SUPPLEMENTAL MATERIAL

Supplement to: Mahmoodi et al. Association of Factor V Leiden with Subsequent Atherothrombotic Events: A GENIUS-CHD Study of Individual Participant Data.

Contents

Supplemental Methods and Data **2**
Summary of the individual studies . . . 2
Supplemental Table I: Study-level characteristics . . . 9
Supplemental Table II: Baseline within study characteristics. . . . 10
Supplemental Table III: Number of outcomes per study . . . 11

Association of factor V Leiden with the primary outcome **12**
Supplemental Figure I: Associations of factor V Leiden with myocardial infarction and CHD death in overall CHD population. . . . 12
Supplemental Figure II: Associations of factor V Leiden with myocardial infarction and CHD death in ACS population. . . . 13
Supplemental Figure III: Associations of factor V Leiden with myocardial infarction and CHD death in MI population. . . . 14
Supplemental Figure IV: Associations of factor V Leiden with myocardial infarction and CHD death in non-MI CHD population. . . . 15
Supplemental Figure V : Associations of factor V Leiden with myocardial infarction and CHD death in the pooled data of CURE and PLATO trials. . . . 16

Association of factor V Leiden with the secondary outcomes **17**
Supplemental Figure VI: Associations of factor V Leiden with non-fatal myocardial infarction in overall CHD population. . . . 17
Supplemental Figure VII: Associations of factor V Leiden with any stroke in overall CHD population. . . . 18
Supplemental Figure VIII: Associations of factor V Leiden with ischemic stroke in overall CHD population. . . . 19
Supplemental Figure IX: Associations of factor V Leiden with revascularization in overall CHD population. . . . 20
Supplemental Figure X: Associations of factor V Leiden with cardiovascular mortality in overall CHD population. . . . 21
Supplemental Figure XI: Associations of factor V Leiden with all-cause mortality in overall CHD population. . . . 22

References **23**

Supplemental Methods and Data

Summary of the individual studies

ANGES - Angiography and Genes Study
The ANGES study population consists of 1,000 Finnish individuals who underwent coronary angiography at Tampere University Hospital to detect coronary artery disease between September 2002 and July 2005. Data were collected on age, sex, body mass index, alcohol consumption, smoking, medication as well as traditional risk factors of atherosclerosis. A clinical diagnosis of myocardial infarction was based on symptoms, electrocardiographic findings and biochemical marker tests measuring troponin I and creatine kinase. Previous cardiovascular diseases, therapeutic procedures and data on coronary artery disease and myocardial infarction were retrieved from patient records at Tampere University Hospital. Follow-up data were derived from the national health care registers maintained by the National Institute for Welfare and Health. The local ethical committee has approved the study and a written informed consent was obtained from all participants.

CABGenomics - Coronary Artery Bypass Genomics
The CABG Genomics Research Study is a prospective, ongoing two institution collaborative study conducted by investigators at the Department of Anesthesiology at Brigham and Women's Hospital, Boston, MA and at the Division of Cardiovascular Anesthesiology, Texas Heart Institute, St. Luke's Episcopal Hospital, Houston, TX. To date enrolled >3000 subjects undergoing primary coronary artery bypass graft (CABG) surgery for the primary purpose of identifying important genetic predictors of adverse postoperative outcomes. The study has active Institutional Review Board approval and patients signed written informed consents.

CDCS - Coronary Disease Cohort Study
The Coronary Disease Cohort Study (CDCS) is a cohort study of 2,140 patients with unstable angina or myocardial infarction admitted to Christchurch or Auckland Hospitals (New Zealand) from 2002-2009. Inclusion criteria were ischaemic discomfort plus one or more ECG change (ST-segment depression or elevation of at least 0.5mm, T-wave inversion of at least 3mm in at least 3 leads or left bundle branch block), elevated levels of cardiac markers, a history or coronary disease, age of at least 65 years and a history or diabetes or vascular disease. Patients were excluded if they had a severe comorbidity that reduced their life expectancy to <3 years. Anthropometric and clinical measures, including echocardiography and a large number of neurohormonal markers, were documented at baseline once patients were stable (approximately 1 month after hospital admission). Clinical outcomes were recorded by direct follow-up and from the New Zealand Health Information Service for a minimum of 3 years after admission (median 5 years, maximum 9.5 years). The study was approved by the New Zealand Multi- region Ethics Committee (CTY/02/02/018) and all patients provided written informed consent. The study was registered on the Australian New Zealand Clinical Trials Registry

(ACTRN12605000431628).

CTMM - Circulating Cells
The Center for Translational Molecular Medicine (CTMM) – Circulating Cells is a prospective cohort study conducted in four Dutch medical centers. Between March 2009 and September 2011, the study enrolled 730 patients with stable or unstable angina pectoris undergoing coronary angiography. Details on the study design have been described elsewhere. Median follow-up was 300 days. Cardiovascular events during follow-up were verified by a clinical event committee. The study was approved by the ethical committees of the participating hospitals and was conducted in accordance with the Declaration of Helsinki.

CURE
CURE was an international, multicentre, randomized, parallel group trial of the combination of clopidogrel plus aspirin vs placebo plus aspirin in patients with acute coronary syndrome (unstable angina and non-Q wave myocardial infarction). The study involved 12,562 patients from 508 centres across 28 countries.

FASTMI2005 – The French Registry of Acute ST-Elevation MI
FAST-MI (French Registry of Acute ST-Elevation or non-ST-elevation Myocardial Infarction) 2005 (NCT00673036) was a nationwide French registry that consecutively included patients with STEMI or NSTEMI admitted to cardiac intensive care units (ICU) within 48 hours of symptom onset. The primary objective was to evaluate the characteristics, management, and outcomes of AMI patients, as seen in routine clinical practice, on a country-wide scale. Of all centres managing AMI patients in France , including university teaching hospitals, general and regional hospitals, and private clinics receiving AMI emergencies, 60% (223 centres, 3059 patients during one month period and 3670 patients overall) participated in the study between October and December 2005. AMI was defined by increased levels of cardiac biomarkers together with either compatible symptoms or ECG changes. Exclusion criteria were (1) refusal to participate; (2) iatrogenic MIs, defined as occurring within 48 hours of any therapeutic procedure and (3) AMI diagnosis invalidated in favour of another diagnosis. Follow-up information was collected through contacts with the patients' physicians, the patients or their family, and registry offices of their places of birth. Events were adjudicated by a scientific committee whose members were unaware of patients' genotypes. The study was conducted in accordance with the guidelines on good clinical practice and French law. A written consent was obtained from all participants. Additional written consent was obtained for those participating in the DNA bank. The study protocol was reviewed by the relevant Committee for the Protection of Human Subjects (CPP). Data file collection and storage were approved by the Commission Nationale Informatique et Liberte.

FINCAVAS - Finnish Cardiovascular Study
The Finnish Cardiovascular Study (FINCAVAS) includes 4,567 patients who underwent exercise stress tests at Tampere University Hospital. Study participants were followed up for major cardiovascular events, coronary procedures and cause of death with follow-up data gathered at 2, 5 and 10 years post- recruitment.

GENEBANK - Cleveland Clinic Genebank Study
The Cleveland Clinic GeneBank study is a single site sample repository generated from consecutive patients undergoing elective diagnostic coronary angiography or elective cardiac com-

puted tomographic angiography with extensive clinical and laboratory characterization and longitudinal observation. Subject recruitment occurred between 2001 and 2007. Ethnicity was self-reported and information regarding demographics, medical history, and medication use was obtained by patient interviews and confirmed by chart reviews. All clinical outcome data were verified by source documentation. CAD was defined as adjudicated diagnoses of stable or unstable angina, myocardial infarction (MI) (adjudicated definition based on defined electrocardiographic changes or elevated cardiac enzymes), angiographic evidence of 50% or more stenosis of one or more major epicardial vessel, and/or a history of known CAD (documented MI, CAD, or history of revascularization). Prospective cardiovascular risk was assessed by the incidence of major adverse cardiac events (MACE) during three years of follow-up from the time of enrollment, which included nonfatal MI, nonfatal stroke, and all- cause mortality. Nonfatal events were defined as MI or stroke in patients who survived at least 48 hours following the onset of symptoms. Adjudicated outcomes ascertained over the ensuing 3 years for all subjects following enrollment were confirmed using source documentation. The GeneBank Study has been used previously for discovery and replication of novel genes and risk factors for atherosclerotic disease. The present analysis included 3703 Caucasian subjects for whom imputed genotype and CAD-related outcome data were available, depending on the phenotype in question.

GoDARTS incident/prevalent
The Genetics of Diabetes Audit and Research in Tayside Scotland (GoDARTS) cohort profile has been described previously. At the point of recruitment, all participants in GoDARTS provided, by invitation, informed consent for their data to be used for research purposes and explicit consent for use in collaboration with industry. The study complies with the Declaration of Helsinki.

INVEST - INternational VErapamil SR Trandolapril Study Genetic Substudy
INVEST (INternational VErapamil SR Trandolapril STudy) was an international, multicenter, randomized controlled clinical trial of 22,576 hypertensive individuals with documented coronary artery disease aged 50 years or older. Patients were randomized to either a calcium channel blocker (Verapamil SR)-based treatment strategy (CCB strategy) or a beta-blocker (atenolol)-based treatment strategy (beta-blocker strategy), with HCTZ and trandolapril available as add-on agents in both strategies. The genetic substudy of INVEST (INVEST-GENES) includes DNA samples from 5,979 INVEST participants from the United States, including Puerto Rico. All study protocols were approved by local or central institutional review boards and all participants provided separate, voluntary, written informed consent for participation in INVEST and INVEST-GENES.

JUMC - Krakow-GENIUS-CHD
Between 2010-2015 in Jagiellonian University Medical College (Krakow, Poland), patients were enrolled into one of the two following studies: VISION (Vascular Events in Noncardiac Surgery Patients Cohort Evaluation study; 900 patients from Polish cohort undergoing vascular surgery) or LTIMI (Leukotrienes and Thromboxane In Myocardial Infarction; 261 MI patients). Protocols for recruitment have been described elsewhere. From these 2 cohorts, patients with documented coronary artery disease (both acute coronary syndromes and stable coronary artery disease) were eligible to participate in the GENIUS project (n=747). DNA samples for genetic analyses were available for 704 subjects (94%). Cardiovascular mortality was defined as any death related to cardiovascular reasons obtained in the follow-up, including: sudden cardiac death, fatal myocardial infarction, death due to congestive heart failure, or death immediately after intervention to treat CAD, as well as fatal stroke. The median follow-up of study participants was 360 days with 0.3% of the sample lost to follow-up. All patients signed written

informed consent to participate according to the local ethics committee and with accordance with the Helsinki Declaration.

LIFE-HEART - Leipzig Heart Study
The LIFE-Heart study is an observational study of patients recruited at the Leipzig Heart Center, Germany. Patients with suspected coronary artery disease (CAD), stable CAD or myocardial infarction were recruited. Patients received a comprehensive assessment of vessel status and cardiologic function including coronary angiography, carotid ultrasound, ankle-brachial index, echo-cardiography and electrocardiography. Details of the study can be found in Beutner et al. Genotyping information including quality control can be found in Pott et al. The study was approved by the Ethics Committee of the Faculty of Medicine of Leipzig University, Germany (Reg. No 276-2005) and is registered at ClinicalTrials.gov (NCT00497887). Written informed consent was obtained from all participants included in the study.

LURIC - The LUdwigshafen RIsk and Cardiovascular Health Study
The Ludwigshafen Risk and Cardiovascular Health (LURIC) study is a monocentric hospital based prospective study including 3316 individuals referred for coronary angiography recruited in the Ludwigshafen Cardiac Center, southwestern Germany from 1997-2000. Clinical indications for angiography were chest pain or a positive non-invasive stress test suggestive of myocardial ischemia. To limit clinical heterogeneity, individuals suffering from acute illnesses other than acute coronary syndrome, chronic non-cardiac diseases and a history of malignancy within the five past years were excluded. All participants were completed a detailed questionnaire which gathered information on medical history, clinical, and lifestyle factors. Fasting blood samples were obtained by venipuncture in the early morning and stored for later analyses. Information on vital status during follow-up was obtained from local registries. Death certificates, medical records of local hospitals, and autopsy data were reviewed independently by two experienced clinicians who were blinded to patient characteristics and who classified the causes of death. Coronary heart disease (CHD) at baseline was defined as the presence of a visible luminal narrowing (more than 50% stenosis) in at least one of 15 coronary segments according to the classification of the American Heart Association. These patients were included in the current analysis. Samples were genotyped on an Affymetrix 6.0 array. Study protocols were approved by the ethics committee of the Landesarztekammer Rheinland-Pfalz and the study was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants.

OHGS longitudinal - Ottawa Heart Genomics Study longitudinal
A total of 956 individuals were recruited to The Ottawa Heart Genomics Study (OHGS) longitudinal from the John and Jennifer Ruddy Canadian Cardiovascular Genetics Centre at The University of Ottawa Heart Institute, Ottawa, Canada, between 2010 and 2013, when recruitment ended. Recruited individuals were later sent a survey to follow-up on risk factors and behaviours related to CAD and hypertension. Participants with both survey and GWAS data available for the Lp(a) locus were included in the analysis. Institutional Research Ethics Board (REB) approval was obtained for this study. A total of 755 individuals participated in the survey and of those there were 522 with GWAS data available. Information related to cause of death of the patients during follow-up were obtained, with prior patient approval, from physician(s) at The University of Ottawa Heart Institute and/or any other institution were the patient would have sought medical attention for their cardiac condition. Median follow-up was 1.76 years with 21% of those recruited not participating in the follow-up survey. Cardiovascular mortality was defined as death related to CAD, death due to valve failure and death due to stroke.

PLATO - The study of Platelet Inhibition and patient outcomes
The PLATO trial was an international randomized double blind, double dummy phase III study comparing ticagrelor with clopidogrel in patients with either ST-elevation MI intended for primary PCI or with non- ST-elevation ACS, regardless if aimed for an initial invasive or non-invasive treatment strategy. A total of 18,624 patients were included. Follow up was 6 to 12 months, with a median of 9 months. The outcome events were centrally adjudicated and included cardiovascular and total death, myocardial infarction, stent thrombosis, stroke and major bleeding. DNA for genetics analyses is available from 9340 patients.

PMI - Post Myocardial Infarction Study
The Post Myocardial Infarction Study (PMI) is a cohort study of 1,063 patients with acute myocardial infarction admitted to Christchurch Hospital (New Zealand) from 1994-2001. Inclusion criteria were acute myocardial infarction (ST-elevation myocardial infarction and non-ST-elevation myocardial infarction) as defined by the presence of typical cardiac symptoms, ischaemic change on ECG in 2 or more contiguous leads and peak elevation of creatinine kinase of at least twice normal (400U/L). Anthropometric and clinical measures, including echocardiography and a large number of neurohormonal markers, were documented during the index hospital admission Clinical outcomes were recorded from the New Zealand Health Information Service over a median 9.3 years after admission (maximum 13.4 years). The study was approved by the Canterbury Ethics Committee (CTY/94/08/783/AM04) and all patients provided written informed consent. The study was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12606000212550).

POPULAR - The POPular Study
POPular is a prospective, observational, single-center cohort study of 1069 (75% male, mean age 64 years) consecutive patients taking clopidogrel plus aspirin or vitamin K antagonists undergoing elective coronary stent implantation between December 2005 and December 2007. The purpose of this study was to investigate whether the level of platelet inhibition as assessed with five point-of-care platelet function assays correlates with clinical (periprocedural) outcomes such as acute myocardial infarction, death, target vessel revascularization and/or stroke in patients undergoing elective percutaneous coronary intervention. All participants are residents of European descent. The local ethics committee approved conduct of the POPULAR study. A written informed consent was obtained from all participants.

SMART - Second Manifestations of ARTerial disease
The Second Manifestations of ARTerial disease (SMART) study is an ongoing prospective cohort study at the University Medical Center Utrecht (UMCU) in the Netherlands. From September 1996 onwards, more than 12,000 patients were referred to the UMCU with clinically manifested vascular disease (coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm) or vascular risk factors (dyslipidemia, hypertension or diabetes mellitus) and were asked to participate in the study. Written informed consent was obtained from all patients. After inclusion, patients underwent a standardized vascular screening protocol consisting of a health questionnaire including medical history and risk factors, physical examination and laboratory testing. All patients are biannually asked to fill in a short questionnaire regarding hospitalization and outpatient clinical visits. If a patient reports a possible event, all available relevant data are collected and an outcome committee of three staff members assesses whether study outcomes (primary events: myocardial infarction, stroke and vascular death) occurred.

STABILITY - Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy trial
The STABILITY trial was an international prospective randomised, double-blind of darapladib versus placebo in patients with stable coronary heart disease and an indicator of increased risk. 15,828 patients were included. Follow-up was 3-5 years with a median of 3.7 years. The outcome events were centrally adjudicated and contained cardiovascular and total death, myocardial infarction and stroke. DNA for genetics analyses is available from 10,786 patients.

TRIUMPH - Translational Research Investigating Underlying Disparities in Acute Myocardial Infarction Patient's Health Status
The TRIUMPH study was designed to explore racial differences in prognosis for myocardial infarction patients. Between June 1, 2005 and December 31, 2008, 31,567 patients with MI were prospectively screened of whom 6,152 had an eligible MI. Of eligible patients, 4,340 (71%) patients were enrolled into TRIUMPH from across 24 US centers with genetic data available for 2,979 (69%) of patients. Centralized follow-up interviews sought to quantify patients' post-discharge care and outcomes, with a focus on their health status (symptoms, function, and quality of life). At 1, 6 and 12 months, 23%, 27% and 24% were lost to follow-up. Vital status was available for 99% of patients at 12-months.

UCORBIO - Utrecht Coronary Biobank Study
The Utrecht Coronary Biobank Study (UCORBIO) enrolled 2,591 patients who underwent coronary angiography for any indication at the University Medical Center Utrecht (UMCU). Baseline assessment and blood sampling took place between 2011 and 2014. Patients were followed up (maximum: 3years) for the occurrence of major adverse cardiovascular events (stroke, myocardial infarction, coronary revascularization, death). The study was approved by the Ethics Committee of the UMCU and was conducted according to the Declaration of Helsinki. UCORBIO is registered with clinicaltrials.gov (ID: NCT02304744)

UCP - Utrecht Cardiovascular Pharmacogenetics Study
Participants of the Utrecht Cardiovascular Pharmacogenetics (UCP) studies were enrolled through the Dutch population-based Pharmaco-Morbidity Record Linkage System (PHARMO) database. The PHARMO database links drug dispensing history from a representative sample of Dutch community pharmacies to the national registry of hospital discharge diagnoses. Several nested case-control studies to assess the interaction between SNPs, drug use and the risk of myocardial infarction were performed using UCP data. The UCP studies received ethical approval from the Medical Ethics Committee of the University Medical Center Utrecht, the Netherlands. A written informed consent was obtained from all participants.

UKB - UK Biobank
UK Biobank is a large-scale cohort study, including 502,655 participants aged between 40-69 years. Study participants were recruited from 22 recruitment centres across the United Kingdom between 2006 and 2010. A sub-sample of the cohort (N = 10,287) of European descent with coronary heart disease at baseline, phenotyped using ICD10 and OPS codes, were included in GENIUS analyses.

WTCCC - Welcome Trust Case Control Consortium CAD study
Cases were European Caucasians who had a validated history of either myocardial infarction

(MI) or coronary revascularisation (coronary artery bypass surgery or percutaneous coronary angioplasty) before their 66th birthday. Recruitment was carried out on a national basis through: (i) responses to a sustained UK-wide media campaign, (ii) through responses to posters placed within hospitals and GP (family physician) surgeries throughout the UK, and (iii) in a pilot-phase contacting patients listed on computer based coronary artery disease databases, in the two lead centres (Leeds and Leicester). The recruitment period was from April 1998 to November 2003. The primary purpose was to recruit families with two or more available siblings with CAD, for a linkage study called the BHF Family Heart Study (BHF- FHS). During the course of the project we however, also recruited subjects with CAD who had a family history of premature CAD (in parents or another sibling), but in whom a further affected sib was not available, for a related project called the GRACE Study.

Supplemental Table 1: Study-level characteristics

Study	Country	Recruit. years	Study design	CHD type	Reference number
ANGES	Finland	2002-2005	Cohort	Any	28
CABGenomics	USA	2001-2014	Cohort	Any	29
CDCS	NewZealand	2002-2009	Cohort	ACS	30
CTMM	Netherlands	2009-2011	Cohort	Any	31
CURE	Canada	1998-2000	RCT	ACS	32
FASTMI2005	France	2005-	Cohort	ACS	33
FINCAVAS	Finland	2001-2008	Cohort	Any	34
GENEBANK	USA	2001-2007	Cohort	Any	35
GoDARTSincident	Scotland	2004-2012	Case-Cohort	Stable	36
GoDARTSprevalent	Scotland	2004-2012	Case-Cohort	Stable	37
INVEST	USA	1997-2003	RCT	Stable	38
KRAKOW	Poland	2010-2014	Cohort	Any	39
LIFE-Heart	Germany	2006-2014	Cohort	Any	40
LURIC	Germany	1997-2000	Cohort	Any	41
OHGS	Canada	2010-2013	Case-Cohort	Any	-
PLATO	International	2006-2008	RCT	ACS	42
PMI	NewZealand	1994-2001	Cohort	ACS	43
POPULAR	Netherlands	2005-2007	Cohort	Stable	44
SMART	Netherlands	1999-2010	Cohort	Any	45
STABILITY	International	2008-2010	RCT	Any	46
TRIUMPH	USA	2005-2008	Cohort	ACS	47
UCORBIO	Netherlands	2011-2014	Cohort	Any	48
UCP	Netherlands	1985-2010	Cohort	Any	49
UKB	UK	2006-2010	Cohort	Any	50
WTCCC	UK	1998-2003	Cohort	Any	51

Recruit.=recruitment period, CHD=coronary heart disease, ACS= acute coronary syndromes, Any CHD included both ACS and Stable CHD. For study acronyms and short discription of the participating studies see pages 2-8 of this supplemental material. Refernces to the key publications of these studies are listed at the end of this supplemental material and in the main paper (Ref 28-51).

Supplemental Table 2: Baseline within study characteristics

Study	N	FVL (n)	MAF/HO (%/n)	Age (yrs)	Male (%)	Cauc. (%)	BMI (kg/m^2)	Smoking (%)	Hyperlip. (%)	Hypert. (%)	Diabetes (%)	MI hist. (%)	Statins (%)	Antipl. (%)
ANGES	608	20	1.64/0	64.1*	65.5	100	28.1	14.6	80.9	63.3*	30.8	24.7	69.4	-
CABGenomics	1054	51	2.42/0	64.2	78.5	86	29.4	12.7*	74.9	76.0	10.3	45.7	53.8	-
CDCS	1941	82	2.11/0	66.7	71.2	91	27.5	6.3	62.4	65.8	16.7	30.0	46.1	53.1
CTMM	604	28	2.32/0	63.0	68.7	96	27.6	20.9	0.0	62.9	20.5	30.1	-	-
CURE	5301	258	2.48/5	64.1	59.5	80	27.9	22.8	43.1	61.4	22.0	32.2	-	71.5
FASTMI2005	2360	91	1.97/2	67.1	69.1	100	27.1	30.2	76.8*	58.7	31.7	17.3	75.5	95.8
FINCAVAS	1671	48	1.44/0	60.9	69.4	100	27.8	24.3	59.4	31.6	18.4	39.0	57.2	-
GENEBANK	2345	5	0.11/0	61.5	74.3	93	29.4	16.8	90.6	72.2	11.8	51.6	71.8	81.0
GoDARTSincident	812	30	1.85/0	71.2	58.6	100	31.4	0.0	54.2	0.2	95.1	1.4	54.2	50.6
GoDARTSprevalent	1613	44	1.36/0	68.9	64.6	100	30.9	11.8	67.1	34.0	92.4	48.8	67.1	65.1
INVEST	2238	59	1.34/1	67.4	44.8	38	-	9.7	56.7*	100.0	17.6	-	38.1	49.2*
KRAKOW	704	37	2.63/0	68.3*	71.6	100	26.3	27.4	21.3	82.4	36.9	17.3	73.9	54.1
LIFE-Heart	4330	277	3.21/1	64.0*	75.5	100	29.0	28.9	36.3*	84.5	34.4	0.1	36.5*	54.2
LURIC	2136	125	2.95/1	63.9	76.5	100	27.5	23.9	72.8	54.7	44.3	57.4	58.8	82.1*
OHGS	392	19	2.42/0	65.3	73.0	100	28.6	19.1	93.4	64.8*	6.9	21.9	92.3	16.6
PLATO	9980	580	2.99/17	62.5	69.5	98	28.2	35.2	45.4	66.0	23.0	20.6	79.7	96.3
PMI	797	40	2.51/0	61.9	77.5	91	26.7	26.1*	61.2	71.4	12.5	16.6	47.8	95.2
POPULAR	1013	57	2.86/1	64.1	74.7	100	27.2	10.8	80.6	77.1	19.1	55.4	79.4	100
SMART	2658	137	2.60/1	60.2	76.6	100	27.3	22.5	29.3	16.4	15.6	40.6	63.7	82.6
STABILITY	10786	498	2.36/12	64.3	81.9	86	29.4	21.1	-	72.8	39.3	59.0	97.2	92.2
TRIUMPH	1974	64	1.62/0	59.8	72.4	100	29.5	37.4	94.1	61.2	28.6	18.3	89.0	97.9
UCORBIO	1485	70	2.36/0	64.7	74.4	94	27.3	23.1	64.6	58.8	22.9	28.4	63.2	-
UCP	1519	86	2.86/1	64.1	75.4	100	-	-	-	-	-	-	27.0	34.6
UKB	9455	421	2.25/4	69.9	80.6	-	29.4	75.4	83.3	53.7	21.9	-	83.3	86.5
WTCCC	1905	63	1.68/1	60.0	79.4	100	27.6	12.8	78.2*	42.6	11.4	71.7	71.0	85.6

N=total number of participants, FVL= factor V Leiden (heterozygotes and homozygotes combined), MAF/HO=minor allele frequency in %/ number of homozygotes individuals; BMI=body mass index, Smoking= current smoking, Hyperlip= hyperlipidemia, Hypert= hypertension, MI hist= myocardial infarction history, antipl= antiplatelet drugs. Values for age and BMI are mean values. For study acronyms and short discription of the studies see pages 2-8 above. * Denotes P-value <0.05 for the difference in proportion/mean value in participants with versus without FVL.

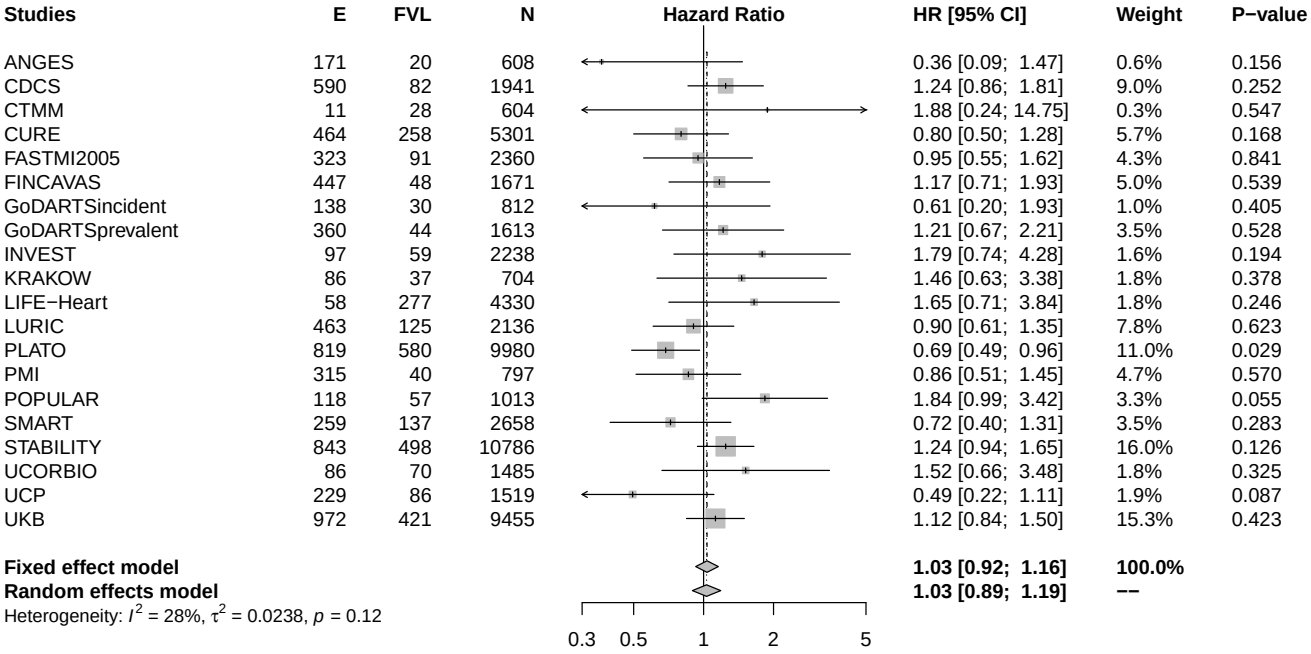
Supplemental Table 3: Number of outcomes per study

Study	N	FVL	Follow-up	Overall MI	Non-fatal MI	Any stroke	Isch. stroke	CV mortality	AC mortality	Revascularization
ANGES	608	20	9.9	171	84	66	60	-	178	201
CABGenomics	1054	51	6.9	-	-	-	-	-	314	-
CDCS	1941	82	5.2	590	578	152	120	270	469	542
CTMM	604	28	0.8	11	9	-	-	-	4	70
CURE	5301	258	0.9	464	321	-	-	104	331	192
FASTMI2005	2360	91	2.0	323	93	59	-	285	384	210
FINCAVAS	1671	48	9.3	447	309	214	191	185	440	399
GENEBANK	2345	5	3.0	-	-	-	-	-	-	857
GoDARTSincident	812	30	3.2	138	111	69	32	103	253	118
GoDARTSprevalent	1613	44	6.9	360	288	149	70	275	635	150
INVEST	2238	59	2.8	97	97	80	-	36	131	-
KRAKOW	704	37	1.0	86	72	14	14	29	78	46
LIFE-Heart	4330	277	0.5	58	-	-	-	62	391	-
LURIC	2136	125	9.9	463	146	42	-	449	722	-
OHGS	392	19	1.8	-	-	-	-	17	18	117
PLATO	9980	580	1.0	819	586	113	92	339	382	2182
PMI	797	40	9.1	315	314	87	66	226	372	350
POPULAR	1013	57	2.5	118	96	22	-	23	39	-
SMART	2658	137	6.9	259	163	57	-	-	257	868
STABILITY	10786	498	3.7	843	505	204	181	457	722	1155
TRIUMPH	1974	64	1.0	-	-	-	-	-	-	-
UCORBIO	1485	70	2.1	86	86	-	-	37	80	143
UCP	1519	86	7.5	229	229	55	-	-	-	550
UKB	9455	421	6.8	972	303	135	13	750	947	273
WTCCC	1905	63	10.6	-	-	-	-	-	406	-

Values are counts, except follow-up values. Values for follow-up represent median follow-up in years. N=number of participants, FVL= number of factor V Leiden carriers, Overall MI=fatal and non-fatal myocardial infarction (primary outcome), Isch. stroke= ischemic stroke, CV mortality= cardiovascular mortality, AC= all-cause mortality. For study acronyms and short discription of the participating studies see pages 2-8 of this supplemental material.

Association of factor V Leiden with the primary outcome

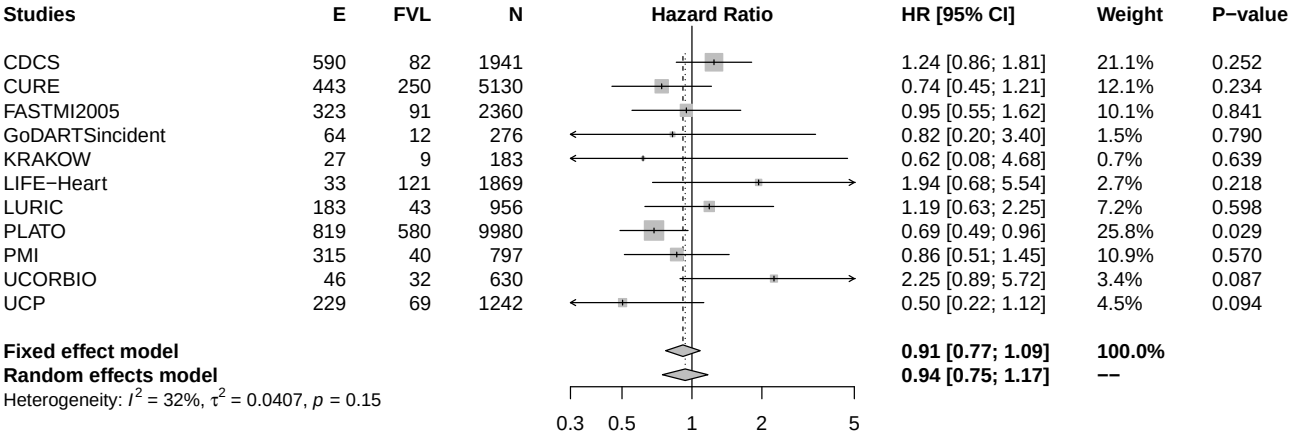
Associations of factor V Leiden with myocardial infarction and CHD death in overall CHD population.



Supplemental Figure I: Adjusted hazard ratios for the associations of factor V Leiden with myocardial infarction and CHD death in overall CHD population.

Estimates are adjusted for age and sex. E = number of events/outcomes; FVL= number of factor V Leiden; N= overall sample-size; HR = hazard ratio.

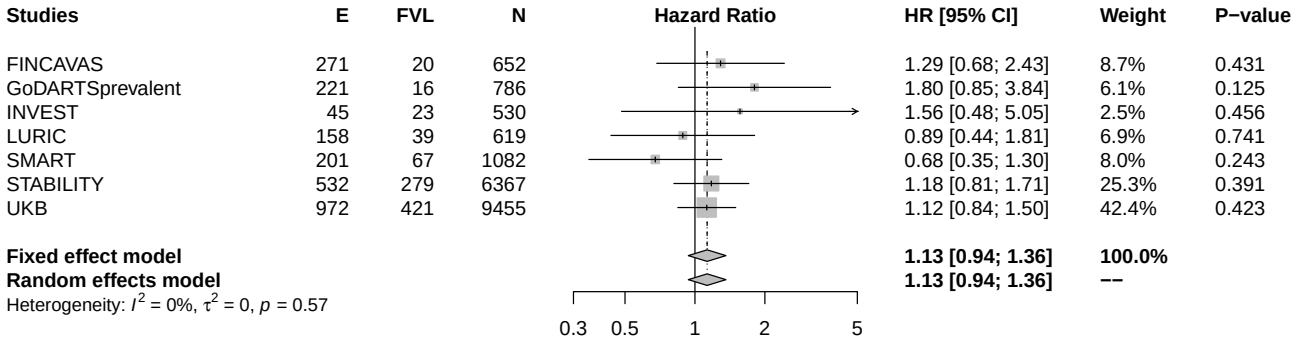
Associations of factor V Leiden with myocardial infarction and CHD death in ACS population.



Supplemental Figure II: Adjusted hazard ratios for the associations of factor V Leiden with myocardial infarction and CHD death in ACS population.

Estimates are adjusted for age and sex. E = number of events/outcomes; FVL= number of factor V Leiden; N= overall sample-size; HR = hazard ratio.

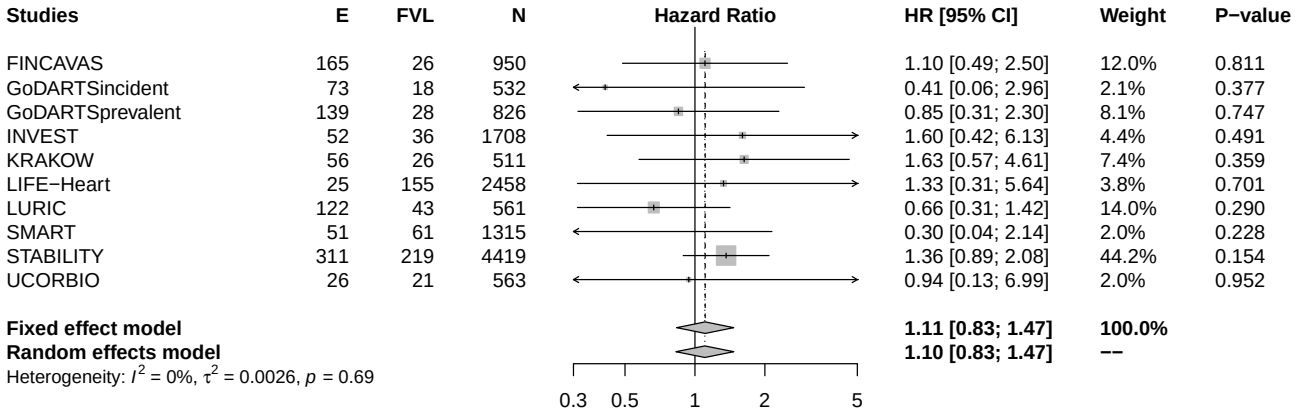
Associations of factor V Leiden with myocardial infarction and CHD death in MI population.



Supplemental Figure III: Adjusted hazard ratios for the associations of factor V Leiden with myocardial infarction and CHD death in MI population.

Estimates are adjusted for age and sex. E = number of events/outcomes; FVL= number of factor V Leiden; N= overall sample-size; HR = hazard ratio.

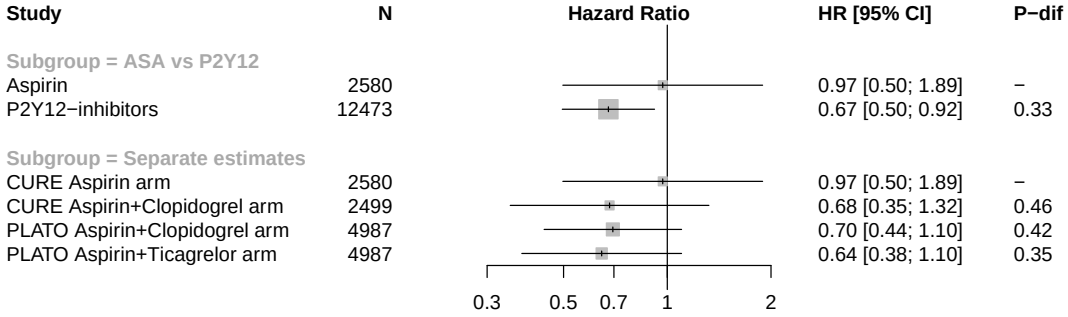
Associations of factor V Leiden with myocardial infarction and CHD death in non-MI CHD population.



Supplemental Figure IV: Adjusted hazard ratios for the associations of factor V Leiden with myocardial infarction and CHD death in non-MI CHD population.

Estimates are adjusted for age and sex. E = number of events/outcomes; FVL= number of factor V Leiden; N= overall sample-size; HR = hazard ratio.

Associations of factor V Leiden with myocardial infarction and CHD death in the pooled data of CURE and PLATO trials.

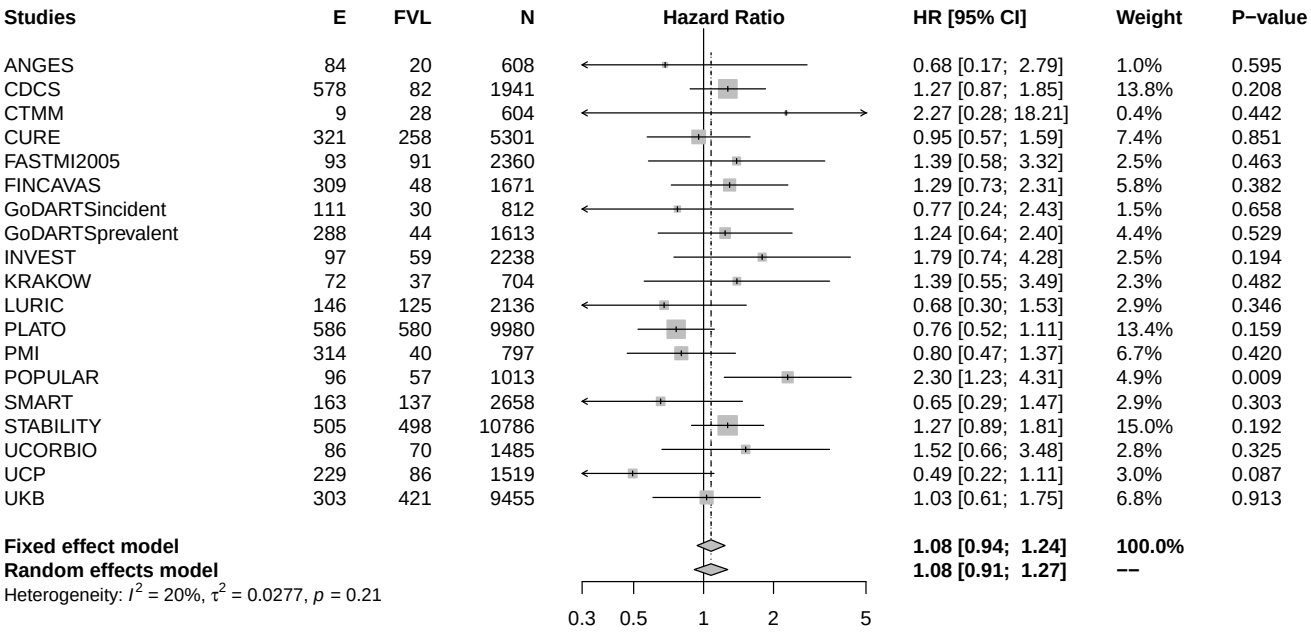


Supplemental Figure V: Adjusted hazard ratios for the associations of factor V Leiden with myocardial infarction and CHD death in pooled data of CURE and PLATO trials.

Estimates are from fixed-effect meta-analysis and adjusted for age and sex. N = number of participants; ASA= aspirin; P2Y12= P2Y12 inhibitors (i.e., Clopidogrel and Ticagrelor); HR = hazard ratio; P-diff= P for difference/interaction.

Association of factor V Leiden with the secondary outcomes

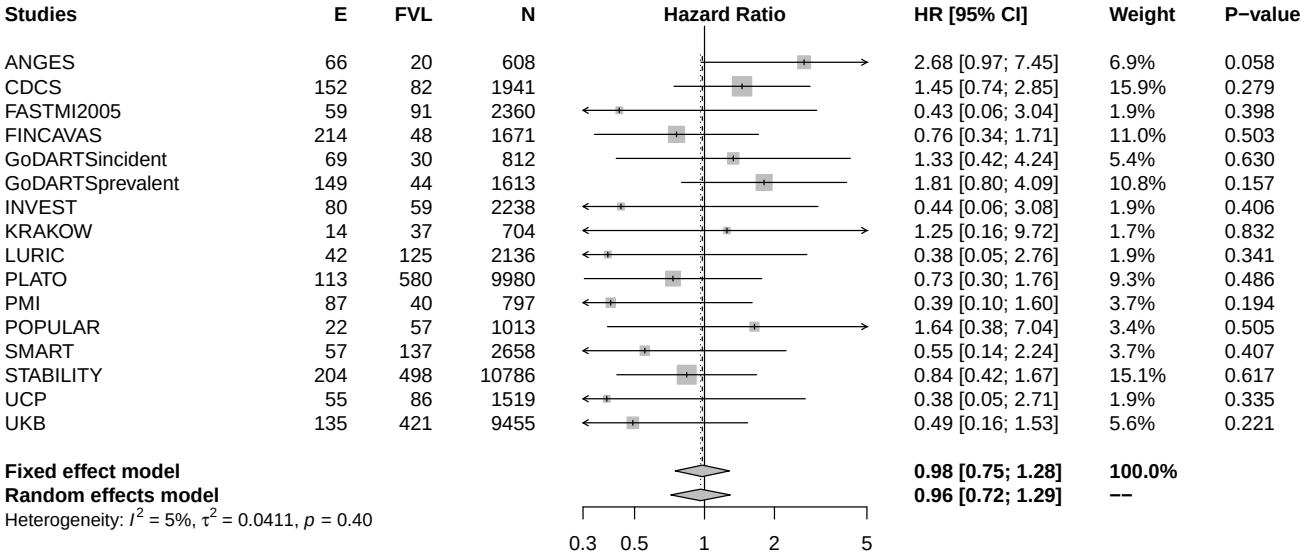
Associations of factor V Leiden with non-fatal myocardial infarction in overall CHD population.



Supplemental Figure VI: Adjusted hazard ratios for the associations of factor V Leiden with non-fatal myocardial infarction in overall CHD population.

Estimates are adjusted for age and sex. E = number of events/outcomes; FVL= number of factor V Leiden; N= overall sample-size; HR = hazard ratio.

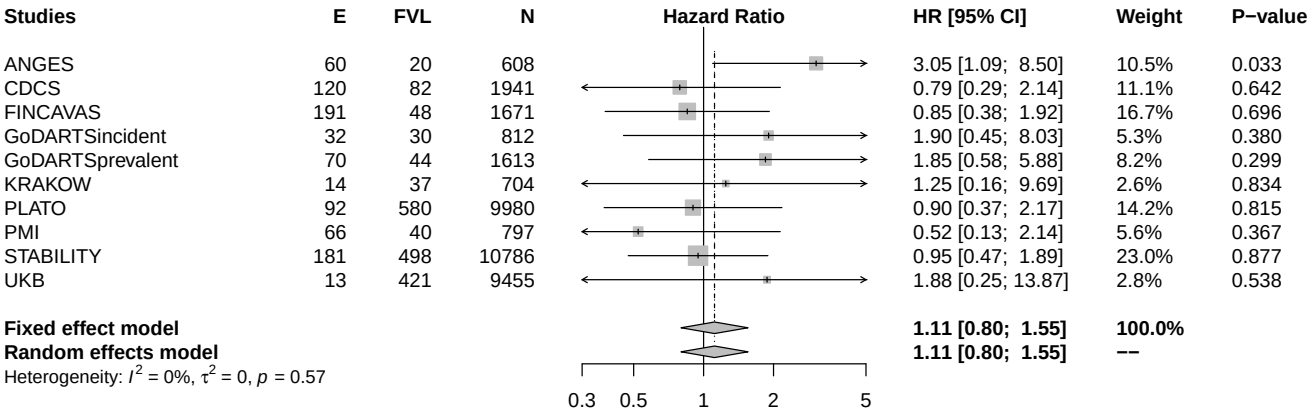
Associations of factor V Leiden with any stroke in overall CHD population.



Supplemental Figure VII: Adjusted hazard ratios for the associations of factor V Leiden with any stroke in overall CHD population.

Estimates are adjusted for age and sex. E = number of events/outcomes; FVL= number of factor V Leiden; N= overall sample-size; HR = hazard ratio.

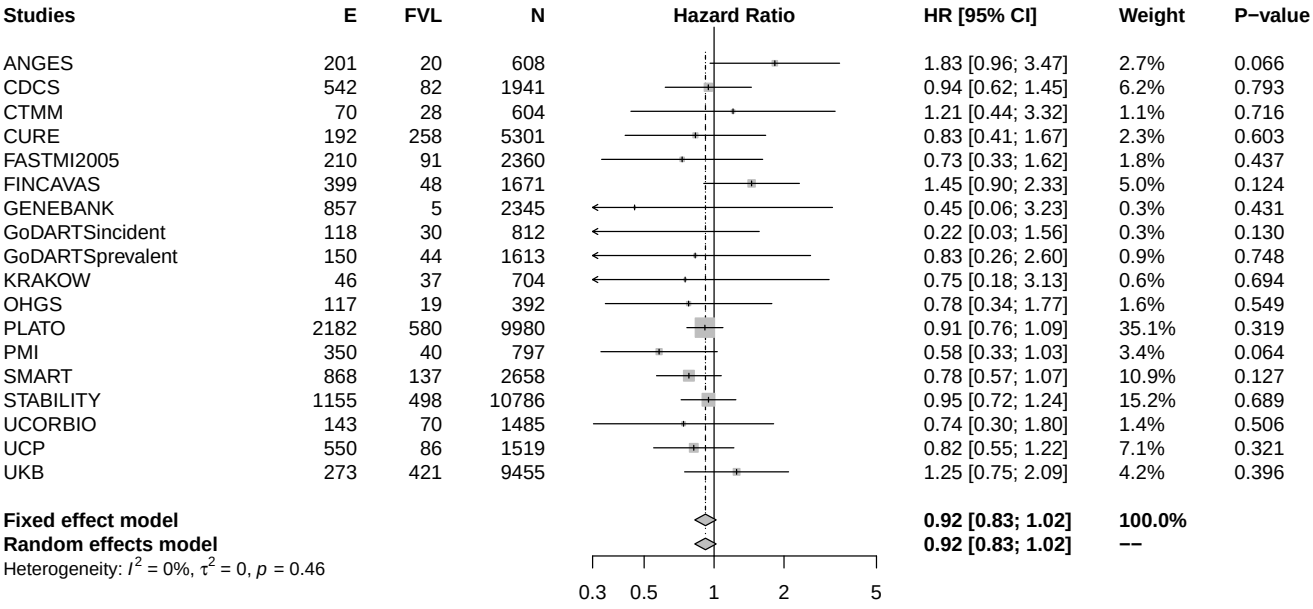
Associations of factor V Leiden with ischemic stroke in overall CHD population.



Supplemental Figure VIII: Adjusted hazard ratios for the associations of factor V Leiden with ischemic stroke in overall CHD population.

Estimates are adjusted for age and sex. E = number of events/outcomes; FVL= number of factor V Leiden; N= overall sample-size; HR = hazard ratio.

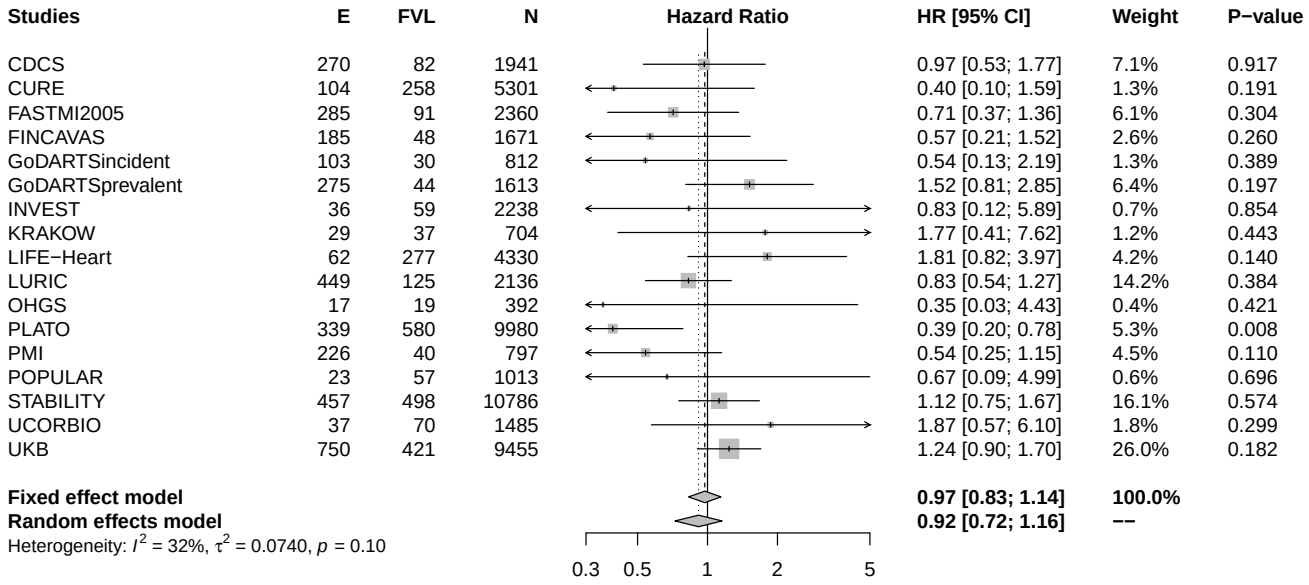
Associations of factor V Leiden with revascularization in overall CHD population.



Supplemental Figure IX: Adjusted hazard ratios for the associations of factor V Leiden with revascularization in overall CHD population.

Estimates are adjusted for age and sex. E = number of events/outcomes; FVL= number of factor V Leiden; N= overall sample-size; HR = hazard ratio.

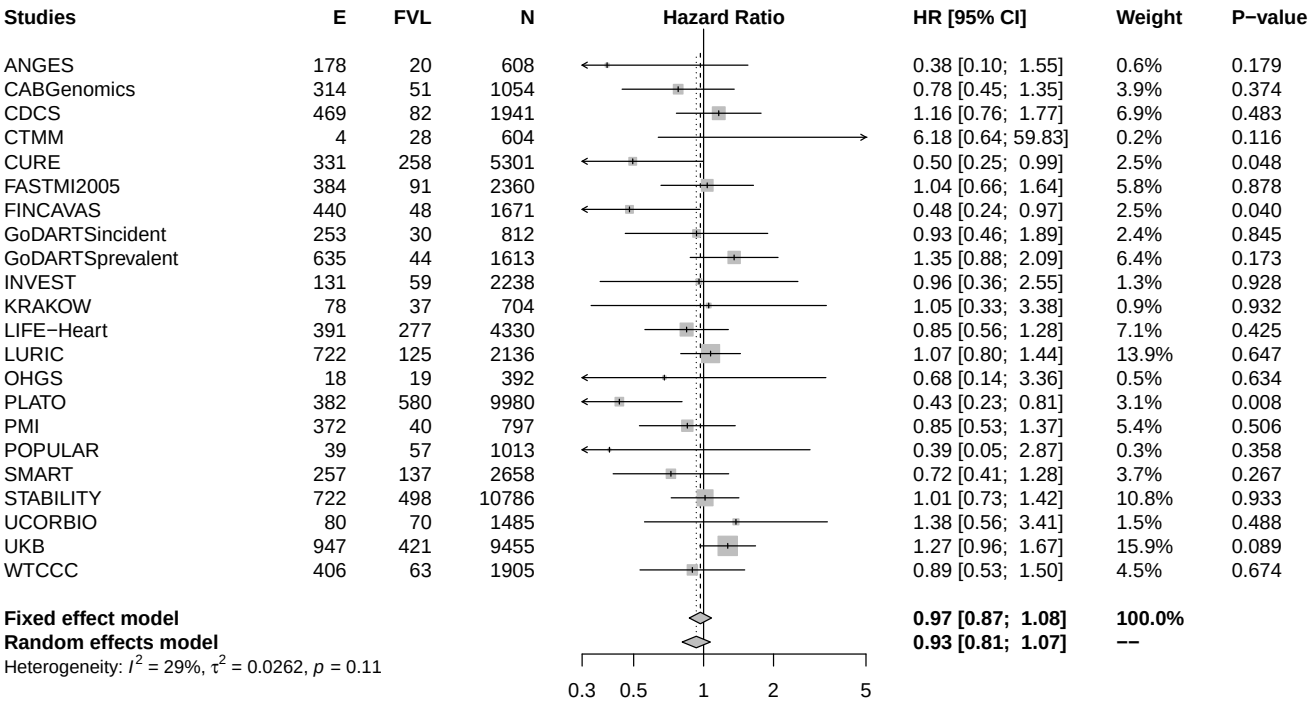
Associations of factor V Leiden with cardiovascular mortality in overall CHD population.



Supplemental Figure X: Adjusted hazard ratios for the associations of factor V Leiden with cardiovascular mortality in overall CHD population.

Estimates are adjusted for age and sex. E = number of events/outcomes; FVL= number of factor V Leiden; N= overall sample-size; HR = hazard ratio.

Associations of factor V Leiden with all-cause mortality in overall CHD population.



Supplemental Figure XI: Adjusted hazard ratios for the associations of factor V Leiden with all-cause mortality in overall CHD population.

Estimates are adjusted for age and sex. E = number of events/outcomes; FVL= number of factor V Leiden; N= overall sample-size; HR = hazard ratio.

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