Circulation

ORIGINAL RESEARCH ARTICLE

Association of Factor V Leiden With Subsequent Atherothrombotic Events

A GENIUS-CHD Study of Individual Participant Data

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BACKGROUND: Studies examining the role of factor V Leiden among patients at higher risk of atherothrombotic events, such as those with established coronary heart disease (CHD), are lacking. Given that coagulation is involved in the thrombus formation stage on atherosclerotic plaque rupture, we hypothesized that factor V Leiden may be a stronger risk factor for atherothrombotic events in patients with established CHD.

METHODS: We performed an individual-level meta-analysis including 25 prospective studies (18 cohorts, 3 case-cohorts, 4 randomized trials) from the GENIUS-CHD (Genetics of Subsequent Coronary Heart Disease) consortium involving patients with established CHD at baseline. Participating studies genotyped factor V Leiden status and shared risk estimates for the outcomes of interest using a centrally developed statistical code with harmonized definitions across studies. Cox proportional hazards regression models were used to obtain age- and sex-adjusted estimates. The obtained estimates were pooled using fixed-effect meta-analysis. The primary outcome was composite of myocardial infarction and CHD death. Secondary outcomes included any stroke, ischemic stroke, coronary revascularization, cardiovascular mortality, and all-cause mortality.

RESULTS: The studies included 69 681 individuals of whom 3190 (4.6%) were either heterozygous or homozygous (n=47) carriers of factor V Leiden. Median follow-up per study ranged from 1.0 to 10.6 years. A total of 20 studies with 61 147 participants and 6849 events contributed to analyses of the primary outcome. Factor V Leiden was not associated with the combined outcome of myocardial infarction and CHD death (hazard ratio, 1.03 [95% CI, 0.92–1.16]; I^2=28%; *P*-heterogeneity=0.12). Subgroup analysis according to baseline characteristics or strata of traditional cardiovascular risk factors did not show relevant differences. Similarly, risk estimates for the secondary outcomes including stroke, coronary revascularization, cardiovascular mortality, and all-cause mortality were also close to identity.

CONCLUSIONS: Factor V Leiden was not associated with increased risk of subsequent atherothrombotic events and mortality in high-risk participants with established and treated CHD. Routine assessment of factor V Leiden status is unlikely to improve atherothrombotic events risk stratification in this population.

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Key Words: coronary artery disease ■ genetic association studies ■ thrombosis ■ prognosis ■ single nucleotide polymorphism ■ myocardial infarction ■ secondary prevention

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Clinical Perspective

What Is New?

- In a large-scale individual-level data meta-analysis of 25 studies recruiting nearly 70 000 patients with established coronary heart disease, factor V Leiden was not associated with an increased risk of further atherothrombotic events or death compared with noncarriers.
- A post hoc analysis, however, suggests that factor V Leiden carriers with established coronary heart disease may gain greater protection from subsequent coronary heart disease death or myocardial infarction through dual antiplatelet therapy compared with noncarriers.

What Are the Clinical Implications?

- The routine assessment of factor V Leiden genotype to improve risk stratification in secondary prevention settings is unlikely to be of value and is not recommended.
- Further work is required to elucidate whether there may instead be a pharmacogenomic role for factor V Leiden status, to help personalize treatment with intensive antiplatelet therapy.

Factor V Leiden, is a genetic variant leading to alteration of the inactivation site of factor V, which in turn leads to activated protein C resistance and a prothrombotic state.[1] Affecting almost 5% of the White population,[2] carriers of factor V Leiden have a 4-fold higher risk of venous thromboembolism.[3] However, the risk of arterial atherothrombotic events, such as myocardial infarction or stroke, conferred by the presence of this variant is less certain.[4–10] Association analyses of factor V Leiden with atherothrombotic events have been mostly conducted in case-control studies and limited to the occurrence of a first cardiovascular event in young or disease-free individuals at low risk of adverse outcomes.[4–10]

In contrast, studies examining the role of factor V Leiden among patients at higher risk of atherothrombotic events, such as those with previous events or established coronary heart disease (CHD), are lacking. In such individuals, who may have a greater atheroma burden and more vulnerable plaques, we hypothesized that carriage of factor V Leiden could manifest as a greater risk of subsequent atherothrombotic events, given the role of coagulation cascade in the acute thrombus formation following plaque rupture or erosion. Furthermore, the synergistic interaction between factor V Leiden and traditional cardiovascular risk factors as reported in some previous studies,[11–13] suggests the possibility of a greater effect in populations with greater atheroma burden. Given the high prevalence of Factor V Leiden, if an association exists, this could support screening of patients with established cardiovascular disease for considering use of anticoagulant therapies,[14] for a targeted precision medicine approach to treatment.

We therefore assessed the association of the factor V Leiden polymorphism with subsequent atherothrombotic events including mortality, in individuals with established CHD using an individual-level data meta-analysis of 25 prospective studies from the GENIUS-CHD Consortium (Genetics of Subsequent Coronary Heart Disease).

METHODS

In accordance with Transparency and Openness Promotion Guidelines, the authors declare that all summary level data used for meta-analysis are available within the article and its online Data Supplement. Individual participant level data for each study were not collected through the federated analysis approach used by the consortium and will therefore not be made available. Further details and contact information are available at www.genius-chd.org.

Study Selection Criteria

The GENIUS-CHD consortium is an international collaboration of prospective studies selectively including individuals with established CHD at baseline and following them for future subsequent CHD events.[15]

The primary criteria for inclusion in the consortium are studies that recruited individuals with: (1) established CHD, defined as a history of or presence at baseline of acute coronary syndrome, or of coronary artery disease as evidenced by any revascularization procedure such as percutaneous coronary intervention or coronary bypass surgery, or a significant (50%) coronary artery plaque at angiography affecting any major epicardial vessel; (2) availability of prospective follow-up and ascertainment of at least 1 clinical cardiovascular outcome including all-cause mortality; and (3) availability of samples or biomarkers or in-silico genotyping data. Full details about the GENIUS-CHD Consortium have been published elsewhere.[15]

A short description of the individual studies from the consortium, participating in this specific analysis of factor V Leiden are listed in the Data Supplement. Participating studies received local institutional review board approval and included participants who had provided informed consent at the time of enrolment. The central analysis sites also received waivers from their local institutional review board for collating and analyzing summary level data from the participating studies.

Outcomes

The primary outcome of interest was a composite of CHD death or myocardial infarction (CHD death/myocardial infarction), whichever came first during follow-up. Myocardial infarction included both ST-segment elevation and non-ST segment elevation myocardial infarction. Secondary outcomes consisted of nonfatal myocardial infarction, any stroke, ischemic stroke, coronary revascularization by means of percutaneous coronary intervention or bypass surgery, cardiovascular mortality, and mortality from any cause.

Exposure Variable Definition

Factor V Leiden was defined as the presence of a single nucleotide mutation; G-to-A substitution at nucleotide 1691 in the factor V (factor V R506Q) gene (single-nucleotide polymorphism rs6025), documented by individual genotyping assays or direct DNA sequencing using various commercially available whole genome or targeted sequencing kits.

Statistical Analysis

Analyses were performed in 2 stages. First, individual studies participating within the GENIUS-CHD Consortium and with available genotype data, evaluated the association between factor V Leiden and subsequent events assuming a dominant genetic model and using time-to-event Cox proportional hazards regression. All analyses were adjusted for age and sex and were performed using shared statistical scripts and harmonized datasets, under a federated analysis approach, as described previously.[15] Study-specific summary estimates were then shared with the study coordination centers (University College London, UK, and University Medical Center Utrecht, the Netherlands) for meta-analysis.

Differences in baseline characteristics by factor V Leiden status were assessed using z-value based approach of mean/proportion differences in participants with and without factor V Leiden in each study. Study-level hazard ratios (HRs) for the association between factor V Leiden and the primary outcome and their corresponding standard errors were pooled in an inverse variance weighted fixed-effect meta-analysis. Estimates of random-effects meta-analysis were also reported in the forest plots. Between-study variance in the random-effects meta-analysis was calculated with the restricted maximum likelihood approach. Heterogeneity was quantified using a χ^2 test for heterogeneity and the I^2 statistic. Study-level effect-modification by baseline characteristics and follow-up length were evaluated with random-effects meta-regression analysis. Global *P* values for study-level effect-modification were on the basis of a χ^2 omnibus test.

In addition to the overall analyses, to assess consistency of effects, stratified estimates according to type of baseline CHD at enrollment (acute coronary syndrome and coronary artery disease with and without previous myocardial infarction) were assessed. Factor V Leiden association with the primary outcome was also stratified on patient-level characteristics measured at baseline, including: age (< or ≥ 65 years), sex, hypertension (physician diagnosed or treated), type 2 diabetes mellitus (physician diagnosed or treated), body mass index (categorized as <18.5; 18.5 to <25; 25 to <30; ≥30.0 kg/m^2), statin use, and antiplatelet drug use. Studies contributing to only 1 level of these strata were excluded from the stratified analyses to simplify comparison. *P* values for the differences across the levels of the stratifying factor were calculated using a Wald test. A *P* value <0.05 was considered statistically significant. All analyses were conducted using the R software package.[16]

RESULTS

Twenty-five studies contributed to this analysis and included 69 681 individuals with established CHD. Of the 25 studies, 18 were cohort studies, 3 case-cohort, and 4 randomized clinical trials (Tables I and II in the Data Supplement). The majority of participants who were included were male (73%) and White (92%), with a mean age ranging from 60 to 71 years per study. Prevalence of traditional cardiovascular risk factors (ie, hypertension, hyperlipidemia, diabetes mellitus, and current smoking) across the studies was as expected for a CHD population (Table II in the Data Supplement).

Among the participants, 3190 (4.6%) were heterozygous and 47 (0.07%) homozygous carriers of factor V Leiden (Table II in the Data Supplement). The median follow-up ranged from 1.0 to 10.6 years per study. Whereas the majority of studies had data on all outcomes, some studies had data on only 1 outcome (Table III in the Data Supplement).

Association of Factor V Leiden With Primary Outcome

A total of 20 studies with 61 147 participants and 6849 events contributed to the age- and sex-adjusted associations with the primary outcome (ie, composite of myocardial infarction and CHD death). Factor V Leiden was not associated with the primary outcome (HR, 1.03 [95% CI, 0.92–1.16]) and showed absence of significant heterogeneity (I^2 =28%; *P*-heterogeneity=0.12) in the overall CHD population (Figure 1 and Figure I in the Data Supplement). In subgroup analysis of patients by type of CHD at baseline, among those with acute coronary syndrome and with or without previous myocardial infarction, the associations of factor V Leiden with the primary outcome were close to identity (Figure 1 and Figures II through IV in the Data Supplement).

Sensitivity Analyses

The associations of factor V Leiden with the primary outcome stratified by sex, age (≥65 versus <65 years) and traditional cardiovascular risk factors including hypertension, diabetes mellitus, and overweight/obesity were similar (*P* for difference ≥0.07; Figure 2). Stratification by statin use and antiplatelet agents use also did not reveal any significant differences (Figure 2). Further comparison by study-level features such as study-type, CHD type, follow-up duration, and proportion of history of myocardial infarction revealed no clear differences (Figure 3).

Study level associations between factor V Leiden and the primary outcome (Figure I in the Data Supplement) revealed a significant but paradoxically inverse risk association (HR, 0.69 [95% CI, 0.49–0.96]) for the PLATO study (Platelet Inhibition and Patient Outcomes), a randomized, controlled trial of ticagrelor plus aspirin versus clopidogrel plus aspirin. A similar but nonsignificant nominal association (HR, 0.80 [95% CI, 0.5–1.28]) was observed for the CURE study (Clopidogrel in the

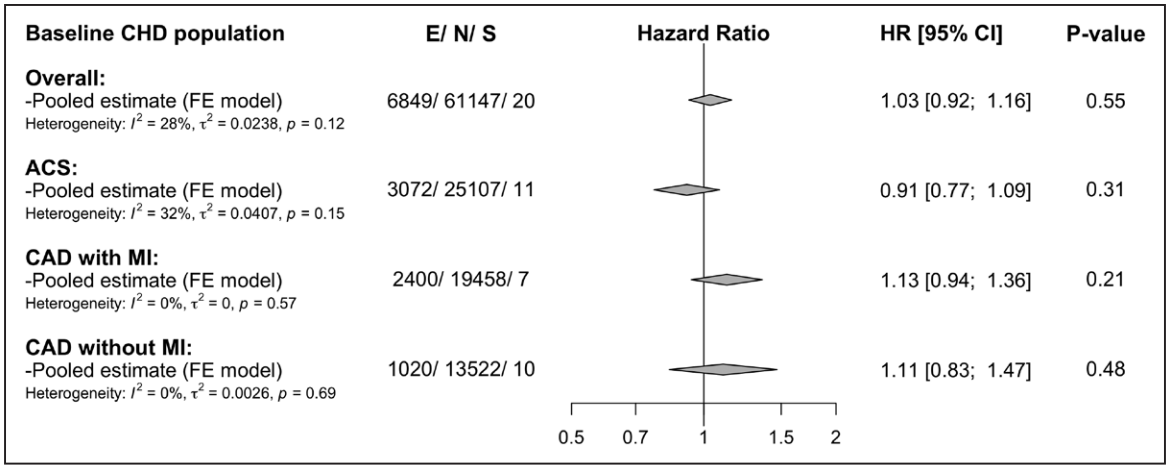

Figure 1. Pooled associations of factor V Leiden with the primary outcome in patients with overall and subtypes of baseline coronary heart disease.
Estimates are adjusted for sex and age and are based on fixed-effect (FE) meta-analysis. ACS indicates acute coronary syndrome; CAD, coronary artery disease; CHD, coronary heart disease; E, number of the primary outcome (ie, composite of myocardial infarction and CHD death); HR, hazard ratio; MI, myocardial infarction; N, total number of included participants; and S, number of studies contributing to the pooled estimates.

Unstable Angina to Prevent Recurrent Events), a randomized, controlled trial of clopidogrel plus aspirin versus aspirin alone. We therefore conducted a post hoc analysis in both studies, to assess for a potential interaction between dual antiplatelet drugs use (ie, aspirin plus a P2Y12 inhibitor clopidogrel or ticagrelor) and factor V Leiden status. Based on the combined PLATO and CURE trials data, whereas there was a nominal

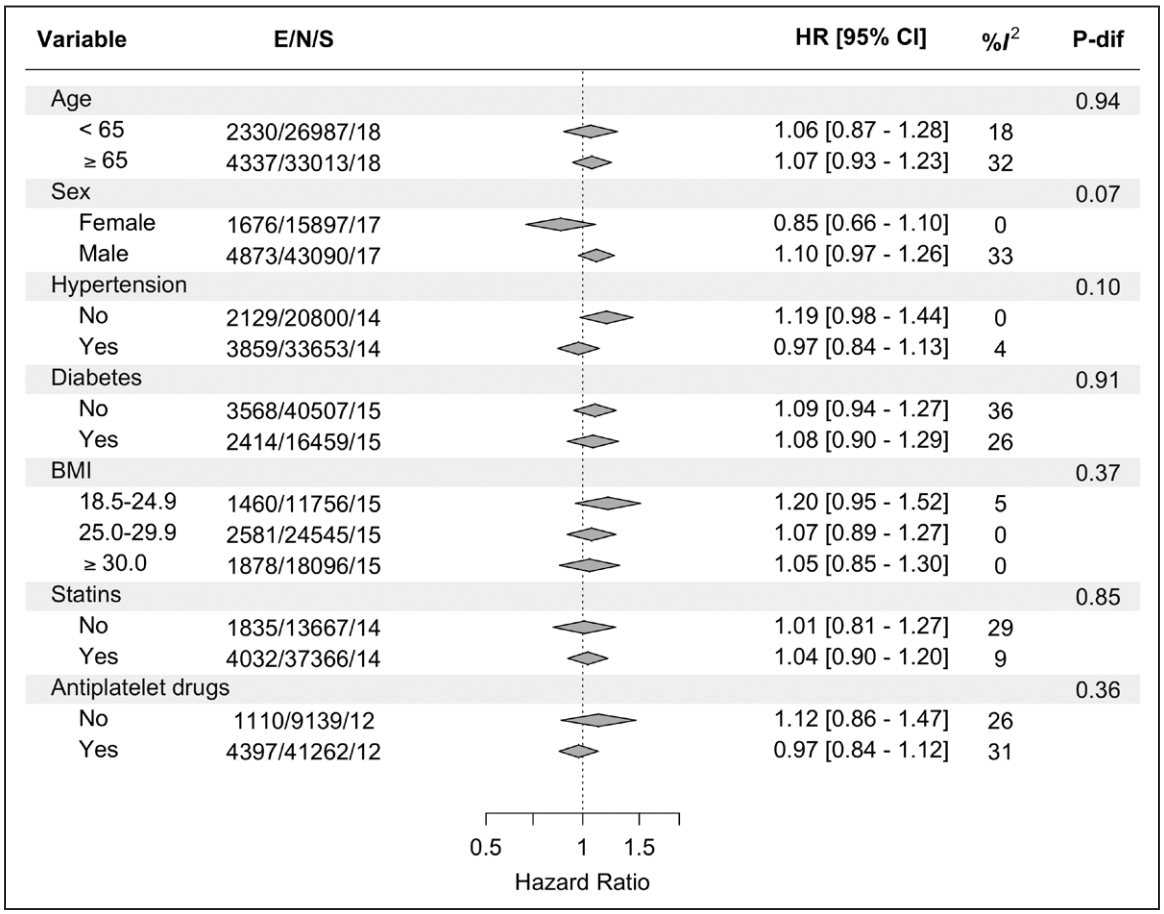

Figure 2. Pooled associations of factor V Leiden with the primary outcome across traditional cardiovascular risk factors strata in the overall coronary heart disease population.
Estimates are adjusted for sex and age, when appropriate, and are based on fixed-effect meta-analysis. BMI indicates body mass index; E, number of the primary outcome (ie, composite of myocardial infarction and coronary heart disease death); HR, hazard ratio; N, total number of included participants; *P*-dif, *P* for difference across the strata of the variable; and S, number of contributing studies.

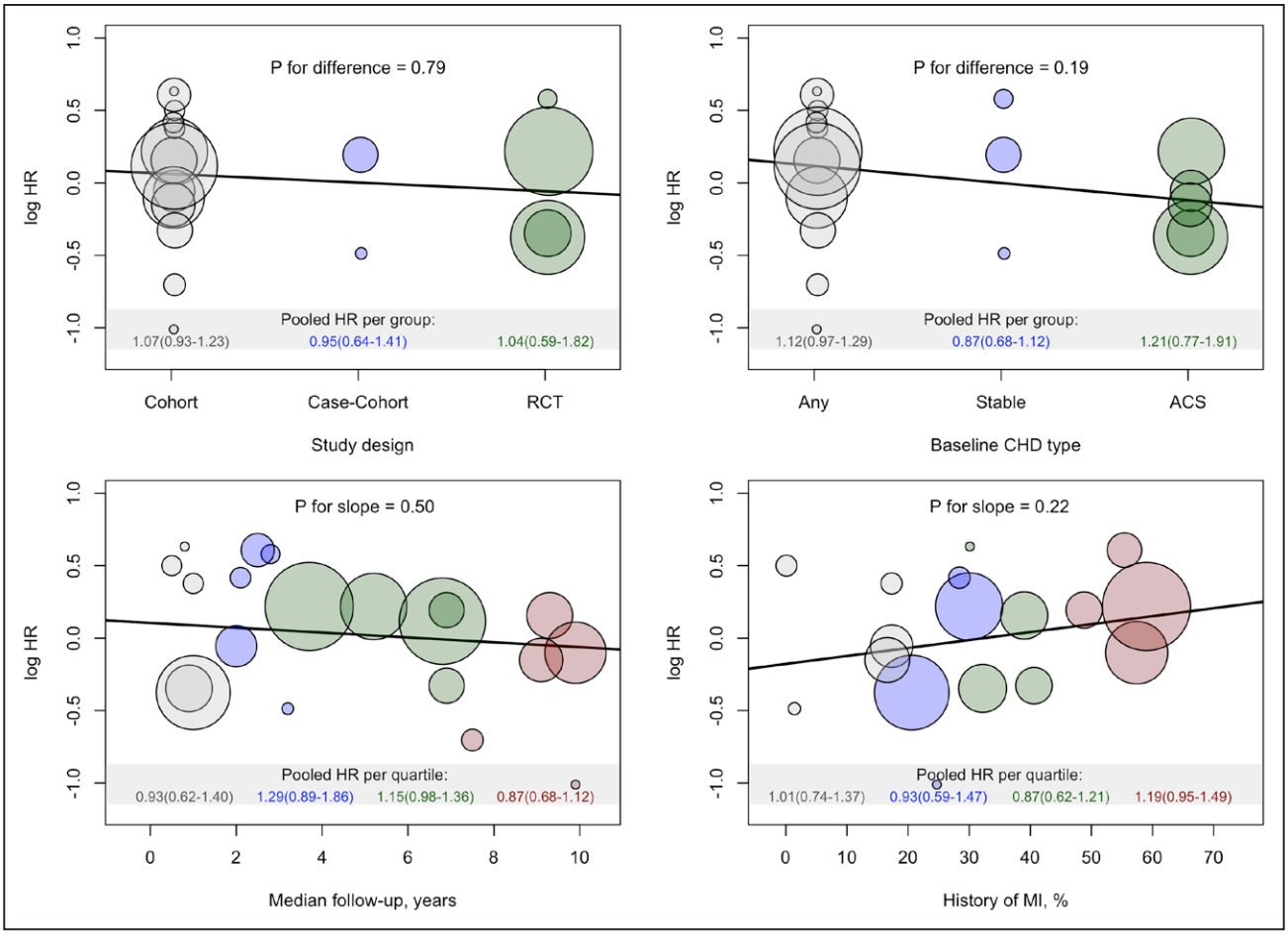

Figure 3. Association between study-level characteristics and the log-hazard ratios for the primary outcome in the overall coronary heart disease population.

The middle of each bubble represents the log-hazard ratio (log HR) of the primary outcome from the individual studies against the study-characteristics shown on the *x* axis. The sizes of the bubbles are proportional to the inverse of the standard-errors of the log-hazard ratios. ACS indicates acute coronary syndrome; MI, myocardial infarction; and RCT, randomized controlled trials.

association toward a greater protective benefit in factor V Leiden carriers taking dual antiplatelet agents (HR, 0.67 [95% CI, 0.50–0.92]), compared with aspirin alone (HR, 0.97 [95% CI, 0.50–1.89]), the statistical test for interaction was nonsignificant (*P*-interaction=0.33; Figure V in the Data Supplement).

Association of Factor V Leiden With Secondary Outcomes

Pooled estimates for the secondary outcomes including nonfatal myocardial infarction, any stroke, ischemic stroke, coronary revascularization, cardiovascular mortality, and all-cause mortality, accompanied by heterogeneity statistics, number of events, number of participants, and studies are shown in Figure 4. In line with the primary outcome, the associations of factor V Leiden with the various secondary outcomes were close to identity and nonsignificant with low heterogeneity (I^2 ≤32%; *P*-heterogeneity≥0.10). The estimates of the individual studies contributing to these pooled estimates are shown in Figures VI through XI in the Data Supplement.

DISCUSSION

In this large-scale individual-level data meta-analysis, we did not find evidence of an association between factor V Leiden and subsequent or recurrent atherothrombotic event risk in nearly 70 000 patients with established CHD. Furthermore, in subgroup analyses no statistically significant interactions to suggest differences by type of baseline CHD, study level or patient level factors were found. These findings suggest there is limited value in assessing factor V Leiden status for risk stratification once CHD is established and treated.

Previous studies on the association of the factor V Leiden polymorphism with atherothrombotic outcomes, including myocardial infarction and stroke, have been limited to case-control studies or to the occurrence of a first event in asymptomatic individuals.[4–10] They showed contradictory results ranging from no risk to a ≈20%

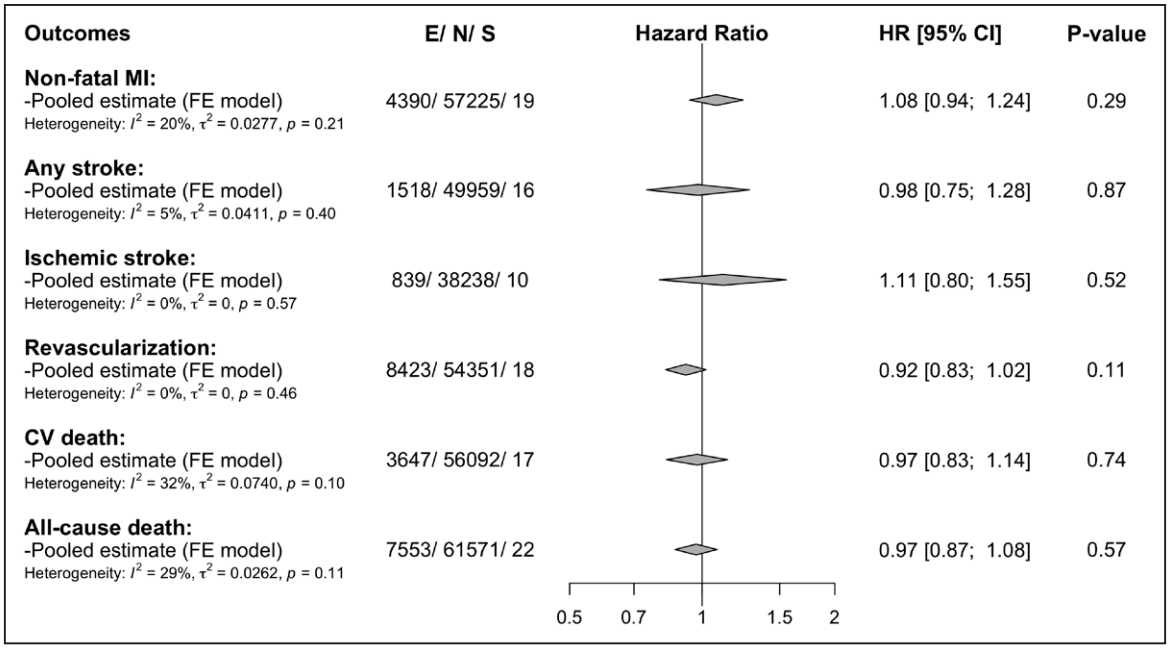

Figure 4. Pooled associations of factor V Leiden with the secondary outcomes in the overall coronary heart disease population.
Estimates are adjusted for sex and age and are based on fixed-effect (FE) meta-analysis. For the estimates of the individual studies contributing to these pooled estimates see Figures VI through XI in the Data Supplement. CV indicates cardiovascular; E, number of the outcome; HR, hazard ratio; MI, myocardial infarction; N, total number of included participants; and S, number of contributing studies.

relative risk increase for myocardial infarction or stroke, as summarized in several meta-analyses.[4–6,8] In prospective cohort studies, factor V Leiden was not associated with incident myocardial infarction or stroke.[6,9,10] Concordant with these cohort studies, but studying only those with established CHD, who are at high risk for atherothrombotic events, we found no association of factor V Leiden with subsequent myocardial infarction, stroke, coronary revascularization, or mortality. There were no significant subgroup effects, including follow-up duration, study design, and baseline history of myocardial infarction. Furthermore, in contrast to previous studies that identified a greater risk association of factor V Leiden with stroke compared with myocardial infarction,[17] we did not find such heterogeneity in analysis of our secondary outcomes.

There could be several reasons for our findings. First, it is possible that factor V Leiden has no impact on the risk of atherothrombotic events and development of acute thrombosis in relation to plaque rupture or erosion in the arterial system. Second, the present analysis may have been underpowered to detect a small association and our results are therefore prone to type 2 error. However, the 95% confidence interval for the primary outcome (95% CI, 0.92–1.16) excludes any clinically relevant association. Third, the effects of factor V Leiden may be masked in the presence of other substantial cardiovascular disease risk factors driving the risk of subsequent events, although a synergistic interaction of factor V Leiden with traditional cardiovascular risk factors has been reported.[11–13]

It is important that medication usage, in particular antiplatelets and anticoagulants may blur any small elevated risk from factor V Leiden. We noted that the PLATO trial,[18] enrolling only patients with acute coronary syndromes and comparing dual antiplatelet agents (ie, aspirin plus ticagrelor versus aspirin plus clopidogrel), showed a significant inverse association of factor V Leiden with the primary outcome. A similar but nonsignificant trend was also noted for the CURE trial comparing clopidogrel plus aspirin versus aspirin alone. Combining these trial data, we found a trend favoring a paradoxically protective effect for carriers of factor V Leiden taking a P2Y12 inhibitor (ie, clopidogrel or ticagrelor) plus aspirin, compared with aspirin alone, but without statistical evidence for an interaction, although this may be caused by the low numbers of participants in the aspirin arm compared with the P2Y12 inhibitors groups. Indeed, a potential interaction of factor V Leiden with antiplatelet agents may be biologically plausible given that ≈20% of human factor V is contained within platelet-granules, is released on platelet activation, and is more hemostatically potent than circulating factor V.[19,20] Although a post hoc finding, this is hypothesis generating and warrants further assessment in existing trials of intensive dual antiplatelet and even combined antiplatelet and anticoagulant strategies,[14] as it opens the intriguing pharmacogenomic possibility that factor V Leiden carriers may derive greater outcome benefit from intensive and prolonged, rather than standard, antiplatelet therapy. If confirmed, then assessment of factor V Leiden status

could help personalize treatment decisions and improve net clinical benefit in high-risk patients.

A further explanation for our overall neutral findings, as with all studies on disease progression is the impact of selection bias, as described previously.[21] Selection biases may include survival bias, with loss of more severe phenotypic manifestations of factor V Leiden not entering the cohort for study. An alternative is that index event bias may be at play. Indeed, the association of heterozygous factor V Leiden with the risk of recurrent venous thromboembolism (odds ratio 1.4) is also much weaker than its association with a first venous thromboembolism (odds ratio 4.2),[3,22] indicating either selection biases or potential effect-modification by disease-status or treatment effects may attenuate associations in the second event context.

Among the known hereditary thrombophilic defects, factor V Leiden is generally considered as a moderate prothrombotic risk factor.[23] However, one of the strongest known hereditary thrombophilic defects (ie, antithrombin deficiency) has also failed to demonstrate a significant association with risk of atherothrombotic events,[24] leaving gaps in our understanding as to why hypercoagulable defects fail to associate with atherothrombotic event risk. In contrast, anticoagulant drugs targeting the coagulation cascade seem to be at least as effective, for prevention and treatment of atherothrombotic events, as the widely used antiplatelet agent (ie, aspirin).[14,25–27]

Our study has some limitations. First, although care was taken to harmonize the definitions across studies, it is possible that residual differences remained among studies. Second, detailed patient level information on the concurrent use of antiplatelet agents, anticoagulant drugs, dual versus single antiplatelet agents use, and its duration was not available in most of the cohorts. This, along with the absence of data on other P2Y12 inhibitors (eg, prasugrel) within the Consortium, limited further exploration of the possible interaction between factor V Leiden and clopidogrel/ticagrelor we found in the CURE and PLATO studies. It is also possible that treatment with any antiplatelet agent may have attenuated overall findings and given that most patients with established CHD are on aspirin this could account for our findings. It is important that if risk from factor V Leiden is indeed attenuated by aspirin use, the value of measuring the genotype among those on aspirin remains questionable in any case. Third, we lacked sufficient data on incident venous thromboembolism events among patients with established CHD to demonstrate a suitable positive control association with factor V Leiden in this setting. Last, our results may not be generalizable to non-White populations given that in most studies primarily White individuals were enrolled.

In conclusion, the prothrombotic hereditary coagulation defect, factor V Leiden, does not show a clear association with increased risk of subsequent atherothrombotic events or mortality, among high-risk individuals with established and treated CHD. Routine assessment of factor V Leiden status is unlikely to improve risk stratification in this population. However, whether there is pharmacogenomic value for factor V Leiden status guiding intensive antiplatelet therapy warrants further study.

ARTICLE INFORMATION

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Supplemental Materials

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REFERENCES

1. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, van der Velden PA, Reitsma PH. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature.* 1994;369:64–67. doi: 10.1038/369064a0
2. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women: implications for venous thromboembolism screening. *JAMA.* 1997;277:1305–1307.
3. Simone B, De Stefano V, Leoncini E, Zacho J, Martinelli I, Emmerich J, Rossi E, Folsom AR, Almawi WY, Scarabin PY, et al. Risk of venous thromboembolism associated with single and combined effects of factor V Leiden, prothrombin 20210A and methylenetethraydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. *Eur J Epidemiol.* 2013;28:621–647. doi: 10.1007/s10654-013-9825-8
4. Bentley P, Peck G, Smeeth L, Whittaker J, Sharma P. Causal relationship of susceptibility genes to ischemic stroke: comparison to ischemic heart disease and biochemical determinants. *PLoS One.* 2010;5:e9136. doi: 10.1371/journal.pone.0009136
5. Hamedani AG, Cole JW, Mitchell BD, Kittner SJ. Meta-analysis of factor V Leiden and ischemic stroke in young adults: the importance of case ascertainment. *Stroke.* 2010;41:1599–1603. doi: 10.1161/STROKEAHA.110.581256
6. Juul K, Tybjaerg-Hansen A, Steffensen R, Kofoed S, Jensen G, Nordestgaard BG. Factor V Leiden: the Copenhagen City Heart Study and 2 meta-analyses. *Blood.* 2002;100:3–10. doi: 10.1182/blood-2002-01-0111
7. Mannucci PM, Asselta R, Duga S, Guella I, Spreafico M, Lotta L, Merlini PA, Peyvandi F, Kathiresan S, Ardissino D. The association of factor V Leiden with myocardial infarction is replicated in 1880 patients with premature disease. *J Thromb Haemost.* 2010;8:2116–2121. doi: 10.1111/j.1538-7836.2010.03982.x
8. Ye Z, Liu EH, Higgins JP, Keavney BD, Lowe GD, Collins R, Danesh J. Seven haemostatic gene polymorphisms in coronary disease: meta-analysis of 66,155 cases and 91,307 controls. *Lancet.* 2006;367:651–658. doi: 10.1016/S0140-6736(06)68263-9
9. Cushman M, Rosendaal FR, Psaty BM, Cook EF, Valliere J, Kuller LH, Tracy RP. Factor V Leiden is not a risk factor for arterial vascular disease in the elderly: results from the Cardiovascular Health Study. *Thromb Haemost.* 1998;79:912–915.
10. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. *N Engl J Med.* 1995;332:912–917. doi: 10.1056/NEJM199504063321403
11. Doggen CJ, Cats VM, Bertina RM, Rosendaal FR. Interaction of coagulation defects and cardiovascular risk factors: increased risk of myocardial infarction associated with factor V Leiden or prothrombin 20210A. *Circulation.* 1998;97:1037–1041. doi: 10.1161/01.cir.97.11.1037
12. Mahmoodi BK, Veeger NJ, Middeldorp S, Lijfering WM, Brouwer JL, Ten Berg J, Hamulyák K, Meijer K. Interaction of hereditary thrombophilia and traditional cardiovascular risk factors on the risk of arterial thromboembolism: pooled analysis of four family cohort studies. *Circ Cardiovasc Genet.* 2016;9:79–85. doi: 10.1161/CIRCGENETICS.115.001211
13. Rosendaal FR, Siscovick DS, Schwartz SM, Beverly RK, Psaty BM, Longstreth WT Jr, Raghunathan TE, Koepsell TD, Reitsma PH. Factor V Leiden (resistance to activated protein C) increases the risk of myocardial infarction in young women. *Blood.* 1997;89:2817–2821.
14. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O, Diaz R, Alings M, Lonn EM, Anand SS, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med.* 2017;377:1319–1330. doi: 10.1056/NEJMoa1709118
15. Patel RS, Tragante V, Schmidt AF, McCubrey RO, Holmes MV, Howe LJ, Direk K, Åkerblom A, Leander K, Virani SS, et al. Subsequent event risk in individuals with established coronary heart disease. *Circ Genom Precis Med.* 2019;12:e002470. doi: 10.1161/CIRCGEN.119.002470
16. R Development Core Team. R: A language and environment for statistical computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2017.
17. Maino A, Rosendaal FR, Algra A, Peyvandi F, Siegerink B. Hypercoagulability Is a stronger risk factor for ischaemic stroke than for myocardial infarction: a systematic review. *PLoS One.* 2015;10:e0133523. doi: 10.1371/journal.pone.0133523
18. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al; PLATO Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med.* 2009;361:1045–1057. doi: 10.1056/NEJMoa0904327
19. Duckers C, Simioni P, Spiezia L, Radu C, Dabrilli P, Gavasso S, Rosing J, Castoldi E. Residual platelet factor V ensures thrombin generation in patients with severe congenital factor V deficiency and mild bleeding symptoms. *Blood.* 2010;115:879–886. doi: 10.1182/blood-2009-08-237719
20. Ren M, Li R, Chen N, Pang N, Li Y, Deng X, Wang L, Luo M, Liu Y, Hao H, et al. Platelet-derived factor V is a critical mediator of arterial thrombosis. *J Am Heart Assoc.* 2017;6:e006345. doi: 10.1161/JAHA.117.006345
21. Hu YJ, Schmidt AF, Dudbridge F, Holmes MV, Brophy JM, Tragante V, Li Z, Liao P, Quyyumi AA, McCubrey RO, et al. Impact of selection bias on estimation of subsequent event risk. *Circ Cardiovasc Genet.* 2017;10:e001616.
22. Marchetti M, Pistorio A, Barosi G. Extended anticoagulation for prevention of recurrent venous thromboembolism in carriers of factor V Leiden–cost-effectiveness analysis. *Thromb Haemost.* 2000;84:752–757.
23. Makris M. Thrombophilia: grading the risk. *Blood.* 2009;113:5038–5039. doi: 10.1182/blood-2009-02-203281
24. Mahmoodi BK, Brouwer JL, Veeger NJ, van der Meer J. Hereditary deficiency of protein C or protein S confers increased risk of arterial thromboembolic events at a young age: results from a large family cohort study. *Circulation.* 2008;118:1659–1667. doi: 10.1161/CIRCULATIONAHA.108.780759
25. Anand SS, Yusuf S. Oral anticoagulant therapy in patients with coronary artery disease: a meta-analysis. *JAMA.* 1999;282:2058–2067. doi: 10.1001/jama.282.21.2058
26. Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, Maeng M, Merkely B, Zeymer U, Gropper S, et al; RE-DUAL PCI Steering

Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med.* 2017;377:1513–1524. doi: 10.1056/NEJMoa1708454
27. Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, Birmingham M, Ianus J, Burton P, van Eickels M, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med.* 2016;375:2423–2434. doi: 10.1056/NEJMoa1611594
28. Raitoharju E, Seppälä I, Levula M, Kuukasjärvi P, Laurikka J, Nikus K, Huovila AP, Oksala N, Klopp N, Illig T, et al. Common variation in the ADAM8 gene affects serum sADAM8 concentrations and the risk of myocardial infarction in two independent cohorts. *Atherosclerosis.* 2011;218:127–133. doi: 10.1016/j.atherosclerosis.2011.05.005
29. Barnet CS, Liu X, Body SC, Collard CD, Shernan SK, Muehlschlegel JD, Jarolim P, Fox AA. Plasma corin decreases after coronary artery bypass graft surgery and is associated with postoperative heart failure: a pilot study. *J Cardiothorac Vasc Anesth.* 2015;29:374–381. doi: 10.1053/j.jvca.2014.11.001
30. Ellis KL, Pilbrow AP, Frampton CM, Doughty RN, Whalley GA, Ellis CJ, Palmer BR, Skelton L, Yandle TG, Palmer SC, et al. A common variant at chromosome 9P21.3 is associated with age of onset of coronary disease but not subsequent mortality. *Circ Cardiovasc Genet.* 2010;3:286–293. doi: 10.1161/CIRCGENETICS.109.917443
31. Hoefer IE, Sels JW, Jukema JW, Bergheanu S, Biessen E, McClellan E, Daemen M, Doevendans P, de Groot P, Hillaert M, et al. Circulating cells as predictors of secondary manifestations of cardiovascular disease: design of the CIRCULATING CELLS study. *Clin Res Cardiol.* 2013;102:847–856. doi: 10.1007/s00392-013-0607-9
32. Mehta SR, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Study Investigators. The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial programme: rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. *Eur Heart J.* 2000;21:2033–2041. doi: 10.1053/euhj.2000.2474
33. Cambou JP, Simon T, Mulak G, Bataille V, Danchin N. The French Registry of Acute ST Elevation or Non-ST-Elevation Myocardial Infarction (FAST-MI): study design and baseline characteristics. *Arch Mal Coeur Vaiss.* 2007;100:524–534.
34. Nieminen T, Lehtinen R, Viik J, Lehtimäki T, Niemelä K, Nikus K, Niemi M, Kallio J, Kööbi T, Turjanmaa V, et al. The Finnish Cardiovascular Study (FINCAVAS): characterising patients with high risk of cardiovascular morbidity and mortality. *BMC Cardiovasc Disord.* 2006;6:9. doi: 10.1186/1471-2261-6-9
35. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, Feldstein AE, Britt EB, Fu X, Chung YM, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. *Nature.* 2011;472:57–63. doi: 10.1038/nature09922
36. Doney AS, Fischer B, Lee SP, Morris AD, Leese G, Palmer CN. Association of common variation in the PPARA gene with incident myocardial infarction in individuals with type 2 diabetes: a Go-DARTS study. *Nucl Recept.* 2005;3:4. doi: 10.1186/1478-1336-3-4
37. Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMJ.* 2002;324:939–942. doi: 10.1136/bmj.324.7343.939
38. Gong Y, Beitelshees AL, Cooper-DeHoff RM, Lobmeyer MT, Langaee TY, Wu J, Cresci S, Province MA, Spertus JA, Pepine CJ, et al. Chromosome 9p21 haplotypes and prognosis in white and black patients with coronary artery disease. *Circ Cardiovasc Genet.* 2011;4:169–178. doi: 10.1161/CIRCGENETICS.110.959296
39. Devereaux PJ, Biccard BM, Sigamani A, Xavier D, Chan MTV, Srinathan SK, Walsh M, Abraham V, Pearse R, Wang CY, et al; Writing Committee for the VISION Study Investigators. Association of postoperative high-sensitivity troponin levels with myocardial injury and 30-day mortality among patients undergoing noncardiac surgery. *JAMA.* 2017;317:1642-1651. doi: 10.1001/jama.2017.4360
40. Beutner F, Teupser D, Gielen S, Holdt LM, Scholz M, Boudriot E, Schuler G, Thiery J. Rationale and design of the Leipzig (LIFE) Heart Study: phenotyping and cardiovascular characteristics of patients with coronary artery disease. *PLoS One.* 2011;6:e29070. doi: 10.1371/journal.pone.0029070
41. Winkelmann BR, März W, Boehm BO, Zotz R, Hager J, Hellstern P, Senges J; LURIC Study Group (LUdwigshafen RIsk and Cardiovascular Health). Rationale and design of the LURIC study–a resource for functional genomics, pharmacogenomics and long-term prognosis of cardiovascular disease. *Pharmacogenomics.* 2001;2(1 Suppl 1):S1–73. doi: 10.1517/14622416.2.1.S1
42. James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, Skene A, Steg PG, Storey RF, Harrington R, et al. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the Platelet Inhibition and Patient Outcomes (PLATO) trial. *Am Heart J.* 2009;157:599–605. doi: 10.1016/j.ahj.2009.01.003
43. Richards AM, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, Frampton C, Turner J, Crozier IG, Yandle TG. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation.* 2003;107:2786–2792. doi: 10.1161/01.CIR.0000070953.76250.B9
44. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruven HJ, Bal ET, Deneer VH, Harmsze AM, van der Heyden JA, Rensing BJ, et al. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. *JAMA.* 2010;303:754–762. doi: 10.1001/jama.2010.181
45. Simons PC, Algra A, Bots ML, Grobbee DE, van der Graaf Y. Common carotid intima-media thickness and arterial stiffness: indicators of cardiovascular risk in high-risk patients. The SMART Study (Second Manifestations of Arterial Disease). *Circulation.* 1999;100:951–957. doi: 10.1161/01.cir.100.9.951
46. White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, Budaj A, Harrington RA, Steg PG, Ardissino D, et al; STABILITY Investigators. Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med.* 2014;370:1702-1711. doi: 10.1056/NEJMoa1315878
47. Arnold SV, Chan PS, Jones PG, Decker C, Buchanan DM, Krumholz HM, Ho PM, Spertus JA; Cardiovascular Outcomes Research Consortium. Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patients' Health Status (TRIUMPH): design and rationale of a prospective multicenter registry. *Circ Cardiovasc Qual Outcomes.* 2011;4:467–476. doi: 10.1161/CIRCOUTCOMES.110.960468
48. Gijsberts CM, den Ruijter HM, de Kleijn DP, Huisman A, ten Berg MJ, van Wijk RH, Asselbergs FW, Voskuil M, Pasterkamp G, van Solinge WW, et al. Hematological Parameters Improve Prediction of Mortality and Secondary Adverse Events in Coronary Angiography Patients: A Longitudinal Cohort Study. *Medicine (Baltimore).* 2015;94:e1992. doi: 10.1097/MD.0000000000001992
49. Kröger E, Van Marum R, Souverein P, Carmichael PH, Egberts T. Treatment with rivastigmine or galantamine and risk of urinary incontinence: results from a Dutch database study. *Pharmacoepidemiol Drug Saf.* 2015;24:276–285. doi: 10.1002/pds.3741
50. Rutten-Jacobs LCA, Tozer DJ, Duering M, Malik R, Dichgans M, Markus HS, Traylor M. Genetic study of white matter integrity in uk biobank (n=8448) and the overlap with stroke, depression, and dementia. *Stroke.* 2018;49:1340–1347. doi: 10.1161/STROKEAHA.118.020811
51. Samani NJ, Burton P, Mangino M, Ball SG, Balmforth AJ, Barrett J, Bishop T, Hall A; BHF Family Heart Study Research Group. A genomewide linkage study of 1,933 families affected by premature coronary artery disease: The British Heart Foundation (BHF) Family Heart Study. *Am J Hum Genet.* 2005;77:1011–1020. doi: 10.1086/498653