12]	

MACE, major adverse cardiovascular events; MI, myocardial infarction.

apolipoprotein B levels were significantly higher in younger compared with older MI patients, whereas HDL-C levels were lower.[37]

Adolescents with a parental history of premature MI have increased lipoprotein-a [Lp(a)] levels. Likewise, a high level of Lp(a) has described as an independent risk factor for MI in all age groups.[38] Rallidis *et al.*[39] showed that high levels of Lp(a) increase by three-fold the odds of MI in individuals <45 years, with a lesser association in individuals between 45 and 60 years. An increase of 10 mg/dL results was associated with a 4% higher relative risk of having Type 1 MI at a younger age (<45 years) and 2% in middle age (45–60 years).

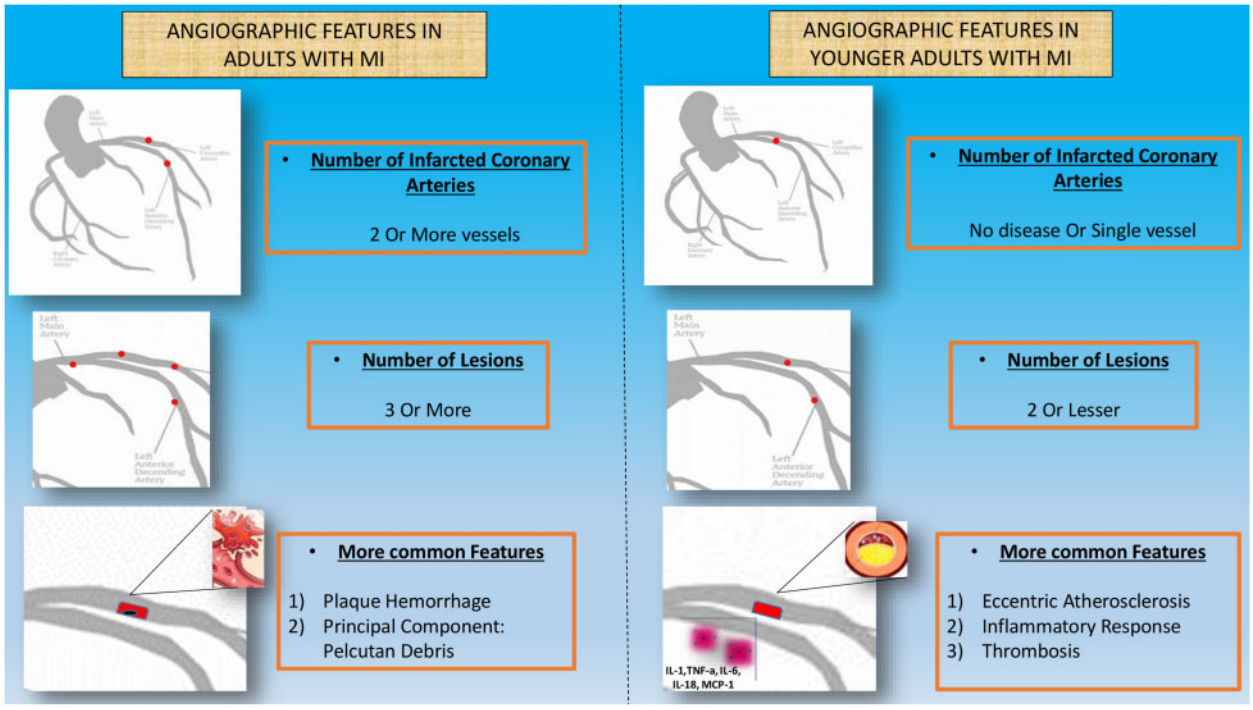


Figure 2 Comparison of angiographic features between young and elderly patients. IL-1/IL-6/IL-18, interleukin-1/-6/-18; TNF-a, tumour necrosis factor-a; MCP-1, monocyte chemoattractant protein-1.

3.3 Obesity

Liu *et al.*[40] analysed the correlation between healthy lifestyle factors (HLFs) and MI in younger patients, such as (i) average body mass index <25 kg/m^2; (ii) no or moderate alcohol intake; (iii) higher healthy diet score; (iv) higher physical activity score; and (v) never smoking. The prevalence of CAD in combination with age, sex, and race were 3.0%, 14.6%, 29.5%, 39.2%, and 60.7% for people with 0–1, 2, 3, 4, and 5 HLFs, respectively, with similar graded relationships being observed for each sex-race group. Compared with older (>45 years) MI patients, younger patients were more likely to be male and had higher body mass index (31 kg/m^2 vs. 29 kg/m^2).[40] Adiposopathy is comprised by adipocyte hypertrophy, decreased adipose tissue blood flow, altered oxygen levels within the tissue, a state of chronic low-grade inflammation and blunted lipid metabolism.[41,42] With obesity levels increasing, the risk of premature Type 1 MI is likely continue increasing, with further research needed on the effect of adiposopathy on young subjects.[43]

3.4 Sex

Most young MI patients are men. Young men have higher levels of cardiac biomarkers and more classic electrocardiogram findings while women tend to present with more atypical symptoms and fewer STEMI cases.[44,45] Specifically, among patients with MI presenting with chest pain, female patients reported more often additional symptoms, such as palpitations, shortness of breath, and epigastric pain. Moreover, females often interpret their anginal symptoms as high anxiety levels and this results in delayed hospital presentation and potentially worse prognosis of female patients with acute MI.[44]

Recent data suggest a rising incidence of MI among young women with spontaneous coronary artery dissection being the cause in a significant proportion of STEMI.[45,46] Young women with MI are more likely to have chronic obstructive pulmonary disease, congestive heart failure, morbid obesity, diabetes, hypertension, and renal failure while they usually suffer from higher levels of anxiety and have altered mental health and physical status.[47] As far as changes in trends are concerned, the prevalence of hypertension has increased while smoking was less frequently observed in young women in the course of time.[45]

Women experience their first MI 6–10 years later than men and a protective effect of their natural oestrogen status prior to menopause has been suggested. Female sex hormones have been associated with a less atherogenic lipid profile and a more healthy fat distribution.[48] Several studies are trying to identify the protective role of oestrogens on cardiovascular system with further research needed.[49]

With regards to management, important disparities are present between sexes. Specifically, young women are less likely to undergo an early invasive strategy, primary percutaneous coronary intervention or CABG compared to their male counterparts irrespective of MI type, even though improvements are noted in the course of time.[50] This translates into worse prognosis (in-hospital mortality, vascular complications, and major bleeding) compared to male patients. Interestingly, increasing age in females was associated with improved outcomes in comparison to elderly males.[50]

3.5 Diabetes mellitus

Although DM is rare in young patients with MI, it is nevertheless associated with a higher MI risk in both sexes.[47] DM, hypertension, dyslipidaemia, and the previous history of MI were more common among elderly patients, 37%, 60%, 43%, and 42%, respectively, vs. 10%, 24%, 36%, and 25% in the younger population.[28,51] In the setting of Type 1 DM, age of

Table 3 Differences and similarities in risk factors between young and elderly patients with MI

Risk factor	Studies	Age <45 years	Age >45 years	Results
Smoking	Shah *et al.*[119] Hbejan[30] Larsen *et al.*[29] Deligiannis *et al.*[32] Liu *et al.*[40] Zgheib *et al.*[28]	(+)(+)(+)(+)	(+)(+)	A dose–effect response is associated with young MI incidence. Younger patients with MI were more likely to be smokers (80% vs. 57%) compared to the elderly.
Male gender	Bucholz *et al.*[47] Shah *et al.*[119] Liu *et al.*[40]	(+)(+)(+)(+)	(+)(+)(+)	The patients of the young MI group were more likely to be male (80%). The dominance of men vs. women is frequently reported (80% vs. 71%).
Diabetes mellitus	Zgheib *et al.*[28,51]	(+)	(+)(+)	DM is more common among elderly patients (10% vs. 37%).
Obesity (BMI > 25kg/m^2)	Matsis *et al.*[120] Liu *et al.*[40] Shah *et al.*[119]	(+)(+)(+)(+)	–	80% of young patients with MI have a higher BMI. Compared to older MI age group (>45 years), patients in the younger group were more likely to be male and have a higher BMI (31 kg/m^2 vs. 29 kg/m^2).
Homocysteine	Karim *et al.*[51,70]	–	–	Homocysteine levels are increased in younger infarcted patients compared to the elderly (16.36 ± 7.8 mmol/L vs. 11.7 ± 5.6 mmol/L).
Hypertension	Zgheib *et al.*[28,51]	(+)	(+)(+)(+)	Hypertension is more common among elderly patients (24% vs. 60%).
Dyslipidaemia	Zhang *et al.*[37]	(+)(+)	(+)(+)	Dyslipidaemia has a stronger correlation with MI incidence in the elderly compared to young individuals (43% vs. 36%).
FCHL	Hovingh *et al.*[35] Singh *et al.*[121] Shah *et al.*[119] Wiesbauer *et al.*[36]	(+)(+)	(+)	FCHL reduced the age onset of first MI by as much as 15 years. Approximately 10% of young MI patients present with elevated LDL-C levels. The EUROASPIRE IV cohort study of 7044 patients with MI, showed that 8.3% had probable FCHL, increasing to >15% in patients with premature event.
PHPMI	Rallidis *et al.*[39] Gaeta *et al.*[38] Shah *et al.*[119]	(+)(+)(+)	–	Lp(a) levels are increased in healthy young patients with parental history of premature MI. PHPMI is reported in the vast majority of young MI cases (41–71%).
Previous MI	Zgheib *et al.*[28,51]	(+)	(+)(+)	Incidence of previous MI is more common in the elderly (25% vs. 42%).
Hereditary Coagulopathies/ Genetic mutations	Redondo *et al.*[62,63] Clarke *et al.*[80]	–	–	Latest studies demonstrate that hereditary coagulopathies have a significant association with premature MI. Genetic mutations are part of differential diagnosis in cases with unexpected CAD occurring at a young age.
Illicit/performance-enhancing drugs	Lisowska *et al.*[57] Deligiannis *et al.*[32]	–	–	Cardiovascular toxicity includes atherogenic, thrombotic and haematological effects as well as direct myocardial injury.

(+): Every cross represents an incidence of the risk factor in the age group of subjects with myocardial infarction of 20–25%.
MI, myocardial infarction; FCHL, familial-combined hyperlipidaemia; PHPMI, parental history of premature myocardial infarction; CAD, coronary artery disease; DM, diabetes mellitus; BMI, body mass index; Lp(a), lipoprotein-a; –, N/A.

onset and gender are important determinants of survival and MI outcomes in young subjects. Specifically, women who developed Type 1 DM before 10 years of age had a hazard ratio of 91.07 with the corresponding hazard ratio in men being 15.11. These differences, however, were mitigated with increasing age of onset, as the lowest hazard ratio for MI in women with Type 1 diabetes was observed with disease onset between 26 and 30 years.[52,53] The above-mentioned finding could be explained by the action of glycosylated haemoglobin A1c, which is described as an independent determinant for microvascular perfusion, suggesting tight glycaemic control is potentially important for the prevention of cardiovascular disease.[54–56]

4. Risk factors for MI at a younger age

4.1 Anabolics and stimulants

Substance abuse, such as cocaine and cannabis, is among the less common MI risk factors for MI.[57] Specifically for cannabis, which is the most frequently abused substance, it has been linked with incident MI independently of traditional cardiovascular risk factors, with the effect being more pronounced in younger patients.[58] Similarly for cocaine use, which is reported in ∼10% of MIs at a young age, has been associated with an increased risk of cardiovascular mortality. The responsible mechanisms include increased myocardial oxygen demand, lower peripheral vascular reflex response, as well as coronary artery vasospasm, meeting the Type 2 MI criteria. The risk of MI due to cocaine is dose–independent, in contrast to cannabis.[58]

Moreover, the use of stimulating substances, mainly androgenic anabolic steroids (AASs) among elite as well as amateur athletes is widespread, with high doses leading to numerous side-effects. AASs increase the odds for MI in young patients due to a decrease in HDL-C and apolipoprotein A1 (by 20–70%) and a significant increase of LDL-C and apolipoprotein B (up to 20%).[59] Besides, long-term use of AASs could lead to the development of hypertension and a high concentration of C-reactive protein.[59] The main pathway of thrombosis is due to erythrocytosis (9.6% increase in haematocrit within ∼26 weeks of use), thrombocytosis, and platelet hyperactivity.[59] Furthermore, AAS increase levels of procoagulant factors (especially fibrinogen, factor VIII and X), homocysteine as well as endothelium release of proteins C and S, with the decreased fibrinolytic activity (decreased levels of a-2-macroglobulin and plasminogen activator inhibitor 1 as well as increased levels of tPA and plasminogen) and prostacyclin synthesis further enhancing their prothrombotic action.[59]

Erythropoiesis-stimulating agents (ESAs) are erythropoietin derivatives that have been widely used as performance-enhancing drugs. Induced erythrocytosis can be achieved through the use of erythropoietin and analogues, blood transfusion in the form of homologous or autologous administration as well as by red blood cells-mimicking synthetic biomaterial particles.[60] There is limited data regarding ESAs in the setting of CAD and MI, but it is speculated that their combination with dehydration during physical activities could lead to adverse cardiovascular events.[60] According to the above mentioned, using of AASs and ESAs lead to acute coronary atherothrombosis via multiple pathways, following the Type 1 MI criteria.[61]

4.2 Thrombotic/fibrinolytic factors

Thrombotic and fibrinolytic pathways are complex and display a particular interaction between them. Redondo *et al.*[62] showed that high levels of factor V or factor VII in serum plasma are associated with higher MI risk. The presence of smoking or arterial hypertension magnified the risk by 50-fold. Factor V Leiden, the most common hereditary hypercoagulability factor has been associated with premature MI Type 1, while a higher activity of factor XIII was also detected in young MI survivors. Moreover, Factor XI can activate coagulation factors X, V, and VIII, and inhibit the anti-coagulant tissue factor pathway inhibitor, therefore being recognized as an independent risk factor for MI.[63] The higher risk associated with these hypercoagulable states could be related to unfavourable lipidaemic profile, as demonstrated by abnormal Lp(a) levels in a group of patients with antiphospholipid syndrome.[62,64,65] Furthermore, Butt *et al.*[66] demonstrated that the Factor II 20210A allele, the Factor XIII-A Leu34 allele, and their synergistic effect are additional risk factors for MI.[62] A recent meta-analysis demonstrated an unfavourable role of hypercoagulable states with previous MI without such an association in the setting of stable CAD.[67]

4.3 Homocysteine

Hyperhomocysteinaemia causes the production of proinflammatory cytokines, namely interleukin-1β and -6, tumour necrosis factor-α, monocyte chemoattractant protein 1, and intracellular adhesion molecule-1, leading to increased oxidative damage.[68] There are conflicting reports on the association between homocysteine—or its lowering with treatment—and the incidence of CAD. Numerous studies showed that hyperhomocysteinaemia is associated with increased MI risk, classifying it as an independent risk factor and a possible marker of preclinical disease state.[68,69] Some studies have shown higher homocysteine levels in younger infarcted patients compared with the elderly.[51,70]

4.4 Genetic factors

There is strong evidence that CAD in early life is associated with the patient's genetic background. The non-Mendelian heritability of MI and CAD makes the issue more complex. A study in 2017—which examined prothrombotic risk factors—showed that polymorphisms G20210A of prothrombin [FII] gene are associated with increased risk of premature ST-segment elevation MI.[71] Prothrombin (FII), the precursor of thrombin, is a vitamin K-dependent glycoprotein whose primary function is to convert fibrinogen to fibrin, activating factor XIII in the development of clots that are more resistant to fibrinolysis. The expression of the mutation G20210A results in slightly higher levels of prothrombin, which can be easily converted to thrombin as required, predisposing to hypercoaguable state.[72] If the above polymorphism is combined with casual smoking, the risk is increased 22-fold (95% CI: 9.192–66.517).[71] Hmimech *et al.*[73] showed that polymorphisms G20210A of prothrombin [FII] gene—even if there is a single or double copy of the 20210A allele—is highly associated with premature MI. A recent meta-analysis found that the polymorphism raises MI risk in an age-related way, with youngs under the age of 55 experiencing the most (OR = 1.76, 95% CI: 1.32–2.35).[74] Burzotta *et al.*'s[75] meta-analysis showed that the G20210A prothrombin gene polymorphism can be a minor but substantial risk factor for MI at a young age (<45 years) (OR = 2.3, 95% CI: 1.27–4.59), favouring the expression of ischaemic cardiac disease in persons with a small degree of coronary atherosclerosis on angiography. Other polymorphisms that seem to play a significant role are these of factor V Leiden—especially the homozygote phenotype—, plasminogen activator inhibitor 1 polymorphism 4G/5G, and glycoprotein VI (GP6, 13254 TC, Ser219Pro). Generally, FV activates factor X in the process of transforming prothrombin to thrombin. FV is activated by thrombin, and its active

form is vulnerable to protein C cleavage and inactivation. The V Leiden mutation altered FV structure, leading to protein C tolerance with a longer half-life and increased thrombin production.[76] Mannucci *et al.*[77] showed that the minor A allele of F5 G1691A was associated with an increased risk of MI, noting the important role of hypercoagulability in the pathogenesis of MI in young individuals (<45 years). Studies in youngs under 45 years old with V Leiden mutation showed that the risk for MI was 32-fold higher in smoking than the non-smokers, but no sex association has been proved until now.[78,79] Congenital deficiencies of AT, PC, and PS belong to rare diseases, the few available case reports refer to young individuals with MI. This could imply that hereditary deficiencies of the natural anticoagulants are significant enough to induce early onset of thrombotic complications.[80] The above mentioned suggests that thrombophilia might be an important part of the differential diagnosis in MI cases with otherwise unexpected coronary disease occurring at a young age.

Titov *et al.*[81] analysed genotype frequencies of single nucleotide polymorphisms (SNPs) in genes whose protein products are involved in the pathogenesis of atherosclerosis. In the group of age <60 years SNPs of FGB, TGFB1, ENOS, and CRP are associated with high risk of MI, with the higher risk to be observed in their combinations [FGB + TGFB1; FGB + LPL + IL4; FGB + ENOS]. The genome-wide association studies identified six new loci associated with CAD: on 2q37 (KCNJ13-GIGYF2), 6p21 (C2), 11p15 (MRVI1-CTR9), 12q13 (LRP1), 12q24 (SCARB1), and 16q13 (CETP) with odds ratio per copy of the risk allele ranging from 1.04 to 1.09.[82] The ADAMTS7 polymorphism exhibited a significant effect on MI risk, with hypertensives, non-diabetics and patients with hyperlipidaemia possessing the greatest risk.[82] Analysis of 2967 early-onset MI cases identified SNPs at nine loci: three are newly identified (21q22 near MRPS6-SLC5A3-KCNE2, 6p24 in PHACTR1, and 2q33 in WDR12) and six replicated prior observations[83–85] (9p21, 1p13 near CELSR2-PSRC1-SORT1, 10q11 near CXCL12, 1q41 in MIA3, 19p13 near LDLR, and 1p32 near PCSK9).[86] The role of ADAMTS-7 in neointima formation is mediated via increased smooth muscle cell (SMC) migration caused by cartilage oligomeric protein degradation and impaired re-endothelialization. Higher levels of ADAMTS-7 correlated with high levels of lipid content, but with low SMC and collagen content in atherosclerotic plaque formation, both of which are indicators of a vulnerable phenotype.[87] Further studies are needed to clarify the exact mechanism for this association.

As discussed above, high Lp(a) levels are associated with incident MI. Lp(a) prevents endothelial cell plasmin production and disrupts the fragile equilibrium between thrombus formation and fibrinolysis. Lp(a)'s gene is one of the strongest monogenic risk factors for CAD. Clarke *et al.*[88] identified two Lp(a) variants associated with increased levels, located on chromosomal region 6q26-27 with odds ratio for coronary disease being 1.70 and 1.92, respectively. Genetic data support Lp(a) levels <20 mg/dL as optimal, and as atherothrombotic range >30–50 mg/dL. Clarke *et al.*[88] established the causative relation between Lp(a)'s genotype and CAD via extended genetic research.[89–91] Methylenetetrahydrofolate reductase polymorphism-homozygotes (C677T MTHFR and 1298 AC) with or without casual smoking is a major risk factor, whereas heterozygotes have no statistically significant association with premature MI. According to the findings of a recent meta-analysis, the MTHFR C677T polymorphism is associated with an increased incidence of MI in young/middle-aged Caucasians. This connection could not be established in the elderly population.[92] In the group of people with a mutation in the gene MTHFR with alleles C677T or A1298C—particularly the homozygotes—has been observed an increase of their plasma homocysteine and the vascular damage, but exceptions have been published for these mutations, with absence of elevated homocysteine levels in countries where food is fortified with folic acid, i.e. USA.[93–95] The European Prospective Cohort on Thrombophilia findings indicated no substantial elevated risk of mortality in individuals neither those with thrombosis occurrence[96] (*Table 4*).

5. Clinical implications

Taking into account the differences in the profile of young and older MI patients, customization of the established primary and secondary prevention strategies may be considered. Since, it is rather difficult to identify hereditary atherosclerotic burden in young population, clinicians have to prevent the thrombotic events. Clinical awareness for the development of CAD even at younger age is required. The value of asymptomatic screening for CAD has to be explored especially in subgroups of patients with strong family history of premature CAD or presence of non-traditional risk factors [e.g. increased Lp(a) or C-reactive protein serum levels]. Surveillance and monitoring for the early onset of arterial hypertension, an abnormal lipid profile, central obesity, and strong counselling against smoking should be implemented, especially when other predisposing thrombotic factors co-exist e.g. use of oral contraceptives in young women.[97] Clinicians must be conscious of the prevalence of drug abuse among young people, which has been steadily growing over the years.[98] According to studies, the majority of young people with premature CAD would not have received statin medication prior to their first MI event.[99–101] This would be disastrous, evidence suggests that the advantage of statin therapy increases with treatment duration; young people with early onset of CAD may derive the largest benefit from timely administration of preventive measures (like statins) given the higher average life expectancy.[99–101] The declining costs of genetic tests and whole-genome sequencing may also lead to the implementation of genetic screening to patients with strong family history of premature CAD.

Younger people are also less likely to be recommended for statin therapy following a MI injury than older people, despite having a significantly greater potential life expectancy for repeated events.[102] These findings point to the need for active secondary preventive interventions in young adults who suffer from MI, especially young patients, who are only rarely candidates for statin therapy. Even so, no clinical trials have been conducted to evaluate the positive benefits of anticoagulation in patients with hereditary thrombophilia and arterial thrombotic events, such as MI.[103] A timely treated incident has better outcome and prognosis for young counterpants.[104] The major area of concern is that ~50% of total young MI patients may not receive any reperfusion therapy due to late diagnosis.[105] Due to a more patent infarct-related artery and non-significant disease in non-infarct vessels, young MI patients have a considerably greater likelihood of revascularization when thrombolysis occurs within 6 h of an event.[105] On the other hand, developments in plaque imaging provide the opportunity to discern the intrinsic pathophysiological cause of thrombosis.[106] Plaque erosion, the dominant mechanism of coronary thrombosis in young individuals, can now be reliably detected by intracoronary imaging, implying that treatment could be individualized based on pathophysiology of MI; pharmacological rather than mechanical intervention could provide an optimal treatment for patients with plaque erosion.[106,107] The EROSION study showed that MI patients with eroded plaques receiving anti-thrombotic therapy without stenting (heparin for 3 days with concurrent aspirin and ticagrelor, glycoprotein IIb/IIIa antagonists, tirofiban) showed >50% decrease in thrombus volume and approximately no major adverse cardiac events occurred.[25] Larger,

Table 4 Genetic mutations implicated in MI incidence

Gene of	Polymorphism-mutation	Studies report on MI risk in young population	OR	Action
Factor II	G20210A[73]	• Li *et al.* (2017)[74] • Burzotta *et al.* (2004)[75]	• Particularly in youngs (≤55 years) and in Caucasians (OR=1.76, 95% CI: 1.32–2.35) • Moderate risk factor in young individuals (≤45 years) (OR = 2.3, 95% CI: 1.27–4.59)	Hypercoagulation
Factor V	V Leiden (rs6025)[80]	• Juul *et al.* (2002)[122] • Mannucci *et al.* (2010)[77]	• Potential moderate risk factor in young individuals (<50 years) (OR = 1.54, 95% CI: 1.07–2.22) • Moderate risk factor (<45 years) (OR = 1.61, 95% CI: 1.16–2.22)	Hypercoagulation
Antithrombin deficiency	p.Arg79Cys p.Pro73Leu nt9788G>A g.5924delC	Several cases reports	NA	Hypercoagulation
Protein C deficiency	p.Pro369Leu p.Gly109Arg p.Lys193del c.565C/T p. Arg147Trp	Several cases reports	NA	Hypercoagulation
Protein S deficiency	p.Thr673fsX10 p.Ser501Pro (Heerlen) p.Asp496	Several cases reports	NA	Hypercoagulation
Methylenetetrahydrofolate reductase	C677T MTHFR or 1298 AC[93–95]	Chao *et al.* (2011)[92]	• Moderate risk in young/middle-aged (<50 years) Caucasians (OR=1.275, 95% CI: 1.077–1.509)	Increase of plasma homocysteine
Lp(a)	rs10455872 or rs3798220[88]	NA	NA	Lp(a) variants
ADAMTS7 tagSNP	rs3825807[82]	NA	NA	Affects ADAMTS7 maturation
• FGB • TGFB1 • ENOS • CRP	rs1800788*T[81] rs1982073*T/T[81] rs2070744*C[81] rs1130864*T/T[81]	NA	NA	Their protein products are involved in the pathogenesis of atherosclerosis

randomized studies will confirm this proposition and evaluate the use of anti-thrombotic treatment in cases of eroded plaques.[107] On the other hand, a randomized trial in 2020 showed that prophylactic stenting of vulnerable plaques (lesions with visually estimated diameter stenosis 40%, but with plaque burden by intravascular ultrasound of ≥65%) was safe with enlarged minimum lumen area and favourable clinical outcomes (MACE) during the follow-up.[108]

6. Conclusion

Young MI patients have a cluster of risk factors including eccentric atherosclerotic plaques with inflammatory features, higher incidence of tobacco use, obesity, and increased healthy lifestyle risk factors, such as inactivity and alcohol intake. Compared with older patients where MI is prevalent among men and women, young MI patients are more likely to be men, have a family history of FCHL and higher levels of Lp(a). In addition, cannabis and cocaine use, as well as the use of AASs are risk factors for MI in young patients. Genomic differences, especially in the pathways of coagulation and lipid metabolism, have also been identified between young and older patients with MI. The relative contributions of gene pathways related to lipid metabolism, inflammation, cellular proliferation, vascular tone, or other as yet undiscovered pathways may provide important insights. Both familial hypercholesterolaemia mutations and high polygenic scores are associated with increased odds of early-onset MI. The different pathophysiology and risk factor profile of young and older MI patients could help identify young subjects at increased risk and guide primary and secondary prevention strategies.

Funding

This research received no specific grant from any funding agency in the public, commercial or not for profit sectors.

Conflict of interest: The authors declare that there is no conflict of interest.

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