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RESEARCH ARTICLE

Genetic Risk Stratification Will Enhance Primary Prevention of Coronary Artery Disease

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ABSTRACT

Coronary artery disease, the number one cause of death in the world, is highly amenable to primary and secondary prevention. Primary prevention is limited because of lack of biomarkers to detect CAD in its asymptomatic phase. Conventional risk factors such as hypertension, are not evident until the 6th or 7th decade, which may be late for primary prevention particularly in males. The recent discovery of genetic risk variants for CAD has the potential through risk stratification to detect individuals most appropriate for primary prevention. First, genetic risk accounts for about 50% of predisposition to CAD; second, it is determined at conception and not influenced by age since DNA does not change in one's lifetime. Thirdly, genetic risk can be determined at any time from birth onward which is close to ideal for early primary prevention. A review of the literature show genetic risk can be summarized in a single number, referred to as polygenic risk score (PRS), and used to risk stratify for CAD. The PRS has been evaluated in over 1 million individuals and those in the top 20% exhibit a one-to-four-fold greater risk for CAD than those in the bottom 20%. More importantly, clinical studies have shown that decreasing plasma LDL-C or modifying lifestyle decreases the genetic risk for CAD by 50%. The polygenic risk score, obtained from a single blood sample, does not need to be repeated in one's lifetime. Furthermore, the genetic risk captured by the PRS is relatively independent of the conventional risk factors including family history. The current PRS was determined primarily in individuals of European decent which can be a limitation to its use in other ethnic groups. However, results of trials ongoing in several ethnic groups will soon be available. We propose primary prevention to be initiated early in life in individuals in the top 20% of the PRS. The test is relatively inexpensive and generic drug therapy is also inexpensive. The use of the PRS to risk stratify for CAD would be a paradigm shift for implementation of early primary prevention of CAD.

Objectives of the Review

The overall objective of this review is to determine whether the genetic risk score for CAD is an appropriate method to risk stratify for early primary prevention. We reviewed the results of studies that have evaluated the genetic risk score for CAD in over one million cases and controls. Individuals with a high genetic risk score (top 20%) exhibited a one to four fold increased risk of CAD. The genetic risk score should be considered as an additional enhancer to stratify for risk in the primary prevention of CAD.

Introduction

In the past 30 years, prevention and treatment of coronary artery disease (CAD) in the U.S. has reduced mortality and morbidity by 50%[1]. The prevention was based on reducing the risk associated with known conventional risk factors including hypertension, smoking, plasma cholesterol, obesity, diabetes, and unfavorable lifestyle. A major factor was the reduction of plasma LDL-C achieved by lifestyle changes and statin drugs. A similar trend in reduction of cardiac mortality and morbidity through prevention has been observed in most if not all Western countries. The observation that CAD is largely a preventable disease is based on well-designed randomized placebo controlled clinical trials[2–4]. Yet, CAD remains the main cause of death in the USA and also in other high income countries[1]. Furthermore, since 2013, CAD has also become the most common cause of death in middle and low income countries[5]. CAD is currently the most common cause of death in the world accounting for nearly a third of all deaths[5]. In the U.S., 50% of the population is expected to encounter at least one cardiac event in their lifetime[5].

Coronary Atherosclerosis Develops Early in Life with Gradual Progression

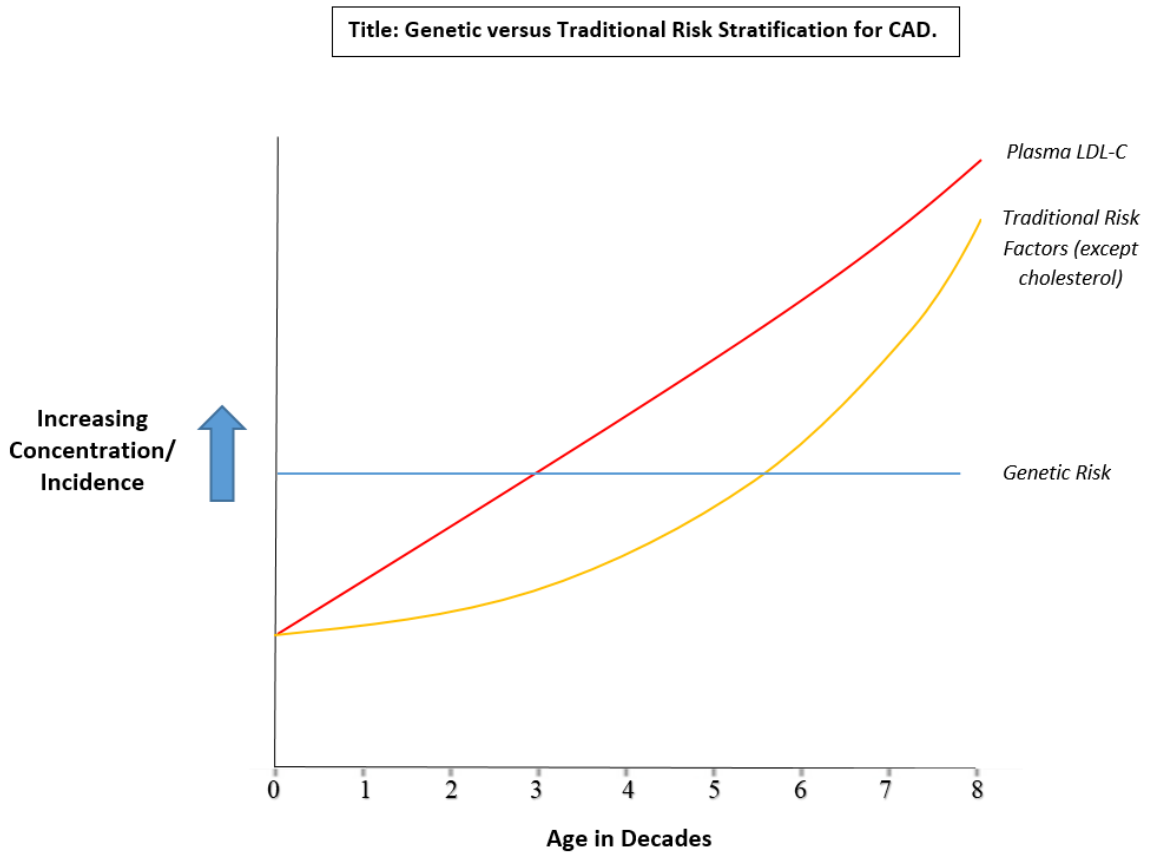
It has been observed for decades that coronary atherosclerosis, the cause of CAD, has a long subclinical period initiated in childhood followed by a very gradual progression, which is generally not manifested clinically until the 6th or 7th decade[6]. In women, this progression is further delayed by 10 years. Coronary atherosclerosis is a residual disease of living which increases with age due in part to deposition of oxidized cholesterol followed by an inflammatory response in the arteries that continues throughout one's life. So, the longer you live the more likely you are to develop the clinical manifestations, of myocardial infarction, angina, heart failure, and death. This is corroborated by the results of Navar-Boggan et al[7], who showed the risk of CAD increases as the duration of exposure to plasma low-density lipoprotein cholesterol (LDL-C) increases such that every additional 10 years of exposure doubles the risk of CAD. This is also in keeping with the observation by Ference et al[8], who showed decreasing the concentration of plasma LDL-C was much more effective in reducing cardiac events when initiated early in the 3rd or 4th decade of life.

Clinical Guidelines Are Less Than Adequate for Early Primary Prevention

The American College of Cardiology (ACC)/American Heart Association (AHA) clinical guidelines[9] for primary prevention of CAD have been codified. An estimated ≥7.5% risk of a cardiac event within the next 10 years as determined by the pooled cohort equation (PCE) is the minimum threshold required to recommend primary prevention. However, in individuals in their 40s it usually requires two or more risk factors to have a 10-year risk for CAD of 7.5%. These conventional risk factors are age dependent and often not present until the 6th or 7th decade (Figure 1)[10]. This is somewhat late for early primary prevention, particularly in males. Furthermore, subclinical coronary atherosclerosis correlates poorly with conventional risk factors[11]. The inadequacy of conventional risk factors for primary prevention is further confirmed by a retrospective analysis of 2733 individuals with premature acute myocardial infarction[12] (<55 years of age). Analysis utilizing the clinical cardiac guidelines indicated only 39.4% of these patients based on the PCE 10-year risk would have been detected for primary prevention before the event.

Genetic Risk Stratification of Coronary Artery Disease Is Superior to Conventional Risk Stratification

This limitation of conventional factors to risk stratify for CAD was one of the reasons to pursue genetic risk. Genetic risk is claimed to account for about 50% of predisposition for CAD[13]. The discovery of 9p21, the first genetic risk variant[14,15], was followed by a cascade of investigations utilizing genome wide association studies (GWAS). These studies led to the discovery of over 200 risk variants predisposing to CAD[16–18]. The genetic risk is determined at conception and does not change during one's lifetime. Thus, genetic risk for CAD unlike conventional risk factors is not age dependent and can be determined at birth if required[18]. In contrast to the conventional risk factors for CAD, the genetic risk variants correlates highly with subclinical coronary atherosclerosis[11] making it a highly sensitive biomarker for risk stratification.



Roberts R, Chavira J, Venner E. Genetic risk and its role in primary prevention of CAD. *Journal of Translational Genetics and Genomics*. 2022; 6(4):388-402. http://dx.doi.org/10.20517/jtgg.2022.07

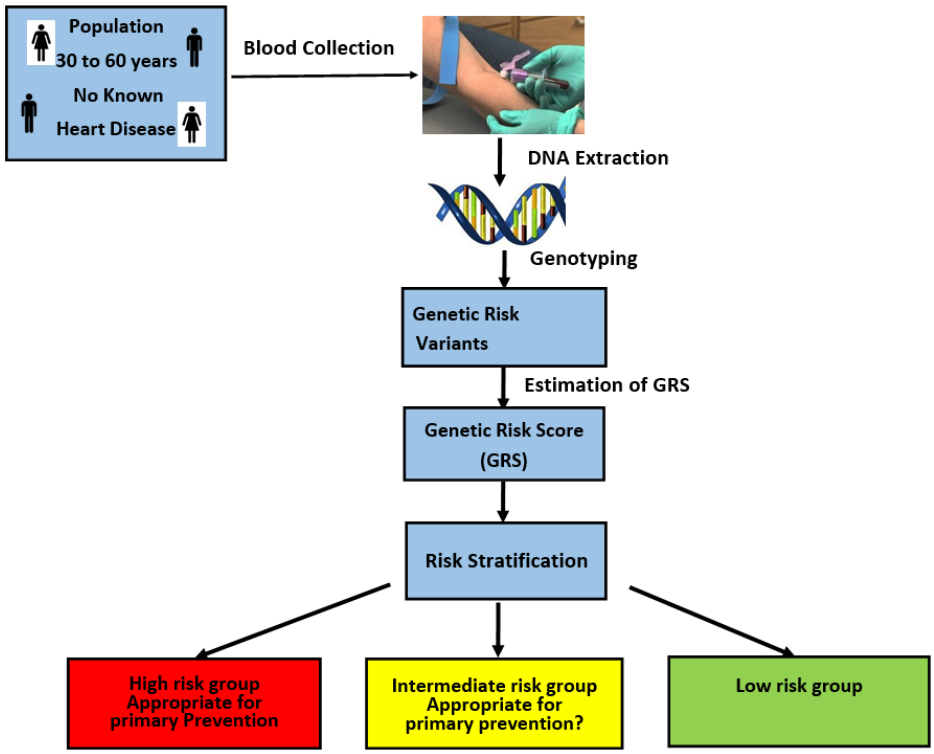
Figure 1: The traditional risk factors have limited application in selecting asymptomatic individuals at risk for CAD. These conventional risk factors such as age, hypertension, or diabetes are infrequent until the 50's or 60's.Plasma LDL-Cholesterol is an exception which increases early in life and 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.

The genetic risk can be expressed in a single number referred to as the genetic risk score by determining the number of genetic risk variants inherited by the individual multiplied by the CAD risk ratio of each variant[19–21]. This risk score variously referred to as genetic risk score or polygenic risk score (PRS) has been evaluated in several studies, totaling over a million individuals[10]. A high genetic risk score was shown to correlate with high risk for CAD. Individuals in the top 20% had a one to four fold increased risk for CAD[20,21]. The genetic risk is virtually independent of conventional risk factors and as such is complementary[21]. Most of the individuals detected in the top 20% would not be detected by conventional risk factors[21]. Retrospective analysis of clinical trials[22–25] showed individuals with the greatest benefit from statin therapy also had the highest PRS. Prospective studies[26,27] showed individuals with the highest PRS had a 50% reduction in genetic risk on a favorable lifestyle compared to those with high PRS on an unfavorable lifestyle. This indicated that the risk for CAD detected by the PRS can be reduced by lowering the risk of conventional predisposing factors.

Prevention of Coronary Artery Disease Based on Polygenic Risk Score Stratification (Clinical Trial)

Utilizing the history and a blood sample one can obtain comprehensive risk stratification of CAD by combining both the conventional and genetic risk factors. One such study was initiated in 2021 at St. Joseph's Hospital and Medical Center in Phoenix, Arizona. Genetic Risk Stratification for Primary Prevention of CAD in Men and Pre & Post-menopausal Women, is registered (NCT05169840) with the federal government and available at this website

(https://clinicaltrials.gov/ct2/show/study/NCT05169840?term=robert+roberts&draw=2&rank=1). The trial is currently enrolling males and females aged 30 to 60 years without known CAD as illustrated in Figure 2. A short history is obtained along with a blood sample. The PRS is determined from a microarray containing 6.6 million risk variants and the conventional risk score is calculated utilizing the PCE. Individuals with a PRS in the high risk range (top 20%) will receive genetic counseling and appropriate treatment (lifestyle changes and cholesterol lowering drugs). They will be followed annually for 10 years.



Roberts R, Chavira J, Venner E. Genetic risk and its role in primary prevention of CAD. *Journal of Translational Genetics and Genomics*. 2022; 6(4):388-402. http://dx.doi.org/10.20517/jtgg.2022.07

Figure 2: The population to be recruited are individuals from age 30 to 60 without known heart disease. DNA sample can be obtained from blood specimen. The DNA will be isolated and genotyped for the genetic risk variants predisposing to CAD. The genetic risk score (GRS) is calculated as a single number. Based on the GRS, the patients are stratified into three separate groups; high, intermediate, and low risk. Those in the high risk group will be counseled and appropriate preventative measures recommended. The population will be followed annually for 10 years.

The PRS will continue to improve as more DNA risk variants predisposing to CAD are discovered. The search for additional genetic risk variants for CAD is continued by the International Consortium – Coronary Artery Disease Genome Wide Replication and Meta Analysis (CARDIoGRAMplusC4D). We recently completed a GWAS on a sample size of over 1.3 million cases and controls and identified an additional 53 genetic risk variants for CAD[28]. The risk variants discovered by GWAS have been based primarily on populations of European origin. Blood samples from multiracial and multiethical populations have, however, been collected and are in the process of being analyzed.

The Genetic Risk Score Could Transform Primary Prevention of Coronary Artery Disease

The screening and application of primary prevention of CAD despite its proven value has been disappointing. In a recent published consensus[12] only about 50% of patients post myocardial infarction with elevated plasma LDL-C were receiving statin therapy. It is expected that primary prevention of CAD is even more neglected given the lack of biomarkers to detect asymptomatic individuals in the subclinical phase of CAD. We spend billions of healthcare dollars on expensive devices inserted in the last month or year of one's life. The cardiovascular community has a significant inexpensive, safe, and efficacious armamentarium to prevent the number one cause of

death but it is seldom implemented for early primary prevention. One of the barriers is the lack of biomarkers to risk stratify those with asymptomatic CAD. Individuals at high risk would benefit most from lowering plasma LDL-C. Since the PRS is not age dependent it provides a method of detecting those at high genetic risk early in the evolution of the disease. Individuals in the top 20% of the PRS score have one to four fold increased risk, all of whom would be expected to benefit from the lowering of plasma LDL-C[20,21]. However, the clinical guidelines do not mention the PRS but do recommend the use of other means to risk stratify for CAD and mention as an example the use of the coronary calcium score. Widespread implementation would require the collaboration of the primary care physician and internists as well as the cardiologists.

Armamentarium for Lowering Plasma Cholesterol

The main culprit causing CAD is cholesterol, primarily LDL-C[29,30]. In addition to lifestyle changes, a significant armamentarium of drugs approved by the FDA are now available to lower plasma LDL-C. These drugs act through four separate mechanisms which in combination would be complementary and expected to have a summation effect. The statins act by inhibiting the synthesis of cholesterol through inhibition of the rate limiting enzyme (3-hydroxy-3-methylglutarylcoenzymeA), often referred to as HMGCOA, and until the last few years, was the only effective agent available[4,8,31]. The PCSK9 inhibitors[24,25], available by injection only, inhibit the degradation of the LDL-C receptor. The angiopoietin-like 3 protein (ANGPTL3) decreases plasma LDL-C by inhibiting the lipases[32,33]. Zetia prevents cholesterol absorption from the intestine[34]. Recently, bempedoic acid administered orally was approved by the FDA. It lowers plasma LDL-C by inhibiting the synthesis of cholesterol through inhibition of the enzyme adenosine triphosphate-citrate lyase (ACL)[35], which is upstream of HMGCOA enzyme.

The Relevance of Cholesterol Metabolism to the Safety and Efficacy of Prevention of Coronary Artery Disease

There is still concern in the medical and cardiological communities about decreasing plasma cholesterol and its safety. Randomized placebo controlled clinical trials have documented the efficacy and safety of decreasing plasma cholesterol with drugs such as statins[2–4]. The safety and efficacy of lowering plasma LDL-C is not unexpected perhaps when one is reminded of the synthesis and metabolism of cholesterol in the human. Cholesterol is needed to make membranes and hormones. All cells in the body synthesize the cholesterol they need and if more cholesterol is synthesized than needed, it must be removed from the cell[36,37]. If cholesterol accumulates within the cell, it is deleterious and also lethal. The cells cannot metabolize cholesterol so it must be dumped into the circulation for transport to the liver. The liver is essentially the only organ that can metabolize cholesterol and convert it into bile pigments of which the latter is secreted into the intestine to facilitate digestion. Thus, the cholesterol dumped into the blood from the cells is excess cholesterol that is not needed and is essentially garbage being transported to the liver for degradation. Normally, the level of plasma cholesterol is 65-75% determined by one's genes[36,37]. The statin drugs target only the cholesterol derived from genetic control. A statin inhibits the HMGCOA enzyme that is necessary for the synthesis of cholesterol. The enzyme HMGCOA is encoded by a gene and through its expressed protein (the enzyme) regulates the synthesis of cholesterol. It should be understood that although dietary cholesterol under unusual circumstances can greatly increase plasma cholesterol, normally the diet contributes only 25-35% of plasma cholesterol. This is why it usually requires drug therapy in addition to diet to significantly reduce plasma cholesterol.

Lower Is Better but the Precise Plasma Low-Density Lipoprotein Level Is Unsettled

Ference et al[30], summarized 200 studies involving over two million participants experiencing more than 150,000 cardiac events. He observed a consistent dose dependent, log linear association between the plasma LDL-C concentration and the risk of CAD. He concluded the effects of statins on cardiac events or other cholesterol lowering drugs such as PCSK9 inhibitors are due solely to lowering of plasma LDL-C and not due to pleotropic effects[38]. Furthermore the reduction in cardiac events per unit of reduction in plasma LDL-C is virtually identical regardless of the agent used to reduce the plasma cholesterol. However, cardiac events while related to the concentration of plasma LDL-C, are also related to the duration of exposure with the risk of CAD doubling with each additional 10 years of exposure to LDL-C[7]. This increased risk of exposure is corroborated by the effect of LDL-C lowering on cardiac events. Ference et al[8], using Mendelian Randomization showed genetic variants that lower the risk for CAD, randomly assigned at conception, were associated with a 54.5% reduction in cardiac risk for each reduction of plasma LDL-C of 1 mmol (38.7 mg/dl). This is a threefold greater reduction than observed in clinical

trials in whom the average age is in the 50s or 60s. This shows risk from plasma LDL-C is also related to the duration of exposure and early primary prevention is significantly more effective than late primary prevention. There is no agreement on the most effective and safe level of plasma LDL-C[39] but meta-analysis of large clinical trials[4,31,40] showed a reduction in cardiac events at all lower levels of plasma LDL-C without an obvious decrease in safety.

The AHA and ACC clinical guidelines in 2004[41] after the publication of the randomized clinical trial Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT)[42] recommended a plasma LDL-C of less than 70 mg/dl. This was further confirmed by TNT (Treating to New Targets)[43]. The guidelines also stated "lower is better". The European Society of Cardiology (ESC) clinical guidelines[44] recommended much lower plasma levels of LDL-C for secondary and primary prevention with a goal of less than 55 mg/dl for those at high risk for CAD and less than 40 mg/dl for familial hypercholesterolemia. The guidelines state "even lower is better". Clinical trials indicate cardiac mortality and morbidity decrease directly proportional to the decrease in plasma LDL-C from 70-20 mg/dl, and the lower values are equally safe. These results are based on several well designed randomized prospective clinical trials. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)[45] compared Simvastatin alone with Simvastatin plus Ezetimibe. The plasma LDL-C with combination therapy was reduced to an average of 54 mg/dl versus 69.5 mg/dl in the group with Simvastatin alone. There was a significant reduction in cardiac events. The PCSK9 inhibitor trials[46,47] reduced the plasma LDL-C to 30-40 mg/dl and was associated with significant reduction in cardiac events. Giugliano[40] did an analysis of 500 individuals with plasma LDL-C reduced to less than 10 mg/dl and the cardiac event rate was the lowest compared to patients of any greater plasma LDL-C concentration. He also showed a linear reduction in cardiac events is expected all the way to a plasma LDL-C of zero. Thus, prospective clinical trials strongly support a plasma LDL-C of 30-40 mg/dl as significantly more efficacious than 70 mg/dl and equally safe. Despite these results the ACC/AHA guidelines have not changed the therapeutic target established in 2004 of 70 mg/dl. It is expected that the ACC and AHA guidelines will in the next revision recommend plasma LDL-C in the range of 30-40 mg/dl as the new therapeutic target. Plasma levels of LDL-C in the 30-40 mg/dl are considered physiological since they are in keeping with the plasma levels found in newborns[48,49].

We are now entering the era in which comprehensive risk stratification for primary prevention of CAD is possible. Stratification based on environmental, lifestyle, and genetic risk factors is necessary to effectively combat and prevent CAD. Changes in lifestyle and lowering plasma cholesterol have been shown to be effective but are not comprehensively applied. Utilizing the PBS it will be possible to initiate primary prevention in the secondary or third decade of life rather than awaiting for more extensive development of the disease. The recent introduction of a 6 month vaccine with the possibility of an annual vaccine has the potential to also decrease lack of compliance with oral therapy[33]. The combination of genetic risk stratification with conventional risk could transform primary prevention of CAD.

Conclusion

The genetic risk score has been evaluated as a means to risk stratify for CAD in a series of studies involving over one million individuals. The top 20% of the genetic risk score is associated with one to four fold increased risk of CAD. The genetic risk is relatively independent of conventional risk factors and unlike conventional risk factors, can be determined as early as birth. The genetic risk was reduced 50% by drug therapy or a favorable change in lifestyle. The test is inexpensive as are the therapies to prevent CAD. The inclusion of the genetic risk score into routine management of CAD could have a paradigmal shift in the primary prevention of CAD.

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