Contents list available at www.heartscience.ub.ac.id

Heart Science Journal

Journal Homepage : www.heartscience.ub.ac.id

Review Article

The Complexity of Premature Coronary Artery Disease

Nikhen Noverike[1*], Anna Fuji Rahimah[2], Mohammad Saifur Rohman[2]

[1]Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[2]Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.

ARTICLE INFO

Keyword :
Coronary Angiography;
Premature Coronary Artery Disease;
Risk Factor.

ABSTRACT

Premature Coronary Artery Disease presents a significant health concern globally, characterized by the onset of coronary atherosclerosis at an early age, typically before the age of 55 in men and 65 in women. This review provides a comprehensive examination of the various aspects of premature CAD, ranging from its underlying pathophysiology to diagnostic modalities such as coronary angiography. Beginning with an overview of the risk factors contributing to premature CAD, including genetic predispositions, lifestyle factors, and metabolic disorders, the review delves into the intricate mechanisms involved in the initiation and progression of atherosclerosis. Furthermore, the review discusses the clinical manifestations and challenges associated with diagnosing premature CAD, particularly in asymptomatic individuals. It examines the utility of non-invasive imaging techniques, stress testing in identifying coronary artery stenosis, cardiovascular risk and the principles of coronary angiography. The review outlines the principles of coronary angiography, including patient preparation, procedural techniques, and interpretation of angiographic findings. In conclusion, this comprehensive review provides insights into the multifaceted nature of premature CAD, elucidating its pathogenesis, clinical presentation, and diagnostic evaluation, with a focus on the pivotal role of coronary angiography in guiding therapeutic interventions and optimizing patient outcomes.

1. Introduction

Coronary Artery Disease (CAD) is one of the most common heart diseases and one of the world leading causes of death until today. There are estimated more than 350.000 deaths every year.[1] According to data from the Global Burden of Disease, the prevalence of CAD is roughly 154 million cases, which represents around one-third of the total burden of CAD worldwide and contributes to 2% of the entire Global Burden of Disease.[2] In 2019, one out of every five adults under the age of 65 died from coronary artery disease (CAD). Over the past three decades, the mortality rate from coronary artery disease (CAD) in adults aged 65 and older has decreased, reaching 5% in women and 4% in men.[3]

Premature coronary artery disease (PCAD) refers to the occurrence of CAD in individuals below the ages of 45 and 55, although the specific threshold may vary between the ages of 45 and 65 based on several research studies.[4] The term PCAD is frequently used interchangeably with early onset CAD or commonly described as coronary artery disease occurring in young individual.[5] Late-onset coronary artery disease (CAD) is defined by medical standards as the occurrence of CAD in males who are 55 years old or older and women who are 65 years old or older. A thorough investigation conducted at a cardiac rehabilitation facility in Germany revealed that the occurrence of PCAD among males below 55 years old and females below 65 years old was documented at a rate of 37%. Conversely, a significant proportion of CAD cases, including 67%, were seen in males aged 55 and above and females aged 65 and above.[6]

On a global scale, PCAD poses a substantial burden and presents a notable public health challenge. Over 80% of individuals diagnosed with PCAD exhibit at least one risk factor that can be modified.[7] In general, there has been a minimal decline in the occurrence of PCAD, but the prevalence of individuals under the age of 65 with three prominent established risk factors has witnessed an increase from 2000 to 2016.[8,9]

2. Definition

Premature coronary artery disease (PCAD) refers to a form of coronary artery disease (CAD) that occurs in individuals who are younger than 45 years old. It is alternatively referred to as early or premature atherosclerotic coronary artery disease (ASCAD).[10] The age limit for PCAD varies from 35 to 55 years old, according to various studies.[11,12] Recently, despite the specific number of biomarkers on CAD, many new markers specifically related to PCAD have already been discovered.[13] The ACC/AHA 2019 guidelines and the ESC 2021 guideline have different age limits for PCAD diagnosis. As to the ACC/AHA 2019 recommendations, premature coronary artery disease (PCAD) is defined as the occurrence of coronary artery disease in men below the age of 55 and women below the age of 65. Conversely, the ESC 2021 guideline establishes that men should be under the age of 55 and women should be under the age of 60.[13]

* Corresponding author at: Brawijaya Cardiovascular Research Center, Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
E-mail address: nikhen@student.ub.ac.id (N. Noverike).

https://doi.org/10.21776/ub/hsj.2024.005.03.2
Received 17 March 2024; Received in revised form 26 March 2024; Accepted 9 April 2024.
Available online 25 July 2024

3. Epidemiology

Research has indicated that individuals with a familial background of PCAD are more prone to developing coronary artery disease when compared to the general population (35% vs 14%).[14] Data from the Framingham study, a cohort study conducted by the National Heart Lung and Blood Institute (NHLBI) from 1880 to 2003, demonstrated that the yearly occurrence of prevalence cardiovascular disease among men aged 35 to 44 is three cases per 1000 individuals. Based on prevalence data gathered by the disease control centre in 2010, the occurrence rate of coronary artery disease varies across different age groups as follows: among individuals aged 18 to 44 years, the prevalence is 1.2%, while for those aged 45 to 64 years, it is 7.1%, and for individuals above the age of 65 years, it rises to 19.8%.[15] According to epidemiological data from England, the occurrence of CAD among males and females aged 35 to 44 years is 0.5% and 0.18%, respectively. Research in Korea states among 112 asymptomatic individuals under the age of 40, the occurrence of hidden CAD was recorded at 11%, with 9 people having single-vessel disease and 3 people having multi-vessel disease.

In Southeast Asia, the average age at which CAD manifests is around 53 years, whereas in Europe it is typically occurs at the age of 63.[16] South Asian populations, particularly Indians, are at an increased risk of developing CAD during early adulthood (5%~10%) than other ethnic groups (1%~2%). A study published in India in 1991 found that 5% to 10% of people under the age of 40 suffered from PCAD. It is possible that Indians' higher risk of developing coronary disease is in consequence of combination of lifestyle, environmental factors, and genetic predisposition.[17]

In the female young population, the mean age at which CAD occurs is higher than in male population. In Asian populations, 9.7% of males and 4.4% of females experience their initial myocardial infarction (MI) before the age of 40. The Singapore Myocardial Infarction Registry of CAD on <65 years age group showed that men had an increase risk up to four times of experiencing CAD compared to women.[13]

4. Risk Factor and Pathogenesis

Early-onset coronary artery disease is the result of both genetic predisposition and traditional risk factors, suggesting a complex process involving multiple components. Roughly a third of CAD patients have a family history of the disease. In early adulthood people, a meta-analysis has shown an association between the disease and a genetic background of the disease, diabetes mellitus, dyslipidaemia, tobacco use, and high blood pressure. Although PCAD is affected by multiple factors, genetic predisposition is often a crucial factor in young people with the disease. It is therefore important to study the risk factors associated with PCAD patients in comparison with the people without the disease.[18]

Autopsy investigations, which may be inclined towards fatal cases, suggest that the main reason for deadly coronary thrombosis is the total rupture of the fibrous cap that shields the plaque. Most cases of acute coronary thrombosis are caused by the rupture of the atherosclerotic plaque. Disrupted plaques trigger thrombosis through many pathways. Initially, the presence of collagen in the extracellular matrix of the plaque can induce platelet activation. Additionally, the coagulation cascade is initiated by tissue factor (TF) secreted by macrophages and smooth muscle cells (SMCs). As a result, the disturbed plaque acts as a stimulant for both thrombosis and coagulation, and these pathways strengthen each other. Thrombin production enhances the activation of platelets and other cells in the lesion. The transformation of fibrinogen into fibrin and the liberation of von Willebrand factor from active platelets aid in the creation of molecular connections between platelets. This process results in the formation of a compact, three-dimensional structure of platelets that are caught in fibrin. This structure is a defining feature of the "white" arterial thrombus.[19]

PAI-1 obstructs the body's inherent process of breaking down blood clots, known as fibrinolysis, by blocking urokinase-like and tissue-type plasminogen activators. Elevated levels of PAI-1 in the circulatory system have been observed in illnesses such as diabetes and obesity. Additionally, drugs associated with hypertension, such as angiotensin II, can stimulate the production of PAI-1 in different cell types. In addition, when plaques are ruptured, they can release TF in the form of particles, which can make the blood more prone to forming clots. The alterations in the fluid composition played a role in deepening our comprehension of the "vulnerable patient" notion, augmenting our awareness of the so-called "vulnerable plaque." In the context of coronary artery disease, the rapid disruption of a plaque can causes the release of debris rich in TF into the bloodstream. This can result in the production of blood clots (thrombi) in the smaller blood arteries (microcirculation), leading to distal thrombosis. The occurrence of the "no-reflow" phenomenon, which can complicate both spontaneous and procedure-related plaque disruption and prevent the successful restoration of blood flow in the distal microcirculation, is largely explained by the process of distal embolization.[20]

PCAD is a complex illness that includes a genetic predisposition as well as modifiable risk factors such as smoking, high blood pressure, diabetes, obesity, and abnormal lipid levels. persons with PCAD demonstrate a higher prevalence of hypertension, elevated blood glucose levels, and increased body mass index (BMI) as compared to healthy persons. According to a meta-analysis, having one is significantly and favourably correlated with CAD in young adults, as are having diabetes, dyslipidaemia, smoking, and hypertension in the family. There is a strong association between ethnicity and persistent smoking with repeated occurrences of acute obstructive or steady PCAD, and these factors have the most significant influence on the disease prognosis in comparison to other factors contributing to the risk.[20]

Genetic predisposition and several modifiable factor that increases the risk, for instance tobacco use, hypertension, overweight, diabetes, and dyslipidaemia, contribute to the development of PCAD. In comparison to healthy people, individuals diagnosed with PCAD exhibit increased occurrence of high blood pressure, high glucose levels, and an elevated BMI. A meta-analysis revealed that CAD, tobacco use, high blood pressure, diabetes mellitus, dyslipidaemia, and familial background of the condition all favourably correlate with CAD in early adulthood people.[21] Tobacco use, diabetes, and high blood pressure are all observed in 11.5%, 22.8%, and 17.1% of instances, respectively. Obesity increases the chance for the development of PCAD and hypercholesterolemia increases the risk up to 10 to 20 times.[21] Race or ethnicity and continuous smoking are strongly linked to recurrent episodes of acute obstructive or steady PCAD, exerting the most substantial impact on the disease outcome compared to other risk factors.[20]

The inclusion of 35 risk alleles in a genetic risk score (GRS) for BMI highlights the concern of genetic factors in both overweight and complication of cardiovascular. This finding aligns with a comprehensive randomized study assessing the influence of obesity risk associated with genetic on the likelihood of developing CAD. Furthermore, a positive family history was related to an overall higher chance of experiencing cardiovascular and cerebrovascular events. It is still necessary to determine the paradox of the genetic basis. Therefore, more research into the genetic factor contributing to risk that impact the progression of CAD is needed.[18]

5. Genetic Variant

Genetic polymorphisms at specific nucleotide locations in the signaling pathway of interleukin (IL)-1/IL-6 play a role in the development of PCAD. Genetic polymorphisms in IL-6-147 g/c, IL-17A, and IL1-CCC are linked to the accumulation of plaque in the arteries and PCAD via affecting the C-reactive protein (CRP), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) inflammatory pathway. Activation of the cytoplasmic multiprotein complex inflammasome results in the creation of IL-1β, which subsequently influences the synthesis of IL-6 and C-Reactive Protein (CRP) in the liver. IL-17, produced by activated T lymphocytes, promotes the production of IL-6, hence strengthening the inflammatory response locally.[22]

The genetic underpinnings of CAD are thought to be equally significant as environmental variables. The Framingham Offspring Study found that the incidence of coronary artery disease (CAD) increased by more than two times in those having a family history of early illness, even accounting for conventional CAD risk factors. Young patients with early-onset coronary atherosclerosis often have a higher occurrence of a positive family history of coronary artery disease (CAD) and lipid abnormalities. Around 40% of individuals with PCAD have a close family member who has also experienced early-onset atherosclerosis.[23]

1. Family Based Study

Some researches have provided the inaugural opportunity to comprehend the genetic foundation of CAD by investigating the role of individual genes in its formation. The identification of a genetic connection between high cholesterol levels and coronary artery disease (CAD), now known as familial hypercholesterolemia, can be traced back to 1938. In 1985, scientists discovered a deletion of 5 kilobases (kb) in the LDLR gene, which is responsible for producing the low-density lipoprotein (LDL) receptor. This loss was found in a patient and his mother, both of whom had familial hypercholesterolemia. This important discovery presented the initial proof that a particular biochemical anomaly in a solitary gene could contribute to the susceptibility of CAD.[24]

Genetic factors influence the development of early atherosclerosis. Lipoprotein(a) [Lp(a)] is widely acknowledged as a firmly established risk factor for the early development of atherosclerosis. Multiple studies have demonstrated that elevated levels of Lp(a) significantly and independently increase the likelihood of coronary artery disease (CAD) in young persons. It is essential to identify cases of early coronary artery disease (CAD) that are genetically inherited, especially when there are no other risk factors present. Preliminary findings from an Italian study indicate that some apolipoprotein(a) [apo(a)] phenotypes, specifically those linked to low molecular weight types, could potentially be used as predictive indicators for the development of coronary artery disease (CAD) in young adulthood. The occurrence of premature atherosclerosis is quite common, affecting almost all persons with familial hypercholesterolemia (FH), a disorder defined by the inefficient elimination of low-density lipoprotein (LDL) cholesterol from the blood. A significant proportion of early-onset coronary artery disease (CAD) can be ascribed to both a family history and familial combination hyperlipidemia (FCHL). According to a recent study, nearly half of the individuals under the age of 40 who survived acute myocardial infarction (AMI) were identified as having one of these two conditions. Moreover, FCHL in isolation demonstrated a 24-fold higher risk for acute myocardial infarction (AMI).[21]

2. Common variant association studies

CAD is a prevalent and intricate disorder, even though it tends to exhibit familial clustering. To explore the genetic factors involved in CAD, genotyping chips have been developed to encompass a substantial portion of commonly occurring genetic variations between individuals. These chips serve as the foundation for common variation association studies (CVAS) or genome-wide association studies (GWAS). Common variants occur with sufficient frequency to enable individual testing, wherein the frequency of each variant is compared between persons affected by the disease and those unaffected. In this context, a precise operational meaning of 'common' is a variant that occurs with a frequency of at least 0.5%, which is comparable to one carrier per 100 persons.[25]

In 2007, the first Cardiovascular Autonomic System (CVAS) reports from three distinct groups, all highlighting the existence of shared genetic variations at the 9p21 locus. These variations were discovered to have an association with a roughly 30% higher risk of CAD for each copy of the risk allele. Follow-up investigations have not only confirmed these findings but have further broadened the connection to additional vascular illnesses, such as carotid atherosclerosis, peripheral arterial diseases, and stroke. Despite thorough examination conducted in the past ten years, the precise mechanism that links 9p21 and CAD is still not fully understood.[24]

Since 2007, extensive research has been conducted on the genetic structure of CAD, employing increasingly larger sample sizes. As a result, approximately 60 specific genetic loci associated with CAD have been identified. These findings have led to several key observations. Most of these variations are prevalent in the population, with a minor allele frequency greater than 5%. They have a correlation with mild increases in CAD risk, usually resulting in a rise in risk of less than 20% per allele. Together, these variations contribute about 30-40% of the heritability of coronary artery disease (CAD). On the other hand, a smaller group of 15 variations with lower frequencies (below 5%) only accounts for 2% of the heredity of CAD, as assessed by using a false-discovery rate threshold.[26] This pattern of results aligns with what has been observed in other complex diseases, including type 2 diabetes mellitus and schizophrenia.[28] Most of the identified variations are located in non-protein coding regions. A new CVAS, employing a genotyping chip specifically tailored to identify coding variations in individuals of European ancestry, unveiled robust relationships with coding variants at only four distinct loci. These findings indicate that CAD risk variants primarily affect gene expression by modifying regulatory areas, as demonstrated by the substantial concentration of variations in these regions.[25]

Roughly 20% are known to play a role in the metabolic processes of low-density lipoproteins (LDL), triglyceride-rich lipoproteins (TRL), or lipoprotein(a) - a modified version of LDL. This observation strengthens the significant significance of these pathways in the development of CAD, offering internal confirmation for the findings acquired using CVAS. Furthermore, around 5-10% of the genetic markers are linked to blood pressure, which is a well-established and adjustable causative risk factor for coronary artery disease (CAD). Two crucial regulators of vascular tone and platelet aggregation are Guanylate Cyclase 1, Soluble, Alpha 3 (GUCY1A3) and Nitric Oxide Synthase 3 (NOS3). Genetic variations at the GUCY1A3 and NOS3 loci have been associated with both blood pressure and coronary artery disease (CAD).[26] Furthermore, it was discovered that in a sizable family with a notable occurrence of early coronary artery disease (CAD), the presence of GUCY1A3 mutations that result in loss of function were linked to a heightened susceptibility to myocardial infarction. Mutations in mice that matched those observed in humans were shown to accelerate the development of blood clots in the small blood vessels after a local injury.[24]

3. Rare variant association studies

The significant reduction in cost has paved the way for extensive genetic sequencing initiatives, facilitating studies focused on the association of rare variants (RVAS). Unlike common variants captured by genotyping chips, rare variants are typically excluded from these chips as they are not prevalent in the general population.[29] In order to increase the statistical power of RVAS, current and future studies are utilizing whole-exome or whole-genome sequencing in a sizable group of individuals. This approach will provide additional insights and strength in conducting association studies for rare variants. Research has revealed the existence of a minimum of 9 genes in which the accumulation of rare mutations impacts the susceptibility to CAD.[24]

In a comprehensive study utilizing whole-exome sequencing, approximately 5,000 cases of early-onset CAD were compared to CAD-free controls, allowing for an unbiased exploration of gene associations with CAD. Not surprisingly, the most significant signal was observed in the LDLR gene, where damaging mutations were found to increase the risk of CAD fourfold.[29] The prevalence of these mutations in people with early-onset CAD was approximately 2%. Another significant discovery was the detection of inactivating mutations in PCSK9. Contrary to the gain-of-function mutations linked to familial hypercholesterolemia, two harmful PCSK9 variants were identified using genome sequencing. These mutations are found in approximately 2% of individuals with African ancestry. Individuals carrying any of these two mutations displayed significantly decreased levels of LDL cholesterol and a diminished susceptibility to CAD and leading to a reduced likelihood of developing coronary artery disease (CAD).[24]

The utilization of high-throughput DNA microarray technology has been important in enhancing our comprehension of intricate disorders such as CAD. These microarrays employ chips containing a vast array of DNA markers, which can encompass as many as one million single-nucleotide polymorphisms (SNPs). In genome-wide association studies (GWASs), commercial arrays utilize single nucleotide polymorphisms (SNPs) with a concentration of generally 0.5-1 mol/L to detect frequent genetic variants (SNPs that are present in at least 5% of the population) across the whole human genome. It is crucial to acknowledge that these Single Nucleotide Polymorphisms (SNPs), referred to as tag SNPs, typically signal a particular position but are rarely functional variations themselves. Furthermore, the effective implementation of GWAS is highly dependent on the cooperation of multiple research teams globally and the enrolment of many individuals with or without clinical indications of CAD, all of whom must undergo thorough phenotyping.[27]

6. Prognosis

Young adults who are diagnosed with PCAD have a negative long-term prognosis. Between 4% and 10% of acute myocardial infarction (AMI) occurrences occur within this age group. Patients diagnosed with CAD and acute coronary syndrome (ACS) who have a genetic predisposition for PCAD demonstrate enhanced long-term survival rates, which contradicts initial expectations. A genetic connection is also linked to a higher overall risk of adverse cardiovascular and cerebrovascular events. Individuals diagnosed with PACD exhibit an elevated level of cardiovascular risk factors that can be modified. PCAD is a rapidly changing condition with the 10-year mortality rate for premature CAD is 21%.[20]

Tobacco use stands out as a prevalent risk factor among individuals affected by early-onset coronary artery disease. The combination of active smoking and additional cardiovascular risk factors often completing each other, increasing the risk of atherosclerosis and early death.[28] As reported by the US population between 2007 and 2014, 10% to 30% of the population had obesity, which indicates that obesity plays a role as an early atherosclerosis risk factor. Obesity contributes to the development of metabolic syndrome, which includes insulin resistance and hypertriglyceridemia, in addition to the typical risk factors for cardiovascular disease in middle-aged individuals.[32] The most essential thing is that the prevalence of type 2 diabetes in young people with CAD also increased in America. There is a contrast finding from a French population perspective cohort with premature CAD, whereas people rarely experienced excess body weight and diabetes but actively smoked and had elevated LDL cholesterol levels. Overall, this research assistance the assumption that there are multiple factors within an individual's control that can be modified with PCAD. In addition, early intervention through pharmacological treatment to help quit smoking and lowering LDL cholesterol or modifying lifestyle to lose body mass and adopt a balanced dietary intake is crucial to apply.[29]

One PCAD patient out of five died on the first ten years of follow-up. These youngsters also experience many recurrent events, especially the development of atherosclerosis that causes stable angina or recurrent myocardia infarct. PCAD patients have worse outcomes than CAD patients over the age of 50, with almost 10 out 100 patients annually suffered from MI or death.[30] This low prognosis suggests that young adults with risk factors require more assertive approach to initial and subsequent prophylaxis, including suitable quitting smoking techniques and reduced LDL-C target objectives. Another important point spotlight is that over 50% of patients continue to smoke regardless of PCAD. This finding aligns with the results of the YOUNG-MI registry, which shows a distinct relationship with following death. It is also crucial to consider the elevated risks in the form of hereditary biomarkers like lipoprotein (a), which may cause early cardiovascular disease. Another factor that requires assessment in this specific population with a minimal risk of bleeding and frequent early subsequent ischemic events is necessity for extended dual antiplatelet therapy. Another unmet condition for this population is a guideline that provides specific cardiovascular risk assessments and direct intensive therapy which barely qualifies.[31] A recent evaluation of the blood cholesterol guidelines issued by the American College of Cardiology and American Heart Association in 2018 revealed that less than 50% of patients under the age of 55 who were being treated for their first heart attack would meet the criteria for statin therapy for primary prevention. In contrast, most older patients who had experienced a heart attack, ranging from 75% to 85%, would qualify for such therapy. Age has a significant role in the risk score for atherosclerotic cardiovascular disease over a 10-year period.[32]

Females with PCAD have higher rates of ischemic recurrence compared to males with PCAD. Across a range of cardiovascular illnesses, sex-specific findings for this prognosis have been documented. Most of them are related to unoptimized secondary prevention and insufficient intensive therapy.[33] According to this study, more than 1 in 4 patients in the cohort were female and had high levels of premature atherosclerotic CAD. Compared to white people, Black and Hispanic people typically exhibit a higher risk of recurrence. Socioeconomic factors, inadequate secondary prevention, a lack of availability of medical services, and insufficient proactive approaches and methodologies have been recognized as elements that impact diverse outcomes.[34]

Due to the fact that environmental factors and genetic predisposition commonly intersect and convey a significant aggregate risk for heart-related results, controlling cardiovascular risk factors is critical for the better outcome. Young patients must receive multiple modes and involving various interventions targeting multiple factors include prolonged evaluation of social factors, mental, and medical aspect in order to successfully encourage a healthy lifestyle. [33]

7. Coronary Lession Characteristics in PCAD

Previous research by Avis et al. supports the notion that hypertension is a significant risk factor for CAD. Their study found a strong association between hypertension and the development of coronary artery disease, emphasizing the importance of hypertension management in CAD prevention.[35] Furthermore, a meta-analysis conducted by Bays et al. concluded that while family history may contribute to CAD risk to some extent, its influence is relatively modest compared to other established risk factors such as hypertension and smoking. These studies corroborate the findings of the current analysis, providing additional evidence on the relationships between these variables and CAD risk.[36] Previous studies exploring the intricate link between diabetes and CAD. For instance, Arnold et al. reported a twofold increase in CAD risk among diabetic individuals,[37] while Jin et al. documented a heightened incidence of CAD in diabetic cohorts.[38] Such findings underscore the critical importance of effectively managing diabetes to mitigate the risk of CAD development, emphasizing the need for comprehensive preventive strategies and diligent medical management. Dyslipidemia Study by Gaman et al. identified dyslipidemia as a key contributor to CAD risk,[39] while the secondary dyslipidemia study by Yanai & Yoshida highlighted its association with acute myocardial infarction.[40] Conversely, studies such as the meta-analysis by Panahiazar et al. and research conducted by Regitz-Zagrosek et al. indicate that gender does not independently contribute to CAD development, with comparable CAD-related event rates observed between genders.[41]

Coronary angiography serves as a crucial diagnostic and therapeutic tool in identifying blockages or narrowing within the coronary arteries. Through the strategic use of specialized dye and X-ray technology, clinicians can visualize these arteries in detail, allowing for timely intervention to mitigate potential risks such as heart attacks or other cardiovascular complications.[42]

In our analysis of the studies conducted by Ibrahim Shah et al. and Badran et al., we observed a notably greater incidence of mild coronary lesions among the premature group. This finding contradicts the results published by S. Sadiq Shah et al., who showed no significant difference in the severity of coronary lesions between premature and mature CAD. The finding in the current study may be associated with a brief period of clustering of risk variables among the preterm group. Tahir et al. found no significant disparity in the types of coronary lesion between premature and mature CAD. This study demonstrated a notably elevated prevalence of type A lesions among individuals with PCAD. Consistent with the findings of Badran et al., Almayali, and Christus et al., this study observed a higher prevalence of single vessel disease among patients with PCAD. On the other hand, the study revealed a notably increased prevalence of triple vessel disease (3VD) and quadruple vessel disease (4VD) among the older age group. Various research, like the one conducted by Tewari et al., have revealed similar findings. Unlike the findings of Farhan et al., this investigation demonstrated a notably elevated prevalence of 3VD and 4VD in males with PCAD. Based on the studies conducted by Abu Siddique et al. and Nafakhi, the distribution of significant blockages in the major arteries surrounding the heart in this research was not influenced by age. The therapeutic alternatives, such as coronary artery bypass grafting (CABG), were shown to be more feasible in patients with multivessel coronary artery disease, while medicinal treatments were more commonly used in patients with single-vessel coronary artery disease, given the less complicated angiographic profile observed in PCAD. These findings align with the study conducted by Chrustus et al. Renowned for its safety and effectiveness, coronary angiography not only serves as a diagnostic tool but also facilitates therapeutic interventions. Furthermore, coronary angiography plays a pivotal role in the comprehensive management of CAD.[43]

8. Conclusion

In summary, while variables like being overweight, family medical history, smoking habits, and gender appear to have minimal influence on the likelihood of coronary lesions, hypertension, diabetes mellitus, and dyslipidemia emerge as significant determinants of risk. These results emphasize the necessity of effectively controlling hypertension, diabetes, and dyslipidemia to mitigate the chances of developing coronary artery disease. Further exploration and implementation of interventions targeting these risk factors hold promise in both prevention and management of CAD. In essence, coronary angiography stands as a pivotal diagnostic and therapeutic measure in addressing cardiac ailments, thereby potentially enhancing outcomes for individuals afflicted with CAD and other cardiovascular conditions.

Hence, it's paramount for individuals to have comprehensive discussions with their healthcare provider to fully understand the potential risks and benefits before undergoing the procedure. Meanwhile, coronary artery disease (CAD) continues to pose a significant health challenge on a global scale. The development of CAD is influenced by a variety of risk factors, ranging from lifestyle choices such as diet and exercise habits to genetic predispositions. These findings underscore the multifaceted nature of CAD risk factors, emphasizing the importance of tailored preventive strategies and targeted interventions to mitigate the burden of this cardiovascular disease.[44]

9. Declaration

9.1 Ethics Approval and Consent to participate
Not applicable.

9.2. Consent for publication
Not applicable.

9.3 Availibility of data and materials
Data used in our study were presented in the main text.

9.4 Competing interests
Not applicable.

9.5 Funding Source
Not applicable.

9.6 Authors contributions
Idea/concept: NN. Design: NN. Control/supervision: AFR, MSR. Data collection/processing: NN. Analysis/interpretation: NN, AFR. Literature review: NN. Writing the article: NN. Critical review: AFR, MSR. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

9.7 Acknowledgements
We thank to Brawijaya Cardiovascular Research Center

References

1. Benjamin EJ, Muntner P, Alonso A, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation*. 2019;139(10):e56-e528. doi:10.1161/CIR.0000000000000659

2. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet*. 2018;392(10159):1789-1858. doi:10.1016/S0140-6736(18)32279-7

3. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary Heart Disease Mortality Declines in the United States From 1979 Through 2011: Evidence for Stagnation in Young Adults, Especially Women. *Circulation*. 2015;132(11):997-1002. doi:10.1161/CIRCULATIONAHA.115.015293

4. Mohammad AM, Jehangeer HI, Shaikhow SK. Prevalence and risk factors of premature coronary artery disease in patients undergoing coronary angiography in Kurdistan, Iraq. *BMC Cardiovasc Disord*. 2015;15(1):1-6.

5. Christiansen MK. Early-onset Coronary Artery Disease Clinical and Hereditary Aspects. *Dan Med J*. 2017;64(9):1-18.

6. Reibis R, Treszl A, Wegscheider K, Bestehorn K, Karmann B, Völler H. Disparity in risk factor pattern in premature versus late-onset coronary artery disease: A survey of 15,381 patients. *Vasc Health Risk Manag*. 2012;8(1):473-481. doi:10.2147/VHRM.S33305

7. Pillay AK, Naidoo DP. Atherosclerotic disease is the predominant aetiology of acute coronary syndrome in young adults. *Cardiovasc J Afr*. 2018;29(1):36-42.

8. Vikulova DN, Grubisic M, Zhao Y, et al. Premature atherosclerotic cardiovascular disease: trends in incidence, risk factors, and sex-related differences, 2000 to 2016. *J Am Heart Assoc*. 2019;8(14):e012178.

9. Khoja A, Andraweera PH, Lassi ZS, et al. Risk factors for premature coronary artery disease (PCAD) in adults: a systematic review protocol. *F1000Res*. 2021;10.

10. Egred M, Viswanathan G, Davis GK. Myocardial infarction in young adults. *Postgrad Med J*. 2005;81(962):741-745.

11. Christus T, Shukkur AM, Rashdan I, et al. Coronary artery disease in patients aged 35 or less–a different beast? *Heart Views*. 2011;12(1):7.

12. Konishi H, Miyauchi K, Kasai T, et al. Long-term prognosis and clinical characteristics of young adults (≤ 40 years old) who underwent percutaneous coronary intervention. *J Cardiol*. 2014;64(3):171-174.

13. Aggarwal A, Srivastava S, Velmurugan M. Newer perspectives of coronary artery disease in young. *World J Cardiol*. 2016;8(12):728.

14. Kang MK, Chang HJ, Kim YJ, et al. Prevalence and determinants of coronary artery disease in first-degree relatives of premature coronary artery disease. *Coron Artery Dis*. 2012;23(3):167-173.

15. CDC C for DC and P. Prevalence of coronary heart disease--United States, 2006-2010. *MMWR Morb Mortal Wkly Rep*. 2011;60(40):1377-1381.

16. Ha EJ, Kim Y, Cheung JY, Shim SS. Coronary artery disease in asymptomatic young adults: its prevalence according to coronary artery disease risk stratification and the CT characteristics. *Korean J Radiol*. 2010;11(4):425-432.

17. Sharma M, Ganguly NK. Premature coronary artery disease in Indians and its associated risk factors. *Vasc Health Risk Manag*. 2005;1(3):217-225.

18. Poorzand H, Tsarouhas K, Hozhabrossadati SA, et al. Risk factors of premature coronary artery disease in Iran: A systematic review and meta-analysis. *Eur J Clin Invest*. 2019;49(7):e13124.

19. Libby P, Theroux P. Pathophysiology of coronary artery disease. *Circulation*. 2005;111(25):3481-3488.

20. Collet JP, Zeitouni M, Procopi N, et al. Long-term evolution of premature coronary artery disease. *J Am Coll Cardiol*. 2019;74(15):1868-1878.

21. Kumbhalkar SD, Bisne V V. Clinical and angiographic profile of young patients with ischemic heart disease: A central India study. *J Clin Prev Cardiol*. 2019;8(1):6.

22. Wang H, Liu Z, Shao J, et al. Pathogenesis of premature coronary artery disease: Focus on risk factors and genetic variants. *Genes Dis*. 2022;9(2):370-380.

23. Ahmadi SH, Abbasi SH, Ugurlucan M, Bina P. Positive family history as the single traditional risk factor for developing extensive very premature coronary artery disease: a case report. *The Journal of Tehran University Heart Center*. 2013;8(1):54.

24. Khera A V, Kathiresan S. Genetics of coronary artery disease: discovery, biology and clinical translation. *Nat Rev Genet*. 2017;18(6):331-344.

25. Zuk O, Schaffner SF, Samocha K, et al. Searching for missing heritability: designing rare variant association studies. *Proceedings of the National Academy of Sciences*. 2014;111(4):E455-E464.

26. Cole CB, Nikpay M, Stewart AFR, McPherson R. Increased genetic risk for obesity in premature coronary artery disease. *European Journal of Human Genetics*. 2016;24(4):587-591.

27. McPherson R, Tybjaerg-Hansen A. Genetics of coronary artery disease. *Circ Res*. 2016;118(4):564-578.

28. Hu Y, Zong G, Liu G, et al. Smoking cessation, weight change, type 2 diabetes, and mortality. *New England Journal of Medicine*. Published online 2018.

29. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *New England Journal of Medicine*. 2018;379(22):2097-2107.

30. Biery DW, Berman AN, Singh A, et al. Association of smoking cessation and survival among young adults with myocardial infarction in the partners YOUNG-MI registry. *JAMA Netw Open*. 2020;3(7):e209649-e209649.

31. Singh A, Collins BL, Gupta A, et al. Cardiovascular risk and statin eligibility of young adults after an MI: partners YOUNG-MI registry. *J Am Coll Cardiol*. 2018;71(3):292-302.

32. Navar-Boggan AM, Peterson ED, D'Agostino RB, Pencina MJ, Sniderman AD. Using age-and sex-specific risk thresholds to guide statin therapy: one size may not fit all. *J Am Coll Cardiol*. 2015;65(16):1633-1639.

33. Lichtman JH, Leifheit EC, Safdar B, et al. Sex differences in the presentation and perception of symptoms among young patients with myocardial infarction: evidence from the VIRGO study (variation in recovery: role of gender on outcomes of young AMI patients). *Circulation*. 2018;137(8):781-790.

34. Schultz WM, Kelli HM, Lisko JC, et al. Socioeconomic status and cardiovascular outcomes: challenges and interventions. *Circulation*. 2018;137(20):2166-2178.

35. Avis SR, Vernon ST, Hagström E, Figtree GA. Coronary artery disease in the absence of traditional risk factors: A call for action. *Eur Heart J*. 2021;42(37):3822-3824. doi:10.1093/eurheartj/ehab474

36. Bays HE, Kulkarni A, German C, et al. Ten things to know about ten cardiovascular disease risk factors – 2022. *Am J Prev Cardiol*. 2022;10. doi:10.1016/j.ajpc.2022.100342

37. Arnold S V., Bhatt DL, Barsness GW, et al. Clinical Management of Stable Coronary Artery Disease in Patients with Type 2 Diabetes Mellitus: A Scientific Statement from the American Heart Association. *Circulation*. 2020;141(19):E779-E806. doi:10.1161/CIR.0000000000000766

38. Jin JL, Zhang HW, Cao YX, et al. Association of small dense low-density lipoprotein with cardiovascular outcome in patients with coronary artery disease and diabetes: A prospective, observational cohort study. *Cardiovasc Diabetol*. 2020;19(1). doi:10.1186/s12933-020-01015-6

39. Găman MA, Cozma MA, Dobrică EC, Bacalbaşa N, Bratu OG, Diaconu CC. Dyslipidemia: A trigger for coronary heart disease in Romanian patients with diabetes. *Metabolites*. 2020;10(5). doi:10.3390/metabo10050195

40. Yanai H, Yoshida H. Secondary dyslipidemia: its treatments and association with atherosclerosis. *Glob Health Med*. 2021;3(1):15-23. doi:10.35772/ghm.2020.01078

41. Regitz-Zagrosek V, Gebhard C. Gender medicine: effects of sex and gender on cardiovascular disease manifestation and outcomes. *Nat Rev Cardiol*. 2023;20(4):236-247. doi:10.1038/s41569-022-00797-4

42. Carvalho V, Pinho D, Lima RA, Teixeira JC, Teixeira S. Blood flow modeling in coronary arteries: A review. *Fluids*. 2021;6(2):1-15. doi:10.3390/fluids6020053

43. Jayaram AA, Shah S. Risk factors, clinical features, angiographic characteristics and treatment outcomes of young myocardial infarction patients. *journal of indian college of cardiology*. 2015;5(3):203-208.

44. Riaz T, Akram M, Laila U, et al. Causes, risks factors and medical consequences of obesity. *IAIM*. 2023;10(8):39-48. http://iaimjournal.com/