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Review Article

ARCHIVES OF
CLINICAL AND
BIOMEDICAL RESEARCH

ISSN: 2572-5017

Plant-Based Diet in Regressing/Stabilizing Vulnerable Plaques to Achieve Complete Revascularization

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Abstract

Coronary artery disease (CAD) has emerged as a significant concern in Indonesia, resulting in a substantial number of fatalities and illnesses. In the United States, the latest guidelines for managing patients with chronic coronary syndrome (CCS) have undergone significant changes, including the recommendation for conducting percutaneous coronary intervention (PCI) only for patients who continue to experience symptoms despite receiving optimal medical treatment (OMT). However, this approach may lead to increased morbidity and mortality due to the presence of vulnerable plaques (VPs). During coronary angiography, VPs are characterized by intermediate obstruction (40-70%) and normally do not produce ischemia during physiological studies. Determining the presence of VPs is crucial, even for asymptomatic individuals. Various methods can be employed to achieve this, with computed tomography coronary angiography (CTCA) being the most effective, practical, and cost-effective approach. To manage VPs, experts have recently utilized different techniques, either with stents or drug-coated balloons (DCB), demonstrating the safety and efficacy of these methods. Achieving complete revascularization (CR) in order to minimize the likelihood of future major adverse cardiac events (MACE) and mortality for patients with CCS is a significant challenge. One of the factors contributing to the inability to perform CR is the presence of VP. Both approaches, identifying and intervening in the vulnerable plaque, are difficult to implement in developing countries due to the lack of necessary tools and financial constraints. Studies have shown that plant-based diets (PBD) can reverse and stabilize VP, potentially leading to CR. PBD is an affordable and effective approach that requires healthcare providers skilled in educating and implementing this dietary approach with their patients. Hence, we introduce the most efficient, feasible, and cost-effective solution for managing VP and avoiding MACE and mortality in CCS patients.

Keywords: Plant-based diet; Vulnerable plaque; Complete revascularization; Optimal medical treatment; Percutaneous coronary intervention; Chronic coronary syndrome

Introduction

The prevalence of CAD is growing in Indonesia, making it the most widespread form of heart disease and the primary cause of death and illness in the country. The burden of CAD in Indonesia is significantly higher than in other Southeast Asian countries [1]. In the past, PCI was believed to be the solution to decrease the morbidity and mortality of patients with CAD. Historically, interventional cardiologists typically performed stent procedures

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Citation: Dasaad Mulijono. Plant-Based Diet in Regressing/Stabilizing Vulnerable Plaques to Achieve Complete Revascularization. Archives of Clinical and Biomedical Research. 8 (2024): 236-244.

Received: May 06, 2024
Accepted: May 15, 2024
Published: June 07, 2024

Mulijono D., Arch Clin Biomed Res 2024
DOI:10.26502/acbr.50170404

for patients with blockage ≥ 70%, representing the largest proportion of PCI. This practice placed a high burden on the government since the majority of CAD patients utilized government-funded healthcare to cover the cost of their health problems. Recently, the US government recognized the opposition to this practice and has started implementing an alternative approach, i.e., OMT and lifestyle changes, instead of performing PCI as the first indication for patients with CAD [2].

Experts claim that the invasive approach may not be superior to OMT alone, primarily due to the inability of interventionalists to diagnose and manage VP appropriately. Consequently, this paper will discuss the current state-of-the-art technology for diagnosing and managing VP. Furthermore, the dilemma of incorporating such an approach will be addressed. Next, we will present a solution for diagnosing VP noninvasively and accurately and discuss options for practically, effectively, and safely managing them. Finally, we will address the dilemma of applying OMT and lifestyle modifications and propose solutions to overcome such challenges.

Discussion

Current problems in managing CCS patients

According to the latest recommendations [2], patients diagnosed with CCS should initially try OMT and lifestyle modifications. Please note that individuals who have been diagnosed with atherosclerosis in their coronary arteries yet remain asymptomatic should be classified as CCS patients [3]. The use of PCI in combination with OMT should only be considered in a few specific cases, as research has shown that OMT often produces similar cardiovascular outcomes compared to PCI plus OMT. The decisions were informed by several studies, notably the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, the Objective Randomized Blinded Investigation with Optimal Medical Therapy of Angioplasty in Stable Angina (ORBITA) trial [4,5], and the most recent study, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHAEMIA) trial. This randomized controlled trial involved 5179 patients with CCS and compared PCI and OMT. The study results showed no significant difference in ischemic CV events or mortality between the treatment groups over 3.2 years of follow-up [6]. It is crucial to emphasize that ISCHEMIA excluded individuals who had left main disease of at least 50%, left ventricular systolic function of less than 35%, New York Heart Association Class III or IV heart failure, and estimated glomerular filtration rate (eGFR) of less than 30 ml/min, or those with unacceptable angina despite optimal medical therapy. Moreover, according to the ISCHAEMIA study, patients who underwent PCI had better quality of life measures than those in the OMT arm [7]. Recently, Stone et al. conducted a sub-analysis of the ISCHAEMIA trial and concluded that the clinical outcomes of patients in the PCI arm may be improved if CR, particularly anatomic complete revascularization or ACR, is achieved [8]. The result was not surprising given that various studies have indicated higher survival rates and a decreased incidence of MACE after achieving CR in patients with multivessel disease through either coronary artery bypass graft surgery (CABG) or PCI, as opposed to incomplete revascularization (ICR). Achieving CR might not always be feasible due to factors such as the patient's comorbidities, inadequate management of vulnerable plaques, anatomical constraints, technical limitations, procedural considerations, and financial constraints. According to certain studies, ACR is considered to have been achieved if all coronary vessels larger than 2 mm with stenoses greater than 50% are treated [9]; in real situations, this criterion was often not followed. Therefore, the standards for performing ACR often omit the treatment of intermediate stenosis (<70%), which may comprise VPs. Moreover, a considerable number of VPs exhibited non-significant ischemia during functional studies. Hence, functional complete revascularization (FCR) may not be an appropriate method for evaluating and treating VPs adequately. It is comprehensible that comparative trials of invasive treatments against OMT often reveal that invasive treatments are not superior due to VP miscalculation, which is typically not addressed during interventions [7-10]. Furthermore, it is essential to consider the cost-effectiveness of invasive approaches for managing VPs and their potential future risks, such as in-stent restenosis (ISR) and stent thrombosis (ST). Despite the ongoing debate, experts argue that integrating CR through invasive techniques is essential to surpass the achievements of OMT, particularly in managing VPs that may lead to future cardiac events [7-10]. The argumentation is based on the tendency to underestimate low-grade stenosis (less than 50%), which is actually responsible for 68% of acute myocardial infarctions (AMI) [10]. Stenosis of this type may indicate a VP, which is often ignored and may not receive the appropriate treatment. If asymptomatic individuals exhibit stenosis ranging from 40-70%, according to the 2023 ACC/AHA guideline for managing CCS, they should receive OMT rather than undergoing additional testing to identify VP [2]. Evading such testing could compromise certain patients, leading to an increased risk of future MACE or mortality. To add to the complexity of the situation, it has been demonstrated that nearly half of individuals who undergo PCI have remaining VPs [11].

Accordingly, a plethora of advanced diagnostic technologies are currently available for detecting VPs, such as IVUS (intravascular ultrasound) in tandem with OCT (optical coherence tomography), hybrid IVUS-OCT/

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DOI:10.26502/acbr.50170404

OFDI, NIRS-IVUS (near-infrared spectroscopy), NIRF-IVUS (near-infrared fluorescence), IVPA-IVUS (molecular imaging intravascular photoacoustics), and TRFS-IVUS (time-resolved fluorescence spectroscopy) [12,13]. However, despite their sophistication, these tools are not widely accessible even in the United States. We propose utilizing CTCA as an alternative, which can accurately identify vulnerable plaques, but this approach may necessitate the expertise of an experienced radiologist.

Park SJ et al. recently published a noteworthy paper titled "Preventive PCI versus OMT alone for the treatment of vulnerable atherosclerotic coronary plaques (PREVENT)." This study was a multicenter randomized controlled trial that demonstrated that patients with non-flow-limiting VPs (angiographic stenosis of 47-66%) experienced a reduction in MACE when they received preventive PCI using stenting, as opposed to the OMT-only approach. Given that PREVENT is the first large trial involving 1606 patients to show the potential effect of the local treatment on VPs, these findings support consideration to expand indications for PCI to include non-flow-limiting high-risk VPs [14,15]. Considering the challenges faced when implanting stents, various researchers find the technology of DCB appealing, as it offers the advantage of not leaving anything behind, allowing the endothelium of the coronary vessel to heal properly and retain its vasomotor function. In late 2023, a study conducted by van Veelen et al. (DEBuT-LRP) demonstrated the safety and viability of using DCBs to stabilize VPs, thereby preventing future MACE [16]. However, the study comprised a limited number of participants and utilized NIRS-IVUS, a technology that is not widely accessible, as previously mentioned. The full report of DEBuT-LRP is expected to be published in the near future. To adequately justify the implementation of PCI using either a stent or DCB, the interventionalist must ensure that the potential risks associated with such procedures are significantly lower than those associated with VPs. The potential long-term risks, including those associated with ISR and ST, should also be considered when making this determination.

The management of coronary VP burden in patients with intermediate obstruction (40-70%) but who are clinically or physiologically asymptomatic presents a significant challenge in the field of cardiology. Despite not causing significant arterial narrowing, these lesions have been shown to cause MACE and mortality [17]. Considering the aforementioned points, it is crucial to closely monitor and manage these patients to reduce their risk of unfavorable outcomes, as current guidelines have not provided adequate attention to VP patients. It is important to recognize that although guidelines offer valuable recommendations, they are not mandatory and are subject to revision as new ideas and inventive approaches arise from individuals who seek to improve the academic world. Without such challenges to the existing order, guidelines would remain unchanged since their initial release. Ensuring patient safety is of paramount importance, particularly in preventing MACE and fatalities associated with VPs, which serves as the underlying objective of our paper.

CTCA as a gold standard for diagnosing VPs in developed countries

More than 50% of fatalities caused by AMI occur in CCS individuals who are not exhibiting any symptoms, which is referred to as silent ischemia [18]. Furthermore, more than half of AMI occur as a result of a lesion in the vessel that is less than 50% occluded, which is most likely due to the rupture of a VP [9]. There has been considerable debate over the screening of asymptomatic patients who may have CAD in order to prevent MACE or death [19]. Critics have expressed concerns about the dependability of using a dynamic exercise test (DET) as an economical screening method for specific individuals, emphasizing the limited negative predictive values associated with these tests. One reason is that some individuals may not be able to reach the test target, which could affect the accuracy of the results [20]. Moreover, individuals with VP may display normal results on physiological tests, including the fractional follow reserve (FFR) [21]. Hence, numerous experts have advocated for screening asymptomatic individuals for CAD using CAC and CTCA, particularly those with a significant risk, as indicated in studies [22-25]. Nowadays, it is easy to access such tests. This tool and risk stratification are crucial for determining the appropriate preventive therapy for asymptomatic patients [26].

Consequently, if the current international guidelines, which recommend managing such asymptomatic individuals based on a negative treadmill test, are followed, they may have unfavorable consequences for such patients [27-29]. Individuals who have received negative results from DET screenings have frequently experienced cardiac incidents, including fatalities, causing unease within our community. In order to tackle this issue, our community has been incorporating the utilization of CAC and CTCA as part of coronary risk assessments for asymptomatic patients in Indonesia for several years. It is essential to point out that the majority of health insurance policies cover the expenses of conducting these tests. On the other hand, CAC and CTCA are generally only reserved for patients exhibiting symptoms in many European nations and the United States. Some worldly experts also recommend conducting CAC and CTCA screenings for high-risk CAD patients [22-25]. Therefore, it is necessary to examine more closely the current recommendations for cardio-prevention in managing asymptomatic patients. It is important to recognize the shortcomings of these guidelines, including the lack of personalized care, the slow assimilation

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of new knowledge, and the conservative therapeutic strategies employed. Moreover, the guidelines are typically voluminous and intricate, rendering them inaccessible to numerous practitioners who must grapple with multiple sets of recommendations [26]. Another important consideration is that a substantial proportion of individuals with CAD may actually be experiencing cardiac symptoms, but they are often misclassified as asymptomatic or labeled as having atypical non-cardiac chest pain. It is essential to consider these factors when managing asymptomatic patients with CAD.

Undoubtedly, it is essential to evaluate the use of CTCA for individuals engaged in occupations that pose a considerable threat to the well-being of others, such as pilots [30]. In these situations, the possibility of experiencing a cardiac event during work duties makes the implementation of CTCA an imperative consideration. Similarly, it would be prudent to consider the feasibility of this screening approach for medical practitioners who carry out procedures where the operator's sudden cardiac event during the procedure could jeopardize the life of their patients. The notion of entitlement to medical tests based on one's occupation and social standing raises questions of double standards that may be debated. As previously stated, when a diagnosis of coronary stenosis is made through CTCA, these patients will be categorized as CCS patients [3], and the management of CCS patients, which includes lifestyle modification and OMT, should be carried out in accordance with the established guidelines.

Previously, it has been observed that advanced technologies like NIRS-IVUS or IVUS/OCT combined have demonstrated exceptional abilities; however, they are not yet universally accessible, even in affluent and developed nations. The primary reasons for the limited utilization of these alternatives include their high expense, scarcity, intrusive nature, and the fact that they are still in the research and development stage. Considering these factors, we suggest that CAC and CTCA are practical, cost-effective, secure, and dependable alternatives for diagnosing VP, as they are noninvasive and effective.

PBDs as the solution to treat vulnerable plaque in CCS patients

Numerous studies have underscored the critical significance of PBDs in managing chronic inflammatory diseases, including atherosclerosis, hyperlipidemia, obesity, non-insulin-dependent diabetes mellitus (NIDDM), and hypertension. It has been widely acknowledged that PBD may not only contribute to the prevention of atherosclerosis but may also cause regression of coronary plaques that have occurred [31-37]. Previous studies have suggested that PBDs possess the potential to remedy metabolic irregularities, restore endothelial function, lessen systemic inflammation, enhance the availability of nitric oxide (NO), exhibit anti-thrombotic properties, combat reactive oxygen species (ROS), exhibit immune-modulating effects, promote healthy microbiota, correct mitochondrial dysfunction, and improve telomere as part of epigenetic adjustments. PBDs may potentially reverse or stabilize atherosclerosis and the VP [38-44].

VP, a particularly dangerous form of atherosclerosis, is characterized by a large lipid core, a thin fibrous cap, and neovascularization, all of which exacerbate the plaque's susceptibility to rupture and increase the likelihood of MACE and death [16]. Pathobiologically, VP is a systemic disease resulting from metabolic dysfunction and chronic inflammation rather than a localized process. It, therefore, should be classified as a metabolic chronic inflammatory condition. Patients who have experienced coronary obstruction due to the VP typically exhibit a state of metabolic disorder and systemic inflammation for an extended period of time. Cardiologists who exclusively utilize interventions, including stent implantation and DCB technology, to manage systemic disorders may be deemed inappropriate if they neglect to address the underlying systemic issues. Although these interventions may provide short-term relief, they do not ensure the prevention of future VP development. Furthermore, it is essential to recognize that treating VPs with either stenting or DCB comes with the potential risk of future restenosis and thrombosis. This risk should not be overlooked when considering treatment options. Our previous publication highlighted the significant reduction in the likelihood of developing ISR and ST in individuals who have received PCI with stenting and adhered to PBD [45]. Despite this, we still favor noninvasively managing VPs with OMT and lifestyle changes over interventions.

Results from clinical trials comparing PCI plus OMT versus OMT alone have been disappointing for PCI plus OMT, as interventional cardiologists often disregard the systemic and metabolic issues of their patients, leading to increased MACE and mortality following PCI. Additionally, it is possible that some individuals may be unable to undergo CR due to complex and difficult coronary anatomies or high-risk interventions that can only be performed at specialized centers with minimal complications. In numerous cases, addressing intricate situations with OMT and lifestyle changes will generally pose a lower risk to patients when compared to performing interventions in certain subpar cardiac facilities. It is also important to note that the presence of VPs may also be overlooked in many cases. Despite this, studies have shown that CR has the potential to reduce the incidence of MACEs and cardiac death. However, it is achieved in approximately 50% of PCI cases, as reported in studies [46-52]. Thus, the concept of systematically managing CAD with PBDs not only presents a strategy to either regress or stabilize VP but also offers the possibility of achieving complete revascularization following coronary interventions.

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DOI:10.26502/acbr.50170404

Eating poor-quality food high in sugar (refined carbohydrate), devoid of fiber-phytonutrients, highly processed, and contains saturated and trans fats, cholesterol, and chemicals that promote chronic inflammation is a major contributor to the development of VPs in the first place. The consumption of these unhealthy foods has been demonstrated to increase LDL cholesterol levels, triglycerides, apolipoprotein (a), apolipoprotein (b), C-reactive protein (CRP), pro-inflammatory mediators, pro-inflammatory chemokines/ cytokines, Trimethylamine N-oxide (TMAO), persistent organic pollutants (POPs), oxidative stress, tumor promotion, and cell proliferation, among other factors will make plaque progress and become more vulnerable [53,54]. On the contrary, eating healthy PBD with adequate supplementation will enhance our body's ability to fight against inflammation. Healthy foods such as vegetables, fruits, and legumes contain carotenoids, isoflavones, phytoestrogens, and phytosterols, which have been shown to prevent atherosclerosis. These polyphenols and phytochemicals' role in molecular signaling are anti-inflammatory, antiplatelet aggregation, inhibitor to VSMCs proliferation and migration, and safeguard for lipid oxidation [55,56]. Oxidized LDL (ox-LDL), in addition to its infamous role in causing atherosclerosis, also plays a significant part in developing VPs [57]. Healthy PBD can also help improve endothelial function, which is essential to maintaining plaque stability.

Adopting a diet abundant in PBD can effectively counteract atherosclerotic plaque and bolster VP stability by preventing the consumption of foods that contribute to the formation of VP in the first place. These unhealthy eating habits have also been implicated in dyslipidemia, insulin resistance, hypertension, glucose intolerance, endothelial dysfunction, chronic systemic inflammation, heightened oxidative stress, elevated TMAO, low NO, gut dysbiosis, mitochondrial damage, and shortened telomeres (accelerating aging) [45,58-62]. All of these factors are widely recognized as risk factors for the development of atherosclerosis, including VP. Figure 1 illustrates the various mechanisms through which PBD plays a role in reversing atherosclerosis and hampering VPs.

Supplements are compulsory for PBD followers

It is crucial for individuals who utilize PBD for regressing VP purposes to pay close attention to their food choices and consume items that possess properties that suppress inflammation, combat oxidative stress, increase NO availability, support healthy microbiota, strengthen mitochondria, heal telomeres, and exhibit anti-thrombotic properties [45]. The precise quantity of these foods must also be determined to prevent nutrient deficiencies (protein, Omega 3, B12, D, K2, Fe, Zn, Cu, and Se), and the food processing method should be carefully considered to ensure maximum benefit. For instance, to obtain the highest NO

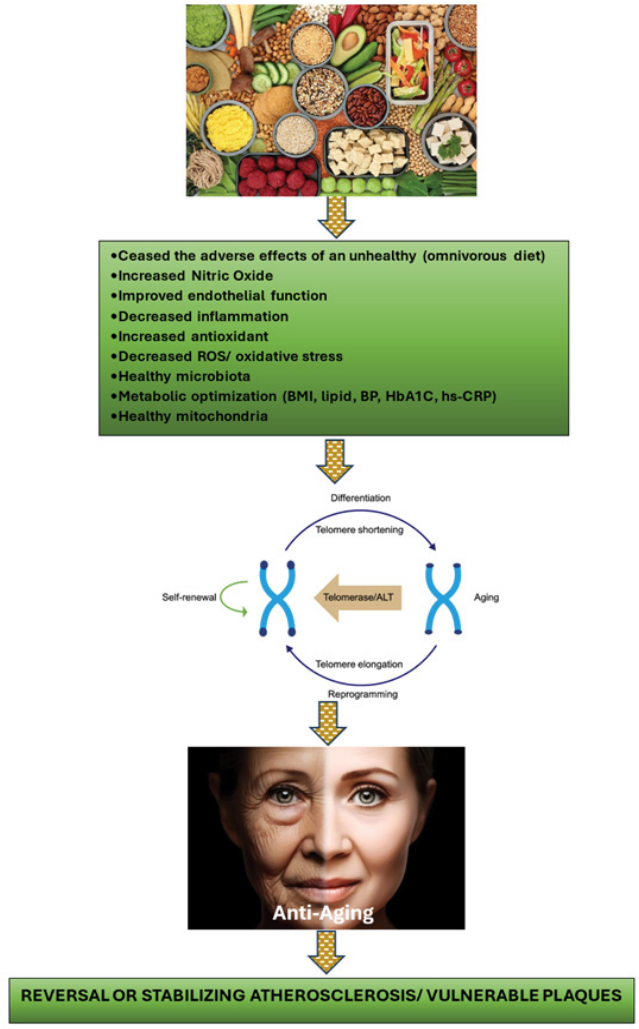

Figure 1: Mechanisms of how PBD stabilizes/ regresses the vulnerable plaque

source from vegetables, consuming them raw rather than cooked is recommended.

Many nutrition experts have specifically emphasized the deficiency of essential nutrients in PBDs, such as vitamins B12 and D, and minerals, like iodine, iron, zinc, selenium, and calcium, which can have detrimental effects [63,64]. In this context, in addition to employing the PBDs program, it is recommended to include supplementations with vitamin C, vitamin D, vitamin K2, vitamin B3/NAD+, zinc, copper, selenium, and natural anti-inflammatory products, such as astaxanthin, curcumin, quercetin, CoQ10, taurine, and multivitamins (containing various small doses of minerals and vitamins as recommended for daily RDA). These supplements ensure no nutrient deficiency occurs when following PBDs and enhance the anti-inflammatory, antioxidant, immunomodulator, repair mitochondria, and strengthen telomere, which will be useful in the anti-aging process, including regressing coronary plaques.

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DOI:10.26502/acbr.50170404

Changing lifestyle: the most difficult area in medicine to implement

In most primary and secondary prevention guidelines, almost all international guidelines recommend lifestyle modification for CAD patients [10,65-67]. Daily practice often neglects to advise CAD patients to follow healthy lifestyle guidelines. Even doctors themselves do not always adhere to healthy lifestyles, regardless of their coronary status. Many health professionals resist promoting healthy eating behavior, which is a crucial component of a healthy lifestyle. There are several reasons for this negative culture, including the fact that proper nutrition is not taught in medical school education, and many doctors do not believe that PBDs can provide significant benefits, particularly in regressing atherosclerosis [68]. Kim A. Williams, former American College of Cardiology president, expressed his disappointment with the medical community's view of PBDs. He has made a powerful assertion, namely that there are two types of cardiologists: vegans and those who have not thoroughly examined the relevant data. Previously, I used to believe that individuals like Kim were prone to hyperbole in their statements. However, since I have become a pioneer in PBDs in my country, I have faced similar problems in promoting PBDs. Cardiologists who advocate for healthier lifestyles among their patients are not afforded the same level of recognition or esteem as those who employ cutting-edge cardiac interventions. Furthermore, the financial remuneration for incorporating lifestyle medicine into patient care is not commensurate with that of performing invasive procedures. Hence, very few publications have been made by interventional cardiologists regarding the role of PBDs in CAD patients.

Conclusion

Being diagnosed with coronary stenosis of 40-70% on CTCA or coronary angiography does not necessarily imply that it is benign, as it does not require any intervention. Studies have shown that 68% of AMIs are caused by coronary obstruction of less than 50%. This peculiar phenomenon is likely due to a VP. Recent developments have suggested that identifying the presence of a VP and intervening before it causes MACE or mortality is beneficial. Nevertheless, advanced diagnostic instruments are not accessible in healthcare facilities in underprivileged countries, such as Indonesia, where the healthcare budget is limited. Consequently, employing PCI to treat such plaques may not be financially and medically viable. Similarly, applying CR with PCI may not be possible except for certain patients. It is important to note that high-risk asymptomatic patients or CCS patients can benefit from receiving CAC and CTCA evaluations to assess their risk for future coronary events and to identify the presence of VPs. The evaluations are non-invasive and boast several benefits, including effectiveness, practicality, reliability, affordability, and high patient tolerability. Furthermore, they are widely accessible in many countries.

In managing VP in asymptomatic or CCS patients, invasive treatments may not always be necessary. Evidence suggests that lifestyle changes, such as implementing PBD, can offer regression and stabilization of plaques in conjunction with OMT. However, OMT alone has been deemed insufficient in managing chronic inflammation associated with CAD, which is widely recognized as a chronic inflammatory disease and systemic condition. Therefore, a method that can regress and stabilize atherosclerotic plaques (VPs) will likely provide CR as well. In light of these findings, we support current guidelines recommending managing high-risk asymptomatic CCS patients with OMT and a healthy lifestyle. The misdiagnosis and mismanagement of high-risk asymptomatic individuals are especially concerning, as many of these individuals have presented with sudden death, which often garners attention from the media, particularly if the deceased is a prominent figure in society.

Effective patient education regarding dietary adjustments necessitates an extensive understanding of PBDs, knowledge of vitamins, minerals, and nutraceuticals, and specialized communication skills and techniques. Moreover, physicians must be willing to educate and follow up with patients despite the limited rewards associated with such efforts. Physicians who have witnessed the significant benefits of PBD interventions in treating CAD patients can serve as influential role models for the future adoption of lifestyle medicine, which, in this case, involves the application of PBDs.

Author Contributions: D.M.; Conceptualization, and Writing-review and editing

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

Conflict of Interest: The authors declare no conflict of interest.

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