Genetic Predisposition to Higher Blood Pressure Increases Coronary Artery Disease Risk


Abstract—Hypertension is a risk factor for coronary artery disease. Recent genome-wide association studies have identified 30 genetic variants associated with higher blood pressure at genome-wide significance (P<5×10\(^{-8}\)). If elevated blood pressure is a causative factor for coronary artery disease, these variants should also increase coronary artery disease risk. Analyzing genome-wide association data from 22,233 coronary artery disease cases and 64,762 controls, we observed in the Coronary ARtery DIsease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) consortium that 88% of these blood pressure–associated polymorphisms were likewise positively associated with coronary artery disease, that is, they had an odds ratio >1 for coronary artery disease, a proportion much higher than expected by chance (P=4×10\(^{-5}\)). The average relative coronary artery disease risk increase per each of the multiple blood pressure–raising alleles observed in the consortium was 3.0% for systolic blood pressure–associated polymorphisms (95% confidence interval, 1.8%–4.3%) and 2.9% for diastolic blood pressure–associated polymorphisms (95% confidence interval, 1.7%–4.1%). In substudies, individuals carrying most systolic blood pressure– and diastolic blood pressure–related risk alleles (top quintile of a genetic risk score distribution) had 70% (95% confidence interval, 50%–94%) and 59% (95% confidence interval, 40%–81%) higher odds of having coronary artery disease, respectively, as compared with individuals in the bottom quintile. In conclusion, most blood pressure–associated polymorphisms also confer an increased risk for coronary artery disease. These findings are consistent with a causal relationship of increasing blood pressure to coronary artery disease. Genetic variants primarily affecting blood pressure contribute to the genetic basis of coronary artery disease. (Hypertension. 2013;61:995-1001.) • Online Data Supplement

Key Words: blood pressure ■ coronary artery disease ■ genetics ■ polymorphism

Hypertension is a major cardiovascular risk factor\(^1\) that is determined by multiple environmental and inherited factors.\(^2\) Indeed, weight, physical activity, nutrition, age, and sex have all been shown to affect the variability of blood pressure (BP) in the population.\(^3\^-\(^7\) Identification of the precise genetic underpinnings of BP has been challenging, in part attributable to the complex character of the trait. Recently, genome-wide association studies (GWAS) reported several single nucleotide...
polymorphisms (SNPs) associated with modest interindividual differences in systolic BP (SBP) and diastolic BP (DBP).8–11

BP-associated variants offer a novel approach to study the causality of the association between BP and cardiovascular risk. This is based on the assumption that any relationship between a SNP and a complex disease cannot be secondary to exogenous nongenetic factors, because such potential confounders should be evenly distributed between the respective genotype groups.12 In other words, if higher BP was causally related to cardiovascular disease, then one would expect to find an association between BP-associated SNPs and clinically apparent cardiovascular events, such as coronary artery disease (CAD).

Recently, genetic predisposition to higher BP, based on an aggregate score of genetic variants, was found to be positively associated with CAD, stroke, and alterations in cardiac structure.13 Beyond such a risk score, a more detailed investigation of the contribution of each of these SNPs to CAD risk is of potential interest to better understand the role of BP variability in predisposition to CAD as well as to better define the genetic architecture of the disease. Indeed, the currently known genetic loci primarily associated with CAD explain only about 10% of its heritability.13 In the present analyses, we assessed the associations of 30 BP-related SNPs with CAD in the Coronary ARtery DIsease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) consortium.14 Furthermore, we aimed to evaluate whether the combined evidence of all currently known BP-SNPs (SNPs associated with BP on a genome-wide fashion) displays association with CAD.

Methods

Study Samples

CARDIoGRAM Consortium

Genetic analyses were performed within the CARDIoGRAM consortium, a large consortium on the genetics of myocardial infarction (MI)/CAD.14 In essence, the study includes data from several community–based and patient cohorts with >22,000 CAD cases and >60,000 controls of apparent CAD. The community-based cohorts include, for example, the Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE), deCODE, and Cooperative Research in the Region of Augsburg (KORA); the CAD/MI case–control samples include, for example, Atherosclerotic Disease, Vascular Function, and Genetic Epidemiology (ADVANCE), the German MI Family Studies I–III, The Welcome Trust Case Control Consortium (WTCCC), PennCATH, the Ottawa Heart Genomics study, the Myocardial infarction Genetics Consortium, MedStar, and the Ludwigshafen Risk and Cardiovascular Health Studies 1 and 2.14

Each cohort was genotyped using arrays from either Affymetrix or Illumina, mostly followed by imputation of the genotyped SNPs to HaploType Map (HapMap) CEU samples to achieve the best possible coverage of the genome. On average, 2.2 million SNPs were available per cohort.14 A previous meta-analysis relating a genetic score of BP-related SNPs to CAD was in part based on the CARDIoGRAM data set.10

Framingham Heart Study Sample

The Framingham Heart Study is a multigenerational prospective cohort study of the determinants of cardiovascular disease.15–17 Using a pooled sample from the Original and the Offspring cohort, we quantified the association between BP levels and incident CAD as part of estimating the predicted effect of BP-SNPs on CAD risk (please see below and Figure 1). CAD was defined as one of the following conditions: MI, coronary insufficiency, angina, or coronary death before age 75, consistent with previous publications.18

German MI Family Studies (GerMIFS) I, II, and WTCCC-Study

For studying the cumulative effect of individual SNPs, we used a previously described weighted score in the German MI Family Studies (GerMIFS) I and II as well as in the WTCCC sample that have all been described elsewhere.19–22 Cases of the GerMIFS I and II as well as the WTCCC sample were selected based on a strong familial basis for MI. The index patients of GerMIFS I and II had a premature MI (before the age of 60 years) and ≥1 first-degree relative with an MI/CAD before the age of 70 years, in most cases a sibling.19,20 The controls for the GerMIFS I and II participated in the KORA/MONItoring trends and determinants In CArdiovascular disease (MONICA) F3/F4 study, a follow-up of a sex- and age-stratified random sample of German residents of the Augsburg area (age range, 25–74 years).19,20,22 Cases of the WTCCC CAD study19 had a validated MI or coronary revascularization before the age of 66 years and a positive family history for CAD.23 Within the WTCCC project, controls were chosen from the British 1958 Birth Cohort and from the UK Blood Services (healthy blood donors).19

All studies were approved by institutional review committees, and all participants gave informed consent. All studies adhered to the principles of the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, revised November 13, 2001, effective December 13, 2001.

SNP Selection

A total of 29 SNPs associated with SBP or DBP traits at a genomewide significant threshold (P<5×10−8) were taken from a recent GWAS meta-analysis on 69,395 individuals (replication of top signals in up to 133,661 additional individuals), mostly from population-based studies of individuals of Western European descent.10 This meta-analysis also confirmed 12 of the previously reported genetic loci associated with SBP and DBP.8–11 Because the previously described association of the PLCδ3 locus8 did not replicate in the much larger study by Ehret et al,10 this locus was not considered in the present analysis. One SNP (rs17477177) associated with SBP and 2 SNPs (rs1446468 and rs319690) associated with SBP and DBP at a genome-wide significant level (P<5×10−8) were added from a GWAS on pulse pressure and mean arterial pressure, because they were likewise genome-wide significant for SBP and DBP, respectively.11

Statistical Analyses

Proportion of BP-SNPs With a Positive Association With CAD

We assessed the proportion of BP-raising alleles with a positive association with CAD (odds ratio [OR] >1) in CARDIoGRAM, and we tested whether this proportion differed from 0.5 (proportion of SNPs with an OR>1 for CAD by chance) using an exact binomial test. We also tested whether the proportion of SNPs tested showing nominally significant (P<0.05) association with CAD was higher than expected by chance (exact binomial test for P<0.05).

\[
\beta_{\text{observed}} (\text{CARDIoGRAM}) = \beta_3
\]

Figure 1. Graphical display of how the predicted and observed effect sizes for the association of blood pressure (BP)-associated single nucleotide polymorphisms (SNPs) with coronary artery disease (CAD) were derived. The effect estimates quantifying the association between SNP and BP-trait (β1) were obtained from the literature10,11; the effect estimates for the association of BP with CAD were estimated in the Framingham Heart Study (β2). The observed effect sizes (β3) were obtained from the Coronary ARtery DIsease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM) consortium.
**Observed Effect of BP-SNPs on CAD in CARDIoGRAM**

Within each participating CARDIoGRAM cohort, the association between SNPs and CAD was assessed using a logistic regression model, adjusting for age, sex, and principal components.\(^{13,14}\) Cohort-specific effect estimates and their \(P\) values were meta-analyzed using a fixed-effects model.\(^{14}\) From this meta-analytic database, the association of each individual BP-related SNP with CAD was assessed. This effect is referred to as the observed effect of the SNPs on CAD in the CARDIoGRAM Study.

**Estimation of Predicted Effect of BP-SNPs on CAD**

To estimate the changes in CAD risk associated with relatively small BP changes as observed for the BP-raising alleles, we analyzed pooled data from the Original cohort and the Offspring cohort of the Framingham Heart Study (\(n=7872\)). Using logistic regression models, we quantified the association of baseline SBP and DBP with CAD over a 10-year time horizon, adjusting for age and sex (\(\beta_2\) in Figure 1). The baseline BP was the mean of 2 BP measurements in seated participants, taken \(\approx 5\) minutes apart.

Based on this association between BP levels and incident CAD in the Framingham data set (\(\beta_2\) in Figure 1) and the reported effects of the selected SNPs on BP levels (from the literature\(^{10,11}\); \(\beta_1\) in Figure 1), we calculated the estimated effect size for each SNP on BP risk. Furthermore, we report this analysis correcting the beta estimate \(\beta_2\) for regression dilution, as described previously.\(^{23}\)

**Comparing Observed and Predicted Effects of SNPs on CAD Risk in CARDIoGRAM**

We graphically displayed the predicted effect (after correcting for regression dilution) and the observed effect (both quantified as OR) of each individual SNP on CAD by connecting the predicted and the observed OR by a straight line. Furthermore, the significance for the difference between mean predicted and the mean observed effects (\(\beta_3\)) for SBP-related and DBP-related SNPs was compared using a Mann-Whitney \(U\) test.

**Calculation of Genetic Risk Score of BP-SNPs**

For the present analyses, individual-level genotypic data were available in 4030 cases and 5826 controls from the German MI Family Studies I and II and from the WTCCC sample. These data were used to generate a genetic risk score. In a first step, each risk allele was multiplied by its effect size on CAD providing weighted risk alleles. To generate a genetic risk score, in a first step, each risk allele was multiplied by its effect size on CAD providing weighted risk alleles. In a second step, the weighted risk alleles that each individual carries were summed up across all SNPs. If a given SNP was missing in any of the samples, this SNP was imputed in the respective sample by the most common genotype. This was the case for 1 SNP (rs13107325) in the German MI Family Study II and for 4 SNPs (rs13107325, rs17367504, rs1458038, rs13184504) in the German MI Family Study I. Quantiles of the genetic risk score distribution were compared between CAD cases and controls using a Cochran-Armitage test for trend. C.L. and I.R.K. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Results**

In the literature, we identified 32 SNPs associated with either SBP or DBP or both at a genome-wide significance threshold (\(P<5\times10^{-8}\))\(^{10,11}\); 28 SNPs were associated with each trait, respectively. 24 SNPs displayed associations with both SBP and DBP.\(^{10,11}\) From these 32 SNPs, 2 (MAP4 and FURIN-FES) were not represented in CARDIoGRAM; thus, we analyzed a total of 30 SNPs (26 SNPs for each trait, SBP and DBP).

**Proportion of BP-SNPs Associated With CAD**

For both BP traits, 23 of 26 (88%) SNPs displayed a positive association (OR>1) with CAD in a direction consistent with their effect on BP, a proportion much higher than the 50% expected by chance (\(P=0.00004\)). Furthermore, for SBP, 12 of 26 (46%) SNPs and for DBP, 13 of 26 (50%) SNPs were associated with CAD at nominal significance (\(P<0.05\)) and consistent directionality; a greater proportion than the 5% expected by chance (\(P=1\times10^{-9}\) for SBP-SNPs; and \(P=7\times10^{-11}\) for DBP-SNPs).

Figure 2A and 2B display the association with CAD of each BP- and DBP-associated SNP. Four loci (SH2B3, GOSR2, CYP17A1-NT5C2, CUCY1A3-GUCY1B3) displayed significance for association with CAD at a Bonferroni-corrected threshold (after correction for 30 tests, \(P<0.0016\)). There were only 4 BP-SNPs (representing the loci SLC39A8, PLCE1, ATP2B1, and ULK4) that were not positively related to CAD (OR<1).

**Comparison of Observed and Predicted Effects of BP-SNPs on CAD**

For most SBP- and DBP-associated SNPs, the effect on CAD risk observed in CARDIoGRAM was larger than the predicted effect, that is, the effect that could be predicted given the effects of these SNPs on BP, and the related CAD risk (associated with BP) as observed in the Framingham Heart Study. In fact, the average observed SNP effects on CAD for SBP-SNPs and DBP-SNPs (mean \(\beta_{\text{observed}_\text{SBP}}=0.0299\); mean \(\beta_{\text{observed}_\text{DBP}}=0.0284\)) were almost 3-fold higher than the average predicted effects (mean \(\beta_{\text{predicted}_\text{SBP}}=0.0102\); mean \(\beta_{\text{predicted}_\text{DBP}}=0.0104\); \(P\) for difference, 0.0013 [SBP] and 0.0039 [DBP]). This relationship was attenuated after adjustment for regression dilution bias, a method that corrects for the failure to account for variability or imprecision in BP measurements.\(^{23}\) After such adjustment, the average predicted effects increased markedly (mean \(\beta_{\text{predicted}_\text{SBP}}=0.018\); mean \(\beta_{\text{predicted}_\text{DBP}}=0.019\)), such that the difference to the observed effects was no longer statistically significant for DBP (\(P\) for difference 0.0751). For SBP-associated SNPs, however, the average observed effect remained statistically significantly higher (\(P\) for difference 0.0382). In Figure 3A and 3B, the predicted and observed ORs for CAD for each SNP are shown after correction for regression dilution.

**Cumulative Effect of DBP- and SBP-Associated SNPs on CAD**

Subjects in the highest quintile of the distribution of a weighted score of BP-SNPs had an elevated genetic risk for CAD in CARDIoGRAM (Figure 4A and 4B). For SBP-associated SNPs, patients in the fifth quintile of risk score quintile had 70% (95% confidence interval, 50%–94%) greater odds of having CAD as compared with patients in the bottom quintile (Figure 4A; \(P=3.3\times10^{-13}\) for trend across quintiles). A relatively similar pattern was observed for a genetic risk score based on DBP-related SNPs (Figure 4B). Compared with the lowest genetic risk quintile, individuals in the top quintile had 59% (95% confidence interval, 40%–81%) higher odds of having CAD (\(P=9.0\times10^{-13}\) for trend across quintiles).

**Discussion**

We assessed the individual and joint effects of BP-related SNPs on the risk of CAD. In previous studies, these SNPs have been associated with mild increases in SBP (range, 0.34–1.1 mm Hg per allele) or DBP (range, 0.22–0.68 mm Hg per allele).\(^{10,11}\) Despite the fact that the average effect on SBP...
was only about 0.6 mmHg per allele, almost all of these SNPs were also observed to increase the odds of CAD in CARDIoGRAM. And although there was some variation in the extent by which individual SNPs were associated with BP and CAD risk, the overall evidence from all SNPs examined indicates a directionality-consistent association with CAD for the great majority of BP-raising alleles. Consistent with this finding, individuals in the top quintile of a genetic risk score, based on SBP- and DBP-effects of the SNPs carried by the individual, were at increased risk of having CAD as compared with individuals in the bottom risk quintile.

These results agree with the concept that BP is an important causal risk factor for CAD. Our genetic-epidemiological data add to a large body of population-based and clinical evidence that higher BP, even within the normal range, is associated with higher risk of cardiovascular events. The present study design is different, though, in that our analysis is not based on BP measurements. Rather, we investigate as instrumental variables the effects of SNPs known to be associated with BP. Therefore, our analysis is free of potential nongenetic confounders, because these should be evenly distributed between the genotype groups.

If we focus on the respective allele that goes along with lower BP, our approach is similar to a series of randomized trials, such that each allele associated with lower BP matches the effects of a BP-lowering intervention. A difference
between randomization to a BP-lowering allele and randomization to a pharmacological agent is that the SNP-related effects are likely to have an effect for a much longer period of time, potentially a lifetime. This may explain why we observed an average CAD risk decrease of \( \approx 3\% \) per allele (with average SNP-effects on SBP and DBP of \( \approx 0.6 \) and \( 0.4 \) mm Hg, respectively), whereas a mean BP decrease of 1.04 mm Hg was found to decrease CAD risk by only 2.3\% in a recent meta-analysis of pharmacological studies.\(^26\) Thus, relative to the decrease in BP, the SNP-related effects on CAD were stronger than the drug-related effects in clinical trials. It is conceivable that SNP-related BP effects capture a lifetime exposure to a difference in BP, whereas clinical studies reflect medium-term effects.

Likewise, epidemiological studies may underestimate the true risk mediated by BP, because inherent inaccuracies in the measurements of this risk factor may lead to a regression dilution bias.\(^25\) Indeed, after adjustment for such bias, the effects on CAD risk estimated for small changes in BP increased by about 2.3\% in a recent meta-analysis of pharmacological studies.\(^26\) Thus, relative to the decrease in BP, the SNP-related effects on CAD were stronger than the drug-related effects in clinical trials. It is conceivable that SNP-related BP effects capture a lifetime exposure to a difference in BP, whereas clinical studies reflect medium-term effects.

Figure 3. Plots displaying the predicted and observed effect sizes for the association of each systolic blood pressure (BP; A) and diastolic BP (B)-associated single nucleotide polymorphisms (SNP) with coronary artery disease (CAD). For each BP-related SNP, the predicted and the observed effects on CAD, quantified as odds ratios, are connected by a straight line. The predicted effects were calculated based on (1) the effects of the SNPs on BP levels (as reported in the literature)\(^10,11\) and (2) the respective changes in BP on CAD risk (in the Framingham Heart Study) adjusted for regression dilution bias.\(^23\) The observed effects were derived from the Coronary ARtery Disease Genome-Wide Replication And Meta-Analysis (CARDioGRAM) meta-analysis on CAD GWAS studies.\(^13,14\)

Figure 4. Association of genetic risk scores (consisting of systolic blood pressure [BP]-related single nucleotide polymorphisms [SNPs; A] and of diastolic BP-related SNPs [B]) with coronary artery disease (CAD). Odds ratios and 95\% confidence intervals for the association with CAD for individuals in the 1 to 5 risk score quintile, using the bottom risk score quintile as the reference.

BP-SNPs affect primarily endothelial function, properties of the vascular wall, such as arterial stiffness, or other important intermediate phenotypes. These alterations may be more closely related to CAD risk than the variability in BP in itself. Likewise, CAD risk may be modulated by pleiotropic effects of these SNPs. Although for some loci (eg, the \( SH2B3 \) locus\(^28\) or the \( CYP17A1-NT5C2 \) locus\(^29\)) such pleiotropic effects are described, it is unlikely that they explain overall our findings, because such pleiotropic effects are not expected (1) to be in effect for almost all BP-related SNPs and (2) to affect CAD risk always in the same direction.

Our data are also consistent with the notion that some of the BP-mediated CAD risk is genetically determined. Indeed, the findings strongly suggest that a large number of genetic variants, primarily affecting BP, are also secondarily involved in the manifestation of CAD. Because of the exploratory and descriptive character of our CAD analyses, we did not focus on individual SNP effects. It is remarkable, however, that 4 loci (\( SH2B3, GOSR2, CYP17A1-NT5C2, CUCY1A3-GUCY1B3 \)) displayed study-wide significant association with CAD after adjustment for the number of SNPs tested. Nevertheless, for individual SNP data, our results should be replicated in other cohorts. This applies specifically to the SNPs that achieved nominally significant \( P \) values in our study. Accordingly, subsequent studies need to test whether the BP-related SNPs can be used to identify individuals susceptible to CAD and whether these individuals benefit from targeted preventive measures.

A weighted genetic risk score based on largely overlapping SNPs was previously associated with incident stroke, left-ventricular wall thickness, and CAD (in a meta-analysis, including
the CARDiOGRAM data set and 2 additional samples). We expand these data in stratifying the risk factor analyses by BP trait, for example, we assessed the aggregate association of SBP-associated SNPs and of DBP-associated SNPs with CAD in separate analyses. Such weighted risk scores, consisting of 26 SNPs associated with either SBP or DBP or both, demonstrated a positive association with CAD. However, because many SNPs display significant overlap in being associated with both SBP and DBP, we cannot conclude that the traits are independently associated with CAD. Furthermore, we provided detailed data on the association of each BP-SNP with CAD in CARDiOGRAM and compared the observed strength of association between each SNP and CAD with the expected strength of association, based on data from the Framingham Heart Study. Our data emphasize the importance of genetics, on the one end, and even small increments of BP, on the other end, with respect to a measurable increase in CAD risk.

**Strengths and Limitations**

A limitation of our approach is that we were not able to study directly the effect sizes linking the SNPs with BP (β in Figure 1), the BP levels with CAD risk (β, in Figure 1), and the SNP with CAD risk (β, in Figure 1) in a single population (also referred to as Mendelian Randomization Study). Rather, we based our analysis on the totality of evidence currently available on subjects of European descent, that is, GWAS meta-analyses studying the associations of SNPs with BP, on the one hand, and with CAD, on the other hand. CARDiOGRAM is a meta-analysis of GWAS for MI and CAD. MI may have profound effects on subsequent BP and mortality, and almost all CAD cases (and many controls) were on BP-lowering therapy at the time of DNA and data sampling. We acknowledge that in population-based samples also a considerable proportion of participants is on antihypertensive medications. However, in the analyses by Ehret et al appropriate adjustments for the intake of medication were performed. Therefore, we believe that the effect estimates for the association between SNPs and BP from the literature (mainly based on the article by Ehret et al) are more valid than those in the different CARDiOGRAM cohorts.

Like recent meta-analysis on the genomics of risk factor traits and CAD risk, we pooled data to maximize power for such analyses. By contrast, the effects of BP on CAD risk were based on observations made in a single prospective study sample, that is, the Framingham Heart Study, and subsequently extrapolated to the effect sizes in the meta-analyses. The strengths of our study include the large sample size (22233 CAD cases and 64762 controls) and the comprehensive set of BP-related SNPs that have been related to CAD. Indeed, our genome-wide data set incorporated almost all SNPs previously identified to affect SBP and DBP with genome-wide significance.

**Perspectives**

Genetic epidemiological studies provide powerful opportunities to assess causality between risk factors and clinically overt cardiovascular disease, based on the principle that the observed associations between true causal genetic variants and CAD should be independent of nongenetic confounders and, as such, exerting larger effects than secondary risk factors or predictors. Applying this principle to the best genetic information currently available for BP and CAD, we demonstrate in the present analyses that many common genetic variants primarily associated with higher SBP and DBP at a population level also confer an increased risk for CAD, consistent with a causal relationship of increasing BP to CAD risk. These results also demonstrate that some of the BP-related CAD risk is genetically determined.

**Sources of Funding**

This work was supported by the EU-funded Integrated Projects Cardiogenics (LSHM-CT-2006-037593) and ENGAGE as well as the BMBF-funded German National Genome Network (NGFN-Plus) Project Atherogenetics (FKZ: 01G0831). W. Lieb has in part been supported by the BMBF-funded (federal ministry for education and research) project GANI_MED. There was support also by the DZHK (German Center for Cardiovascular Research) and by the BMBF (German Ministry of Education and Research and by the Framingham heart core contract N01-HC-25195. Information regarding the CARDiOGRAM members, acknowledgments, funding sources, and disclosures are detailed in the in the online-only Data Supplement.

**Disclosures**

Information regarding disclosures for CARDiOGRAM is detailed in the online-only Data Supplement.

**References**


**Novelty and Significance**

**What Is New?**

- The majority of single nucleotide polymorphisms increasing blood pressure in a genome-wide fashion also confer an increased risk for coronary artery disease.

**What Is Relevant?**

- The average relative risk increase for coronary artery disease for each of the multiple blood pressure–raising alleles was substantial, 3.0% for systolic blood pressure–related single nucleotide polymorphisms (95% confidence interval, 1.8%–4.3%) and 2.9% for diastolic blood pressure–related single nucleotide polymorphisms (95% confidence interval, 1.7%–4.1%).

**Summary**

Single nucleotide polymorphisms primarily affecting blood pressure contribute to the genetic basis of coronary artery disease, consistent with a causal relationship of increasing blood pressure to coronary artery disease.
ONLINE SUPPLEMENT

Genetic predisposition to higher blood pressure increases coronary artery disease risk

Wolfgang Lieb, MD MSc; Henning Jansen, MD; Christina Loley, PhD; Michael J Pencina, PhD; Christopher P Nelson, PhD; Christopher Newton-Cheh, MD MPH; Sekar Kathiresan, MD; Muredach P. Reilly, MD; Themistocles L. Assimes, MD PhD; Eric Boerwinkle, PhD; Alistair Hall, MD PhD; Christian Hengstenberg, MD; Reijo Laaksonen, MD PhD; Ruth McPherson, MD PhD; Unnur Thorsteinsdottir, PhD; Andreas Ziegler, PhD; Annette Peters, PhD; John R Thompson, PhD; Inke R König, PhD; Jeanette Erdmann, PhD; Nilesh J Samani, MD; Ramachandran S Vasan, MD; Heribert Schunkert, MD on behalf of CARDIoGRAM

Sources of Funding, Members, Affiliations, and Disclosures of the CARDIoGRAM Consortium

Sources of Funding of the CARDIoGRAM Consortium (page 2)
Members of the CARDIoGRAM Consortium (page 3)
Affiliations (page 5)
Disclosures (page 6)
Sources of Funding of the Cardiogram Consortium

The ADVANCE study was supported by a grant from the Reynolds's Foundation and NHLBI grant HL087647.

Genetic analyses of CADomics were supported by a research grant from Boehringer Ingelheim. Recruitment and analysis of the CADomics cohort was supported by grants from Boehringer Ingelheim and PHILIPS medical Systems, by the Government of Rheinland-Pfalz in the context of the “Stiftung Rheinland-Pfalz für Innovation”, the research program “Wissen schafft Zukunft” and by the Johannes-Gutenberg University of Mainz in the context of the “Schwerpunkt Vaskuläre Prävention” and the “MAIFOR grant 2001”, by grants from the Fondation de France, the French Ministry of Research, and the Institut National de la Santé et de la Recherche Médicale.

The deCODE CAD/MI Study was sponsored by NIH grant, National Heart, Lung and Blood Institute R01HL089650-02.

The German MI Family Studies (GerMIFS I-III (KORA)) were supported by the Deutsche Forschungsgemeinschaft and the German Federal Ministry of Education and Research (BMBF) in the context of the German National Genome Research Network (NGFN-2 and NGFN-plus), the EU funded integrated project Cardiogenics (LSHM-CT-2006-037593), and the bi-national BMBF/ANR funded project CARDomics (01KU0908A).

LURIC has received funding from the EU framework 6 funded Integrated Project “Bloodomics” (LSHM-CT-2004-503485), the EU framework 7 funded Integrated Project AtheroRemo (HEALTH-F2-2008-201668) and from Sanofi/Aventis, Roche, Dade Behring/Siemens, and AstraZeneca.

The MiGen study was funded by the US National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute’s STAMPEED genomics research program through R01 HL087676. Ron Do from the MiGen study is supported by a Canada Graduate Doctoral Scholarship from the Canadian Institutes of Health Research.

Recruitment of PennCATH was supported by the Cardiovascular Institute of the University of Pennsylvania. Recruitment of the MedStar sample was supported in part by the MedStar Research Institute and the Washington Hospital Center and a research grant from GlaxoSmithKline. Genotyping of PennCATH and Medstar was performed at the Center for Applied Genomics at the Children’s Hospital of Philadelphia and supported by GlaxoSmithKline through an Alternate Drug Discovery Initiative research alliance award (M. P. R. and D. J. R.) with the University of Pennsylvania School of Medicine.

The Ottawa Heart Genomic Study was supported by CIHR #MOP–82810 (R. R.), CFI #11966 (R. R.), HSFO #NA6001 (R. McP.), CIHR #MOP172605 (R. McP.), CIHR #MOP77682 (A. F. R. S.).

The WTCCC Study was funded by the Wellcome Trust. Recruitment of cases for the WTCCC Study was carried out by the British Heart Foundation (BHF) Family Heart Study Research Group and supported by the BHF and the UK Medical Research Council. N. J. S. and S. G. B. hold chairs funded by the British Heart Foundation. N. J. S. and A.H.G are also supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease and the work described in this paper is part of the research portfolio of the Leicester NIHR Biomedical Research Unit.

The Age, Gene/Environment Susceptibility Reykjavik Study has been funded by NIH contract N01-AG-12100, the NIA Intramural Research Program, Hjartaværnd (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament).

The Cleveland Clinic GeneBank study was supported by NIH grants P01 HL098055, P01HL076491-06, R01DK080732, P01HL087018, and 1RO1HL103931-01.

The collection of clinical and sociodemographic data in the Dortmund Health Study was supported by the German Migraine- & Headache Society (DMKG) and by unrestricted grants of equal share from Astra Zeneca, Berlin Chemie, Boots Healthcare, Glaxo-Smith-Kline, McNeil Pharma (former Woelm Pharma), MSD
Sharp & Dohme and Pfizer to the University of Muenster. Blood collection was done through funds from the Institute of Epidemiology and Social Medicine, University of Muenster.

The **EPIC-Norfolk study** is supported by the Medical Research Council UK and Cancer Research UK.

The **EpiDREAM study** is supported by the Canadian Institutes for Health Research, Heart and Stroke Foundation of Ontario, Sanofi-Aventis, GlaxoSmithKline and King Pharmaceuticals.

Funding for Andrew Lottery from the **LEEDS** study was provided by the T.F.C. Frost charity and the Macular Disease Society.

The **Rotterdam Study** is supported by the Erasmus Medical Center and Erasmus University Rotterdam; the Netherlands Organization for Scientific Research; the Netherlands Organization for Health Research and Development (ZonMw); the Research Institute for Diseases in the Elderly; The Netherlands Heart Foundation; the Ministry of Education, Culture and Science; the Ministry of Health Welfare and Sports; the European Commission (DG XII); and the Municipality of Rotterdam. Support for genotyping was provided by the Netherlands Organization for Scientific Research (NWO) (175.010.2005.011, 911.03.012), the Netherlands Genomics Initiative (NGI)/NWO project nr. 050-060-810 and Research Institute for Diseases in the Elderly (RIDE). Abbas Dehghan is supported by a grant from NWO (Vici, 918-76-619).

The **SAS** study was funded by the British Heart Foundation.

The Swedish Research Council, the Swedish Heart & Lung Foundation and the Stockholm County Council (ALF) supported the **SHEEP** study.

SMILE was funded by the Netherlands Heart foundation (NHS 92345). Dr Rosendaal is a recipient of the Spinoza Award of the Netherlands Organisation for Scientific Research (NWO) which was used for part of this work.

The **Verona Heart Study** was funded by grants from the Italian Ministry of University and Research, the Veneto Region, and the Cariverona Foundation, Verona.

The **Atherosclerosis Risk in Communities Study** is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022. The authors thank the staff and participants of the ARIC study for their important contributions.

The **KORA** (Kooperative Gesundheitsforschung in der Region Augsburg) research platform was initiated and financed by the Helmholtz Zentrum München - National Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. Part of this work was financed by the German National Genome Research Network (NGFN-2 and NGFNPlus) and within the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ.

Work described in this paper is part of the research portfolio supported by the Leicester NIHR Biomedical Research Unit in Cardiovascular Disease.

This work forms part of the research themes contributing to the translational research portfolio of Barts and the London Cardiovascular Biomedical Research Unit which is supported and funded by the National Institute of Health Research.

**The CARDioGRAM Consortium**

**Executive Committee:** Sekar Kathiresan¹², Muredach P. Reilly⁴, Nilesh J. Samani⁵, Heribert Schunkert⁷

**Executive Secretary:** Jeanette Erdmann⁷

Statisticians: Inke R. König (chair), John R. Thompson (chair), Devin Absher, Li Chen, L. Adrienne Cupples, Eran Halperin, Mingyao Li, Kiran Musunuru, Michael Preuss, Arne Schillert, Gudmar Thorleifsson, Benjamin F. Voight, George A. Wells


ADVANCE: Devin Absher, Themistocles L. Assimes, Stephen Fortmann, Alan Go, Mark Hlatky, Carlos Iribarren, Joshua Knowles, Richard Myers, Thomas Quertermous, Steven Sidney, Neil Risch, Hua Tang

CADomics: Stefan Blanken, Tanja Zeller, Arne Schillert, Philipp Wild, Andreas Ziegler, Renate Schnabel, Christoph Sinning, Karl Lackner, Laurence Tiet, Viviane Nicaud, Francois Cambien, Christof Bickel, Hans J. Rupprecht, Claire Perret, Carole Proust, Thomas Münzel


decODE: Solveig Gretarsdottir, Jeffrey R. Gucler, Hilma Holm, Augustine Kong, Kari Stefansson, Gudmundur Thorgerisson, Karl Anders, Gudmar Thöllefsson, Unnur Thorsteinsdottir


LURIC/AtheroRemo: Bernhard O. Böhm, Harald Dobin, Tanja B. Gramer, Eran Halperin, Michael M. Hoffmann, Marcus Kleber, Reijo Laaksonen, Winfried März, Andreas Meinitzer, Bernhard R. Winkelmann, Stefan Pilz, Wilfried Renner, Hubert Scharnagl, Tatjana Stojakovic, Andreas Tomaschitz, Karl Winkler


OHGS: Alexandre F. R. Stewart, Li Chen, Sonny Dandona, George A. Wells, Olga Jaronova, Ruth McPherson, Robert Roberts


WTCC: Nilesj. Samani, John R. Thompson, Peter S. Braund, Christopher P. Nelson, Benjamin J. Wright, Anthony J. Balmforth, Stephen G. Ball, Alistair S. Hall, Wellcome Trust Case Control Consortium
Affiliations
1 Cardiovascular Research Center and Cardiology Division, Massachusetts General Hospital, Boston, MA, USA; 2 Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA, USA; 3 Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology (MIT), Cambridge, MA, USA; 4 The Cardiovascular Institute, University of Pennsylvania, Philadelphia, PA, USA; 5 Department of Cardiovascular Sciences, University of Leicester, Glenfield Hospital, Leicester, UK; 6 Leicester National Institute for Health Research Biomedical Research Unit in Cardiovascular Disease, Glenfield Hospital, Leicester, LE3 9QP, UK; 7 Medizinische Klinik II, Universität zu Lübeck, Lübeck, Germany; 8 Department of Medicine, Stanford University School of Medicine, Stanford, CA, USA; 9 University of Texas Health Science Center, Human Genetics Center and Institute of Molecular Medicine, Houston, TX, USA; 10 Division of Cardiovascular and Neuronal Remodelling, Multidisciplinary Cardiovascular Research Centre, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, UK; 11 Klinik und Poliklinik für Innere Medizin II, Universität Regensburg, Regensburg, Germany; 12 Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Lübeck, Germany; 13 Science Center, Tampere University Hospital, Tampere, Finland; 14 The John & Jennifer Ruddy Canadian Cardiovascular Genetics Centre, University of Ottawa Heart Institute, Ottawa, Canada; 15 Department of Health Sciences, University of Leicester, Leicester, UK; 16 deCODE Genetics, 101 Reykjavik, Iceland; 17 University of Iceland, Faculty of Medicine, 101 Reykjavik, Iceland; 18 Hudson Alpha Institute, Huntsville, Alabama, USA; 19 Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, 40 Ruskin Street, Ottawa, Ontario, Canada, K1Y 4W7; 20 Department of Biostatistics, Boston University School of Public Health, Boston, MA USA; 21 National Heart, Lung and Blood Institute's Framingham Heart Study, Framingham, MA, USA; 22 The Blavatnik School of Computer Science and the Department of Molecular Microbiology and Biotechnology, Tel-Aviv University, Tel-Aviv, Israel, and the International Computer Science Institute, Berkeley, CA, USA; 23 Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, USA; 24 Department of Medicine, Harvard Medical School, Boston, MA, USA; 25 Research Methods, Univ Ottawa Heart Inst; 26 Department of Clinical Sciences, Hypertension and Cardiovascular Diseases, Scania University Hospital, Lund University, Malmö, Sweden; 27 Division of Research, Kaiser Permanente, Oakland, CA, USA; 28 Institute for Human Genetics, University of California, San Francisco, San Francisco, CA, USA; 29 Dept Cardiovascular Medicine, Cleveland Clinic; 30 Medizinische Klinik und Poliklinik, Johannes-Gutenberg Universität Mainz, Universitätsmedizin, Mainz, Germany; 31 Institut für Klinische Chemie und Laboratoriumsmedizin, Johannes-Gutenberg Universität Mainz, Universitätsmedizin, Mainz, Germany; 32 INSERM UMR 937, Pierre and Marie Curie University (UPMC, Paris 6) and Medical School, Paris, France; 33 University of Texas Health Science Center, Human Genetics Center, Houston, TX, USA; 34 Cardiovascular Health Research Unit and Department of Medicine, University of Washington, Seattle, WA USA; 35 Cedars-Sinai Medical Center, Medical Genetics Institute, Los Angeles, CA, USA; 36 Erasmus Medical Center, Department of Epidemiology, Rotterdam, The Netherlands; 37 Boston University, School of Public Health, Boston, MA, USA; 38 University of Minnesota School of Public Health, Division of Epidemiology and Community Health, School of Public Health (A.R.F.), Minneapolis, MN, USA; 39 University of Washington, Cardiovascular Health Research Unit and Department of Medicine, Seattle, WA, USA; 40 Icelandic Heart Association, Kopavogur Iceland; 41 University of Iceland, Reykjavik, Iceland; 42 Laboratory of Epidemiology, Demography, and Biometry, Intramural Research Program, National Institute on Aging, National Institutes of Health, Bethesda MD, USA; 43 University of Washington, Department of Epidemiology, Seattle, WA, USA; 44 University of Washington, Department of Biostatistics, Seattle, WA, USA; 45 University of Washington, Department of Internal Medicine, Seattle, WA, USA; 46 University of Texas, School of Public Health, Houston, TX, USA; 47 National Heart, Lung and Blood Institute, Framingham Heart Study, Framingham, MA and Cardiology Division, Massachusetts General Hospital, Boston, MA, USA; 48 Center for Health Studies, Group Health, Departments of Medicine, Epidemiology, and Health Services,
Seattle, WA, USA; 49 The Wellcome Trust Sanger Institute, The Wellcome Trust Genome Campus, Hinxton, Cambridge, UK; 50 Cardiovascular Health Research Unit, Departments of Medicine and Epidemiology, University of Washington, Seattle; 51 Boston University Medical Center, Boston, MA, USA; 52 Department of Internal Medicine, Erasmus Medical Center, Rotterdam, The Netherlands; 53 Department of Medicine, Landspitali University Hospital, 101 Reykjavik, Iceland; 54 Boston University School of Medicine, Framingham Heart Study, Framingham, MA, USA; 55 Institut für Klinische Molekularbiologie, Christian-Albrechts Universität, Kiel, Germany; 56 Institute of Epidemiology, Helmholtz Zentrum München – German Research Center for Environmental Health, Neuherberg, Germany; 57 Institut für Humangenetik, Helmholtz Zentrum München, Deutsches Forschungszentrum für Umwelt und Gesundheit, Neuherberg, Germany; 58 Institute of Medical Information Science, Biometry and Epidemiology, Ludwig-Maximilians-Universität München, Germany; 59 Klinikum Grosshadern, Munich, Germany; 60 Institut für Humangenetik, Technische Universität München, Germany; 61 Division of Endocrinology and Diabetes, Graduate School of Molecular Endocrinology and Diabetes, University of Ulm, Ulm, Germany; 62 Division of Endocrinology, Department of Medicine, Medical University of Graz, Austria; 63 Synlab Center of Laboratory Diagnostics Heidelberg, Heidelberg, Germany; 64 Division of Clinical Chemistry, Department of Medicine, Albert Ludwigs University, Freiburg, Germany; 65 LURIC non profit LLC, Freiburg, Germany; 66 Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Graz, Austria; 67 Institute of Public Health, Social and Preventive Medicine, Medical Faculty Mannheim, University of Heidelberg, Germany; 68 Cardiology Group Frankfurt-Sachsenhausen, Frankfurt, Germany; 69 Cardiovascular Epidemiology and Genetics Group, Institut Municipal d’Investigació Mèdica, Barcelona; Ciber Epidemiología y Salud Pública (CIBERESP), Spain; 70 Chronic Disease Epidemiology and Prevention Unit, Department of Chronic Disease Prevention, National Institute for Health and Welfare, Helsinki, Finland; 71 Department of Molecular Biology and Center for Human Genetic Research, Massachusetts General Hospital, Harvard Medical School, Boston, USA; 72 The Center for Applied Genomics, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; 73 Cardiovascular Research Institute, Medstar Health Research Institute, Washington Hospital Center, Washington, DC 20010, USA; 74 Genetics Division and Drug Discovery, GlaxoSmithKline, King of Prussia, Pennsylvania 19406, USA; 75 The Institute for Translational Medicine and Therapeutics, School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; 76 Department of Cardiovascular Surgery, University of Leicester, Leicester, UK; 77 Division of Cardiovascular and Diabetes Research, Multidisciplinary Cardiovascular Research Centre, Leeds Institute of Genetics, Health and Therapeutics, University of Leeds, Leeds, LS2 9JT, UK; 78 LIGHT Research Institute, Faculty of Medicine and Health, University of Leeds, Leeds, UK; 79 Nordic Center for Cardiovascular Research (NCCR), Lübeck, Germany

Disclosures
Dr Absher reports receiving an NIH research grant for the ADVANCE study. Dr Assimes reports receiving an NIH research grant for the ADVANCE study. Dr Blankenberg reports receiving research grants from NFGNplus for Atherogenomics and from BMBF for CADomics. Dr Boerwinkle received research support from NIH/National Human Genome Research Institute (NHGRI), GWA for gene-environment interaction effects influencing CGD; NIH/NHLBI, Molecular epidemiology of essential hypertension; NIH/NHLBI, Genome-wide association for loci influencing coronary heart disease; NIH/NHLBI, Genetics of hypertension-associated treatment; NIH/NHLBI, Modeling DNA diversity in reverse cholesterol transport; NIH/NHLBI, 20-year changes in fitness and cardiovascular disease risk; NIH/NHLBI, Genetic epidemiology of sodium-lithium countertransport; NIH/National Institute of General Medical Sciences (NIGMS), Pharmacogenomic evaluation of antihypertensive responses; NIH/NIGMS, Genomic approaches to common chronic disease; NIH/NHLBI, Genes of the CYP450-derived eicosanoids in subclinical atherosclerosis; NIH/NHGRI-University of North Carolina, Chapel Hill, Genetic epidemiology of causal variants across the life course; and NIH/NHLBI, Building on GWAS for NHLBI-diseases: the CHARGE consortium. Dr Cupples reports receiving research grants from
NIH/NHLBI, The Framingham Heart Study; NIH/NHLBI, Genome-wide association study of cardiac structure and function; NIH/NHLBI, Functional evaluation of GWAS loci for cardiovascular intermediate phenotypes; and NIH/NHLBI, Building on GWAS for NHLBI-diseases: the CHARGE consortium. Dr Halperin reports receiving research grants from NIH, subcontract Genome-wide association study of Non Hodgkin’s lymphoma; ISF, Efficient design and analysis of disease association studies; EU, consultant AtheroRemo; NSF, Methods for sequencing based associations; BSF, Searching for causal genetic variants in breast cancer and honoraria from Scripps Institute, UCLA. Dr Halperin also reports ownership interest in Navigenics. Dr Hengstenberg reports receiving research grants for EU Cardiogenics. Dr Holm reports receiving a research grant from NIH; providing expert witness consultation for the district court of Reykjavik; serving as member of the editorial board for decodeme, a service provided by deCODE Genetics; and employment with deCODE Genetics. Dr Li reports receiving research grant R01HG004517 and other research support in the form of co-investigator on several NIH-funded grants and receiving honoraria from National Cancer Institute Division of Cancer Epidemiology and Genetics. Dr McPherson reports receiving research grants from Heart & Stroke Funds Ontario, CIHR, and CFI. Dr Rader reports receiving research grant support from GlaxoSmithKline. Dr Roberts reports receiving research grants from the Cystic Fibrosis Foundation, NIH, and Cancer Immunology and Hematology Branch; membership on the speakers bureau for AstraZeneca; receiving honoraria from Several; and serving as consultant/advisory board member for Celera. Dr Stewart reports receiving research grant support from CIHR, Genome-wide scan to identify coronary artery disease genes, and CIHR, Genetic basis of salt-sensitive hypertension in humans; other research support from CFI: Infrastructure support; and honoraria from the Institute for Biomedical Sciences, Academia Sinica, Taipei, Taiwan. Dr Thorleifsson is an employee of deCODE Genetics. Dr Thorsteinsdottir reports receiving research grants from NIH and EU; serving as an expert witness for a US trial; having stock options at deCODE Genetics; and having employment with deCODE Genetics. Dr Kathiresan reports receiving research grants from Pfizer, Discovery of type 2 diabetes genes, and Alnylam, Function of new lipid genes, and serving as consultant/advisory board member for DAIICHI SANKYO Merck. Dr Reilly reports receiving research grant support from GlaxoSmithKline. Dr Schunkert reports receiving research grants from the EU, project Cardiogenics; NGFN, project Atherogenomics; and CADnet BMBF. M. Preuss, L. Chen, and Drs König, Thompson, Erdmann, Hall, Laaksonen, März, Musunuru, Nelson, Burnett, Epstein, O’Donnell, Quertermous, Schillert, Stefansson, Voight, Wells, Ziegler, and Samani have no conflicts to disclose. Genotyping of PennCATH and MedStar was supported by Glaxo-SmithKline. Dawn M. Waterworth, Max C. Walker, and Vincent Mooser are employees of GlaxoSmithKline. PennCath/MedStar investigators acknowledge the support of Eliot Ohlstein, Dan Burns and Allen Roses at GlaxoSmithKline.