International Journal of Family Medicine and Primary Care

Review Article
Published: 06 Apr, 2022

Therapeutic Implications of Genetic Risk Stratification for CAD

Robert Roberts[1], Judith Chavira[2] and Esperanza Acuna[3]*

[1]*Department of Medicine, University of Arizona, USA*

[2]*Biological Sciences/Kinesiology, USA*

[3]*Bachelors of Science in Physiology, USA*

Abstract

CAD, most common cause of death worldwide affects 50% of all Americans. CAD initiates early and slowly develops with clinical manifestations decades later. Primary prevention is most effective if initiated early. Conventional risk factors for CAD are often not present until the 5th or 6th decade too late for primary prevention. 50% of the risk for CAD is genetic. Recent discovery of 200 genetic risk variants enables one to estimate the genetic accumulative risk for CAD in a single number referred to as Polygenic Risk Score (PRS). Retrospective risk stratification with the PRS in clinical trials that evaluate the effect of drugs on cardiac mortality by lowering plasma cholesterol show individuals with the highest PRS have the highest risk for CAD and the most benefit from decreasing plasma LDL-C. The PRS has been evaluated in over 1 million individuals and those with the highest PRS (10% to 20%) have 1 to 4 fold increased risk for CAD. Prospective studies based on risk stratification by the PRS show a favorable lifestyle reduces genetic risk for CAD by nearly 50% in those with the highest PRS, and similar results are observed for physical fitness. The PRS, determined at conception, does not change throughout one's lifetime and so can be estimated at birth or anytime thereafter. Incorporation of the PRS (inexpensive and accessible) into routine clinical practice would be a paradigm shift in the prevention of this pandemic disease.

Introduction

Therapeutic implications of genetic risk stratification for CAD

Early primary prevention of Coronary Artery Disease (CAD) has long been a sought after goal in the Cardiovascular Community. CAD, the number one cause of death in the western world, has now progressed to the number one cause worldwide [1]. It is not surprising that epidemiological studies show about 50% of individuals living an average lifespan in the U.S. will experience a cardiac event. Perhaps more important than its common occurrence is the proven fact that CAD is a preventable disease. Experimental, epidemiological, and clinical studies have proven plasma LDL-Cholesterol (LDL-C) to be the primary culprit in the initiation and progression of coronary atherosclerosis, the underlying cause of CAD [2]. In addition to plasma LDL-C, other conventional risk factors (acquired and lifestyle) that predispose to coronary atherosclerosis have been known since the 60's [3]. Decreasing the risk for CAD associated with these conventional risk factors has been shown in randomized clinical trials to significantly reduce morbidity and mortality [4]. Lastly, reducing the risk of conventional risk factors contributing to coronary atherosclerosis also reduces atherosclerosis of other organ vasculature such as the brain, the limbs, and the kidneys and the incidence of associated diseases such as strokes.

A major limitation to early primary prevention has been the lack of biomarkers to select among asymptomatic individuals those at risk for CAD. The recent discovery of genetic risk variants predisposing to CAD has the potential to select those individuals at high genetic risk for CAD [5-7]. Unlike conventional risk factors, genetic risk is not age dependent and can be determined at birth or any time thereafter since ones DNA does not change in a lifetime. This review will discuss the therapeutic role of the genetic risk score to select individuals at high risk for CAD who would benefit from primary prevention.

Barriers to early primary prevention of CAD

Secondary prevention has been very effective and increasingly so with increased availability of less expensive generic statin therapy. Primary prevention which has the potential to be even more effective is necessary if the goal is to decrease the prevalence of this pandemic disease. It is theoretically possible as others have postulated to eradicate this disease in the 21st century [8]. In the

OPEN ACCESS

Correspondence:
Robert Roberts, Department of Medicine, University of Arizona, USA, E-mail: robert.roberts@commonspirit.org

Received Date: *09 Mar 2022*
Accepted Date: *31 Mar 2022*
Published Date: *06 Apr 2022*

Citation:
Roberts R, Chavira J, Acuna E. Therapeutic Implications of Genetic Risk Stratification for CAD. Int J Fam Med Prim Care. 2022; 3(1): 1059.

US the incidence of myocardial infarction has decreased about 50% in the past 30 years [9,10]. Conventional risk factors, known for several decades, have transformed primary and secondary prevention; however, their role is limited in early primary prevention since they are age dependent and other than cholesterol are often not present until the 5th or 6th decade of life [11-14]. Early primary prevention lacks the necessary biomarkers to risk stratify an asymptomatic population and determine individuals at greater risk for CAD. Plasma cholesterol, the main culprit causing CAD, increases almost linearly with age such that the plasma LDL-C concentration in females in the US average 121 mg/dL, and males 147 mg/dL by the age of 40 years which is approximately twice the recommended plasma level [15]. The Current Clinical Cardiovascular Practice Guidelines (CCCPG) which have played a remarkable role in prevention of CAD, specifically target the age group between 40 and 75 years and recommend using the Pooled Cohort Equations (PCE) to calculate the 10 year risk of a cardiac event, and if >7.5, primary prevention is appropriate including the use of Statins (http://tools.acc.org/ASCVD-Risk-Estimator-Plus/# !/calculate/estimate/) [16]. To have a 10 year risk of 7.5 at middle age usually requires at least 2 risk factors. However, other than cholesterol, the remaining traditional risk factors such as hypertension, diabetes, and obesity are age dependent and often not present until the 6th or 7th decade [14]. This is illustrated by this 40 year old female with plasma LDL-C of 180 mg/dL and no other traditional risk factors. The PCE calculation has a 10 year risk for CAD of 2.1%, which would put her into the category of no specific treatment. Her risk for CAD is low because most of the traditional risk factors such as hypertension or diabetes which would increase her risk for CAD do not develop until later in life (Figure 1). This could be a missed opportunity to prevent CAD and its clinical sequela. A second limitation to the PCE 10 year risk screening for primary prevention for CAD is its dependence on age. The same case discussed previously, now aged 60 years, with the same single risk factor of a plasma LDL-C of 180 mg/dL, has a 10 year risk of 9.2, simply because of the increase in age. The recent ACC/AHA guidelines are less than desirable for early primary prevention.

Early primary prevention is more effective

Genetic studies of rare disorders have provided strong evidence that early primary prevention has the potential to be more effective than late primary prevention. Discovery of a family with familial hypercholesterolemia in the 70s was subsequently shown to be due to a mutation in the LDL receptor [17]. Individuals inheriting this defect had increased plasma LDL-C and developed premature heart disease in the 2nd and 3rd decades of life. Analogous to these Abifadel et al. [18], discovered a gain of function mutation in PCSK9 which caused increased levels of plasma LDL-C [18]. These individuals exhibited premature CAD and heart disease. Subsequently, a loss of function mutation in PCSK9 was associated with low plasma LDL-C levels and 80% reduction in cardiac risk [19].

Utilizing a method referred to as Mendelian Randomization [20], Ference et al. [21], selected 9 genetic variants associated with decreased plasma LDL-C. These genetic variants are randomly assigned at conception which exposes the individual to their genetic influence throughout their lifetime. In this analysis of a population with a mean age of 50, they observed a 54.5% reduction in cardiac risk for each reduction of plasma LDL-C of 1 mmol (38.7 mg/dl) [21]. In contrast multiple clinical trials, assessing the effect of lowering plasma LDL-C, consistently observed that a reduction in plasma LDL-C of 1 mmol (38.7 mg/dl) is associated with on average only 20% reduction in cardiac risk [11–13,22]. These clinical trials enroll individuals' later in life usually in their 5th or 6th decades of life and the duration of prevention is short being only 3 to 5 years. Thus, there is a 3 fold greater reduction in cardiac events when the reduction in the concentration of plasma LDL-C is initiated at birth. In the same study, Ference et al. [21] observed the cardiac risk from LDL-C is not only proportional to the concentration of LDL-C but also the duration of exposure [23]. Nevar Boggan et al.[24], In a follow-up study of the Framingham Offspring cohort enhanced this observation

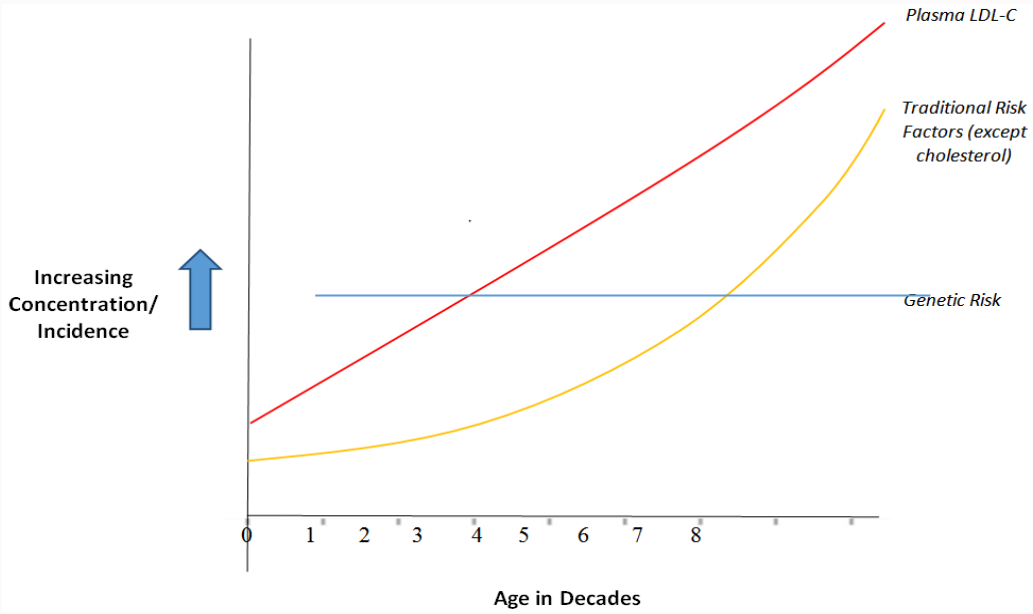

Figure 1: Genetic versus traditional risk stratification for CAD.
Legend: The traditional risk factors have limited application in selecting asymptomatic individuals at risk for CAD. These conventional risk factors such as age, hypertension, or diabetes are infrequent until the 50's or 60's. Plasma LDL-Cholesterol is an exception which increases early in life and the risk for CAD doubles every 10 years. In contrast, the genetic risk score for CAD is independent of age and remains the same throughout life. The genetic risk obtainable at any time after birth provides a major advantage enabling one to predict risk for CAD early in life. This could be a paradigm shift for the implementation of early primary prevention.

by showing the cardiac risk and its clinical manifestations doubled for each additional decade of exposure to increased plasma LDL-C. A corollary of these studies indicates that the earlier one initiates primary prevention the more effective it will be in reducing cardiac risk.

Initiation and progression of CAD is most amenable to early prevention

The need for early intervention in preventing CAD and its clinical sequela is also inherent in the initiation and progression of this disease. Coronary atherosclerosis is a chronic and slowly developing but progressive disease that begins early in life, and evolves clinically over several decades. We know it begins in males as early as the teenage years based on autopsies of soldiers who died during the Korean War [25]. These soldiers already had fatty streaks in their coronary arteries. Recent studies of individuals dying young from trauma further confirm the early development of atherosclerosis [26]. The slow progression of this disease is associated with increasing atherosclerosis. The disease is clinically silent for decades until a threshold is reached and that threshold is usually in the 5th or 6th decade for males and the 6th or 7th decade for females. The threshold that causes clinical manifestations is usually associated with 30% to 40% narrowing of the lumen of the coronary arteries. Despite minimal if any reduction in coronary flow from a 30% to 40% reduction in the lumen, plaque rupture can precipitate a thrombus with complete occlusion of the lumen causing an event such as myocardial infarction or sudden death. The peak incidence of myocardial infarction in the U.S. averages 58 years for males and 68 years for females [1]. It is noteworthy that once the threshold is reached the clinical manifestations tend to follow a numeric progression increasing from 1% at age 40 years, to 2% at age 50 years, to 4% at age 60%, and 16% at age 80 years [23]. Clinical data strongly indicates the premenopausal female is well protected from coronary atherosclerosis, but the progression increases rapidly with the onset of menopause such that the incidence of heart disease of 68 years [1] matches that of males. The opportunity for early primary prevention of CAD in the female has a much later window since current data suggests very little CAD in the female even in the early 40's[9]. Optimal prevention of CAD in the male would probably require intervention in the third decade. The wide spread occurrence of CAD throughout the world should spark the concern for more effective early primary prevention.

Discovery of genetic risk variants

Genetic factors have been claimed for decades to account for up to 50% of predisposition for CAD [27]. However, the technology has been lacking to pursue the responsible DNA sequences. Several innovative techniques contributed to our ability to pursue DNA variants associated with disease. Prominent among these techniques were the sequencing of the human genome by the Human Genome Project and the annotation of Single Nucleotide Polymorphisms (SNP) by the Hap Map Project [28,29]. Simultaneously was the development of computerized platforms to rapidly genotype and sequence DNA [30]. Utilizing these SNPs as DNA markers it was possible to span the human genome with millions of SNPs enabling us to pursue an unbiased approach referred to as the Case Control Association Study (CCAS). In a Case Control Association Study one compares the frequency of each DNA marker in controls to that of its frequency in cases with proven CAD. Markers occurring more frequently in cases indicate that marker is a risk variant for CAD or is in close physical proximity to a sequence that predisposes to CAD. The CCAS coupled with SNPs as markers that span the human genome is referred to as a Genome Wide Association Study (GWAS). Since one is assessing one million markers the difference between the frequency of a marker in cases and controls if relied on a p-value of 0.05 would give 50,000 false positives. A statistical correction factor was needed and the Bonferroni correction was adopted which requires a p-value of 0.00000005 or 10^{-8}. This would become known as a p-value of genome wide significance [31]. It was also required that SNPs with a p-value of 10^{-8} be replicated in an independent population. The genetic risk score for CAD is usually referred to as a Polygenetic Risk Score (PRS) since it is a polygenic disease. The genetic risk can be summarized in a single number by the product of number of risk variants inherited by an individual and the hazard ratio of each risk variant. The number of copies of each genetic variant inherited per person can be 0 (neither parent having a copy), 1 (only one parent transmitting a copy), or 2 (each parent transmitting a copy).

In 2007, we and the decode group in Iceland independently and simultaneously identified the first genetic risk variant for CAD referred to as 9p21 [5,6]. The sample size utilized by us for 9p21 was just over 23,000 cases and controls, and the sample size by Iceland of over 18,000. The 9p21 as a risk variant for CAD was confirmed shortly thereafter by The Welcome Trust Group [7] in a sample size of 17,000. Over the next two years 9p21 was confirmed as a genetic risk variant for CAD in many ethnic groups throughout the world and was recently comprehensively reviewed [32]. The 9p21 risk variant was shown to mediate its risk for CAD independent of all known risk factors and increased the relative risk for CAD of about 25% per copy. It is claimed to occur in about 75% of the world's population. This result suggested the genetic risk predisposing to CAD would be transmitted by many DNA sequences with each variant contributing only minimal risk. The total risk for CAD would require assessing the total accumulative number of variants inherited by the individual.

Given the minimal risk associated with each variant and the stringent p-value it would require even larger sample sizes than we had anticipated. This led to the formation of an international consortium referred to as CARDIoGRAM (Coronary Artery Disease Genome Wide Replication and Meta-analysis) [33] and subsequently CARDIoGRAM PLUS C4D [34]. These efforts along with other groups and individual investigators led to the discovery of over 200 genetic risk variants predisposing to CAD. These efforts to pursue the discovery of genetic risk variants predisposing to CAD are well summarized in several recent reviews [32,35-37]. The key features of these genetic risk variants predisposing to CAD are summarized in Table 1. Each risk variant occurs commonly and on average increases the relative risk for CAD by only 10%. Over 80% of the risk variants occur in the non-protein coding region of the DNA. Lastly, over half of the risk variants mediate their risk through unknown mechanisms.

Evaluation of the PRS

The discovery of the genetic architecture predisposing to CAD has many diagnostic and therapeutic implications. One of the most obvious is the power to predict one's risk for CAD and its application in selecting those who would benefit most from primary prevention. One initial attempt to risk stratifies for CAD was based on utilizing just 12 genetic risk variants. The results were statistically significant but perhaps not clinically significant [38]. The power to predict risk for CAD increased as the number of risk variants increased. Mega et al. [39] utilized 27 genetic risk variants and a sample size of 48,421. The blood samples were retrospectively genotyped in a randomized placebo controlled study performed to assess the effect of statin therapy

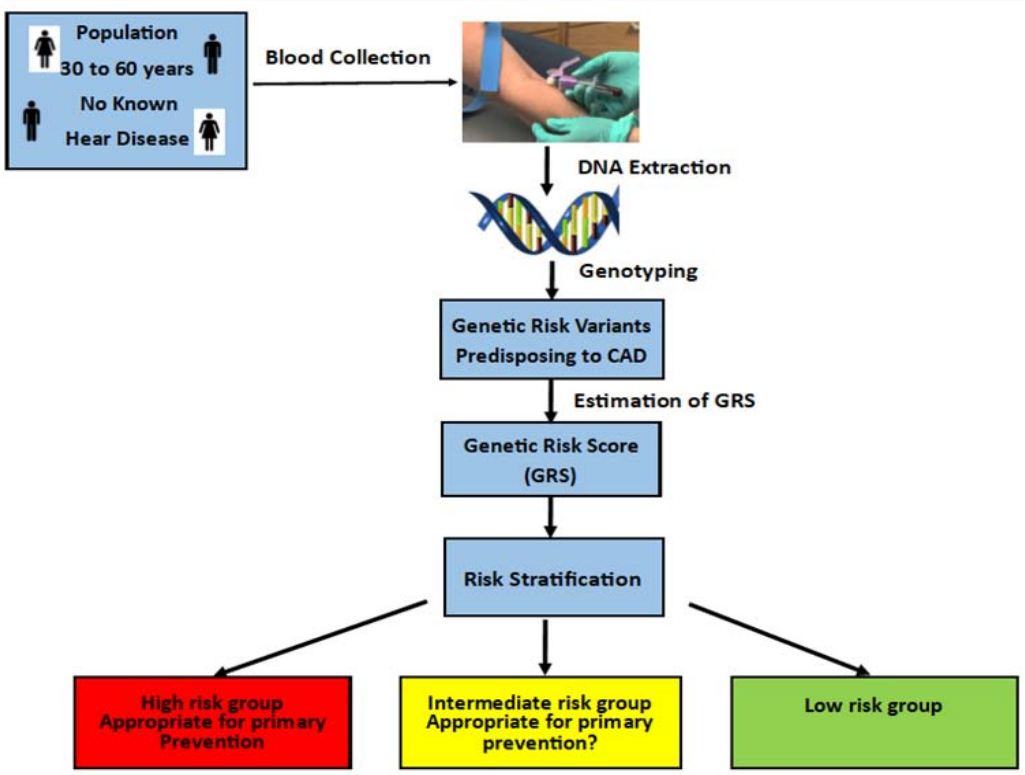

Figure 2: Genetic risk screening for coronary artery disease.
A blood sample is obtained from the patient. The DNA is extracted and genotyped for genetic risk variants predisposing to CAD. The number of genetic risk variants inherited by the person times the associated risk is calculated as a single number GRS. Based on the GRS, the patients are stratified into three risk groups; high, intermediate, and low risk.

on cardiac events. The trials included four well-known clinical trials; Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), Cholesterol and Recurrent Events (CARE), and Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE-IT-TIMI). Two trials assessed statin therapy as primary prevention and the latter two trials as secondary prevention. The individuals with the highest risk were shown to have the highest risk for CAD. The PRS predicted cardiac events independent of traditional risk factors. Individuals with the highest PRS score also received the most benefit from statin therapy. Furthermore, the PRS was equally effective in stratifying risk for CAD for both primary and secondary prevention. Retrospective genotyping of blood samples from another large clinical trial referred to as the West of Scotland Coronary Prevention Study (WOSCOPS) was performed with 57 genetic risk variants for CAD [40]. This study also evaluated the effect of statin therapy to lower cholesterol and reduce cardiac events. Individuals with the highest PRS had a 44% reduction of cardiac events versus only 24% reduction in the intermediate and low risk genetic groups. The number needed to prevent one cardiac event in the high PRS group was 13 individuals versus 38 in the intermediate and low PRS groups.

Recent randomized clinical trials have employed PCSK9 inhibitors which enhanced the removal of LDL-C from the plasma and are complementary to statins. Two of these trials are The FOURIER (Further Cardiovascular Outcomes Research with PCSK9 inhibition in subjects with elevated risk) and The ODYSSEY (Evaluation of Cardiovascular outcomes after an acute coronary syndrome during treatment with Alirocumab). The FOURIER trial evaluated Evolocumab [41] (PCSK9 inhibitor) in 27,564 patients. There was a strong correlation between individuals with intermediate and high PRS and cardiac events with 1.23 and 1.65 hazard ratios respectively. Patients receiving Evolocumab therapy had a 13% reduction in risk in the group stratified by conventional risk factors without high PRS and a 31% reduction in the high PRS groups with or without conventional risk factors. Individuals with the highest PRS had the most benefit from Evolocumab and were independent of conventional risk factors. The ODYSSEY trial enrolled 11,953 individuals [42]. Individuals with the highest PRS had the highest risk for CAD. Alirocumab treatment in the group with the highest PRS was associated with a 37% reduction in cardiac events *vs.* a 13% reduction in the group with the lowest PRS. These results confirm that the PRS is effective in identifying those at greatest risk who will benefit most from lowering plasma cholesterol whether it is achieved by statins or PCSK9 inhibitors.

Evaluation of the PRS in large bio-bank populations

To evaluate the specificity and accuracy of the PRS to risk stratify for CAD one approach was to genotype populations that have been well phenol typed and their samples stored in bio banks for future use. Abraham et al. [43] evaluated 5 prospective cohorts, 3 from the FINRISK group and 2 from the Framingham Heart Study for a combined sample size of 16,082 subjects. The microarray used for genotyping contained 49,310 genetic risk variants for CAD. These investigators observed that the cohort with the highest PRS was associated with more cardiac events independent of traditional risk factors including family history.

Table 1: Features of genetic risk variants for CAD.

1. Genetic risk variants for CAD are due to common DNA variants	3. More than 80% of genetic risk variants for CAD occur in Non protein coding regions
2. Each genetic risk variant for CAD imparts minimal risk (average increased relative risk of less than 10%)	4. More than two-thirds of genetic risk variants for CAD mediate risk independence of traditional risk factors

The UK bio bank has phenotyped over 500,000 individuals which Inouye et al. [44], genotyped using 1.7 million genetic risk variants predisposing to CAD. The individuals with the highest PRS had a fourfold increase risk of CAD which comprised 20% of the population. These investigators claimed stratification based on 1.7 million risk variants was superior to previous studies genotyping with a much smaller number of genetic risk variants. Khera et al. [45] genotyped a sample size of 388, 978 individuals also from the UK bio-bank utilizing 6.6 million risk variants. They observed that the top 8% with the highest PRS had a threefold increase risk for CAD and the top 5% a fivefold increase risk for CAD. The investigators comment on the increased power of the PRS to risk stratifies for CAD over conventional risk factors. In this particular group with the highest PRS only 20% had hypercholesterolemia, 28% hypertension, and 35% a family history, and thus, most would not have been detected by conventional risk factors.

These accumulated studies reflect the evaluation of the PRS to risk stratify for CAD in over a million individuals. These studies would indicate the PRS is more potent than conventional risk factors for risk stratification of CAD and also in large part independent of conventional risk factors.

Genetic risk for CAD is reduced by lifestyle changes and drug induced lowering of plasma cholesterol

It is important to note that therapy reducing genetic risk has been confirmed for decades. The concentration of plasma cholesterol has been proven to be reduced by statin therapy in many randomized placebo controlled clinical trials. It has been recognized for some time that 65% to 70% of the concentration of plasma LDL-C is under genetic control. A statin reduces the plasma concentration of LDL-C by inhibiting a protein which is the rate limiting enzyme (3-hydroxy-3-methylglutarylcoenzymeA) in the synthesis of cholesterol. Inhibiting the synthesis of cholesterol indirectly blocks the function of the gene encoding for this enzyme. The therapeutic approach to genetic and acquired risk factors is similar. Khera et al. [46] analyzed four prospective cohorts involving a sample size of 55,685 individuals. Individuals in the top 20% of the PRS had 90% higher risk of cardiac events than the remainder. The objective of the study was to compare the incidence of cardiac events in individuals with a healthy lifestyle (no current smoking, no obesity, regular physical activity, and a healthy diet) to that of an unhealthy lifestyle (at least two unfavorable features). In the group with the highest PRS and a favorable lifestyle there were 46% fewer cardiac events than those with an unfavorable lifestyle. Tikkanen et al. [47] assessed the effects of physical activity on cardiac events following risk stratification for CAD based on the PRS. In the group with the highest PRS and the most cardio respiratory fit, there was a 49% decrease in the genetic risk for CAD.

Limitations of the PRS

The genetic risk variants on which the PRS is based were determined primarily from individuals of European descent [48]. While these variants are common and occur throughout the world, it is expected there are risk variants unique to ethnic groups and geographical isolated populations. In a study of Southeast Indians the addition of variants obtained specifically from this ethnic group improved the power of the PRS to stratify for CAD [49]. The genetic risk variants discovered predisposing to CAD only account for less than 50% of the expected genetic predisposition. This would indicate there are many more to be discovered and intense efforts are ongoing such as the international consortium, CARDIoGRAMplusC4D, using larger sample sizes and greater saturation of SNPs as markers [50]. Another critique of the PRS is only the top 10% to 20% qualify for high risk with the remainder being in the average range based on the normal bell shaped distribution curve. What percentage of the average would benefit from prevention is unknown. It remains arbitrary as to where the line is drawn to represent significant increased risk for CAD. To date most individuals have over 100 genetic risk variants for CAD are still interpreted to remain in the average or normal risk range. This may have to be interpreted differently as we obtain more experience in the clinical setting. While most of the studies evaluating the PRS as a risk stratify for CAD concluded it is beneficial, there are two studies that recommend it not be used for clinical application [51,52]. In both of these studies the PRS showed a statistical advantage over conventional risk factors but was not of clinical significance. The investigators acknowledged the advantage of the PRS over conventional risk factors to risk stratify for CAD in the young but not in elderly adults. These studies are in contrast to all others evaluating the PRS.

Advantages of PRS genetic risk stratification of CAD for primary prevention

To halt the pandemic of coronary artery disease will require an active global primary prevention program initiated preferably in the preclinical stage of this disease. This requires biomarkers that are reliable in detecting symptomatic individuals who are at increased risk for CAD. The current conventional risk factors with the exception of plasma LDL-C is less than desired because they are not manifested in the early preclinical stage of this disease. It is evident that optimal primary prevention would probably be in the 3rd or 4th decade of life for males and 4th and 5th decade for females. The major advantage of the PRS for genetic risk stratification of CAD is its lack of dependence of age being present at birth and remaining the same throughout life. The current CCCPG do not include PRS but has suggested other techniques, referred to as enhancers, can be used to risk stratify for CAD. The example given by the CCCPG was coronary artery calcium score. A future approach to enhance risk stratification could be the use of the Genetic Risk Score (GRS). The GRS is not age-dependent and thus more appropriate for CAD risk stratification than conventional risk factors for primary prevention in the young. Using GRS to risk stratify would detect risk for CAD much earlier than the development of coronary calcium. If the person at age 40 has a high genetic risk score, one could recommend lifestyle changes and drug therapy to reduce LDL-C. The PRS enables primary prevention to be initiated at any age and can be obtained from a simple blood test. The cost of the genotyping is expected to be in the same range as any blood test and is often quoted at about $200. However, a commercial company is currently charging $350. It would only be necessary to perform the test once since one's DNA does not change in a lifetime. Adoptions of PRS to risk stratify for CAD would make it possible to initiate primary prevention in those at increased risk even

in their 2nd or 3rd decade of life. The blood or saliva can be collected anywhere in the world and shipped to the nearest laboratory that can perform genotyping regardless of the distance since the DNA remains stable for years. Since the plasma LDL-C is elevated in most people early in life it forms a target for primary prevention. Furthermore, the recent availability of inexpensive non-patent drugs to reduce plasma LDL-C makes therapy accessible to all parts of the world. This makes it possible to initiate global early primary prevention of CAD. The incorporation of the PRS into routine clinical practice would be a paradigm shift in the prevention of this disease.

The PRS has been evaluated in over 1 million individuals and individuals with the highest PRS (10% to 20%) had a 1 to 4 fold increased risk for CAD. These evaluations were performed in large cohorts previously phenotyped such as the UK Biobank or retrospectively in large clinical trials. The PRS has not been incorporated into routine clinical use and thus the PRS has not been assessed in individuals or utilized to determine patient management. One such study was initiated in 2021 and is currently enrolling individuals. The clinical trial (NCT05169840) is registered with the federal government and available at this website (https://clinicaltrials.gov/ct2/show/study/NCT05169840?term=robert+roberts&draw=2&rank=1). The study is referred to as genetic risk stratification for primary prevention of CAD in Men and Pre- & Post-menopausal Women as outlined briefly in Figure 2. Criteria for enrollment are males and females between the ages of 30 to 60 years without known heart disease. The PRS is determined based on a microarray containing 6.6 million genetic risk variants. Individuals are classified into low, intermediate, and high risk. Patients at high risk will receive genetic counseling together with appropriate preventive measures to decrease their risk for CAD. It is expected to enroll over 2,000 individuals in a period of two years and an annual follow-up will be continued for 10 years.

Acknowledgment

Dr. Robert Roberts has received research funding from the Dignity Health Foundation (455005033246), the Canadian Institutes of Health Research (MOP P82810), the Canada Foundation for Innovation (11966). The authors declare no competing interests.

References

1. Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med. 2013;369(5):448–57.
2. Borén J, Chapman MJ, Krauss RM, Packard CJ, Bentzon JF, Binder CJ, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: Pathophysiological, genetic, and therapeutic insights: A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2020;41(24):2313-30.
3. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J III. Factors of risk in the development of coronary heart disease six-year follow-up experience: The Framingham study. Ann Intern Med. 1961;55:33-50.
4. The Multiple Risk Factor Intervention Trial Group. Statistical design considerations in the NHLI Multiple Risk Factor Intervention Trial (MRFIT). J Chronic Dis. 1977;30(5):261–75.
5. McPherson R, Pertsemlidis A, Kavaslar N, Stewart A, Roberts R, Cox DR, et al. A common allele on chromosome 9 associated with coronary heart disease. Science. 2007;316(5830):1488-91.
6. Helgadottir A, Thorleifsson G, Manolescu A, Gretarsdottir S, Blondal T, Jonasdottir A, et al. A common variant on chromosome 9p21 affects the risk of myocardial infarction. Science. 2007;316(5830):1491-3.
7. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature. 2007;447(7145):661-78.
8. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. 2003;326(7404):1419.
9. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. The Lancet. 1999;353(9147):89-92.
10. American Heart Association: Heart and Stroke Statistical Update. American Heart Association. 2000 Ed. Dallas: 2000.
11. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). Lancet. 1994;344(8934):1383-9.
12. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.
13. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. The Lancet. 2016;388(10059):2532-61.
14. Roberts R, Fair J. A Less than provocative approach for the primary prevention of CAD. J Cardiovasc Transl Res. 2022;15(1):95-102.
15. Swiger KJ, Martin SS, Blaha MJ. Narrowing sex differences in lipoprotein cholesterol subclasses following mid-life: The Very Large Database of Lipids (VLDL-10B). J Am Heart Assoc. 2014;3(2):e000851.
16. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: A report of the American college of cardiology/American Heart Association task force on clinical practice guidelines. Circulation. 2019;139(25):e1082-e1143.
17. Brown MS, Goldstein JL. Familial hypercholesterolemia: A genetic defect in the low-density lipoprotein receptor. N Engl J Med. 1976;294:1386–90.
18. Abifadel M, Varret M, Rabès JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet. 2003;34(2):154–6.
19. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. Nat Genet. 2005;37(2):161-5.
20. Roberts R. Mendelian randomization studies promise to shorten the journey to FDA approval. JACC Basic Transl Sci. 2018;3(5):690-703.
21. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease. J Am Coll Cardiol. 2012;60(25):2631.
22. Cholesterol Treatment Trialists' (CTT) Collaboration; Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomized trials. Lancet. 2010;376(9753):1670-81.
23. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: A report from the American Heart Association. Circulation. 2015;131(4):e29-322.
24. Navar-Boggan AM, Peterson ED, D'Agostino RB, Neely B, Sniderman AD, Pencina MJ. Hyperlipidemia in early adulthood increases long-term risk of coronary heart disease. Circulation. 2015;131(5):451-8.
25. Virmani R, Robinowitz M, Geer JC, Breslin PP, Beyer JC, McAllister HA. Coronary artery atherosclerosis revisited in Korean war combat casualties. Arch Pathol Lab Med. 1987;111(10):972-6.
26. Joseph A, Ackerman D, Talley JD, Johnstone J, Kupersmith J.

Manifestations of coronary atherosclerosis in young trauma victims--an autopsy study. J Am Coll Cardiol. 1993;22(2):459-67.

27. Chan L, Boerwinkle E. Gene-environment interactions and gene therapy in atherosclerosis. Can J Cardiol. 1994;2(4):130-37.

28. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome. Science. 2001;291(5507):1304-51.

29. Frazer KA, Ballinger DG. A second generation human haplotype map of over 3.1 million SNPs. Nature. 2007;449(7164):851–61.

30. Roberts R. New gains in understanding coronary artery disease, interview with Dr Robert Roberts. affymetrix microarray bulletin. Spring. 2007;3(2):1–4.

31. Risch N, Merikangas K. The Future of genetic studies of complex human diseases. Science. 1996;273(5281):1516-7.

32. Assimes TL, Roberts R. Genetics: Implications for prevention and management of coronary artery disease. J Am Coll Cardiol. 2016;68(25):2797–818.

33. Preuss M, König IR, Thompson JR, Erdmann J, Absher D, Assimes TL, et al. CARDIoGRAM consortium. Design of the coronary artery disease genome-wide replication and meta-analysis (CARDIoGRAM) study: A genome-wide association meta-analysis involving more than 22,000 cases and 60,000 controls. Circ Cardiovasc Genet. 2010;3(5):475–83.

34. The Coronary Artery Disease (C4D) Genetics Consortium. A genome-wide association study in Europeans and South Asians identifies five new loci for coronary artery disease. Nat Genet. 2011;43(4):339–44.

35. Erdmann J, Kessler T, Munoz Venegas L, Schunkert H. A decade of genome-wide association studies for coronary artery disease: The challenges ahead. Cardiovasc Res. 2018;114(9):1241-57.

36. Roberts R, Chang CC. A Journey through genetic architecture and predisposition of coronary artery disease. Curr Genomics. 2020;21(5):382-98.

37. Khera AV, Kathiresan S. Genetics of coronary artery disease: Discovery, biology and clinical translation. Nat Rev Genet. 2017;18(6):331–44.

38. Davies RW, Dandona S, Stewart AF, Chen Li, Ellis SG, Wilson Tang WH, et al. Improved prediction of cardiovascular disease based on a panel of single nucleotide polymorphisms identified through genome-wide association studies. Circ Cardiovasc Genet. 2010;3(5):468–74.

39. Mega JL, Stitziel NO, Smith JG, Chasman DI, Caulfield M, Devlin JJ, et al. Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: An analysis of primary and secondary prevention trials. Lancet. 2015;385(9984):2264-71.

40. Natarajan P, Young R, Stitziel NO, Padmanabhan S, Baber U, Roxana Mehran R, et al. Polygenic risk score identifies subgroup with higher burden of atherosclerosis and greater relative benefit from statin therapy in the primary prevention setting. Circulation. 2017;135(22):2091-01.

41. Nicholas A, Frederick K, Francesco N, Gurmu Y, Roselli C, Sever PS, et al. Predicting benefit from evolocumab therapy in patients with atherosclerotic disease using a genetic risk score. Circulation. 2020;141(8):616-23.

42. Amy D, Gabriel SP, Gregory S, Szarek M, Hagström E, Badimon L, et al. Patients with high genome-wide polygenic risk scores for coronary artery disease may receive greater clinical benefit from alirocumab treatment in the odyssey outcomes trial. Circulation. 2020;141(8):624-36.

43. Abraham G, Havulinna AS, Bhalala OG, Byars SG, De Livera AM, Laxman Y, et al. Genomic prediction of coronary heart disease. Eur Heart J. 2016;37(43):3267–78.

44. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, et al. Genomic risk prediction of coronary artery disease in 480,000 adults. J Am Coll Cardiol. 2018;72(16):1883–93.

45. Khera AV, Chaffin M, Aragam KG, Haas ME, Roselli C, Choi SH, et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. Nat Genet. 2018;50(9):1219–24.

46. Khera AV, Emdin CA, Drake I, Natarajan P, Bick AG, Cook NR, et al. Genetic risk, adherence to a healthy lifestyle, and coronary disease. N Engl J Med. 2016;375(24):2349–58.

47. Tikkanen E, Gustafsson S, Ingelsson E. Associations of fitness, physical activity, strength, and genetic risk with cardiovascular disease: Longitudinal analyses in the UK Biobank study. Circulation 2018;137(24):2583–91.

48. Roberts R, Chang CC, Hadley T. Genetic risk stratification: A paradigm shift in prevention of coronary artery disease. JACC Basic Transl Sci. 2021;6(3):287-304.

49. Wang M, Menon R, Mishra S, Aniruddh Patel P, Chaffin M, Tanneeru D. Validation of a genome-wide polygenic score for coronary artery disease in south Asians. J Am Coll Cardiol. 2020;76(6):703-14.

50. Schunkert H, Erdmann J, Samani SNJ. CARDIo GRAM celebrates its 10th Anniversary. Eur Heart J. 2019;40(21):1664-6.

51. Mosley JD, Gupta DK, Tan J, Yao J, Wells QS, Shaffer CM, et al. Predictive accuracy of a polygenic risk score compared with a clinical risk score for incident coronary heart disease. JAMA. 2020;323(7):627–35.

52. Elliott J, Bodinier B, Bond TA, Chadeau-Hyam MC, Evangelou E, Moons KG, et al. Predictive accuracy of a polygenic risk score enhanced prediction model *vs.* a clinical risk score for coronary artery disease. JAMA. 2020;323(7):636–45.