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STATE-OF-THE-ART REVIEW

Coronary Artery Disease Genetics Enlightened by Genome-Wide Association Studies

Thorsten Kessler, MD,[a,b] Heribert Schunkert, MD[a,b]

HIGHLIGHTS

- **Genetic studies led to a deeper knowledge of the pathophysiological processes in CAD and the identification of novel treatment targets (e.g., in lipid metabolism).**
- **The interplay between genetic factors and traditional risk factors, such as obesity, hypertension, smoking, or hyperlipidemia, but also noise and air pollution, is the subject of extensive research.**
- **In the future, genetic risk scores may improve risk prediction and lead to the development of individualized treatment strategies, the cornerstone of precision medicine.**

SUMMARY

Many cardiovascular diseases are facilitated by strong inheritance. For example, large-scale genetic studies identified hundreds of genomic loci that affect the risk of coronary artery disease. At each of these loci, common variants are associated with disease risk with robust statistical evidence but individually small effect sizes. Only a minority of candidate genes found at these loci are involved in the pathophysiology of traditional risk factors, but experimental research is making progress in identifying novel, and, in part, unexpected mechanisms. Targets identified by genome-wide association studies have already led to the development of novel treatments, specifically in lipid metabolism. This review summarizes recent genetic and experimental findings in this field. In addition, the development and possible clinical usefulness of polygenic risk scores in risk prediction and individualization of treatment, particularly in lipid metabolism, are discussed. (J Am Coll Cardiol Basic Trans Science 2021;6:610–23) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Cardiovascular diseases are the leading killers worldwide (1). Among these, coronary atherosclerosis and its complications, chronic or acute coronary syndromes, and ischemic heart failure are leading entities. A positive family history has been recognized for many years to be a risk factor for coronary artery disease (CAD), whereas the specific genetic variants underlying this observation remained obscure (2). Fifteen years ago, mutations leading to familial hypercholesterolemia were the only known genetic causes of CAD. Recently, advances in biotechnology facilitated large-scale genomic studies, which have led to remarkable discoveries. Currently, the complex etiology of CAD

From the [a]German Heart Centre Munich, Department of Cardiology, Technical University of Munich, Munich, Germany; and the [b]German Centre for Cardiovascular Research (DZHK e.V.), partner site Munich Heart Alliance, Munich, Germany.
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results from an interplay of hundreds of genetic risk variants that infiltrate the entire population, and in a systems biology sense, lay the cellular foundation for disease development. Based on this foundation, several (exogenous) risk factors, such as hypertension, diabetes mellitus, and smoking (3), aggravate the situation. This opens up new vistas on the pathophysiological processes in CAD and raises the hope for novel therapeutic concepts that are able to interfere with these, so far unknown, biological processes. In this review, we discuss recent findings in discovery and mechanistic exploration, as well as the therapeutic exploration of genetic risk variants for cardiovascular diseases with a focus on CAD.

GENETICS OF CAD AND/OR MYOCARDIAL INFARCTION

Marenberg et al. (4) reported in 1994 that monozygotic and dizygotic twins had a higher risk of dying from CAD if their twins died themselves from CAD at young age. The same is true for subjects with a relative who had a myocardial infarction (MI) (5). Early studies designed to unravel the underlying genetic risk factors had limited success. Particularly, candidate gene studies focusing on traditional risk factors or unrelated pathways (e.g., the angiotensin-converting enzyme) (6) resulted in dead-end streets. For a long time, only mutations in the low-density lipoprotein cholesterol receptor (LDLR) (7,8) or proprotein convertase subtilisin/kexin type 9 (PCSK9) (e.g., those leading to hypercholesterolemia) were considered as causal via this intermediate phenotype (9,10).

Since 2007, mainly 2 factors have changed the scenario: first, the introduction of arrays that enabled genome-wide genotyping of an increasing number of genomic variants with subsequent imputation of millions of further variants; and second, the formation of large international consortia jointly investigating the genetics of CAD. As a result, the last several years have provided deep insights into the genetic architecture of the disease with implications for future prevention and treatment strategies (11,12). In the beginning, most of the large-scale genetic studies mainly focused on subjects who had been recruited in Europe and the United States. With efforts as the UK Biobank (13), the CARDIoGRAMplusC4D 1M+ Hearts project (14), and the Million Veteran Program (15), the discovery of genetic risk factors for CAD and/or MI in subjects of European ancestry will continue. Meanwhile, however, several genome-wide association studies (GWASs) in other ethnic groups [e.g., Han Chinese (16) and Japanese (17)] have been performed. A recently published large-scale GWAS also revealed 43 novel loci in Japanese, highlighting the ongoing search for population-specific and trans-ancestry risk factors (18). These studies are of outmost importance, because the implementation of polygenic risk scores in clinical practice will largely depend on the accuracy of predicting effect sizes of risk alleles, which varies with the genetic background (19).

GENETICS OF CAD: OVERVIEW. The first discovery in modern CAD genetics research is exemplary in its success and challenges, the chromosome 9p21 locus. It was unraveled independently by 3 research consortia at the same time (20–23), and together with the *LPA* locus, represents the locus with the strongest effect on CAD risk (24). This is remarkable because how it exerts its molecular effects is not completely understood. The locus has been initially called a "gene desert" because an obvious traditional candidate gene could not be determined. Close-by genes encode the cyclin-dependent kinase inhibitors 2A/2B (*CDKN2A/CDKN2B*), which have been thoroughly investigated but not proven to be involved (25). Another interesting candidate is the long noncoding RNA (lncRNA) *ANRIL* because the risk allele associates with its expression, and increased expression of linear *ANRIL* was linked to enhanced atherosclerosis (26). In contrast, circular *ANRIL* seems to be protective (27). A recent elegant study used genetic engineering in induced pluripotent stem cells and showed that replacement of the non-risk genotype by the risk genotype led to overexpression of *ANRIL* and proatherogenic phenotypes in vascular smooth muscle cells (28).

Since 2007, >200 loci like the one at chromosome 9p21 locus have been reported to be associated with CAD and MI. Comprehensive lists of these loci, including the risk alleles, allele frequencies, and candidates at the loci have been published previously [for an overview, please see (12,29)]. Although initially only a handful of loci could be explained by an influence on classical risk factors such as hypertension or hypercholesterolemia, currently, approximately one-half of the loci can be attributed to pathophysiological pathways, many of them being new "drivers" of CAD and/or MI (**Figure 1**). One example is nitric oxide signaling (43–45), which has been well characterized for modulating vascular tone but also plays a major role in precipitating genetic CAD risk (46,47).

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease

CXCL1 = chemokine (C-X-C motif) ligand 1

GWAS = genome-wide association study

LDLR = low-density lipoprotein receptor

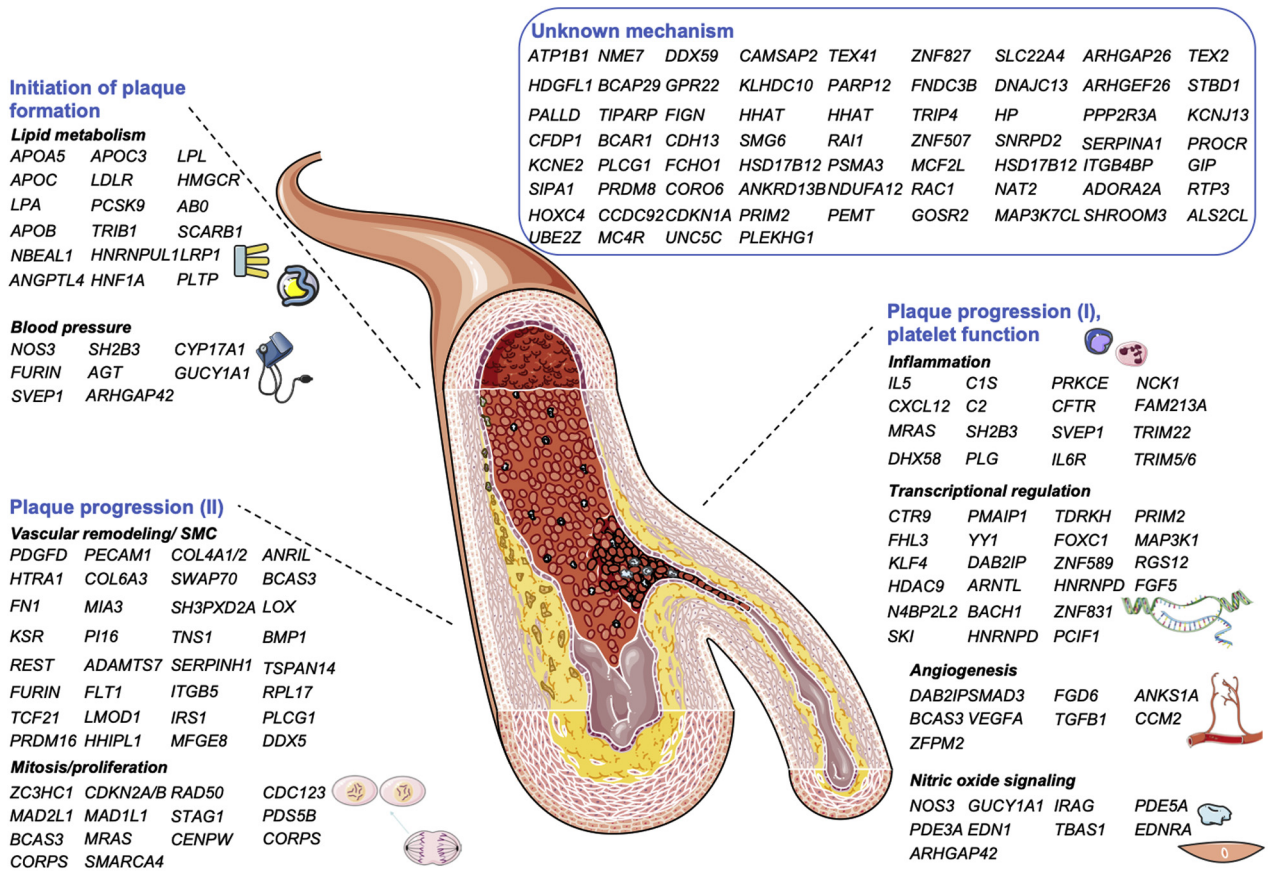
lncRNA = long non-coding RNA

LPL = lipoprotein lipase

MI = myocardial infarction

PCSK9 = proprotein convertase subtilisin/kexin type 9

FIGURE 1 Currently Known CAD Genes and Supposed Mechanisms



Mechanisms were grouped to initiation, plaque progression, and platelet function but are not limited to this rough classification. Previously unknown genes were grouped to the proposed pathways if experimental data (using the queries "gene name" and "atherosclerosis" in PubMed) was published in the meantime: *LMOD1* (30); *NBEAL1* (31); *IRS1* (32); *PLCG1* (33); *NCK1* (34,35); *PRDM16* (36); *HHIPL1* (37); *MFGE8* (38); *HNRNPUL1* (39); *RAC1* (40,41); and *DDX5* (42). CAD = coronary artery diseased. Modified after and updated from Erdmann et al. (12). Modified image material available at Servier Medical Art under a Creative Commons Attribution 3.0 Unsupported License.

CHALLENGES IN THE IDENTIFICATION OF THE MECHANISMS LINKING PHENOTYPE AND GENOTYPE. GWASs detected numerous variants that are associated with CAD. However, the elucidation of the underlying mechanisms remains challenging. Usually, the 'closest gene approach' was used, that is, the genes that are located nearby the detected variant were reported as candidates. This strategy can be complemented by various bioinformatics approaches (e.g., expression data from datasets like GTEx (48)). The GTEx database includes genome-wide genotyping and transcriptome data, making it possible to report expression quantitative trait loci. Because a GWAS variant is associated with differential expression of a more distantly located gene, the closest gene might not be causal. A plethora of studies used such strategies or a combination of strategies to predict the causal genes at GWAS loci (49). Nevertheless, there may be a need to prove causal effects experimentally. A prominent example is the chromosome 6p24 locus. It harbors the *PHACTR1* gene, which, intriguingly, was not only associated with CAD (50) but also with spontaneous coronary artery dissection (51) and coronary artery calcification (52). There are also experimental data that support association of calcification with *PHACTR1* (53). However, an elegant experimental study revealed a rather surprising result. Using CRISPR-based genome editing in stem cell–derived endothelial cells, alteration of a variant at the chromosome 6p24 locus led to expression changes of *EDN1* rather than *PHACTR1* (54). *EDN1* encodes endothelin-1, a well-studied vasoconstrictor and

TABLE 1 CAD Genes Associated With CAD and Lipid Phenotypes in GWASs That Are Used as Therapeutic Targets

Gene	Protein/Mechanism	Clinical Use/Perspective	Ref. #
APOC3	Apolipoprotein C-3/lipoprotein lipase activity ⇓, plasma triglycerides ⇑ → increased CAD risk	Antisense APOC3 inhibitor (Volanesorsen) leads to a dose-dependent 31%–71% reduction in triglycerides, effective triglyceride reduction in familial chylomicronemia syndrome	(60–63)
ANGPTL3/4	Angiopoietin-like protein 3/4/Lipoprotein lipase activity ⇓, plasma triglycerides ⇑ → increased CAD risk	Evinacumab, a monoclonal antibody against ANGPTL3, reduced plasma LDL-cholesterol levels in patients with familial hypercholesterolemia by 47%	(60,64–70)
PCSK9	Proprotein convertase subtilisin/kexin type 9/LDL-cholesterol receptor recycling on the hepatocellular surface ⇓, LDL-cholesterol receptor density ⇓, LDL-cholesterol ⇑ → increased CAD risk	Monoclonal antibodies and antisense molecules reduce PCSK9 function and LDL-cholesterol and cardiovascular events	(9,50,71–75)
LPA	Lipoprotein(a)/lipoprotein with prothrombotic and proinflammatory properties → increased CAD risk	Lipoprotein(a) can be reduced by lipid apheresis; TQJ230, an antisense oligomer, is currently investigated in clinical trials (NCT04023552*)	(76–80)
NPC1L1	Niemann-Pick C1-Like 1/Involved in the resorption of cholesterol from the intestine, LDL-cholesterol ⇑ → increased CAD risk	Ezetimibe, a NPC1L1 inhibitor, was able to reduce LDL-cholesterol and cardiovascular events when added to statin therapy	(78,81,82)
HMGCR	3-Hydroxy-3-methylglutaryl-CoA reductase/pivotal in endogenous cholesterol biosynthesis, LDL-cholesterol ⇑ → increased CAD risk	Statins targeting 3-hydroxy-3-methylglutaryl-CoA reductase have been repeatedly shown to reduce cardiovascular events	(83,84)

*Assessing the Impact of Lipoprotein (a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With CVD [Lp(a)HORIZON].
CAD = coronary artery disease; CoA = coenzyme A; GWASs = genome-wide association studies; LDL = low-density lipoprotein; PCSK9 = proprotein convertase subtilisin/kexin type 9.

modulator of vascular smooth muscle cell function. Even if the results from genome editing are in doubt, the studied variant was also associated with endothelin-1 precursor protein levels in plasma, which validated the finding (54).

Another strategy might be the investigation of transgenic mouse models regarding atherosclerotic plaque formation. Although the limitations of this approach, because of the differences between mice and humans, are obvious, a recent review provided evidence that most of the genes identified by CAD GWASs that were already studied in atherosclerosis-prone mouse models revealed consistent results (55). Nevertheless, results from such studies need to be interpreted with caution because the approach of deleting genes might be too artificial. One example is the *GUCY1A1* locus, which harbors private mutations leading to a loss of function (43), and common non-coding variants that are associated with CAD (56). However, the knockout of the murine counterpart *Gucy1a1* led to enhanced atherosclerotic plaque formation (57), a finding that opposes the genetic associations. However, in a population-based approach in mice, a variant that was associated with reduced *Gucy1a1* expression was also linked to enhanced atherosclerotic plaque formation (44). The approach of investigating genetic variation in mice (e.g., using the Hybrid Mouse Diversity Panel) (58) might be particularly useful. Taken together, these examples illustrate the hurdles on the way from genotype to phenotype that need to be considered when interpreting findings from such analyses.

A NOVEL VIEW ON LIPID METABOLISM. Although most of the genomic loci were not linked to CAD before, GWASs also identified genes that are associated with both CAD and traditional risk factors (e.g., lipid metabolism and blood pressure). While both hypertension and hypercholesterolemia increase CAD risk, lipid metabolism remains unique. Important examples of early associations are *PCSK9* and *LDLR*, as discussed previously (59). However, there are more genes that expanded our view on lipid metabolism and might represent future treatment targets. In this section, we want to discuss 3 promising examples. In addition, **Table 1** lists CAD risk genes in lipid metabolism that are targets of current and future treatment strategies.

SORT1. The chromosome 1p13.3 locus was identified early in the GWAS era (21,50). Subsequently, experimental studies identified sortilin 1 (*SORT1*) (85), a protein that plays an important role in the regulation of plasma LDL cholesterol by interacting with APOB in the Golgi apparatus in hepatocytes (85), as the most likely candidate gene at this locus. The risk variant affects gene expression with the risk allele being linked to lower *SORT1* mRNA levels (86). Its use as a therapeutic target might be complicated because the enzyme affects a variety of phenotypes [for an overview, see (87,88)], including proper function of neurotrophins and neuron viability (89). However, *SORT1* has also been linked with frontotemporal dementia, and clinical trials using a monoclonal antibody targeting SORT1 in this indication (e.g., A Phase 2 Study to Evaluate Safety of Long-term AL001

Dosing in Frontotemporal Dementia [FTD] Patients [INFRONT-2]; NCT03987295; A Phase 3 Study to Evaluate Efficacy and Safety of AL001 in Frontotemporal Dementia [INFRONT-3]; NCT04374136) are currently underway.

Lipoprotein lipase and its modulators. Lipoprotein lipase (LPL) is a vascular enzyme critically involved in metabolizing triglyceride-rich lipoproteins. The locus harbors both common, noncoding, and rare variants that lead to a loss of function and increased risk of CAD. Other variants lead to a gain of function and reduced CAD risk, respectively (90). Importantly, not only the *LPL* gene but also pivotal endogenous regulators of LPL activity are associated with CAD, including APOA5 (8,60), APOC3 (60-62), ANGPTL4 (91), and ANGPTL3 (67). For most of these, treatment approaches are currently being investigated (**Table 1**). ANGPTL3 in particular revealed promising results: evinacumab, an anti-Angptl3 antibody, reduces plasma triglyceride levels and atherosclerotic plaque formation in mice. In humans, the administration of the humanized counterpart confirmed the effect on plasma triglyceride levels (68), and recently, a beneficial effect was also shown for LDL cholesterol (70).

TRIB1. A less mature candidate is represented by the *TRIB1* locus (56,78,92). TRIB1 also seems to influence lipid metabolism with an inverse correlation of hepatocellular *TRIB1* expression and the expression of lipogenic genes; in line targeted overexpression of *Trib1* in wild-type mice reduced cholesterol levels (93). Whether this approach can ultimately be transferred to human treatment will be interesting to follow.

TARGETING THE VASCULAR INTERFACE.

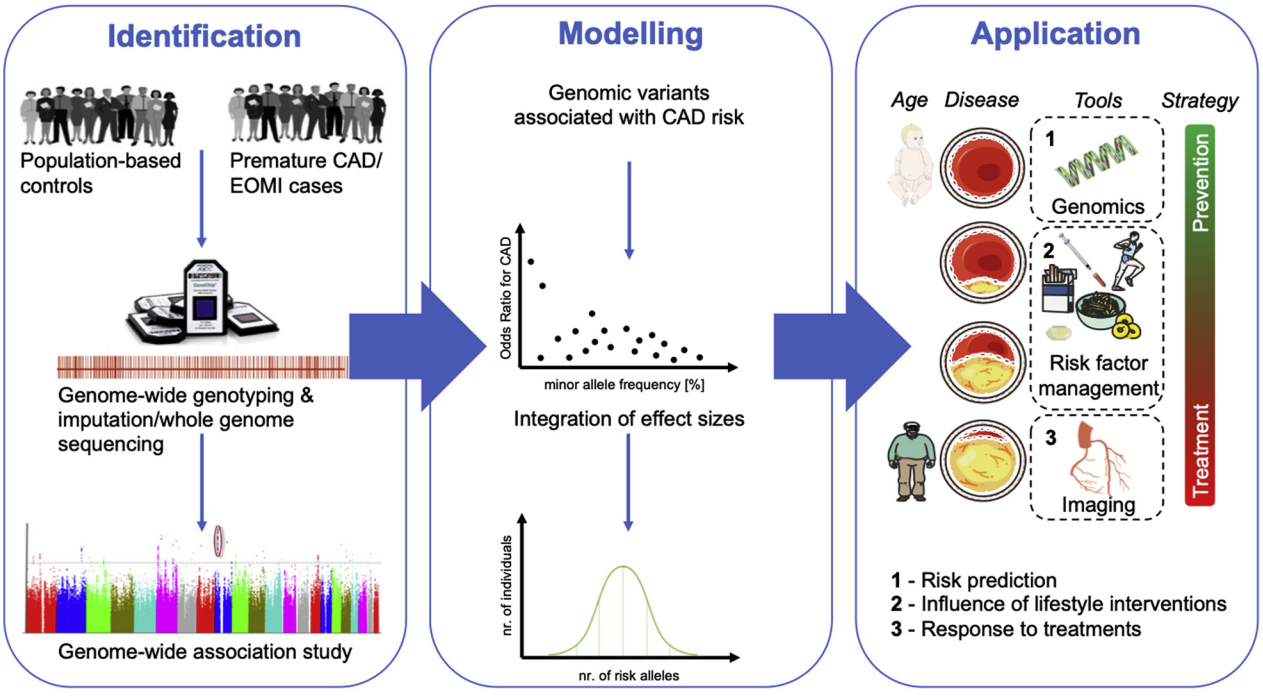
A number of risk genes have been classified to influence processes in the vascular wall. With increasing knowledge about the involvement of immune cells [for an overview, see (94)] and platelets [for an overview, see (95)] in atherosclerosis, it seems prudent to investigate the vascular interface where resident, recruited, and circulating cells, and lipids interact to beget atherosclerotic plaque formation. Some recently investigated genetic examples are discussed in the following section.

Genes involved in vascular smooth muscle cell function. Vascular smooth muscle cells can influence atherosclerosis by at least 2 mechanisms: first, via vascular tone, and thereby, modulation of blood pressure; second, via local processes including inflammation, vascular remodeling, and so on, leading either to stabilization or destabilization of the plaque. As expected, there is significant genetic overlap between these 2 phenotypes. An important example is the previously mentioned nitric oxide signaling pathway, in which, upon release of nitric oxide, vascular smooth muscle cells form the second messenger cyclic guanosine monophosphate (96). This leads to relaxation of vascular smooth muscle cells. Vice versa, mice that lack the nitric oxide receptor in vascular smooth muscle cells show a hypertensive phenotype (97). However, an intracellular increase in cyclic guanosine monophosphate levels also inhibits migration of vascular smooth muscle cells (98), which itself is a hallmark of atheroprogression (99). Another genetic locus mediating its effects most likely through alterations of vascular smooth muscle cell biology is the 9p21 locus (27,28). Further promising putative targets were identified and are discussed in this section.

TCF21. Recently, a comprehensive view on the role of the CAD gene TCF21 (79) in atherosclerosis was published. A disease-associated variant in the 3′ untranslated region of *TCF21* alters its mRNA stability by differential binding of a microRNA (100), which allows insight into the fascinating interaction of disease genetics and gene regulation by noncoding RNAs. Wirka et al. (101) reported that a loss of *Tcf21* resulted in an inhibition of the phenotype switch of vascular smooth muscle cells, and, as a consequence, there were fewer fibromyocytes in the fibrous cap of atherosclerotic plaques, which indicated reduced stability. It is now also known that the molecular mechanism, for example, involves an interaction of TCF21 with the myocardin-serum response factor pathway (102). Increasing the availability of TCF21 might have beneficial effects in the prevention and stabilization of atherosclerotic plaques, but further information about the production and fate of TCF21 is needed. Therapeutic targeting of the mRNA–microRNA interaction by oligomers might be even more complicated by the need for delivering such substances to the vascular smooth muscle cell.

ADAMTS7. A more convenient target in this regard might be the extracellular matrix protease ADAMTS-7 (79,103,104). It is produced by endothelial cells and vascular smooth muscle cells and has been shown to degrade multiple members of the thrombospondin family (105,106). Mice lacking Adamts-7 develop less atherosclerosis and are resistant to neointima formation secondary to vascular injury (106,107). The downstream mechanisms in atherosclerosis so far remain unknown. However, in vitro, ADAMTS-7 degrades the sushi, von Willebrand factor type A, EGF, and pentraxin domain containing 1 (SVEP1) protein (106), another extracellular matrix protein with an important role in development and

FIGURE 2 Generation and Use of Polygenic Risk Scores

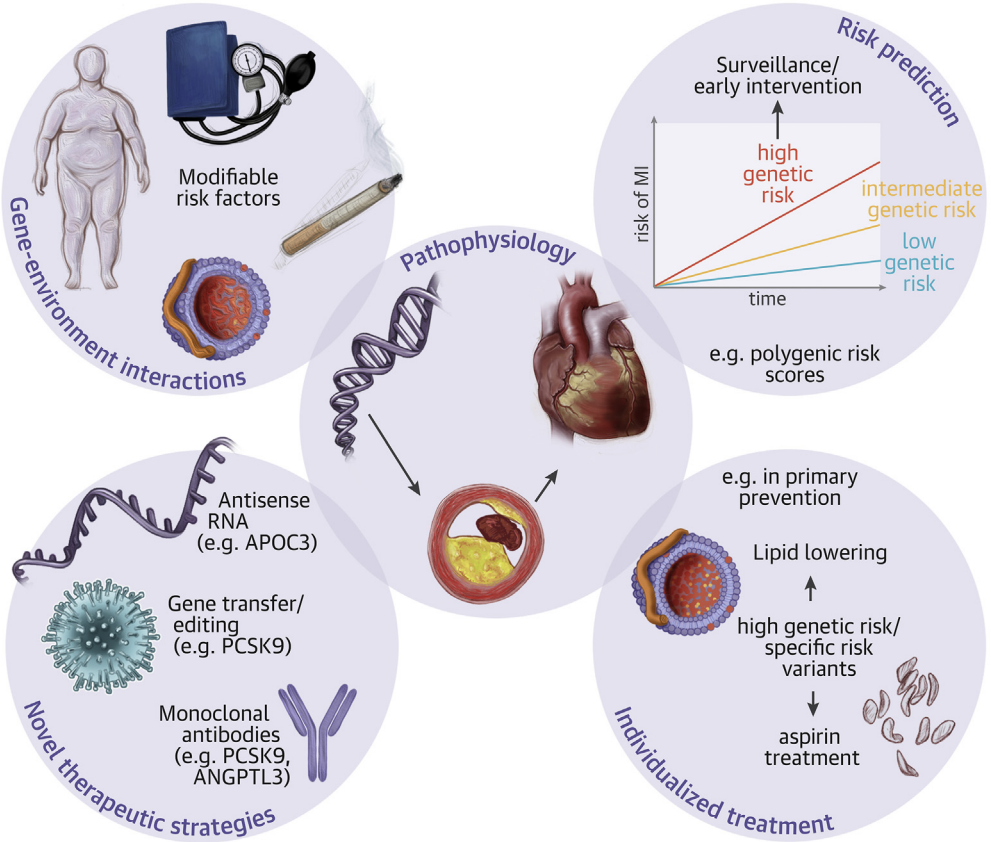


Identification: genome-wide association studies are required to identify variants that are associated with CAD and early-onset myocardial infarction (EOMI). Bioinformatic tools enable the imputation of not directly genotyped variants to increase the numbers of variants that can then be compared between healthy control subjects and cases. Statistical analysis leads to the identification of variants that are associated with CAD at the genome-wide level of significance ($p < 10^{-8}$). Modeling: in a second step, polygenic risk scores are based on modeling the sum of particular risk alleles, integrating their effect sizes. Polygenic risk scores follow a Gaussian distribution with most subjects carrying an intermediate number of risk alleles and a small portion either carrying a small or a large number of risk alleles. Application: genetic information is the only tool in risk prediction and management that is basically available at birth and could be used to predict risk and tailor prevention strategies. During life, the influence of risk factors and their management becomes increasingly important. In older adults, imaging to detect atherosclerosis and its complications remains the main diagnostic tool. Over time, the strategy shifts from prevention in young and middle-aged subjects to treatment and secondary prevention. However, genetic information could, be used at all stages to predict risk in young and middle-aged individuals (1), evaluate the beneficial effects of lifestyle but also pharmacological interventions (2), and predict the response to a given treatment strategy (e.g., statins or PCSK9 inhibitors) (3). For details, see text. Modified image material available at Servier Medical Art under a Creative Commons Attribution 3.0 Unsupported License. Abbreviations as in Figure 1.

lymphatic vessel formation (108). SVEP1 was identified as a CAD gene by an exome-wide association study (91). First results now render an atheroprotective role of SVEP1 possible with Svep1 haploinsufficiency promoting atherosclerotic plaque formation and recruitment of leukocytes to the vascular wall (109). Although there are still open questions regarding the role of circulating SVEP1 as a biomarker or risk modifier and the multiple sources of SVEP1 in the body, SVEP1 further indicates the need for the identification of ADAMTS-7 inhibitors as a possible upstream target to increase therapeutic effects.

HHIPL1. Novel players in the vascular wall with specific drugs available include hedgehog interacting protein-like 1 (HHIPL1) (79). HHIPL1 has been annotated to hedgehog signaling, which is indispensable in embryonic development, in particular for the coronary vasculature, and ischemia-driven neoangiogenesis (110,111). In atherosclerosis, HHIPL1 represents an interactor of hedgehog signaling in vascular smooth muscle cells with a positive influence on vascular smooth muscle cell migration and proliferation. Mice lacking *Hhipl1* present smaller atherosclerotic plaques (37). Further evidence can be drawn from a study in which antagonizing hedgehog signaling led to the opposite effect with larger atherosclerotic plaques (112). Of note, in a recently published analysis of genetic variants that influence atherogenic phenotypes in vascular smooth muscle cells in vitro, there was a considerable overlap of genetic variants that influenced such vascular smooth muscle cell phenotypes and genetic variants that are associated with CAD (113).

CENTRAL ILLUSTRATION The Identification of Genetic Variants Influencing Coronary Artery Disease Risk Affects Several Fields



Kessler, T. et al. J Am Coll Cardiol Basic Trans Science. 2021;6(7):610–23.

From a deeper knowledge of the: 1) pathophysiological processes, 2) novel treatment targets were identified; 3) the interplay between genetic factors and traditional risk factors such as obesity, hypertension, smoking, or hyperlipidemia but also noise and air pollution is the subject of extensive research. Finally, genetic risk scores may in the future 4) improve risk prediction and lead to the development of 5) individualized treatment strategies, the cornerstone of precision medicine. PCSK9 = proprotein convertase subtilisin/kexin type 9. Modified image material available at Servier Medical Art under a Creative Commons Attribution 3.0 Unsupported License.

CIRCULATING CELLS AND VASCULAR INFLAMMATION. In the process of atherosclerotic plaque formation and progression, lipid-laden monocytes are recruited to the intimal layer, giving rise to foam cells, cell necrosis, and apoptosis, as well as plaque progression and/or destabilization (99). The benefits from lipid-lowering therapies are well documented. The inflammatory part of this process was controversially discussed in epidemiology and clinical trials, albeit experimental evidence on the role of inflammation in atherosclerosis was overwhelming. The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) (114) and studies using colchicine in patients with CAD (115,116), however, showed that independent of lipid metabolism, targeting the inflammatory cytokines reduced cardiovascular events in high-risk subjects. This and the experimental evidence, summarized in Schloss et al. (117), is now complemented by genetic evidence. Interestingly, genes with GWAS evidence for association with CAD being classified as playing a role in inflammation do not contain the usual suspects such as interleukin-1β (118), components of the NLRP3 inflammasome (119), or classic proatherogenic chemokines (e.g., chemokine [C-X-C motif] ligand 1 [CXCL1]) (120). However, another member of the CXCL family, *CXCL12*, as well as *IL6R*, are CAD genes (21,79). CXCL12 represents the ligand for CXCR4 and signaling via this receptor influences atherosclerosis

phenotypes. In particular, endothelial cell–derived CXCL12 seems to have pro-atherosclerotic properties (121), whereas the role of CXCR4 is more complex (122), which limits its current value in prevention and therapy.

The role of platelets in mediating the effects of the GWAS loci remains more controversial. However, the observation that antiplatelet therapy with aspirin, a strategy that has no value in primary prevention, reduces the incidence of cardiovascular events in subjects homozygous for the risk allele at the *GUCY1A1* locus will fuel further research (45).

POLYGENIC RISK SCORES

Promises of genetic studies of adding knowledge to the pathophysiology of CAD and identifying novel therapeutic targets seem to be fulfilled. Another promise is to identify subjects at risk with a higher precision than conventional risk scores. Undoubtedly, a polygenic risk score can predict information already at birth (i.e., long before risk factors or imaging modalities may be used in this respect) (**Figure 2**). Therefore, genetic information offers the only tool to guide primordial prevention (i.e., targeted interventions) before onset of traditional risk factors or visible disease manifestations. However, initial results were disappointing [for an overview, see (123)]. The discovery of many more genomic variants that are associated with CAD, the possibility to impute millions of variants throughout the human genome that have not been directly genotyped, biostatistical modeling, and the availability of large cohorts as the UK Biobank (13) have enabled the construction of (genome-wide) polygenic risk scores that changed the scenario. In addition, this recent approach is used to rather discriminate differences in absolute risk between subjects than to differentiate healthy and diseased subjects, which might be more appropriate. The methodological and statistical background cannot be fully addressed in this review and was recently summarized by Aragam and Natarajan (124). In brief, a polygenic risk score is calculated as the sum of a number of genomic variants weighted for their effect estimate, which has been determined by GWASs (125) (**Figure 2**).

Currently, such scores are often used in research: 1) to predict the risk of experiencing CAD or major complications; 2) to identify subjects who may display strong benefit from a given intervention or therapy; and 3) to study the inter-relationship between the risk of CAD and other phenotypes.

PREDICTION OF RISK. One of the first approaches used the chromosome 9p21 locus to predict CAD. In middle-aged men, the genetic information on this locus was added to the Framingham Risk Score and compared the combination to the Framingham Risk Score alone. Although there was an improvement in reclassification (i.e., approximately 13% of men could be more accurately classified to their risk group), there was no substantial value of adding chromosome 9p21 information (126). The same was basically observed for further studies that incorporated >10 risk loci (127). In comparison, a polygenic risk score may incorporate many more variants that do not necessarily meet the criterion of being associated with CAD at the genome-wide significance threshold. Such scores consist of up to 6 million variants. This concept revealed that although all subjects have a given number of risk alleles, only a few subjects have very high or very low numbers. Nevertheless, this means for those at the extreme ends that the risk of suffering from CAD is markedly decreased or increased. In a study published by Khera et al. (128), the risk for those subjects who represented the 8%, 2.3%, and 0.5% of the largest number of risk alleles was increased >3-, 4-, and 5-fold, respectively. This prompted an interesting comparison. Because familial hypercholesterolemia has a prevalence of 0.4% in the population with a 3-fold increase in CAD risk, and the subjects at the top 0.5% of the polygenic risk score display a >5-fold increased CAD risk, the polygenic risk score has a higher predictive power than diagnosis of a monogenic disease as familial hypercholesterolemia (128). Furthermore, this seems to be independent of the information of a positive family history (129). In a cohort of patients who experienced early-onset MI, the prevalence of familial hypercholesterolemia was 1.7%, and the estimated increase in MI risk was estimated as 3.8-fold. A comparable increase in risk of MI was observed for those subjects in the top 5% polygenic risk score. However, with 17%, the prevalence was 10 times higher. Mean LDL cholesterol levels were 206 and 132 mg/dl in those with familial hypercholesterolemia and subjects in the top 5% polygenic risk score, respectively, which indicated independent mechanisms (130). Along this line, genetic risk scores performed better when they were compared with traditional risk factors (e.g., smoking or hypercholesterolemia) (131). Importantly, this concept does not only work in subjects of European ancestry. In a study focusing on South Asian subjects, the top 5% polygenic risk score was also associated with an approximately 3- to 4 times increased risk of CAD (132). Nevertheless, most of the contemporary polygenic risk scores for CAD are derived from studies in subjects of European ancestry and are not necessarily transferable to populations of

African ancestry (133). Together with uncovering novel risk factors, ancestral differences remain a major challenge in this field of genome-driven precision medicine.

A STEP TOWARDS PRECISION MEDICINE? Personalized medicine incorporating genetic information is often regarded as a cornerstone of the term "precision medicine." As 2 examples, we aim to discuss: 1) what polygenic risk scores could provide for subjects to change their lifestyle and behavior; and 2) how polygenic risk could inform decision-making in the use of lipid-lowering drugs specifically in primary prevention.

Genetics and lifestyle. Knowledge of genetic CAD and/or MI risk could tailor prevention and treatment strategies to specific patient groups. Subjects carrying a high genetic risk could more profoundly reduce risk if they follow a healthy lifestyle with regular exercise, healthy diet, and absence of smoking (134). In the UK Biobank, compared with subjects with a low genetic risk and a poor lifestyle, risk of CAD was increased >4-fold in subjects with high genetic risk and a poor lifestyle. Despite this impressive interplay of independent risk factors, subjects with a high genetic risk but a healthy lifestyle also displayed a lower risk of CAD as subjects with a low genetic risk but a poor lifestyle (135). However, the power of genetic risk scores to beneficially influence behavior is challenged by observations that indicate that the communication of genetic risk does not influence smoking, physical activity, or diet (136). Most of the recent studies were small and found no or little effect. For example, Jouni et al. (137) reported no improvement in metrics as participation in decision-making or perception of the quality of discussion in 207 subjects, one-half of whom were informed about traditional risk factors alone or the combination of traditional risk factors with genetic risk. Further prospective studies are needed to determine whether knowledge of genetic risk might translate to a reduction in CAD risk.

Individualized treatment. Genetic risk factors might also influence response to therapeutic strategies. An exciting example is that subjects with a high genetic risk score had larger benefit from statin treatment, both in secondary and primary prevention (138). A genetic score including 57 variants identified subjects at high genetic risk for CAD who also displayed the strongest reduction in CAD risk, with 46% compared with 26% in subjects with a lower genetic risk (139). In addition, knowledge of genetic risk might help to identify undertreated individuals. In patients with high cardiovascular risk (e.g., in patients with hypercholesterolemia), the use of statins is well established and recommended by current guidelines (140). Although a high polygenic risk score is associated with an increase in risk comparable to traditional risk factors, statins were not prescribed as often in such subjects (141,142). Two further studies revealed that polygenic risk scores were also able to identify subjects who benefitted most from treatment with the PCSK9 inhibitors evolocumab and alirocumab (143,144). In a post-hoc analysis of FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial (74), the absolute risk reduction by the monoclonal antibody evolocumab was 1.4% in participants with multiple traditional risk factors but low genetic risk; in contrast, subjects with a high genetic risk displayed an absolute risk reduction of 4.0%, regardless of traditional risk factors (143). Likewise, alirocumab treatment led to an absolute risk reduction of 1.5% in participants with low genetic risk compared with 6% in subjects with a high genetic risk (144). Whether these post hoc results, although encouraging in identifying treatment responders, can be replicated in prospective clinical trials on subjects without previous disease manifestation in line with an acute coronary syndrome is awaited. In addition, we so far only have limited knowledge how genetic risk, which inherently includes alterations in a variety of pathophysiological pathways, is modulated by 1 single therapy. Therefore, although the data on statins are encouraging, we need to be aware that this class of drugs rather represents a role model because the studies and the necessary data are available. Because only a small number of the genes that have been tagged by GWASs variants are involved in lipid metabolism, we currently do not know which other drugs might reveal comparable benefits.

Risk of CAD and other phenotypes. Quantifying the genetic risk of CAD using a genetic score can also be used to study the connection between CAD and other traits on the basis of genetics. A recent example by Ntalla et al. (145) is based on a genetic risk score that incorporated 300 CAD-related variants and found an association with a plethora of cardiovascular phenotypes: 1) traditional CAD risk factors, such as hypercholesterolemia, hypertension, obesity, and type 2 diabetes; 2) diseases that occur as complications of CAD, such as atrial fibrillation, heart failure, and premature death; and 3) other cardiovascular diseases, such as migraine, abdominal aortic aneurysm, aortic stenosis, peripheral artery disease, and stroke. Although the overlap in genetic risk does not necessarily prove causality, it powerfully demonstrates the potential of genetic scores to investigate complex interactions in large-scale datasets.

Education, for example, is known to influence lifestyle behavior, such as smoking, diet, or physical activity (146). As for CAD, a strong genetic component was also shown for intelligence and educational attainment (i.e., the length of school education). In Europe, educational attainment was inversely correlated with the incidence of CAD, meaning that least educated subjects had the highest CAD incidence and mortality rates (147). A genetic score for educational attainment was also correlated with CAD with an inverse relationship. The score was also associated with the traditional risk factors of smoking, obesity, and hypertension. When the model was adjusted for these risk factors, the association between the educational attainment genetic score and risk of CAD was attenuated, indicating that educational attainment mediates CAD risk via lifestyle. Another important finding was that the association was not altered by adjustment for the number of years spent in school (148). Taken together, it was hypothesized that some genetic variants affect lifestyle behavior via educational attainment, and some genetic variants directly influence these lifestyle factors, culminating in increased risk of CAD. Therefore, increasing the duration of school education as a consequence might not be the clue to reduce the impact of education on CAD risk (149).

Limitations and challenges of polygenic risk scores. As mentioned previously, transferability of results from subjects of European ancestry to other ethnicities remains a challenge. In addition, the search for genetic risk variants is still ongoing. The heritability of CAD, which is explained by the currently known risk variants, is still believed to be below approximately 30%, and the concept of "missing heritability" remains an open issue (150). It remains questionable whether it is theoretically possible to identify variants that explain all or even a large portion of the heritability of complex traits. However, is this even necessary, particularly in risk prediction? Perhaps the genetic basis of complex traits as CAD needs to be understood as probabilistic rather than deterministic. In addition, even the risk, which is believed to be determined by monogenic risk variants, seems to be modulated by polygenic risk (151). Besides the hurdles in the medical community to adequately implement genetic risk scores in clinical practice, there are also psychosocial factors that need to be considered. Knowledge of genetic risk could lead to fear, but also, in cases of low genetic risk, to the feeling of invulnerability. In addition, there are also studies that pour some water into the wine. In another analysis of the UK Biobank data that compared standard risk models and models, including polygenic risk scores, the reclassification improvement was present but modest (152). A further comparison of a standard model to determine CAD risk compared with a model that also included a polygenic risk score in the ARIC (Atherosclerosis Risk In Communities) study and the MESA (Multi-Ethnic Study of Atherosclerosis) failed to show improved reclassification of patients (153). Guidelines that address the indication, implementation, and proper genetic counseling are needed before genetic risk scores will enter clinical routine. The basis for this need is prospective clinical trials that definitively evaluate the benefit of genetic risk scores in prevention and treatment.

SUMMARY AND CONCLUSIONS

Within the past 15 years, tremendous success has been made in the elucidation of CAD genetics. Although genetic studies often face the critique that they have not led to a breakthrough in a reduction of CAD incidence, they have certainly led to identification of novel treatment targets. Some of these are already addressed in clinical practice (e.g., PCSK9), whereas others are still a focus of translational studies but may be ready for prime time in the near future. In addition, GWASs give an exciting insight into the pathophysiology of CAD—that most of the identified loci are not associated with traditional risk factors and that the role of almost one-half of the loci in the pathophysiology still remains unknown. It is obvious that our understanding of coronary atherosclerosis remains incomplete and requires further experimental research. Lastly, the rise of polygenic risk scores demonstrates the power of genetics to improve risk prediction and personalize prevention and treatment strategies. The **Central Illustration** summarizes the impact of CAD genetics on these different fields.

OUTLOOK

What can we expect from the near future? Results from ongoing efforts of large international consortia to identify further CAD risk variants are awaited. The opportunity to perform exome or even whole-genome sequencing at low cost will probably lead to the identification of further rare variants with large effects and thereby reduce the "missing heritability." It will furthermore be exciting to see whether polygenic risk scores can overcome the discussed hurdles and be implemented into clinical practice. Lastly, can we expect the discovery of novel therapeutic targets? So far, medications inspired by genetic findings all interact with lipid metabolism. Although the drugs are new, and the clinical results are promising, they

do not represent entirely new therapeutic concepts. This basically also applies to inflammation-related targets. It will be exciting to see whether we will witness the introduction of therapies that address vascular remodeling or cell proliferation to reduce atherosclerotic plaque formation and progression. However, even if this is not the case, findings from genetic studies in CAD and other cardiovascular diseases will continue to expand our view on the biology underlying the diseases, thereby also improving prevention and therapy.

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ADDRESS FOR CORRESPONDENCE: Dr. Heribert Schunkert, German Heart Centre Munich, Department of Cardiology, Technical University of Munich, Lazarettstrasse 36, 80636 Munich, Germany. E-mail: schunkert@dhm.mhn.de.

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