



# Genetic Risk, Adherence to a Healthy Lifestyle, and Ischemic Heart Disease

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## Abstract

**Purpose of Review** The purpose of this review is to investigate and discuss two aspects of coronary artery disease (CAD)—genetic risk and therapeutic lifestyle change (TLC)—both of which have key importance for patients and their care but which actually receive inadequate attention.

**Recent Findings** Genetic risk has generally been relegated to a broad association with the presence of one or more inherited cardiovascular (CV) risk factors such as hypercholesterolemia, family history of atherosclerosis, hypertension, and diabetes mellitus. However, the future of genetic risk is an understanding of specific genes, a genetic risk score, specific genetic loci known as selective nucleotide polymorphisms (SNPs), specific alleles, and microribonucleic acids (miRNAs). Healthy lifestyle is fashionably referred to as TLC and encompasses physical fitness, exercise, behavioral modification, diet, and stress reduction.

**Summary** In the past decade, aggressive treatment of cholesterol with statins has received the major emphasis for CV risk reduction. Genetics, of course, can only be modified by factors that influence epigenetics, and TLC could have an effect on genetics by this mechanism. On the other hand, each individual component of TLC has been shown to contribute to a reduction of CV risk. Although aggressive pharmaceutical approaches are now in vogue, whatever TLC can contribute, depending on the degree of individual patient adherence, should never be forgotten.

**Keywords** Atherosclerosis · Coronary artery disease · Genetics · Hyperlipoproteinemias · Lipoprotein (a) · Low-density lipoprotein cholesterol · Therapeutic lifestyle change

## Abbreviations

AF	Atrial fibrillation	CXCL12	Cell-derived factor 1
CAD	Coronary artery disease	DM	Diabetes mellitus
CIMT	Carotid intima-media thickness	GRS	Genetic risk score
CSF1	Colony-stimulating factor 1	HHS	Health Heart Score
CTA	Computed tomography angiography	hsCRP	High sensitivity C-reactive protein
CV	Cardiovascular	LDL	Low-density lipoprotein
		LDL-C	Low-density lipoprotein cholesterol
		Lp(a)	Lipoprotein (a)
		MedDiet	Mediterranean diet
		MetS	Metabolic syndrome
		MI	Myocardial infarction
		MiRNAs	Microribonucleic acids
		MPO	Myeloperoxidase
		PAD	Peripheral arterial disease
		PCI	Percutaneous coronary intervention
		PCSK9	Proprotein convertase subtilisin/kexin type 9
		SCD	Sudden cardiac death
		SNPs	Selective nucleotide polymorphisms
		TLC	Therapeutic lifestyle change
		UK	United Kingdom

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## Introduction

There is an association of genetics and lifestyle with cardiovascular (CV) disease and coronary artery disease (CAD). Genetics cannot be modified, but understanding the association of genetics with CV disease and CAD is essential. In contrast, epigenetics can be favorably modified. Also, therapeutic lifestyle change (TLC) has multiple components and these can be effectively altered. This review discusses some basic genetics associated with CAD and CV disease and also emphasizes the importance of TLC as significant to patient care in the reduction of CAD and CV disease risk.

## Ischemic Heart Disease

### Coronary Artery Disease

Although hyperlipidemia appears to have the strongest association with CAD, multiple other associated factors must be kept in mind and these include diabetes mellitus (DM), hypertension, tobacco abuse, increased age, family history, and other risk markers of interest including lipoprotein (a) [Lp(a)], apolipoprotein B, remnant lipoproteins, small dense low-density lipoprotein (LDL), high-sensitivity C-reactive protein (hsCRP), oxidized LDL, homocysteine, blood coagulation factors, fibrinolysis factors, and oxidized LDL [1••]. Of inflammatory risk factors, hsCRP appears to be the most clinically useful and increased levels appear to have a significant association with CAD [2].

CAD, which can also be referred to as coronary atherosclerosis, is well established as the major factor involved in CAD events. Although coronary angiography is considered the gold standard for assessing CAD, this angiography has many drawbacks since the technique does not measure actual atherosclerosis or provide an assessment of CAD lesion composition [3]. CAD regression does appear to occur and be demonstrable [4]. However, angiography underestimates atherosclerosis extent, especially if a coronary artery segment appears normal, and even though aggressive lipid-lowering therapy has been associated with CAD regression, angiography is not accurate for actually detecting progression or regression of CAD [3]. Less invasive but involving significant iodine exposure, coronary computed tomography angiography (CTA) also offers visualization of the coronary arteries. As CTA techniques reach increased sophistication, they may become increasingly important in quantifying and detecting vulnerable CAD plaques by semi-quantitative plaque quantification and characterization [5]. When vulnerable coronary plaques can be characterized, it can lead to a prediction of future CAD events [6]. Following disruption, the plaque core results in a potent activation substrate for the coagulation cascade [7]. Identifying vulnerable plaques is important due to the fact that most CAD events associated with

a nonculprit lesion, as identified by intravascular ultrasound, involve a mean angiographic plaque stenosis of 30% [8]. Once detected, high-risk CAD patients with vulnerable plaques would likely benefit from aggressive medical management of CV risk [9]. Surgical or interventional revascularization is likely to be of little value with a vulnerable CAD plaque, and therefore its identification and aggressive medical management are of utmost importance [10]. Of interest, is the fact that increased epicardial fat or adipose tissue is associated with an increased incidence of high-risk vulnerable CAD plaques [11]. For the future, much remains to be learned regarding the vulnerable CAD plaque. For example, matrix metalloproteinases have been noted as mechanisms associated with thinning and subsequent rupture of the vulnerable plaque's fibrous cap [12]. CAD risk factor assessment combined with basic screening for vulnerable plaques (such as determination of the coronary artery calcium score as a simple noninvasive inexpensive test using computed tomography but no iodine dye in high-risk populations) may become increasingly important, as will future imaging tests that offer even greater specificity [13, 14•, 15]. An increased coronary artery calcium score would appear to be grounds for increased CAD and CV risk management, whereas a score of zero would tend to justify less aggressive management [16, 17].

### CAD Is a Metabolic Disease

CAD can be looked upon as a metabolic disease. In line with this, there is convincing evidence that both increased insulin resistance and hyperinsulinemia are linked to CAD [18]. Therefore, metabolic syndrome (MetS), may be considered a unifying concept due to associations with hyperglycemia, decreased high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, hypertension, and obesity with insulin resistance worsened by obesity and increased insulin contributory to hypertension [18]. To decrease CAD risk, TLC such as increased exercise, improved diet, and weight reduction are beneficial while contributing to decreased manifestation of MetS [19]. Both TLC and medications that target the individual components of MetS have been shown to decrease the incidence of CV disease [20]. In addition, to reinforce the association of MetS with CAD and CAD as a metabolic disease, the increased incidence of MetS with DM adds further support [21]. Vitamin D deficiency has been associated with increased MetS risk, with an inverse linear relationship reported in cross-sectional studies, but prior to recommending regular supplementation with the vitamin, randomized clinical trials are indicated [22] with an inverse linear reported in cross-sectional studies. Hyperhomocysteinemia has a general population prevalence of 5–10%, possibly as high as 30–40% in senior citizens, with a 10% association with CAD events, and therefore has to be considered a possibly modifiable CAD risk factor [23]. Unfortunately, thus far, despite the association of hyperhomocysteinemia with increased CAD risk, a vitamin

B combination including folic acid, vitamin B6, and vitamin B12 has yielded disappointing results regarding any decrease in CAD events, with only a small benefit noted regarding decreased stroke when administered to reduce plasma homocysteine, as reported in a recent Cochrane review [24].

## Genetics of CAD

### Low-Density Lipoprotein Cholesterol

The level of low-density lipoprotein cholesterol (LDL-C) has a major association with CV disease risk although some guidelines do not recommend attainment of a specific level [25•, 26], whereas others do, generally around an LDL-C level of 70 mg/dL (1.81 mmol/L) [27–29]. There is good evidence that lowering LDL-C decreases CV risk with a “lower is better” status for high CV risk [30], and there is proof of safety of an LDL-C level down to at least 20 mg/dL (0.52 mmol/L) [31].

### Hyperlipoproteinemias

The hyperlipoproteinemias have a well-established association with CAD [32•, 33•]. Various lipid-related markers have been studied. In the Emerging Risk Factors Collaboration study, which had 165,544 participants with no known baseline CV disease, it was found that the application of a combination of apolipoprotein A-1, apolipoprotein B, lipoprotein (a) [Lp(a)], and lipoprotein-associated phospholipase A<sub>2</sub> mass, in comparison to risk scores with total cholesterol and HDL-C, yielded minimal additional benefit for prediction of CV disease risk [34]. Higher HDL-C levels can be achieved with both TLC and medication. Increased HDL-C has an association with decreased CAD risk and there is increasing evidence that targeting the attainment of its elevation, in addition to reducing LDL-C, offers benefit for decreasing CAD risk [35]. Although statins are the major driver in the medical management of hyperlipoproteinemias, they have generally resulted in inconsistencies regarding HDL-C [36]. Of the statins, pitavastatin and rosuvastatin appear to offer the most consistent and effective increases in HDL-C [36].

### Lipoprotein (a)

The physiological function of Lp(a) has still not been defined, and a randomized trial to test a so-called Lp(a) hypothesis defining that reduction of elevated Lp(a) levels will decrease CV disease risk remains to be performed [37•]. However, there is sufficient evidence to support the significant association of elevated Lp(a) as a causal factor for CV disease, CV disease risk prediction [37•, 38, 39], and calcific aortic valve disease [37•]. Elevated Lp(a) also appears to be associated

with an increase in CV events following percutaneous coronary intervention (PCI) in DM patients [40]. Possible pathophysiological mechanisms associated with Lp(a) may be due to the LDL-like particle structure of Lp(a), along with pro-inflammatory effects of oxidation, antifibrinolytic effects, and prothrombotic effects associated with Lp(a) [37•]. In addition, because of various factors including epigenetics [37•] and genetics, there has been a resurgence in interest in Lp(a) and it has been referred to by Gencer et al. as the “revenant” [41], a term that means one who returns after death or a long absence. The importance of Lp(a) was considered of little value at the end of the twentieth century. These authors believe that recent genetic studies have contributed to the resurgence of interest in Lp(a), following a new Mendelian randomization approach that found support for a role of elevated Lp(a) levels in association with CV disease as well as in aortic stenosis. Previously, concentration has been on lowering LDL-C as the primary effort in CV risk reduction with any decrease in Lp(a) considered secondary, with even some medications effective in lowering Lp(a) not taken to endpoint studies [41]. However, three available therapies appear to have promise: LDC-C apheresis which also markedly lowers Lp(a), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors which decreases Lp(a) approximately 30%, and antisense therapy that targets the apolipoprotein (a) moiety of Lp(a) with up to a 90% decrease in phase 1 and phase 2 trials [41].

### Family History of Atherosclerosis

Family history of atherosclerosis is an important determinant of CAD risk but one that is hard to quantify. In a review of Medline and PubMed databases, Pandey et al. found 32 studies with results where family history of CAD was significantly associated with individuals with multiple nontraditional CAD risk factors such as carotid intima-media thickness (CIMT), coronary artery calcium score, multiple markers of inflammation such as hsCRP, and vascular function, which could appropriately lead to more intensive assessment of patients with a positive family history of CAD [42]. Most clinicians pay some attention to a positive family history of CAD, thereby placing some extra emphasis on TLC and medications that alter CV risk in such patients; but unfortunately, there is no readily available quantitative method to factor in family history when making a 10-year CV risk estimate [43].

### Genetic Architecture and Specific Genes (Table 1)

There is limited understanding of the genetic architecture of CAD. The genetic risk for CAD has been proposed as being able to be expressed as a genetic risk score (GRS) which is determined by the product of the number of high-risk variants inherited by an individual multiplied by the natural log of a previously calculated odds ratio [44••]. In a review of some

**Table 1** Relevant genetic considerations

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Genetic risk score (GRS) is determined by inherited high-risk variants multiplied by the natural log of an odds ratio [44••].
In excess of 60 genetic loci, classified as common selective nucleotide polymorphisms (SNPs), have an association with coronary artery disease (CAD) [45].
Upregulation of microribonucleic acids (miRNAs) is associated with the presence of CAD [46].
Specific alleles can be associated with CAD with also a racial variance [47].
Epigenetics can alter genetics by changing gene expression or cellular phenotype [48].

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large clinical trials, Assimes and Roberts found that GRS yielded an assessment of prognosis that was independent of conventional risk factors [49]. Recently, in excess of 60 genetic loci, classified as common selective nucleotide polymorphisms (SNPs), have been identified for having an association with CAD [45]. Some specific SNPs that have been shown to have a strong association with CAD include +45T>G (rs2241766), -11391G>A (rs17300539, and -4034A>C (rs822395); on the other hand, SNP +276>T (rs1501299) has been associated with decreased CAD [50]. In a 2017 meta-analysis, an association with increased CAD risk was also demonstrated for the myeloperoxidase (MPO) gene as MPO 463G/A gene polymorphism, but this increase CAD risk was not present with MPO 129G/A gene polymorphism [51]. In an Asian population, it was found that miR-146a (rs2910164) polymorphism is associated with CAD in an elderly population [52]. A 2017 literature search of microribonucleic acids (miRNAs), found that upregulation of various miRNAs was associated with the presence of CAD, and downregulation of various miRNA was associated with patients without clinical CAD [46].

There also appear to be racial differences regarding genetics as demonstrated by a Chinese meta-analysis with meta-regression which showed an association of the TT genotype and the T allele with CAD in East Asians whereas this association was not present in an Indian or European population, with further studies indicated [47]. A 2018 Mendelian randomization (MR) analysis linked, for the first time, two biomarkers with increased CAD risk: macrophage colony-stimulating factor 1 (CSF1) and stromal cell-derived factor 1 (CXCL12) [53]. Both CSF1 and CXCL12 were found to be associated with increased CAD risk with, in addition, supportive results noted for these two biomarkers in the United Kingdom (UK) Biobank of 343,735 subjects [53].

The current understanding of these genetic observations is that the effect of genetics on CAD and its severity is the cumulative small individual effect of multiple common CAD risk alleles rather than the existence of rare variants with a significant individual association with CAD risk [45]. Such data emphasize the importance of inheritance and the

possibility of creating future agents to target some of the genetic basis of CAD associated with related traits [49]. Such information can also lead to an understanding of when to increase the intensiveness of current risk prevention strategies even before genetically targeted medications are available [49]. The ideal goal of GRS screening is to take asymptomatic individuals and make an early identification of those with a significant increase in CAD risk in order to facilitate an early primary prevention strategy [44••]. The actual genes themselves cannot be modified but their epigenetics, associated with inheritable alteration in gene expression or cellular phenotype, can be altered by TLC, as discussed in the next section, and by environmental factors and change [48].

## Therapeutic Lifestyle Change (Table 2)

### Physical Fitness and Exercise

Physical fitness and physical activity have long been demonstrated to be beneficial as components of therapeutic lifestyle change (TLC) that have an inverse association with CV disease. The UK Biobank study reported an inverse association of increased physical activity and increased fitness with incident CV disease in a general population [54]. This UK Biobank study used different measures of physical fitness including grip strength, subjective physical activity, objective physical activity, and cardiorespiratory fitness with median follow-up of 6.1 years, and all of these physical modalities showed an inverse association with incident CV disease in their general population [54]. In addition, the UK Biobank study showed benefit for increased fitness and physical activity in decreasing CV disease in individuals with low, intermediate, or high genetic risk for CV disease including CAD and atrial fibrillation (AF) with an inverse association at every level of genetic risk [54]. The only downside for exercise ever established, aside from the occurrence of physical injury, has been the increased risk of a CV event during the period of exercise, especially when intensive [60]. In a 2011 study, it was found that 1 h of additional physical or sexual activity per week was associated with an increased risk of myocardial infarction (MI) of 2–3/10,000 person-years and an increase in sudden cardiac death (SCD) of 1/10,000 person-years [60]. However, the MI and SCD risk were further decreased

**Table 2** Therapeutic lifestyle change (TLC) and its effect

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Physical fitness and physical exercise are key TLC components and have established cardiovascular benefit [54].
Behavioral modification and stress reduction represent favorable mental, nonphysical aspects of beneficial TLC [55, 56].
Diet is a key component of TLC, and the Mediterranean Diet has very well established benefit for cardiovascular risk reduction [57–59].

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by an increase in additional weekly physical activity. Therefore, this very minimal increased CV event rate during the actual period of exercise, especially when intensive, is less in the presence of regular physical activity [60].

Hypertension, as a major CAD risk factor, appears to be benefited by moderate intensity physical activity in association with rhythmic motion of the lower extremities 3–4 times a week with a duration for 50–60 min [61]. Weight loss, when intentional, is a part of beneficial TLC to decrease CAD whereas so-called observational weight loss (such so-called observational weight loss occurs not planned and not on purpose) appears to have an association with increased CV events [62].

### Behavioral Modification

In a study involving 86 outpatients who had previously sustained a MI, a heart camp was established, which was completed by 45 patients who returned 8 weeks later [55]. These heart camps consisted of programs for an entire day that involved educational classes, a health assessment, and sessions for questions and answers, all carried out with a multidisciplinary approach. Upon completion, the participants appeared to have achieved significantly lower cardiac risk factor scores, including better diet and exercise habits as well as significant improvement in motivation [55]. The emphasis can then be made on the possible benefit of group behavioral modification. The use of meditation has also been proposed as a possible CV risk modification, with components of self-reflection, concentration, and contemplation [63]. In a 2013 study of 136 overweight hypertensive African Americans in Atlanta, Georgia, Davis et al. found that a treatment group exposed to a 3-month comprehensive lifestyle intervention vs. a control group with an abbreviated 6-week intervention, resulted in a significant net improvement in body mass index (BMI), amount of exercise each week, and servings of fruits plus vegetables each day [64]. Such results emphasize the power of collective high CV risk group management. Motivation to adhere to TLC appears to be increased when proof of CAD, as with an increased nonzero coronary artery calcium score, is present [65]. Another example of favorable behavioral modification is when a patient has undergone PCI, which appears to be a driver for improved TLC [66].

### Diet

Diet is a key component of TLC and, of course, there are multiple diets available that modify various food components and that are of varying extremes. Regardless of diet, calorie restriction remains important and with this reality in mind, the Mediterranean Diet (MedDiet) appears to be an ideal recommendation and patient guideline, even for a DM patient, as long as decreased simple sugar intake is included. There are

seven components associated with a MedDiet and these include (1) high ratio of monounsaturated to saturated fat, (2) low to moderate red wine intake, (3) high legume consumption, (4) significant cereal/grain intake, (5) significant fruit/vegetable consumption, (6) decreased red meat consumption with increased dietary fish, and (7) decreased milk/dairy products consumption [57]. The *Prevención con Dieta Mediterránea* (PREDIMED) study adds extra virgin olive oil and mixed nuts to the dietary mix [67]. The PREDIMED study resulted in significant reduction in CV risk factors and the incidence of peripheral arterial disease (PAD) [58], with also demonstration of a regression of CIMT after just 2.4 years follow-up [59]. PAD usually refers to atherosclerosis in the lower extremities whereas CIMT strictly deals with carotid atherosclerosis. The Dietary Approaches to Stop Hypertension (DASH) diet, which is rich in fruits, vegetables, and low-fat dairy products, has proven benefit for controlling hypertension as a major CV risk factor [68]. The Ornish diet, which is an example of an extreme very low-fat diet mainly consisting of vegetables, fruits, whole grains, and legumes, has been associated with regression of CAD as measured by quantitative coronary angiography and associated with fewer CAD events [69]. The increased intake of fruits and vegetables has been shown to decrease the incidence of CV disease and to decrease death from stroke and MI [70].

### Stress

The stresses of various situations and various lifestyles have long been associated with the development of CV disease events. Transcendental meditation (TM) has been one method of stress reduction with evidence indicating significant reductions in all-cause morbidity and all-cause mortality [71]. Of interest in this regard is the fact that the Maharishi Vedic Education Development Corporation has US trademarks for ((R))Transcendental Meditation and TM [71]. In the Lifestyle Heart Trial (LHT), improvements in the management of stress in a select group of patients with very high 5-year program adherence were associated with decreases in percent diameter coronary artery stenosis at follow-up [56]. Evidence for an association of stress with CAD and a decrease in CAD events by stress reduction is limited but increasing. In a study of TM, Walton et al. showed in their review that TM can decrease stress as well as reduce hypertension, tobacco abuse, and alcohol abuse [72].

### Possible Best Lifestyle Modifications

In general, TLC is a combination of change, and significant evidence suggests that TLC can reduce CV disease events by up to 80% with major emphasis on targeting a healthy population as a primary health promotion before the development of clinically manifest CV disease [73]. In 2016, an article by

Chu et al. noted the well-accepted evidence that decreasing stress, smoking cessation, and following a healthy diet all have evidence behind them in support of their contribution to a reduction in CV risk [74]. The authors used published literature on decreasing risk factors using a case-based analysis and found that participation in yoga had an association with a significant 10-year decrease in CV risk (16.7% for the highest risk subjects) with complete cessation of smoking for a current smoker even more beneficial. All TLCs appeared of benefit to CV disease prevention but this report fixated on yoga (undoubtedly this has a viable stress reduction component, as well as an exercise component) and complete smoking cessation as most effective measures [74]. In a prospective analysis including 11,527 individuals with type 2 DM (including 8910 women from the Nurse's Health Study and 2557 men from the Health Professionals Follow-Up Study), all of whom were found to be free of CV disease and cancer at the time DM was diagnosed, were followed for TLC factors before and after the diagnosis of DM [75]. An overall healthy TLC was defined in this study following a high-quality diet as in the top two fifths of the Alternative Healthy Eating Index, not smoking, participation in moderate to vigorous physical activity for  $\geq 150$  min/week, and alcohol intake in moderation as modified by sex. It was found that following an overall healthy lifestyle with TLC was associated with significantly decreased incidence of CV disease and mortality from CV disease in these adults with DM [75]. The investigators found that for each additional TLC factor added, there was a 14% lower risk of total CV disease, a 12% decrease in CAD events, a 21% decrease of stroke risk, and a 27% decrease in CV disease mortality (all with  $P < 0.001$ ) [75].

## Conclusions

Genetics contributes significantly to CV disease, and CAD risk and their effect has population variability. Understanding this may help place increased emphasis on risk reduction strategies. Despite available drugs to decrease LDL-C, the contributory value of TLC should never be forgotten, and its additive benefit should always be attempted in patient care to achieve maximum clinical benefit for each patient. One recent study suggested that the Healthy Heart Score (HHS), which includes smoking status, age, alcohol intake, body mass index, exercise program, and a dietary score composed of self-reported daily intake of fruits and/or vegetables, cereal fiber, sugar-sweetened beverages, nuts, and the combination of red or processed meats (alone or together), is an attractive tool for risk assessment and counseling for primary prevention of atherosclerotic CV disease [76]. Furthermore, the reliance of the HHS on self-reported, modifiable lifestyle factors makes it an

attractive tool for risk assessment and counseling for heart disease prevention.

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## Compliance with Ethical Standards

**Conflict of Interest** Thomas F. Whyne, Jr. and Siby P. Saha confirm that there are no conflicts of interest involving any pharmaceutical or medical device company or any other possible conflict.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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