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Mini review

Genetics - Predisposition and Applicastion to Primary Preventions of CADs

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Abstract

The risk of Coronary Artery Disease (CAD) has been recognized to be approximately 50% due to genetic predisposition and the remainder due to lifestyle and acquired causes. The first genetic risk variant was discovered in 2007 and since that time over 200 genetic risk variants predisposing to CAD have been discovered. These risk variants have been encrypted on to a microarray in preparation for their evaluation as a means to predict one's risk for CAD. The Polygenic Risk Score (PRS) derived from these variants provides a single number for the total genetic risk burden. The PRS has been evaluated in several studies, totaling over 1 million individuals. Individuals categorized as high genetic risk for CAD based on PRS stratification show 2-3 fold increase risk for cardiac events. Retrospective analysis of several clinical trials showed lowering plasma LDL cholesterol is associsated with decreased genetic risk and the frequency of cardiac events. A prospective study showed a favorable lifestyle to be associated with 47% reduction in the high genetic risk group and a similar reduction of 50% from physical activity in another prospective study. The PRS unlike acquired factors is not age-dependent but determined at conception and does not change throughout one's lifetime. The several ethical, legal, and social implications associated with the clinical use of a PRS for CAD is fully discussed. The routine clinical application of the PRS for early primary prevention of CAD has the potential to be a paradigm shift in the prevention of this pandemic disease.

Keywords: ***Cardiovascular genetics, Coronary Artery Disease, Genetic Risk Stratification, Genetics, Genomics, Primary Prevention, Genetic Risk Variants***

Genetic Predisposition and Primary Prevention of CAD

The epidemiology and responsibilities of public health are assumed through various international agencies such as the World Health Organization (WHO) or local national agencies such as the Center for Disease Control (CDC). These organizations play a necessary role in the education and control of pandemic diseases. Most of these diseases are infections, such as the current COVID-19 influenza pandemic. These diseases are contagious and the fear associated with them is rapidly appreciated by the public. It is almost self-evident that if not controlled, such infections can spread to paralyze a nation or even the world as proven by the COVID-19 pandemic. There is another kind of pandemic disease, which by definition, must be widespread and growing but not due to an infectious agent, at least not one we have identified. The best example of this is Coronary Artery Disease (CAD) which is the number one cause of death in the world. This is a disease that is secondary to the effects of living. The disease starts early in life, at least in the second decade in males, and progresses slowly and relentlessly with clinical manifestations (angina, heart attacks, sudden death, and heart failure) occurring in the sixth decade of life for males and about 10 years later for females. The overall incidence of CAD is similar for males and females. It is a disease that affects equally the high, middle, and low-income brackets. It is estimated that 60% of CAD is currently in the low-income population [1]. This is in part because living conditions have improved in developing countries, enabling the population to live long enough to develop the clinical manifestations of CAD while in developed countries, prevention of CAD has greatly improved. In the US, in the past 30 years, morbidity and mortality from CAD have decreased about 50% [2]. The well-developed western countries, which used to harbor most of CAD, have now greatly improved their prevention and treatment programs.

Evidence that CAD is preventable

Coronary artery disease was recognized to be associated with increased plasma cholesterol even in the 1950s. It is well documented in animal studies that cholesterol induces coronary atherosclerosis which is the core culprit leading to the clinical manifestations of coronary artery disease. Extensive

epidemiological studies and in particular the longitudinal studies obtained from the Framingham project [3] indicated several risk factors that enhanced CAD. These factors were enumerated and their association with CAD was confirmed in the '60s. These risk factors included plasma cholesterol, diabetes, diet, smoking, obesity, sedentary way of life, family history, and hypertension. In subsequent decades it was confirmed that reducing the risk of these factors was strongly associated with a reduction in cardiac morbidity and mortality. There was further evidence from experimental and clinical observations that plasma cholesterol was a major culprit in the development of coronary atherosclerosis [4]. In 1994, a randomized, placebo, controlled clinical trial, showed the lowering of plasma cholesterol with Simvastatin was associated with a 30% reduction in cardiac mortality [5]. Since 1994, multiple randomized clinical trials have been performed, and results consistently show that the lowering of plasma cholesterol is associated with a 30-40% reduction of cardiac morbidity and mortality [6]. Studies reducing other risk factors such as hypertension or smoking are consistently associated with reduced cardiac morbidity and mortality [7]. The efficacy and safety of statin therapy to reduce plasma low-density lipoprotein cholesterol (LDL-C) has been well documented in recent meta-analyses [8,9].

Genetic predisposition

It has been claimed by epidemiologists for several decades that about 50% of the predisposition for CAD is genetic. This genetic predisposition has been postulated for many other common chronic diseases such as diabetes type II, and hypertension. The studies documenting genetic predisposition have come in large part from the studies of identical twins and family histories of individuals manifesting CAD [10,11]. In a study performed in Iceland, it was estimated that 15% of myocardial infarctions were explained by family history unrelated to other conventional risk factors [12]. The powerful influence of heredity factors was also displayed in a Utah study in which 14% of the population had a family history of heart disease. In this cohort, 72% of all premature myocardial infarctions and 48% of all coronary events occurred [13]. First-degree relatives with CAD are associated with a 2-3 fold increase in the risk for CAD [14,15]. In the Interheart study, a family history of CAD was associated with a 55% increased risk and 45% after correction for other risk factors [16].

Genome-Wide Association Studies

Pursuit of the DNA variants that transmit the genetic risk for CAD has been elusive until recently. The technology necessary to pursue an unbiased approach was lacking until about 2005 [17]. It has also been the hypothesis of both the epidemiologist and the geneticist that genetic predisposition for such common disorders would be associated with genes that occur commonly and each variant would be associated with only minimal risk. The genetic burden of risk for CAD would be transmitted by multiple variants rather than any single risk variant. It was also hypothesized that these variants would be distributed throughout the human genome. It was realized in the 90s that genetic linkage analysis, which had been so successful in discovering genes responsible for single-gene disorders, would not be appropriate for these common polygenic disorders such as CAD. Instead of requiring a few hundred DNA markers, it would require thousands and perhaps hundreds of thousands of markers spanning the whole human genome. The preferred marker would be single nucleotide polymorphisms (SNP's) because they are polymorphic and distributed throughout the genome. Millions of DNA markers in the form of SNPs became available due to the successful efforts of HapMap [18] to annotate the location of these SNPs throughout the human genome. This enabled investigators to use DNA markers spanning the whole genome at high density. This provided the first opportunity to pursue Case-Controlled Association Studies involving the whole of the genome, referred to as Genome-wide association studies (GWAS). The basic approach is genotyping thousands of cases with CAD and thousands without CAD (controls) using millions of SNPs as DNA markers. If the frequency of a particular SNP was more common in the cases than controls, it would be interpreted to be a risk factor or in close proximity to sequences that predispose to the disease. However, since one was using a million markers, if one used a p-value of .05, it would lead to approximately 50,000 false positives. To minimize false positives it was agreed to adopt the Bonferroni statistical correction, requiring a p-value of 10^-8. Utilizing this approach, we [19] and 2 other groups [20,21] independently and almost simultaneously identified the first genetic risk variant for CAD, now referred to as 9p21. This would be the first additional risk factor for CAD to be discovered since the 1960s. A single copy of the 9p21 risk variant was associated with a 25% increased relative risk for CAD and as expected, it is very common, occurring in more than 75% of the world's population. The risk mediated by the 9p21 risk variant for CAD was shown to be independent of all known conventional risk factors, such as hypertension or cholesterol. The features of 9p21 as a genetic risk variant for CAD strongly supported our original hypothesis that each variant was associated with only minimal risk for CAD and occurred in a large proportion of the population. The risk mediated by the 9p21 risk variant for CAD is independent of known risk factors providing further encouragement to pursue the genetic variants with the hope that someday comprehensive prevention would be available by modifying both acquired and inherited risk factors.

Investigators across the world merged their resources in pursuit of genetic risk variants for CAD, led by the international consortium CARDIoGRAMplusC4D [22]. Within a decade of discovering 9p21, hundreds of genetic risk variants for CAD were discovered and confirmed in independent populations. These discoveries are detailed in several recent comprehensive reviews [23-26].

Development and evaluation of the PRS

The discovery of genetic risk variants for CAD significantly elucidated our understanding of the genomic architecture predisposing to CAD. The development of a genetic risk score based on the risk variant for CAD and its application for risk stratification in selecting individuals at risk for CAD was self-evident and one of the earlier goals. The total genetic risk for CAD can be expressed in a single number taking into account the percent risk associated with each variant and the number of genetic risk variants inherited by the individual. The genetic risk of a polygenic disease which by definition is due to many genetic risk variants is referred to as the Polygenic Risk Score (PRS). In an initial study assessing the power of the genetic risk score, we utilized only 12 genetic risk variants which showed only a slight improvement over that of traditional risk factors [27]. As more risk variants became available, the risk stratification power of the PRS increased. Early studies took advantage of the availability of samples from previous clinical trials assessing the effect of lowering plasma LDL-C on cardiac events. Retrospective genotyping of samples was performed on randomized clinical trials (JUPITER, ASCOT,

CARE, and PROVE-IT-TIMI) with a sample size of 48,421. The PRS was determined based on 27 genetic risk variants and was shown to be more powerful than that of the Framingham risk score or that of the Pooled Cohort Equation (PCE) [28]. A similar analysis was performed in the West of Scotland Coronary Prevention Study (WOSCOP) [29], those with the highest PRS had a reduction of risk of 44% associated with statin therapy, compared to a risk reduction of only 24% in others. Two recently randomized clinical trials assessing the effect of (FOURIER and the ODYSSEY Outcomes Trial) PCSK9 inhibitors to lower plasma LDL-C also underwent genetic risk stratification based on a PRS calculated from a microarray of 6 million risk variants predisposing to CAD. FOURIER [29] had a sample size of 27,564 and showed that those with the highest risk for CAD had the highest PRS and received the most benefit from statin therapy. In the ODYSSEY Outcomes Trial [30], with a sample size of 18,924, the group with the highest PRS treated with Alirocumab had a reduction in cardiac events by 37% vs 13% reduction in those with a low PRS. All of these studies mentioned above performed to lower plasma LDL-C showed the PRS to be superior and relatively independent of the conventional risk factors.

In a study of five prospective cohorts by Abraham et al. [31] with a sample size of 16,082, the GRS was superior to traditional risk factors (TRF) and also relatively independent of TRF. Inouye et al. [32] genotyped a population of 500,000 from a UK biobank and observed that the top 20% had a 4 fold increased risk for CAD. In a separate study, Khera et al. [33] observed in 288,978 individuals that 8% of the population with the highest PRS had a 3-fold increased risk for CAD, and the top 5% had a 5-fold increased risk for CAD. The investigators point out that this high-risk group would in large part not be detected by conventional risk factors. In the high PRS group, only 20% had familial hypercholesterolemia, 28% had hypertension, and 25% had a family history of CAD. This group of investigators concluded the genetic risk score is superior to scores based on conventional risk factors.

Genetic Risk is reduced by Lifestyle Changes and Plasma Cholesterol-Lowering Agents

It is often stated that if it is in your genes, one cannot do anything about it. This of course is a myth. We have treated heart disease effectively for decades, whether it is due to genetic predisposition, acquired predisposition, or both. Statins inhibit the rate-limiting enzyme for the synthesis of cholesterol and are only effective against the genetic risk induced by the synthesis of cholesterol. The synthesis of cholesterol is controlled by your genes. A recent study [34] compared a favorable lifestyle with an unfavorable lifestyle with a sample size of 55,685. A favorable lifestyle consisted of no smoking, a healthy diet, no obesity, and routine exercise. An unfavorable diet had at least two unfavorable features such as smoking or obesity. The group with the highest PRS in the favorable lifestyle had 46% fewer cardiac events than the group with an unfavorable lifestyle. Analysis showed individuals in the top 20% of the PRS had a 90% higher risk of cardiac events than in the remainder of the sample.

Tikannen, et al. [35] used a sample size of 468,095 from the UK biobank and showed regular physical activity decreased cardiac events by 49% in the group with the highest PRS. The group with the highest number of cardiac events had the highest PRS.

Legal Ramifications of a Polygenic Risk Score

Clinical use of a PRS-CAD test introduces several practical considerations with ethical, legal, and social implications. In particular, genomic testing of seemingly healthy individuals to identify who has an elevated risk of developing certain diseases will be a seismic shift for advancing preventative medicine but it brings with it a host of ethical and legal concerns that will affect society on a large scale as the technology to establish a genetic profile of individuals based on PRS estimates becomes increasingly prevalent.

Many issues are similar to those raised by traditional genetic testing practices for a single mutation of a disease-associated genetic sequence (eg a monogenetic disease associated with a single base-pair mutation) but in a different context and on a far greater scale. Genomic testing, more so than a single genetic test, could reveal unexpected results (eg secondary or incidental findings) for other diseases, including those not anticipated, specifically ordered, or discussed with the patient. These need careful interpretation through expert mediators or genetic counselors and a decision needs to be made whether or not these findings should be communicated to the patient and any potentially affected family members. These are not new issues but will reinvigorate debates addressing these issues now anticipated to occur by an exponential factor for PRS-testing [36].

A PRS-test for CAD, whether integrated with existing tools such as QRISK or standalone, is not yet available. However, commercially available PRS tests for other diseases do exist through Ambry Genetics for breast and prostate cancer risk, Myriad Genetics for breast cancer, and 23andMe for type 2 diabetes risk [37]. Several companies will produce “polygenic reports” based on a user’s upload of their 23andMe or Ancestry.com data. In the UK, a pilot study for PRS-CAD was initiated 2021 by Genomics Plc and the National Health Services. A US trial will soon be initiated through a partnership between Dignity Health Hospital and Baylor College of Medicine.

In the US fears of genetic discrimination by employers and insurers led to the passage of a federal law called the Genetic Information Nondiscrimination Act (GINA) which makes it illegal for health insurance providers and employers to use genetic information. This means that health insurance companies cannot use the results of a direct-to-consumer genetic test (or any other genetic test) to deny coverage or require you to pay higher premiums. Under Title II of GINA, it is illegal to discriminate against employees or applicants because of their genetic information or that of their family members [38]. GINA applies only to asymptomatic individuals. It was not until 2010 that Congress prohibited all health-based discrimination in health insurance when it enacted the Affordable Care Act.

However, several caveats significantly dilute these protections. For example, GINA does not apply when an employer has fewer than 15 employees and does not apply to funding, education, or any other type of insurance (eg other than standard health insurance), such as disability insurance, long-term care insurance, or life insurance. Although some states have additional legislation, almost all of these states allow insurance underwriting based on genetic information if the findings can be sufficiently associated with higher mortality or morbidity [39,40]. Most notably, GINA is enforceable only by the US government, the Human Health Services Office for Civil Rights, and does not create a private right of action that can be brought by individuals whose data are disclosed [41]. Lastly, GINA brings genetic information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) privacy protections but this general health information privacy act only applies to certain entities and transactions leaving

many situations where genomic PRS results may be used, shared, or required/stored to fall outside its remit. These examples illustrate just a few of the ways the current US protections inadequately address the contemporary use of genomic PRS testing.

It is unclear whether genetic information, including the results of any direct-to-consumer or clinically, offered genomic PRS-testing, will become a standard part of the risk assessment that some insurance companies, small company employers, lenders, or educators undertake when making decisions that affect the opportunities they will extend to that individual and at what cost. Survey evidence of participants in clinical trials indicates that many people will avoid learning about their genetic health risks for fear that their results could be used against them in the future such as by employers or for certain types of insurance pricing or availability.

A key focus globally has been concern over the heterogeneity of quality of genomic services offered to the public. PRS models vary and some services are not transparent on how these scores are calculated. Many governments have focused on the need to establish a direct-to-consumer genomic testing regulatory framework.

Two papers in 2021, one presenting a standards framework, the other a catalog of published PRS models, aim to address these issues with guidance on how to describe PRS models and a repository which researchers can search and compare the various models available to determine which is best suited for a particular clinical need and support translation into clinical practice [42-44]. The UK Parliament also published a comprehensive report in June 2021 on the regulation of direct-to-consumer genomic testing with legislative recommendations [45]. The protections developed in the UK and EU may serve as a useful example to the US and other nations.

Historically, most national regulations focus on anti-discrimination measures based on health data, and many agreed on voluntary industry moratoriums against the use of this data. However, in 2018 the General Data Protection Regulation came into force across the European Union and the UK providing privacy and data protection rights that would extend to genetic information and provides individuals with a mechanism of enforcement. Furthermore, in the EU, on 26 May 2022, a new In Vitro Diagnostic Medical Device Regulation will apply to PRS-genomic tests and require safety and efficacy standards to be met before a test may be provided to the public or patients. These go some distance in a more general sense to improve protections but still have further to go to adequately address the specific issues involved with PRS-genomic testing.

Previously, a UK Code on Genetic Testing and Insurance was published in October 2018, replacing the Concordat and Moratorium on Genetics and Insurance which had been in place since 2001 and 2005 respectively [46]. The code is a voluntary agreement between the government and the Association of British Insurers (ABI) that insurers will never require or pressure any applicant to undertake a predictive or diagnostic genetic test, and only consider the result of a predictive genetic test for an exceptional minority of cases. To date, there is only one approved relevant predictive genetic test for Huntington's disease permitted in applications for life insurance cover which total over the financial limit of £500,000.

The UK Equality Act 2010 restricts employers in a pre-employment context from relying on genetic or genomic testing results. It means that employers can only ask for information that is directly relevant to the applicant's ability to carry out the work, or needed to make 'reasonable adjustments to the workplace to enable a particular person to work there as required under the law (see Joint Statement of Concern 2006) [47].

A critical concern specific to genomic testing that remains is one of equity and access. At the moment clinical use of a PRS-CAD test disproportionately benefits those of European ancestry and is less useful for people of minority demographics. Rather than restricting their use to those of certain ancestry, such as done by Ambry Genetics which restricts the prostate cancer test to males of European ancestry and their breast cancer test to females of Non-Ashkenazi Jewish, Northern European ancestry, there is hope this situation improves as initiatives targeting recruitment of racial and ethnic minorities. For example, the NIH funded the "All of Us" program, which aims to recruit more than 45% of its one million participants from racial and ethnic minorities [48]. Improving the equity of genomic testing will of course not alter structural or systemic challenges of access to these tests.

Upon consideration of the current landscape of genetic privacy, existing legal measures provide inadequate protection and fail to offer individuals meaningful control over genetic information disclosures that may affect their lives. Individual rights and public health and social goods will increasingly need to be balanced.

Given that PRS-genomic testing services are already commercially available and the speed at which the science is advancing, the one certainty is that best practices need to be developed around this emerging branch of genomics.

Significantly more needs to be implemented to address these issues in terms of privacy and data protection, access, equity, and ownership. A regulatory inter cooperative international framework is needed to better guide these actions and the options available, including more comprehensive anti-discrimination measures and protections against surreptitious testing. The challenge will be establishing regulatory guidelines for how PRS should be used and the conditions for access.

The Advantage of the PRS over Conventional Risk Factors

The PRS has now been evaluated in over 1 million individuals and in almost all of the studies it has shown genetic risk stratification for CAD is superior to risk stratification based on conventional risk factors. The PRS was also shown to be relatively independent of conventional risk factors. Comprehensive risk stratification for CAD would benefit from utilizing both the PRS and the risk due to conventional risk factors.

The major advantage of the PRS as a means of risk stratification for CAD is its independence of age. One's genetic risk is determined at conception and does not change throughout one's lifetime. Thus, the PRS for CAD enables one to determine the genetic risk anytime from birth onwards. Genetic risk has also been shown to be reduced by plasma LDL-C lowering agents as well as favorable lifestyle changes. The TRFs are very dependent on age which is a significant disadvantage when selecting patients for early primary prevention of CAD. As illustrated in figure 1 many of the TRFs are not manifested until the fifth, sixth, or even the seventh decade and thus not amenable to primary prevention. Risk stratification for primary prevention of CAD in the male population will probably require primary preventive measures to be initiated in their 20s, while females, afforded by protection from their hormones, could be initiated as late as the fourth or fifth decade.

While traditional risk factors are not manifested until later in life, this does not apply to the main culprit risk factor of plasma LDL-C [49,50]. The male population in the U.S., in their 30s, has an average plasma LDL-C of 140 mg/ dL which is almost twice the recommended level of 70 mg/ dL. The average LDL-C in a female in her 40's is 121 mg/dL, which is also markedly increased over that of the recommended 70 mg/dL. One might argue, why not treat everyone with an increased plasma LDL-C with lifestyle changes and statins if necessary? However, epidemiologist studies document repeatedly that only about 50% of individuals [1] will experience a cardiac event in their lifetime, thus, half of the individuals would be receiving unnecessary therapy, along with the cost and potential side effects. The combination of risk stratification for CAD based on the PRS would be expected to detect those individuals at highest risk and be among that 50% that is vulnerable.

The Current Clinical Cardiology Practice Guidelines (CCCPG) are less than desirable for risk stratification in applying primary prevention of CAD. The authors of the guidelines, in an attempt to avoid treating everyone swith an elevated LDL-C, developed the PCE technique to estimate their 10-year risk for CAD. Someone in their 40s with the only risk factor of plasma LDL-C would be calculated to have a PCE of 2.2%. The cutoff for the PCE ten-year risk for primary prevention is ≥7.5%. For example, a female aged 40 with a plasma LDL-C of 80 mg/dL would have a 10-year risk of 2.2% and thus not qualify for preventive measures. Utilizing the PRS for risk stratification would identify genetic risk factors in addition to the increased plasma LDL-C, enabling primary prssevention to be initiated in those at highest risk before the development of significant CAD. The recent guidelines encourage the use of novel means, referred to as enhancers to improve risk stratification for CAD. The use of the PRS would be analogous to the recent use of the Coronary Calcium Score as an enhancer to detect an increased risk for CAD. The PRS would be effective in idsentifying those at the highest genetic risk who would benefit most from early primary preventive measures. The PRS is expected to improve with the discovery of additional risk variants particularly those unique to certain ethnic, geographical, and racial groups. We believe this discovery effort along with its practical evaluation would benefit from being integrated into clinical application.

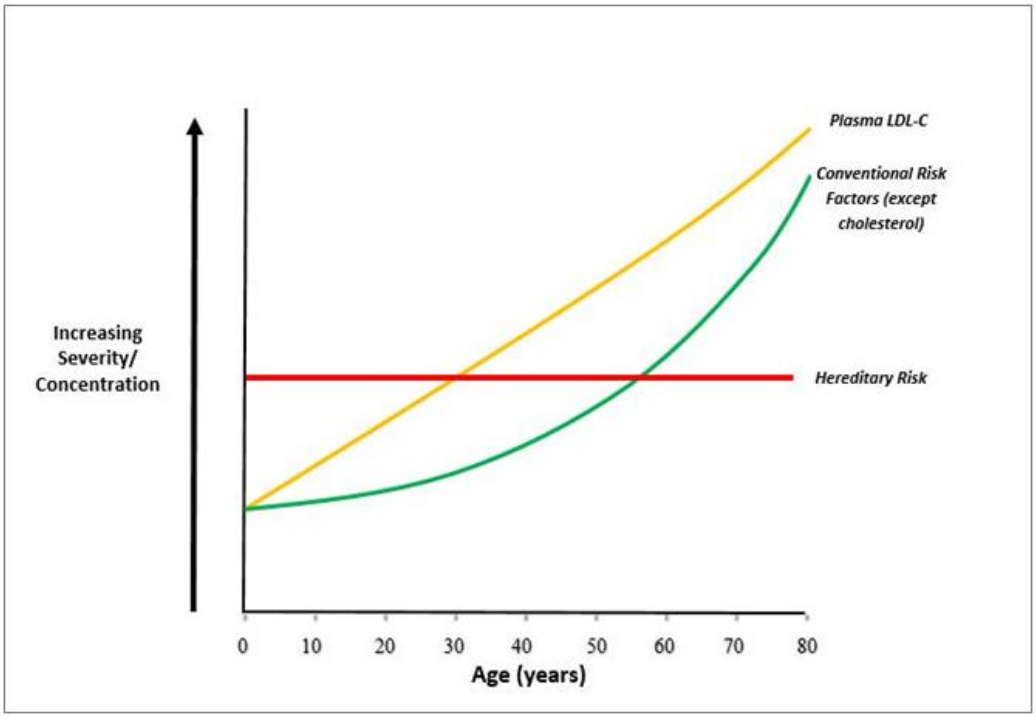

Figure 1: Traditional Risk Stratification for CAD vs Genetic Risk

Legend: Conventional risk factors (green) including age, hypertension, or diabetes are not prevalent until the fifth or sixth decade. Plasma LDL-C (orange) is an exception, increasing early in ones life. The risk for CAD doubles approximately every additional 10 years of exposure to cholesterol. The genetic risk (red) for CAD remains constant throughout one's lifetime and is independent of age. Thus, genetic risk can be calculated at any time after birth and as a risk stratifier for CAD, it provides an advantage in selecting individuals for early primary prevention over that of age-dependent conventional risk factors.

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Conflicts of Interest

Dr. Roberts is a consultant to Cumberland Pharmaceuticals. There is no conflict of interest with this manuscript.

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Authors' contributionss

RR and AM are the main authors of the manuscript. JF and DM researched references and were responsible for the development of the figure. All authors read and approved the final manuscript.

Abbreviations

JUPITER: Justification for the Use of statins in primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial
ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial
CARE: Cholesterol and Recurrent Events
PROVE-IT-TIMI: the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis FOURIER Further Cardiology Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
CARDIoGRAMplusC4D: (Coronary ARtery DIsease Genome-wide Replication and Meta-analysis (CARDIoGRAM) plus The Coronary Artery Disease (C4D) Genetics) consortium
PCSK9: Proprotein convertase subtilisin/Kexin type 9

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