REVIEW ARTICLE

The Inherited Basis of Coronary Artery Disease

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SUMMARY

Investigations of the genetic basis of coronary artery disease have led to advances in mechanistic insights, therapeutics, prevention, and risk prediction. Indeed, most contemporary medicines for coronary artery disease target pathways that promote atherosclerosis due to underpinning genetic mechanisms. Monogenic causes of coronary artery disease occur in approximately 1 out of 250 people and mostly result in massively elevated lipid levels. At the population level, hundreds of common variants with small effect sizes have even greater influence. They can be combined in polygenic risk scores that depict genetic risk in a person relative to the average in the general population. The risk among persons in the highest 5% is 3 to 5 times that among persons with an average score; relative risk derived from the polygenic risk score can be used to multiply the absolute risk derived from a clinical risk score. Key questions remain regarding the clinical value, cost-effectiveness, and implementation strategies required to integrate coronary artery disease polygenic risk scores into clinical practice.

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CME

Coronary artery disease develops from an interplay of behavioral, environmental, genetic, and stochastic factors. Smoking, hypertension, hyperlipidemia, and diabetes mellitus are well-recognized modifiable risk factors for coronary artery disease, which affects almost 1 in 2 men and 1 in 3 women during their lifetime.[1] More than a century ago, Osler posited that inherited factors may cause coronary artery disease after he observed that angina pectoris often clusters in families.[2] Approximately 30 years ago, twin studies indicated that the heritability of fatal coronary artery disease was as high as 50%.[3] Since 2007, large-scale genotyping and gene-sequencing studies have identified hundreds of genetic variants associated with increased susceptibility to coronary artery disease (Fig. 1 and interactive graphic). Protein products of some associated genes already constitute effective treatment targets, and other genes point to currently unexplored disease mechanisms.[8,9]

An inquiry about a family history of coronary artery disease is routine in the clinical assessment of patients presenting with chest pain syndromes. Here we review recent discoveries regarding the molecular genetic origins of coronary atherosclerosis and discuss current and potential clinical uses of this information.

MONOGENIC FORMS OF CORONARY ARTERY DISEASE

The archetypal molecular genetic cause of coronary artery disease is familial hypercholesterolemia, an incompletely dominant monogenic condition.[10] It was first described by Müller in 1938 and remained the only proven genetic cause of coronary

artery disease for approximately 70 years.[11] Familial hypercholesterolemia is found in approximately 4 of every 1000 people who are heterozygous for the disease and in approximately 1 of every 200,000 people who are homozygous for the disease. By their mid-forties, approximately 20% of persons with heterozygous familial hypercholesterolemia have atherosclerotic conditions.[12] Causative genetic variants for familial hypercholesterolemia typically lead to diminished function of low-density lipoprotein (LDL) receptor,[10] altered function of apolipoprotein B, or enhanced function of proprotein convertase subtilisin/kexin type 9 (PCSK9).[9]

Familial hypercholesterolemia is suspected when LDL cholesterol levels are severely elevated (in adults, >190 mg per deciliter [4.9 mmol per liter]; in children, >150 mg per deciliter [3.9 mmol per liter]). The clinical suspicion is particularly strong when these elevations occur in conjunction with a personal or family history of premature coronary artery disease, xanthelasma, or tendon xanthomas; these disorders are given the most weight, after severely elevated LDL cholesterol levels, in clinical scoring systems for familial hypercholesterolemia.[13] The prevalence of pathogenic variants is approximately 0.4% in the general population and approximately 3.5% in persons with LDL cholesterol levels that exceed 190 mg per deciliter.[14,15] Among persons in whom additional findings suggest probable or definite familial hypercholesterolemia, variants are detected in 5% and 24%, respectively.[15]

Establishing the molecular genetic diagnosis of familial hypercholesterolemia has implications, since even at similar LDL cholesterol levels, persons with a familial hypercholesterolemia–defining variant have a risk of coronary artery disease that is 2 to 3 times that among persons who do not have such a variant.[14,15] Moreover, the benefit of LDL cholesterol lowering is even greater in persons with genetically proven familial hypercholesterolemia[16]; this benefit is reflected in society guidelines that recommend lower LDL targets than those for primary prevention among patients with nonfamilial hypercholesterolemia.[13] Unfortunately, genetic assessment of familial hypercholesterolemia is underused worldwide, which results in missed opportunities to implement guideline-recommended cascade screening in first-degree relatives. Population screening for familial hypercholesterolemia in children is currently being analyzed in order to mitigate the risk of coronary artery disease through early preventive treatment.[17,18]

Other monogenic forms of coronary artery disease are very rare and account for only a small fraction of the overall high prevalence of the disease. Autosomal recessive conditions, such as autosomal recessive hypercholesterolemia (caused by variants in *LDLRAP1*),[19] sitosterolemia (*ABCG5* and *ABCG8*),[20] and pseudoxanthoma elasticum (*ABCC6*),[21] are often associated with premature coronary artery disease. Rare variants in genes involved in the nitric oxide pathway (*GUCY1A1* and *PDE5A*),[22,24] triglyceride regulation (*APOA5*),[23] and cholesterol transport (*SCARB1*)[25] have also been linked to premature coronary artery disease. Clinically significant variants in these genes might be considered in expanded panels for molecular genetic evaluation, along with the variants in the usual genes associated with familial hypercholesterolemia — *LDLR*, *APOB*, and *PCSK9*.

An interactive graphic is available at NEJM.org

POLYGENIC CONTRIBUTION TO CORONARY ARTERY DISEASE

Whereas rare damaging variants, such as those in *LDLR*, can profoundly impair health in affected persons, common risk alleles with small effects appear to be more relevant at the population level. In the 1950s, Platt and Pickering argued about whether hypertension is inherited in a monogenic or polygenic fashion. Subsequently, mathematical modeling indicated that multiple common risk alleles with small effects result in more cases of hypertension than do rare variants with strong effects.[26]

Genomewide association studies of coronary artery disease have validated this hypothesis.[27,28] Genotyping arrays assess alleles of hundreds of thousands of single-nucleotide polymorphisms (SNPs) in parallel and, combined with statistically imputed, nongenotyped SNPs, enable efficient genomewide genotyping of common variants. Genomewide association studies compare allele frequencies of each SNP between affected and unaffected persons. To account for multiple testing, a stringent P value of less than 5×10^{-8} establishes genomewide significance. The latest meta-analyses of genomewide association studies included more than 180,000 persons with coronary artery disease and more than 1 million persons in total,[4,5,29] yielding 346 risk regions of genomewide significance, also referred to as loci (Fig. 1 and interactive

graphic).[6] Many more associated variants are predicted to exist. Specifically, risk alleles with lower frequencies,[6] markedly varied frequencies globally, or smaller effect sizes will require even larger and more diverse cohorts to be identified.[4,29] Large-scale sequencing studies may help to fill this gap. It is remarkable that these genetic alterations affect genes that are expressed in a wide spectrum of tissues and cell types, which jointly contribute to the susceptibility of persons to coronary artery disease (Fig. 2). The findings that have emerged from these discovery efforts are being applied in two key areas: prediction of cardiovascular risk and advancement of therapeutic developments.

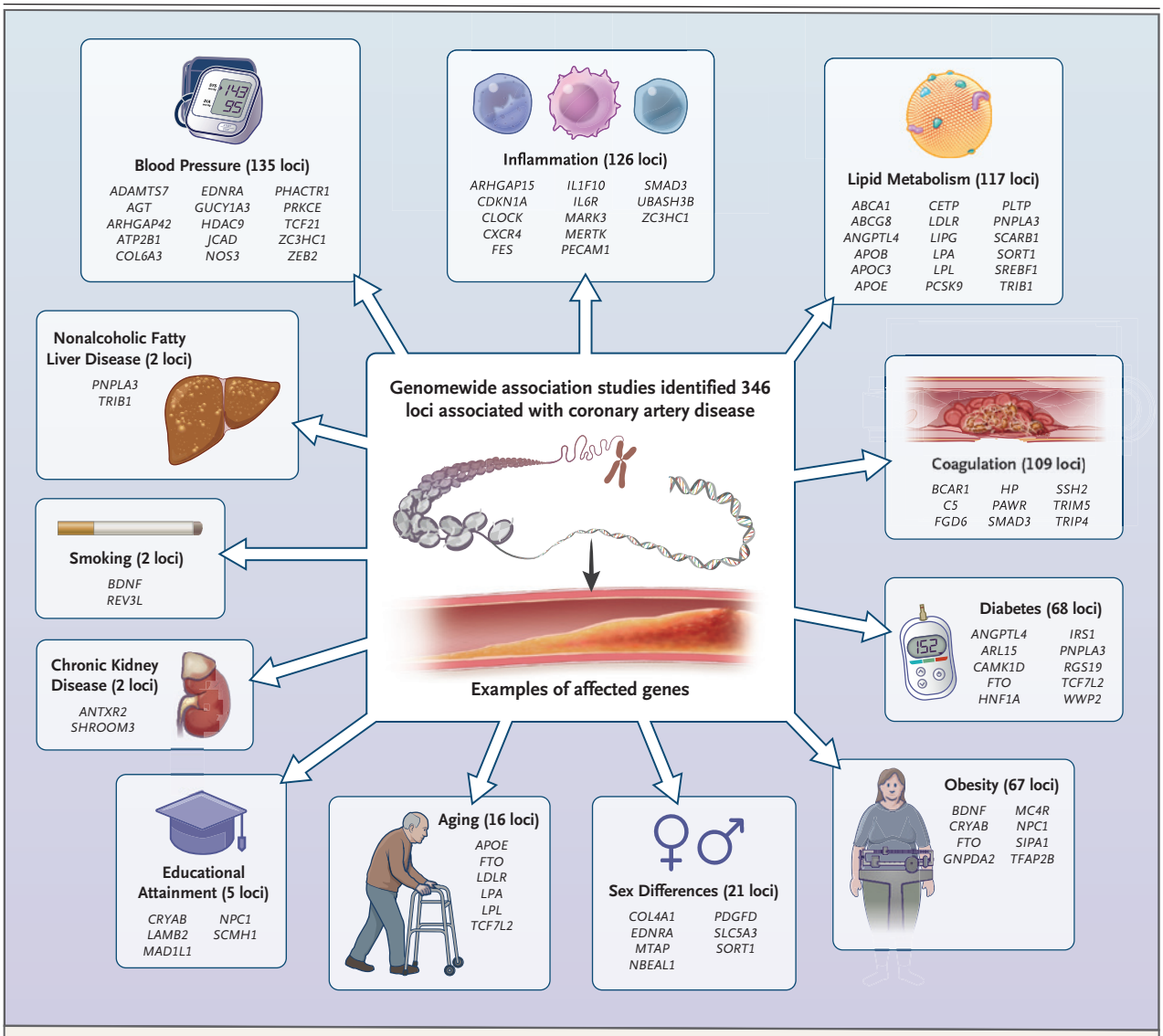

Figure 1. Genomic Loci Associated with Coronary Artery Disease.

Genomewide association studies have shown 346 genomic loci with significant associations with coronary artery disease.[4-7] The figure shows, for some of these loci, the causal genes that have also been found to be significantly associated with established risk factors, risk modifiers, and clinical conditions related to the disease. The total numbers of loci with genomewide signals for both coronary artery disease and the respective traits are shown in parentheses (some loci are significantly associated with several traits). A total of 76 risk loci have no association with these traits; the mechanisms underlying the respective associations with coronary artery disease are yet to be discovered. All 346 candidate genes — or, for loci with uncertain candidate genes, the lead single-nucleotide polymorphisms — are shown in the interactive graphic. Additional information can be found in the Supplementary Appendix, available with the full text of this article at NEJM.org.

PREDICTION OF CARDIOVASCULAR RISK

CLINICAL RISK ASSESSMENT

Calculation of risk scores that integrate clinical factors is recommended for persons without known coronary artery disease in order to identify those who are at sufficiently increased risk for atherosclerotic cardiovascular events to merit preventive therapies.[35,36] These risk estimates are strongly influenced by chronological age, which results in a lower chance of identifying younger persons at high risk.[35,36] Despite the recognition of a family history of coronary artery disease as a major risk factor, this information is not included in current clinical risk

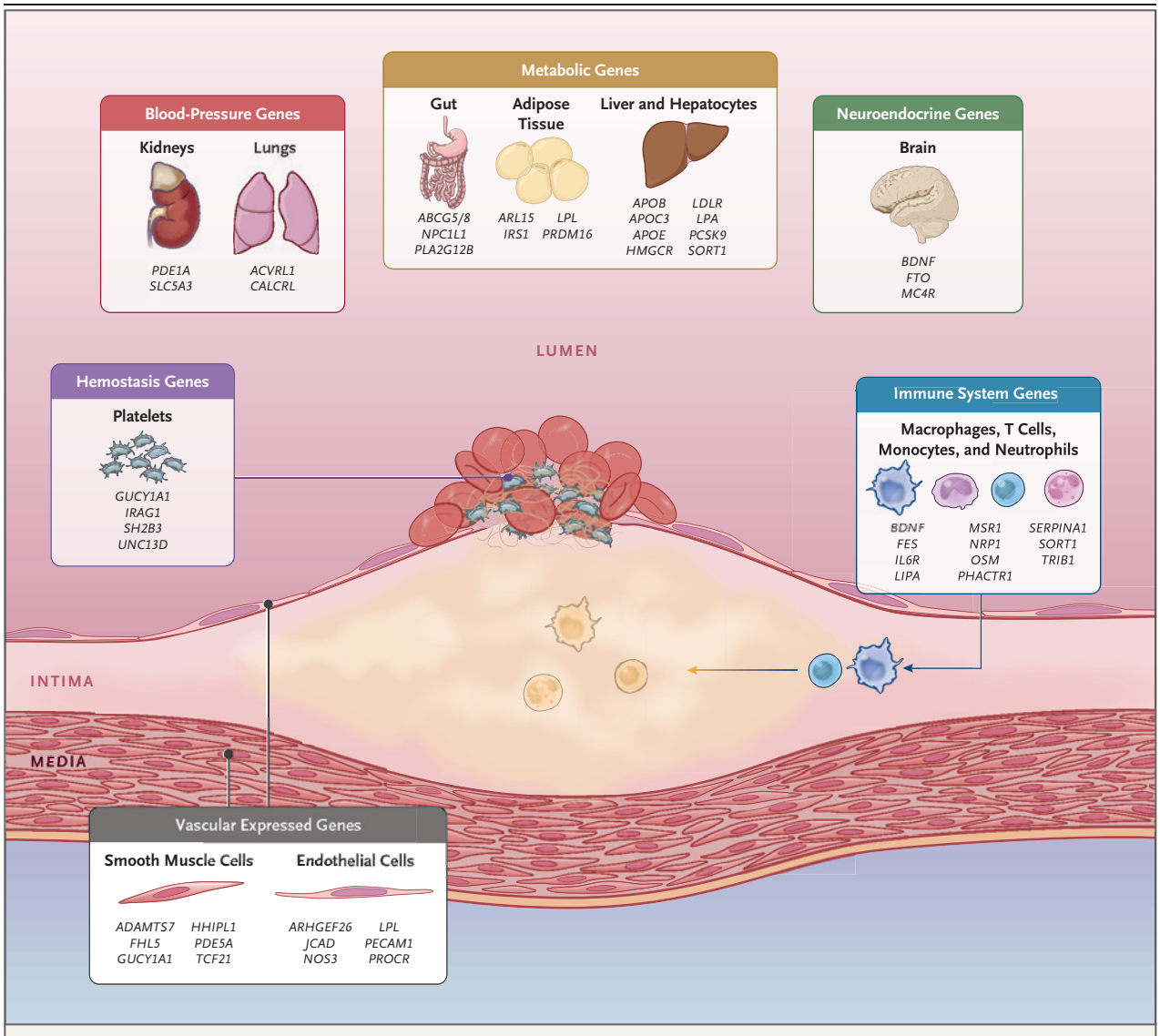

Figure 2. Expression Sites of Genes Affecting Risk of Coronary Artery Disease.

The tissues and organs that most abundantly express genes affecting the risk of coronary artery disease are shown, as are genes at a genomewide level that are significantly associated with coronary artery disease and exemplify those with high tissue-specific expression. The arterial wall is shown at the center, with the key cellular contributors to atherosclerosis highlighted. Additional organs and tissues that are relevant to the pathophysiology of coronary artery disease are shown above the arterial wall. Gene expression was identified with the use of the Human Protein Atlas and was cross-validated with data from the Genotype-Tissue Expression (GTEx) project, STARNET, and the literature.[4,5,7,29-34] Additional information can be found in the Supplementary Appendix.

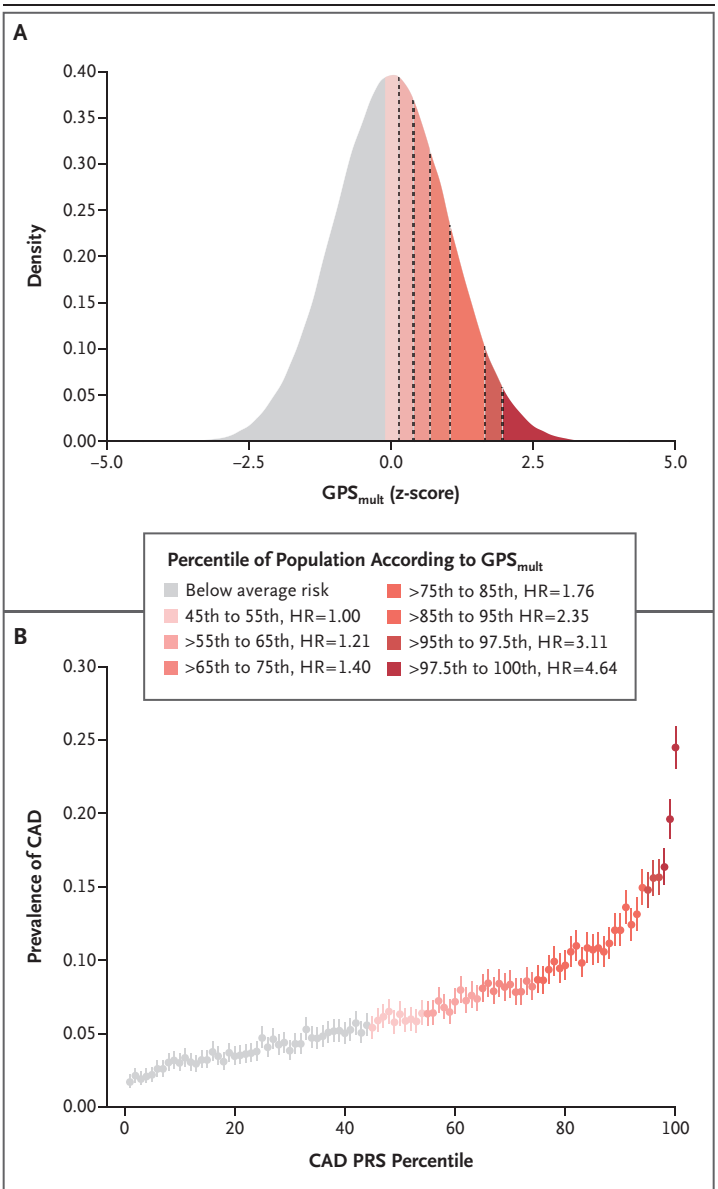

Figure 3. Polygenic Risk Scores (PRSs) for Coronary Artery Disease (CAD).

Each person inherits hundreds of coronary artery disease risk alleles through a play of chance. The numbers of risk alleles carried by persons within a population are distributed under a gaussian curve, as shown in Panel A. Density (y axis) corresponds to the number of observations per GPS_{mult} standard deviation, adjusted for sample size, so that the total area equals one. GPS_{mult} refers to a previously published polygenic risk score for coronary artery disease.[37] Hazard ratios (HR) for coronary artery disease are shown for persons with a PRS above the mean. Panel B shows that although individual risk alleles have small effects, they act multiplicatively, resulting in an exponential increase in risk.[28] Data in both panels are from the U.K. Biobank.

scores because it does not provide sufficient additional discrimination.

POLYGENIC RISK ASSESSMENT

The small effect sizes of coronary artery disease risk alleles are individually not useful for prediction. However, the aggregated information in a polygenic risk score provides the opportunity to refine risk prediction. Independent inheritance of the many common risk alleles results in a gaussian distribution of the polygenic risk score for coronary artery disease in the general population (Fig. 3A). The risk for persons in the top 5% of the distribution is 3 to 5 times as high as that among persons in the middle quintiles of the population (Fig. 3B),[37] a finding that is independent of status with respect to a family history of coronary artery disease.[38] Since variants of genomewide significance (Fig. 1 and interactive graphic) represent only a small fraction of the true number of variants associated with a disease, the current polygenic risk score includes all informative genetic variants, each having small associations with coronary artery disease or stroke, to predict the full genetic predisposition. With increasingly large and diverse genomewide association studies and new methods, the performance of successive polygenic risk scores continues to improve.[39]

COMBINED CLINICAL AND POLYGENIC RISK ASSESSMENT

The polygenic risk score for coronary artery disease is most informative when a baseline clinical risk assessment has been performed.[39] The relative risk derived from the polygenic risk score can be used to multiply the absolute risk derived from a clinical risk score.[40] Accordingly, if the clinical risk is small, then the implications of a polygenic risk score for coronary artery disease are small as well.[39,41] For example, across U.K. Biobank participants who were 45 to 70 years of age, assessment of the polygenic risk score showed that it would prevent only 1 coronary artery disease event for every 5750 persons screened.[42] The diagnostic yield of a high polygenic risk score may be greater when a family history of coronary artery disease is present.[44] Likewise, among persons with an intermediate clinical probability of myocardial infarction or stroke (i.e., 5 to 10% within 10 years), the

polygenic risk score for coronary artery disease puts 10% of these persons in the high-risk category, with twice the risk of a cardiovascular disease event, as compared with those who were not considered to be at high risk on the basis of the polygenic risk score (Fig. 4A).[40] Such a strategy could prevent 1 additional cardiovascular disease event for every 340 persons screened, or approximately 7% of all events.[42]

Use of a polygenic risk score as a means of improving clinical risk assessment harmonizes with current guidelines, which suggest the use of additional factors to further define personalized risk. The guidelines may already inform clinicians about appropriate actions, including further diagnostic tests (e.g., coronary calcium screening) or the preventive use of lipid-lowering therapy for persons moved to a high-risk category, such as those with a high polygenic risk score.[45] Retrospective analyses of randomized trials have shown consistently that persons with a high polygenic risk score for coronary artery disease have a greater absolute and relative benefit from lipid-lowering therapy than those with an average polygenic risk score (Fig. 5). In a single-site, randomized trial involving adults at intermediate risk for coronary artery disease, disclosure of the polygenic risk score led to a reduction in major adverse cardiovascular disease events over a period of nearly 10 years.[48]

Another population in which the polygenic risk score for coronary artery disease has value is young adults, in whom clinical risk scores are not well calibrated and identify only approximately 1 in 4 persons who go on to have a major cardiovascular disease event.[47] Cohort studies have shown that at the age of 40 years, an average man with no clinical risk factors who is in the highest quintile of polygenic risk scores has a 30 to 40% risk of having coronary artery disease by the age of 70 years, as compared with a 10% risk for a man in the lowest quintile (Fig. 4B). Such information may be relevant to clinical care, since preventive therapies, such as statins, are anticipated to be more effective when implemented earlier in the progression of the disease.[47] Furthermore, the relative contribution of polygenic risk to overall long-term risk is greater earlier in life, when traditional risk factors have a lower prevalence. Lifetime risk models that prioritize preventive therapies on the basis of the polygenic risk score require prospective evaluation.[43,47]

The third population that may benefit from assessment of polygenic risk is persons with premature coronary artery disease, in whom high polygenic risk may have contributed to the disease manifestation and thus can help clarify the cause. In such patients, a high polygenic risk score is predictive of recurrent events, albeit less so than in the context of primary prevention.[32,33] Although the clinical actionability of a high polygenic risk score in patients with established coronary artery disease is currently less clear, a high score may call for intensification of therapies when there is otherwise equipoise.

There are relevant limitations in the use of the polygenic risk score for coronary artery disease.[39] First, since the underpinning data are predominantly derived from persons of European ancestry, current polygenic risk scores do not predict risk equally well across ancestries, an issue that is being increasingly addressed in new genomewide association studies of coronary artery disease.[37] Second, there is no single-consensus score, nor are there agreed-on reporting standards.[49] Third, current guidelines have not yet incorporated the polygenic risk score for coronary artery disease.[39,41] Fourth, research and implementation gaps remain, such as assessment of the effect of the polygenic risk score on clinical decision making, determination of cost-effectiveness, and calibration of the score to the population of a health care system.[39,50,51] Finally, until there is uniform insurance coverage, equitable access may be limited because of required out-of-pocket costs.

TREATMENT OF PERSONS AT HIGH GENETIC RISK FOR CORONARY ARTERY DISEASE

FAMILIAL HYPERCHOLESTEROLEMIA

Clinical trials have shown that patients with familial hypercholesterolemia benefit from intensive lipid-lowering treatment even more, in absolute terms, than do other patient groups at risk for coronary artery disease.[16] Accordingly, initiation of lipid-lowering treatment is recommended for primary prevention in patients with familial hyper-

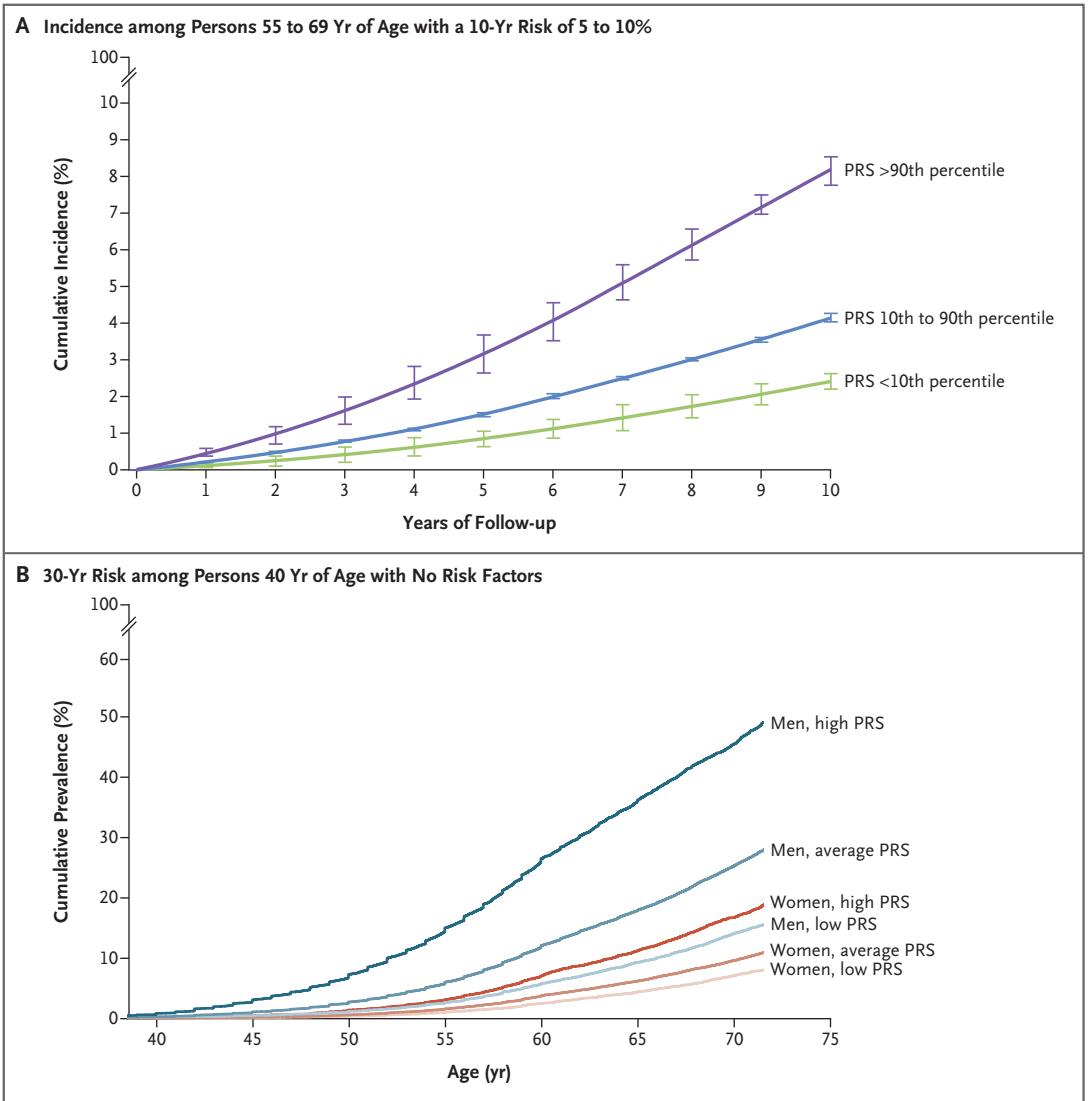

Figure 4. Trajectories for Atherosclerotic Cardiovascular Disease Events According to the Polygenic Risk Category.

Drawing on data from the U.K. Biobank, Panel A shows that among persons 55 to 69 years of age, the risk of an atherosclerotic cardiovascular disease event is 5 to 10%, as calculated with the use of SCORE2. Even though SCORE2 and other risk prediction tools overestimate the incidence among persons included in the U.K. Biobank, the observed incidence largely differs according to the polygenic risk.[43] The samples were randomly split into 10 groups, and the mean cumulative incidence and standard error (I bars) were calculated. Panel B, which also draws on data from the U.K. Biobank, shows that among 40-year-old men and women without clinical risk factors at this age, the long-term risk of coronary artery disease also differs according to the polygenic risk. Currently used clinical risk scores do not adequately predict the long-term risk of coronary artery disease among younger people. In this subgroup of the population, the polygenic risk of coronary artery disease may provide useful information for predicting future risk.

cholesterolemia, even in early adulthood, with a target LDL cholesterol value of less than 70 mg per deciliter (1.8 mmol per liter).[13,46,52] In children with a genetic variant that causes familial hypercholesterolemia and persistent, clinically significant hypercholesterolemia, statin therapy can be initiated to reduce the LDL cholesterol level to less than 135 mg per deciliter (3.5 mmol per liter), according to European guidelines.[13] Homozygous familial hypercholesterolemia is a life-threatening disease, with coronary artery disease often developing during childhood. Severely elevated LDL choles-

terol levels require intensive treatment in specialized centers.

HIGH POLYGENIC RISK

Whereas monogenic conditions such as familial hypercholesterolemia mainly act through a single risk factor, the polygenic risk score for coronary artery disease represents a heterogeneous mix of causal risk factors and unknown risk pathways. Yet the polygenic risk for coronary artery disease can also be substantially modified. Observational studies have suggested that a healthy lifestyle may largely counterbalance a high polygenic risk score (Fig. 5). Moreover, post hoc analyses of several randomized primary and secondary prevention trials showed repeatedly that treatment with statins or PCSK9 inhibitors results in larger absolute as well as relative risk reductions in persons with a high polygenic risk score for coronary artery disease.[31,34] These studies support the premise that LDL cholesterol lowering is a particularly effective strategy for reducing the risk of coronary artery disease in persons with a high polygenic risk score (Fig. 5).[32,33]

TRANSLATING GENETIC ARCHITECTURE INTO NEW THERAPEUTIC STRATEGIES

Leveraging the genetic architecture of coronary artery disease to advance therapeutics is an attractive strategy. Since allele allocation is random and does not change during a person's lifetime, risk alleles point toward causal mechanisms that allow for prioritization of therapeutic targets. Indeed, investigational medicines with support based on human genetics are more likely to obtain regulatory approval than are those that lack genetic support.[53]

Elucidation of *LDLR* variants causing familial hypercholesterolemia and familial clustering of coronary artery disease laid the groundwork for

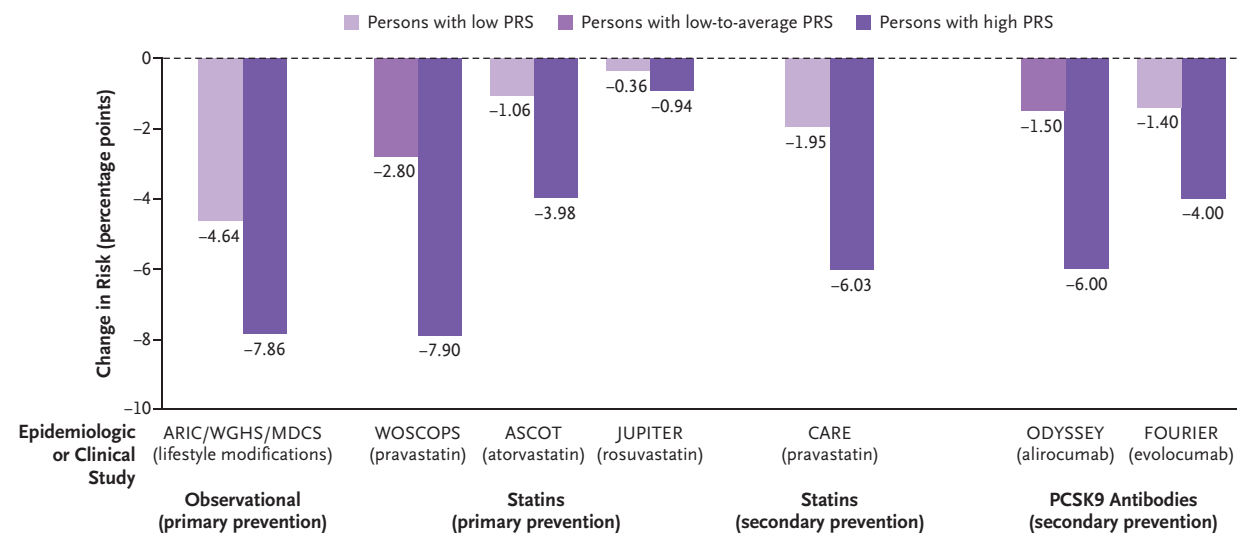

Figure 5. Risk Reduction through Lifestyle Modifications or Lipid-Lowering Treatment, According to the PRS.

Epidemiologic studies and clinical trials have shown that over a span of 20 years, lifestyle modifications are associated with a reduction in incident atherosclerotic cardiovascular disease events, with the greatest risk reduction occurring among persons with a high PRS. Data on lifestyle modifications are from the following epidemiologic studies: Atherosclerosis Risk in Communities (ARIC), the Women's Genome Health Study (WGHS), and the Malmö Diet and Cancer Study (MDCS).[30] Likewise, statin and proprotein convertase subtilisin–kexin type 9 (PCSK9) antibody trials uniformly show a greater absolute risk reduction among persons with a high PRS than among those with a low PRS. Data on lipid-lowering treatment are from the following studies: the West of Scotland Coronary Prevention Study (WOSCOPS),[31] the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), Cholesterol and Recurrent Events (CARE),[34] Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome during Treatment with Alirocumab (ODYSSEY OUTCOMES),[33] and Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER).[32] Additional information can be found in the Supplementary Appendix.

KEY POINTS

THE INHERITED BASIS OF CORONARY ARTERY DISEASE

- Rare loss-of-function variants with large effects have directly implicated specific genes as therapeutic targets, which has provided strong human genetic validation for drug development.
- Genomewide association studies show that common genetic variants account for a substantial proportion of inherited risk for coronary artery disease.
- The variants associated with the risk of coronary artery disease manifest effects across organs and tissues. Many of these variants mediate risk through pathways known to be central to the development of coronary artery disease, but the underlying mechanism for several variants currently remains unknown.
- Genetic association data have enabled causal inference studies through mendelian randomization, which provides a framework for distinguishing causal risk factors from correlated risk markers for coronary artery disease.
- Polygenic risk scores integrate the cumulative effects of common variants into a single measure of inherited coronary artery disease risk, with a continuous population distribution and marked enrichment of events at the upper extremes.
- Polygenic risk scores provide information largely independent of conventional clinical risk factors, including family history, and refine risk stratification for both incident and recurrent coronary artery disease.
- Although genetic risk alleles are fixed at conception, their clinical consequences are modifiable, with evidence that lifestyle interventions and lipid-lowering therapy can attenuate risk among persons with high polygenic risk scores, particularly when applied early.
- There is no consensus about the clinical use of polygenic risk scoring for coronary artery disease, and questions remain regarding robustness across populations, incremental value, cost-effectiveness, and implementation.

the development of medications that up-regulate the LDL receptor in the liver, such as statins. The observation that rare disruptive variants in *PCSK9* reduce LDL cholesterol levels and decrease the risk of coronary artery disease led to the development of PCSK9 inhibitors.[9] The observation that variants in the genes that encode the proteins targeted by ezetimibe and bempedoic acid — *NPC1L1* and *ACLY*, respectively — are associated with coronary artery disease validates the preceding observation that their pharmacologic inhibition decreases LDL cholesterol levels and the risk of coronary artery disease events.[8,54-56]

One of the first loci for coronary artery disease to be identified in genomewide association studies, and the locus with the strongest association, harbors apolipoprotein(a),[57] which determines serum levels of lipoprotein(a), a highly heritable, LDL cholesterol–like macromolecule and a potentially new modifiable risk factor for coronary artery disease. On the basis of compelling genetic data linking *LPA* genetic variation and coronary artery disease, agents that block the transcription or function of its product, apolipoprotein(a), are currently being tested in clinical trials of cardiovascular outcomes. Other drug targets under investigation are products of *ANGPTL3*, *ANGPTL4*, and *APOC3*, which have been shown by genetic means to increase triglyceride levels and the risk of coronary artery disease.[58-60]

Some rare and common variants affecting nitric oxide signaling, such as *NOS3*, *GUCY1A1*, and *PDE5*, are associated with an increased risk of coronary artery disease and increased blood pressure.[22,24] An observational study showed that treatment with a phosphodiesterase-5 inhibitor was correlated with a reduction in coronary artery disease event rates,[61] but data from subsequent trials are lacking. A variant that switches an amino acid in *SVEP1* increases its function, thereby increasing inflammation in vascular smooth muscle cells and the risk of coronary artery disease.[58,62] In addition, experimental studies have shown that the use of antibodies or vaccination to block *ADAMTS7* has therapeutic potential.[63,64] Genetic analyses of related inflammatory molecules have prioritized the likely causal features in the NLRP3 inflammasome, as subsequently shown in clinical trials.[65] A common amino acid switch in *SH2B3* is associated with an increased risk of coronary artery disease through excess neutrophil extracellular traps and arterial thrombosis.[66] Signals in genomewide association studies have also converged on cell-specific signaling pathways, such as *CCM2* and *TLNRD1*, which affect atheroprotective processes in endothelial cells.[67,68]

Elucidating the genetic basis of coronary artery disease has helped to distinguish potentially causal biomarkers from confounded biomarkers. The approach, often referred to as mendelian randomization, makes use of genetic variants that associate solely with a putative exposure of interest; such variants are referred to as instrumental variables. If the association of the exposure with the disease in question is causal, then genetic variants should also be associated with the disease to the extent that it affects the exposure. This approach has been used to validate risk factors for coronary artery disease such as elevated LDL cholesterol and triglyceride levels, hypertension, obesity, elevated lipoprotein(a) levels, and type 2 diabetes.[69] As mentioned above, several drugs that target these risk factors interfere with the function of genes that genomewide association studies have shown to be significantly associated with coronary artery disease, providing confirmation that these drugs address relevant mechanisms.[70] These studies have also helped to deprioritize several risk markers as causal for coronary artery disease, such as low plasma levels of high-density lipoprotein cholesterol and vitamin D and high plasma levels of C-reactive protein and uric acid.[71-74] Despite strong epidemiologic correlations for these latter biomarkers, the genetic variants that modulate their plasma levels show no convincing association with the risk of coronary artery disease.

Mendelian randomization studies have also provided valuable evidence for understanding the risk of coronary artery disease when randomized trials were not easily feasible. For example, randomization studies indicated that the association of shorter height with an increased risk of coronary artery disease is causal and that habitual alcohol consumption may confer a predisposition to an increased risk of coronary artery disease.[75,76]

CONCLUSIONS

Even larger genomewide association studies and sequencing studies across persons globally will provide more precise information on involved DNA variants, causal genes, and downstream mechanisms. These studies will also help to further refine and standardize polygenic risk scores for coronary artery disease. A plethora of genetic findings from genomewide scans, beginning in 2007, continues to change the perception of how coronary artery disease develops. Hundreds of common genetic variants affecting a wide spectrum of disease mechanisms are found in each person; the more a person carries, the higher the risk of coronary artery disease. Many established treatments have been validated on the basis of these data, and several genetically driven disease pathways are currently being interrogated for their therapeutic potential. The totality of the genetic information about coronary artery disease, captured as familial hypercholesterolemia variants or aggregated as a polygenic risk score, continues to open new opportunities for earlier risk prediction, prevention, and treatment.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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