

Genetic Predisposition to Higher Blood Pressure Increases Coronary Artery Disease RiskNovelty and Significance

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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 ($P < 5 \times 10^{-8}$). 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 ($P = 4 \times 10^{-5}$). 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 factor¹ 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

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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.¹⁰ 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 free 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 Wellcome 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.^{19–21} 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.¹⁹ 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 genome-wide significant threshold ($P < 5 \times 10^{-8}$) 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.^{8,9} Because the previously described association of the *PLCD3* 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 ($P < 5 \times 10^{-8}$) 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 $P < 0.05$).

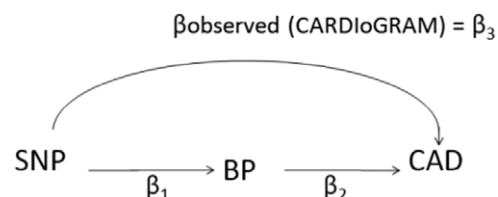


Figure 1. Graphical display of how the predicted and observed effect sizes for the association of blood pressure (BP)-associated single nucleotide polymorphisms (SNPs) with coronary artery disease (CAD) were derived. The effect estimates quantifying the association between SNP and BP-trait (β_1) were obtained from the literature^{10,11}; the effect estimates for the association of BP with CAD were estimated in the Framingham Heart Study (β_2). The observed effect sizes (β_3) 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 (β_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 (β_2 in Figure 1) and the reported effects of the selected SNPs on BP levels (from the literature^{10,11}; β_1 in Figure 1), we calculated the estimated effect size for each BP SNP on CAD risk. Furthermore, we report this analysis correcting the beta estimate β_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 (β s) 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. 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, rs3184504) in the German MI Family Study I. Quintiles 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 ($P < 5 \times 10^{-8}$)^{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 ($P = 1 \times 10^{-9}$ for SBP-SNPs; and $P = 7 \times 10^{-11}$ for DBP-SNPs).

Figure 2A and 2B display the association with CAD of each SBP- 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 $\beta_{\text{observed_SBP}} = 0.0299$; mean $\beta_{\text{observed_DBP}} = 0.0284$) were almost 3-fold higher than the average predicted effects (mean $\beta_{\text{predicted_SBP}} = 0.0102$; mean $\beta_{\text{predicted_DBP}} = 0.0104$; *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 $\beta_{\text{predicted_SBP}} = 0.018$; mean $\beta_{\text{predicted_DBP}} = 0.019$), 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; $P = 3.3 \times 10^{-13}$ 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 ($P = 9.0 \times 10^{-13}$ 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

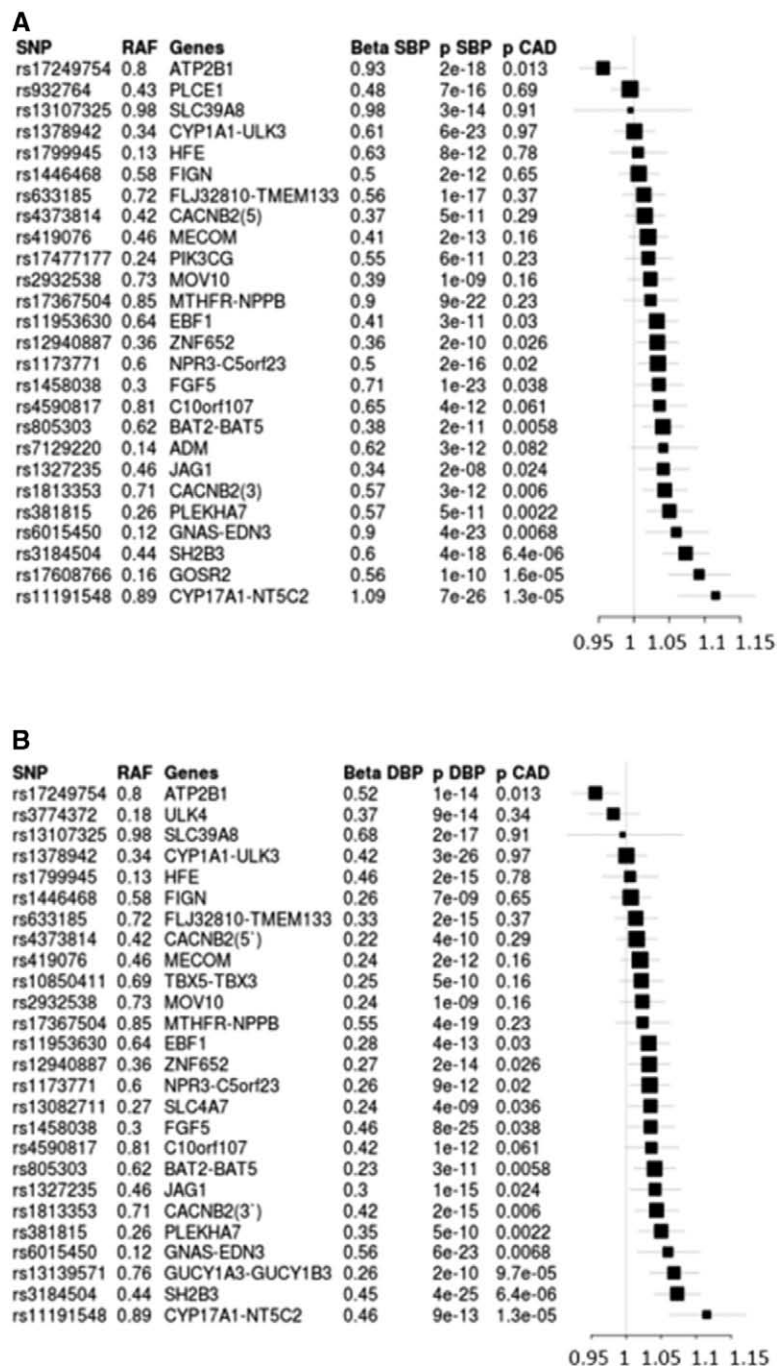


Figure 2. Forest plots displaying the associations of each systolic blood pressure (SBP) single nucleotide polymorphisms (SNP; **A**) and each diastolic BP SNP (**B**) with coronary artery disease (CAD) in Coronary ARtery Disease Genome-Wide Replication And Meta-Analysis (CARDIoGRAM). Boxes represent the odds ratios (ORs) and whiskers 95% confidence intervals. Size of boxes is proportional to the inverse variance of ORs. Genes and respective lead SNPs (rs numbers) are listed. beta SBP/DBP quantifies the effect of the SNP on BP (as reported in the literature).^{10,11} p SBP/DBP indicates the respective *P* value^{10,11}; p CAD, the *P* value for the association of the SNP with CAD as observed in CARDIoGRAM; and RAF, risk allele frequency.

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.¹ In this respect,

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.²⁴ The present study design is different, though, in that our analysis is not based on BP measurements. Rather, we investigate as instrumental variables¹² 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.^{25,26} A difference

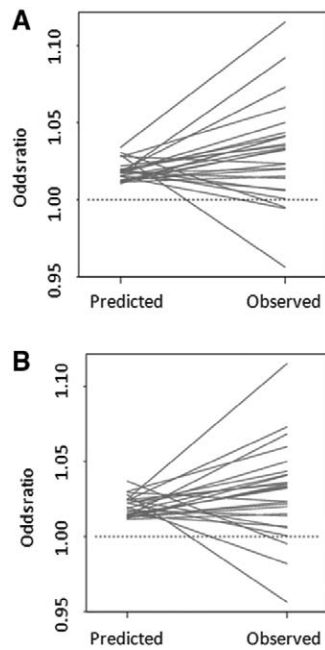


Figure 3. Plots displaying the predicted and observed effect sizes for the association of each systolic blood pressure (BP; **A**)- and diastolic BP (**B**)-associated single nucleotide polymorphisms (SNP) with coronary artery disease (CAD). For each BP-related SNP, the predicted and the observed effects 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}

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 ≈ 0.6 and 0.4 mmHg, respectively), whereas a mean BP decrease of 1.04 mmHg 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.²⁷ Indeed, after adjustment for such bias, the effects on CAD risk estimated for small changes in BP increased by about 80% and were, at comparable changes in BP, no longer significantly different from the effects observed for the DBP-related SNPs; however, for SBP-associated SNPs, the difference remained significant ($P=0.038$).

Another potential explanation for the profound effects of the analyzed SNPs may be related to their biological effects. In other words, it is hypothetically conceivable that these

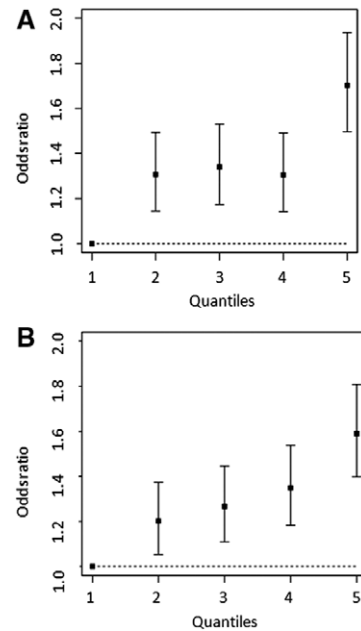


Figure 4. Association of genetic risk scores (consisting of systolic blood pressure [BP]-related single nucleotide polymorphisms [SNPs; **A**] and of diastolic BP-related SNPs [**B**]) with coronary artery disease (CAD). Odds ratios and 95% confidence intervals for the association with CAD for individuals 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* locus²⁸ or the *CYP17A1-NT5C2* locus²⁹) 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).¹⁰ 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_1 in Figure 1), the BP levels with CAD risk (β_2 in Figure 1), and the SNP with CAD risk (β_3 in Figure 1) in a single population (also referred to as Mendelian Randomization Study).¹² 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,^{10,11} on the one hand, and with CAD,¹⁴ 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 al¹⁰ 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 al¹⁰) 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 (22 233 CAD cases and 64 762 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.

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Disclosures

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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

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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)

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