SUPPLEMENTAL MATERIAL.

Material and Methods.

Participants.

Twenty three hospitals from the Spanish territory participated in the GRECOS project, the list of participants is available in the Supplemental Figure I.

Variables definition: cohort A, B and C.

-Hypertension was defined as systolic blood pressure (BP) ≥140 mmHg, diastolic BP≥90 mmHg and/or use of antihypertensive medication.
-Diabetes mellitus was defined as fasting glucose levels over 7 mmol/L and/or the use of oral antidiabetic drugs or insulin.
-Dyslipidemia was defined as total cholesterol over 5.2 mmol/L, triglycerides over 2.3 mmol/L and/or the use of lipid lowering treatments.
-Alcohol abuse was defined as ≥280 grams per week in males and ≥170 grams per week in females.
-Smoking habit was categorized into current, former or never.
-Previous cardiovascular disease includes coronary artery disease (angina and/or myocardial infarction)
Other clinical risk factors were assessed reviewing the clinical records during hospitalization.
Analytical variables such as leukocytes or cholesterol levels were obtained during the acute phase of stroke (<24h).
NIHSS score was obtained during the acute phase of stroke and at discharge.
mRS score was obtained during the acute phase of stroke and at third month.
Stroke subtypes were defined by TOAST classification (1).

VISP project (Cohort D).

The VISP trial was a multi-center, double-blind, randomized, controlled clinical trial which enrolled patients aged 35 or older with homocysteine levels above the 25th percentile at screening and a non-disabling cerebral infarction (NDCI) within 120 days of randomization (2, 3**)**. NDCI was defined as an ischemic brain infarction not due to embolism from a cardiac source, characterized by the sudden onset of a neurological deficit. The deficit must have persisted for at least 24 hours, or if not, an infarction in the part of the brain corresponding to the symptoms must have been demonstrated by CT or MRI imaging. The trial was designed to determine if daily intake of a multivitamin tablet with high dose folic acid, vitamin B_6 and vitamin B_{12} reduced recurrent cerebral infarction and nonfatal myocardial infarction (MI) or mortality. Subjects were randomly assigned to receive daily doses of the high-dose formulation (n=1,827), containing 25mg pyridoxine (B_6), 0.4mg cobalamin (B_{12}), and 2.5mg folic acid; or the low-dose formulation (n=1,853), containing 200µg pyridoxine, 6µg cobalamin and 20µg folic acid. Enrollment in VISP began in August 1997, and was completed in December 2001, with 3,680 participants enrolled from 55 clinic sites across the U.S. and Canada and one site in Scotland.

Exclusion criteria for the VISP trial included the following:

-Stroke due to any form of intracranial hemorrhage, dissection of a cervicocephalic artery, veno-occlusive disease, drug abuse, or vasculitis;
-CT or MRI of the brain showing lesion other than ischemic infarction as cause of syndrome;
-Modified Rankin score of four or five at the time of eligibility determination;

-Presence of specific potential sources of cardiogenic emboli: atrial fibrillation within 30 days of stroke; or history of prosthetic cardiac valve, intracardiac thrombus or neoplasm, or valvular vegetation;
-Presence of major neurological illness apart from stroke that would prevent proper evaluation of recurrent stroke;
-Presence of cancer, pulmonary disease, or other illness which, in the opinion of the study physician, would limit the life expectancy of the patient to less than 2 years;
-Severe congestive heart failure;
-Renal insufficiency requiring dialysis;
-Untreated pernicious anemia or untreated B12 deficiency;
-Uncontrolled hypertension defined as systolic blood pressure>185 mm or diastolic>105 mm on two readings separated by 5 min at time of eligibility determination;
-Conditions that prevent reliable participation in the study, such as refractory depression, severe cognitive impairment, alcoholism, or other substance abuse;
-Use of medications (within the last 30 days) that affect homocyst(e)ine: methotrexate, tamoxifen, L-dopa, or phenytoin or bile acid sequestrants that can decrease folate levels;
-Woman of childbearing potential, defined as not having reached menopause (natural or surgical) or having had tubal ligation;
-Participation in another trial in which active intervention is being received;
-Patients on multivitamin supplements or single vitamins of B6 or folic acid will be excluded unless they are willing to take the study supplements in place of the one(s) they usually take;
-Any surgical procedure requiring a general anesthesia or hospital stay of 3 days or more, any type of invasive cardiac instrumentation, or an endarterectomy, stent placement, thrombectomy, or any other endovascular treatment of an abnormal carotid artery performed within 30 days prior to randomization or scheduled to be performed within 30 days after randomization

Variables definition: VISP project (cohort D).

Alcohol intake was determined from a dietary intake form in which patients were asked whether they drink or do not drink alcohol.
Tobacco use was defined as self-reported smoking at baseline.
Hypertension: Self-reported (i.e. “Has a doctor ever said you had any of the following…. High blood pressure or hypertension”)
Diabetes: Self-reported.
NIHSS score was obtained during hospitalization.
mRS score was obtained during hospitalization.
Analytical values were obtained during hospitalization.

A subset of VISP participants provided consent for inclusion in genetic studies. These participants were included in the GWAS component of VISP, supported by the National Human Genome Research Institute (NHGRI), Grant U01 HG005160, as part of the Genomics and Randomized Trials Network (GARNET). Samples were genotyped at the Johns Hopkins Center for Inherited Disease Research (CIDR), using the Illumina HumanOmni1-Quad_v1-0_B BeadChip (Illumina, San Diego, CA, USA). Individuals were excluded if they were unexpected duplicates or had gender discrepancies. A total of 2,100 individuals were included in the final genetic analyses, the samples with recurrence data were 1,683 (1.501 controls (ischemic stroke patients without ischemic stroke recurrence and 182 cases (ischemic stroke patients with ischemic stroke recurrence)).
Individuals were excluded if they were unexpected duplicates or had gender discrepancies.
Imputation for rs1800168 was performed using MACH version 1.0.16 (http://www.sph.umich.edu/csg/abecasis/MACH/).

Candidate genes selection.

Candidate genes were selected by manual searching Pubmed using the keywords “stroke, hypertension, inflammation, drug metabolism, coagulation, diabetes mellitus or diabetes, angiogenesis, myocardial infarction, atherosclerosis, lipid metabolism” for phenotypes and the keywords “polymorphism, SNP, mutation, variant” for polymorphisms. Pathways analyzed were related to stroke risk (hypertension, diabetes mellitus, lipid metabolism and myocardial infarction), t-PA targets (coagulation) and catabolizers (drugs metabolism) and further processes linked to good (angiogenesis) and bad (inflammation) outcome after ischemia. Only articles in English or Spanish were read. Among candidate genes, SNP selection was performed depending on previous literature, and their functional effect, including those with an already known modification at transcription, translation or protein activity or a hypothetic modification based on an aminoacid substitution. We selected the SNP that has been associated with the risk factor for stroke risk and/or a functional activity observed. Whenever an interesting polymorphism involved more than a single nucleotide change (e.g. Angiotensin I/D variant), a SNP in perfect linkage disequilibrium was chosen for genotyping.

In addition, we followed the recommendations of Pettersson et al (4), indicating that it is important to select those SNPs with an implication in the disease or pathway or with a demonstrated functional association with the activity of the gene or the protein codified in the gene. Candidate genes that are selected entirely on the basis of their supposed biological significance, without any evidence that the region they are located in is implicated, have very low success rates. Candidate gene studies should therefore follow association studies which have already implicated the gene, or follow from the proven involvement of a particular biological pathway in which other associated gene(s) already have been identified, and in which the candidate gene of interest plays a role. Indicating that it is important to select those SNPs with an implication in the disease or pathway or with a demonstrated functional association with the activity of the gene or the protein codified in the gene.

Supplemental references

1-Adams HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. 3rd. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; 24:35-41.

2-Spence JD, Howard VJ, Chambless LE, Malinow MR, Pettigrew LC, Stampfer M, et al. Vitamin Intervention for Stroke Prevention (VISP) trial: rationale and design. *Neuroepidemiology* 2001; 20:16-25.

3-Toole JF. Vitamin intervention for stroke prevention. *J Neurol Sci* 2002; 15;203-204:121-4.

4-Pettersson FH, Anderson CA, Clarke GM, Barrett JC, Cardon LR, Morris AP, et al. Marker selection for genetic case-control association studies. *Nat Protoc* 2009;4:743-752.

Supplemental legends.

Supplemental Figure I: Hospitals that participated in the GRECOS study. Numbers of patients recruited before removing hemorrhagic stroke patients, patients with low DNA concentration, low genotyping, and before exclusion criteria and inclusion criteria checking. Y axis: number of patients, X axis: name of the hospital. VH: Vall d'Hebron Hospital, BH: Bellvitge Hospital, SCH, Hospital Universitari Sagrat Cor, MH: Mataró Hospital, BAH: Basurto Hospital, TH: Josep Trueta Hospital, GTPH: Germans Tries i Pujols Hospital, VAH: Valladolid Hospital, Virgen del Rocio Hospital, DH: Donosti Hospital, RyCH: Ramon y Cajal Hospital, PTH: Parc Taulí Hospital, SPH: Sant Pau Hospital, VdNH: Virgen de las Nieves Hospital, dMH: del Mar Hospital, LLH: Lleida Hospital, GH: Granollers Hospital, MTH: Mutua de Terrassa Hospital, NH: Navarra Hospital, LBH: Lozano Blesa Hospital.

Supplemental Table I: List of SNPs genotyped. SNP: Single nucleotide polymorphism, CHR: Chromosome.

Supplemental Table II Clinical and demographic description variables Discovery cohort (Cohort A). Categorical variables and continuous variables.

Supplemental Table III: SNPs associated with ischemic stroke recurrence in a dominant-recessive model in the Discovery cohort A; SNPs associated with vascular recurrence in a dominant-recessive model in the Discovery cohort A; SNPs associated with vascular recurrence in an additive model in the Discovery cohort A. RG: Risk genotype, OR: Odds Ratio, CI: confidence interval, Dom/Rec: Dominant Recessive model, HZ: Hazard Ratio.

Supplemental Table IV: SNPs associated with ischemic stroke recurrence in an additive model in the Discovery cohort A. Risk allele, HZ: Hazard Ratio, CI: confidence interval.

Supplementary Table V: Clinical and demographic data of VISP cohort, categorical variables and continuous variables.

Supplemental Table VI. Clinical and demographic description variables Replication cohorts B+C, N=1305. Categorical variables and continuous variables.

Supplemental Table I: Polymorphisms genotyped

Biologic Pathway	**GENE**	**SNP**	**CHR**
Angiogenesis	*ABAC*	rs28587567	9
Angiogenesis	*ABAC*	rs2230806	9
Angiogenesis	*EDN*	rs5370	6
Angiogenesis	*FGF*	rs1449683	4
Angiogenesis	*HTR*	rs6311	13
Angiogenesis	*ICAM*	rs1799969	19
Angiogenesis	*PARP*	rs1136410	1
Angiogenesis	*VCAM*	rs1041163	1
Angiogenesis	*VEGFA*	rs2010963	6
Angiogenesis	*VEGFA*	rs3025042	6
Angiogenesis	*VEGFA*	rs3024994	6
Angiogenesis	*VEGFA*	rs3025000	6
Angiogenesis	*VEGFA*	rs3025010	6
Angiogenesis	*VEGFA*	rs3025030	6
Angiogenesis	*VEGFA*	rs3025033	6
Angiogenesis	*VEGFA*	rs3025035	6
Diabetes Mellitus	*ADIPOQ*	rs2241766	3
Diabetes Mellitus	*ADIPOQ*	rs1501299	3
Diabetes Mellitus	*ADAMTS9*	rs4607103	3
Diabetes Mellitus	*CDKAL1*	rs6931514	6
Diabetes Mellitus	*ENPP*	rs1044498	6
Diabetes Mellitus	*GCKR*	rs1260326	2
Diabetes Mellitus	*GRM3*	rs6465084	7
Diabetes Mellitus	*HHEX*	rs5015480	10
Diabetes Mellitus	*HNF4A*	rs2144908	20
Diabetes Mellitus	*CDC123*	rs12779790	10
Diabetes Mellitus	*IGF1R*	rs2229765	15
Diabetes Mellitus	*IGFBP2*	rs4402960	3
Diabetes Mellitus	*IGFBP3*	rs2854744	7
Diabetes Mellitus	*JAZF1*	rs864745	7
Diabetes Mellitus	*LGR5*	rs7961581	12
Diabetes Mellitus	*TCF7L2*	rs7903146	10
Diabetes Mellitus	*THADA*	rs7578597	2
Diabetes Mellitus	*PPARA*	rs1800206	22
Drug metabolism	*CYP11B2*	rs1799998	8
Drug metabolism	*GST*	rs3211206	1
Drug metabolism	*GSTO*	rs4925	10
Drug metabolism	*GSTP*	rs1695	11
Drug metabolism	*MGP*	rs1800801	12
Drug metabolism	*MTHFR*	rs1801131	1
Drug metabolism	*MTHFR*	rs1801133	1
Drug metabolism	*PTGS*	rs3842787	9
Drug metabolism	*PTGS*	rs20417	1
Drug metabolism	*CYP2C19*	rs12571421	10

Drug metabolism	*TP53*	rs1042522	17
Drug metabolism	*VKORC*	rs2359612	16
Fibrinolysis/coagulation	*ANAX5*	rs11575945	4
Fibrinolysis/coagulation	*CYP2C*	rs1057910	10
Fibrinolysis/coagulation	*F12*	rs1801020	5
Fibrinolysis/coagulation	*F2*	rs1799963	11
Fibrinolysis/coagulation	*F8*	rs1800291	23
Fibrinolysis/coagulation	*FGA*	rs6050	4
Fibrinolysis/coagulation	*FGB*	rs1800790	4
Fibrinolysis/coagulation	*PLAT*	rs2020918	8
Fibrinolysis/coagulation	*PLAU*	rs2227564	10
Fibrinolysis/coagulation	*PROC*	rs1799810	2
Fibrinolysis/coagulation	*PROS1*	rs6123	3
Fibrinolysis/coagulation	*RETN*	rs1862513	19
Fibrinolysis/coagulation	*SERPINE*	rs1799768	7
Fibrinolysis/coagulation	*SERPINE*	rs7242	7
Fibrinolysis/coagulation	*TAFI*	rs1926447	13
Fibrinolysis/coagulation	*THBD*	rs1042579	20
Fibrinolysis/coagulation	*VWF*	rs2239162	12
Fibrinolysis/coagulation	*VWF*	rs1063856	12
Hypertension	*ACE*	rs4341	17
Hypertension	*ADRB2*	rs1042713	5
Hypertension	*ADRB2*	rs1042714	5
Hypertension	*ADRB2*	rs1800888	5
Hypertension	*ADRB3*	rs4994	8
Hypertension	*AGTR1*	rs5186	3
Hypertension	*SCNN1A*	rs5742912	12
Inflammation	*CD40*	rs1883832	20
Inflammation	*CRP*	rs1205	1
Inflammation	*CRP*	rs1130864	1
Inflammation	*CRP*	rs1800947	1
Inflammation	*IFNG*	rs2430561	12
Inflammation	*IL10*	rs1800872	1
Inflammation	*IL10*	rs1800896	1
Inflammation	*IL13*	rs1295686	5
Inflammation	*IL1A*	rs1800587	2
Inflammation	*IL1B*	rs1143634	2
Inflammation	*IL1B*	rs1143627	2
Inflammation	*IL1B*	rs16944	2
Inflammation	*IL4R*	rs1805015	16
Inflammation	*IL4R*	rs1801275	16
Inflammation	*IL5*	rs2069812	5
Inflammation	*IL5RA*	rs2290608	3
Inflammation	*IL6*	rs1800797	7
Inflammation	*IL6*	rs1800796	7
Inflammation	*IL6*	rs1800795	7
Inflammation	*IL9*	rs2069885	5
Inflammation	*ITGA2*	rs1126643	5

Inflammation	*MCP1*	rs1024611	17
Inflammation	*MMP1*	rs1799750	11
Inflammation	*MMP10*	rs486055	11
Inflammation	*MMP12*	rs2276109	11
Inflammation	*MMP13*	rs2252070	11
Inflammation	*MMP2*	rs243864	16
Inflammation	*MMP3*	rs3025058	11
Inflammation	*MMP7*	rs11568818	11
Inflammation	*MMP8*	rs1320632	11
Inflammation	*MMP9*	rs3918248	20
Inflammation	*MMP9*	rs2274756	20
Inflammation	*MMP9*	rs8113877	20
Inflammation	*MMP9*	rs3918278	20
Inflammation	*MMP9*	rs3918241	20
Inflammation	*MMP9*	rs3918253	20
Inflammation	*MMP9*	rs2274755	20
Inflammation	*MMP9*	rs2236416	20
Inflammation	*MMP9*	rs3918256	20
Inflammation	*MMP9*	rs3787268	20
Inflammation	*MMP9*	rs2250889	20
Inflammation	*NOS2A*	rs1137933	17
Inflammation	*NOS3*	rs4722204	7
Inflammation	*NOS3*	rs10266564	7
Inflammation	*NOS3*	rs1800779	7
Inflammation	*NOS3*	rs2070744	7
Inflammation	*NOS3*	rs2257073	7
Inflammation	*NOS3*	rs2257090	7
Inflammation	*NOS3*	rs10275136	7
Inflammation	*NOS3*	rs12703116	7
Inflammation	*NOS3*	rs2243428	7
Inflammation	*NOS3*	rs2288649	7
Inflammation	*NOS3*	rs2435609	7
Inflammation	*NOS3*	rs2487151	7
Inflammation	*NOS3*	rs2435608	7
Inflammation	*NOS3*	rs6952465	7
Inflammation	*NOS3*	rs310590	7
Inflammation	*NOS3*	rs310589	7
Inflammation	*NOS3*	rs310588	7
Inflammation	*NOS3*	rs310586	7
Inflammation	*NOS3*	rs310585	7
Inflammation	*NOS3*	rs310584	7
Inflammation	*SELE*	rs5355	1
Inflammation	*SELE*	rs5361	1
Inflammation	*SELP*	rs6133	1
Inflammation	*TIMP1*	rs2070584	23
Inflammation	*TNF*	rs1800629	6
Inflammation	*TNFRSF1B*	rs1061622	1
Lipid Metabolism	*APOB*	rs1367117	2

Lipid Metabolism	*APOB*	rs576203	2
Lipid Metabolism	*APOB*	rs7575840	2
Lipid Metabolism	*APOB*	rs693	2
Lipid Metabolism	*APOB*	rs1713222	2
Lipid Metabolism	*APOC1*	rs10402271	19
Lipid Metabolism	*APOC3*	rs2854117	11
Lipid Metabolism	*APOE*	rs405509	19
Lipid Metabolism	*APOE*	rs7412	19
Lipid Metabolism	*APOH*	rs1801692	17
Lipid Metabolism	*BCL3*	rs4803750	19
Lipid Metabolism	*BCAM*	rs4605275	19
Lipid Metabolism	*CETP*	rs1800775	16
Lipid Metabolism	*CELSR2*	rs646776	1
Lipid Metabolism	*CETP*	rs5882	16
Lipid Metabolism	*HMGCR*	rs12654264	5
Lipid Metabolism	*LEPR*	rs1137101	1
Lipid Metabolism	*LIPC*	rs1800588	15
Lipid Metabolism	*LPL*	rs268	8
Lipid Metabolism	*LPL*	rs328	8
Lipid Metabolism	*LRP1*	rs12307379	12
Lipid Metabolism	*LRP1*	rs11172113	12
Lipid Metabolism	*LRP1*	rs17547610	12
Lipid Metabolism	*LRP1*	rs4759044	12
Lipid Metabolism	*LRP1*	rs715948	12
Lipid Metabolism	*LRP1*	rs1800127	12
Lipid Metabolism	*LRP1*	rs7398375	12
Lipid Metabolism	*LRP1*	rs10876966	12
Lipid Metabolism	*LRP1*	rs1800168	12
Lipid Metabolism	*LRP1*	rs1800159	12
Lipid Metabolism	*LRP1*	rs7956957	12
Lipid Metabolism	*NCAN*	rs16996148	19
Lipid Metabolism	*OLR1*	rs11053646	12
Lipid Metabolism	*PPARGC1*	rs8192678	4
Lipid Metabolism	*PCSK9*	rs11206510	1
Lipid Metabolism	*TOMM40*	rs2075650	19
Lipid Metabolism	*LDLR*	rs2228671	19
Lipid Metabolism	*LDLR*	rs11668477	19
Lipid Metabolism	*SREBF2*	rs2269657	22
Myocardial Infarction	*ESR1*	rs9340799	6
Myocardial Infarction	*ESR2*	rs1255998	14
Myocardial Infarction	*ESR3*	rs1256030	14
Myocardial Infarction	*PLA2G7*	rs1051931	6
Myocardial Infarction	*PON1*	rs662	7
Myocardial Infarction	*PON2*	rs7493	7
Myocardial Infarction	*MIA3*	rs17465637	1
Myocardial Infarction	*SMAD3*	rs17228212	15
Myocardial Infarction	*S100B*	rs1051169	21
Myocardial Infarction	*CXCL12*	rs501120	10

Myocardial Infarction	*CELSR2*	rs599839	1
Myocardial Infarction	*CDKN2A*	rs10757278	9
Stroke	*A2M*	rs669	12
Stroke	*AACT*	rs4934	14
Stroke	*ADD1*	rs4961	4
Stroke	*AIM1*	rs783396	6
Stroke	*ALOX5AP*	rs10507391	13
Stroke	*AMPD1*	rs17602729	1
Stroke	*ANP*	rs5065	1
Stroke	*ASTN2*	rs3761845	9
Stroke	*CD14*	rs2569190	5
Stroke	*CDH1*	rs16260	16
Stroke	*CX3CR1*	rs3732379	3
Stroke	*ELN*	rs17855988	7
Stroke	*GJA1*	rs17653265	6
Stroke	*GJA4*	rs1764391	1
Stroke	*GNB3*	rs5443	12
Stroke	*HIF1AN*	rs2295778	10
Stroke	*IMPA2*	rs7506045	18
Stroke	*KCNK17*	rs1078911	6
Stroke	*KCNK17*	rs10807204	6
Stroke	*LTA*	rs909253	6
Stroke	*NEUROD1*	rs1801262	2
Stroke	*P2RY1*	rs1065776	3
Stroke	*PDE4D*	rs1396476	5
Stroke	*PDE4D*	rs2910829	5
Stroke	*PDE4D*	rs966221	5
Stroke	*PDE4D*	rs702553	5
Stroke	*PDE4D*	rs152312	5
Stroke	*ROCK2*	rs9808232	2
Stroke	*PITX2*	rs2200733	4
Stroke	*PITX2*	rs10014124	4
Stroke	*PITX2*	rs10033464	4
Stroke	*Intergenic*	rs9536591	13
Stroke	*Intergenic*	rs10486776	7
Stroke	*ZFHX3*	rs7193343	16
Stroke	*COL11A2*	rs1799908	6
Other Processes	*ICT1*	rs1044228	17
Other Processes	*CHD2*	rs10520716	15
Other Processes	*LOC643339*	rs11106995	12
Other Processes	*CHD2*	rs12438635	15
Other Processes	*Intergenic*	rs12732417	1
Other Processes	*Intergenic*	rs12777823	10
Other Processes	*CDKN2B-ABS*	rs1333049	9
Other Processes	*Intergenic*	rs1338500	1
Other Processes	*MC4R*	rs17782313	18
Other Processes	*Intergenic*	rs180117	17
Other Processes	*A2M*	rs1805651	12

Other Processes	*ADAMTS7*	rs1994016	15
Other Processes	*Intergenic*	rs2184006	1
Other Processes	*CDKN2B-AS1*	rs2383206	9
Other Processes	*Intergenic*	rs2824292	21
Other Processes	*CHD2*	rs3826035	15
Other Processes	*CELSR1*	rs4044210	22
Other Processes	*Intergenic*	rs4450014	1
Other Processes	*Intergenic*	rs563280	2
Other Processes	*DMPK*	rs572634	19
Other Processes	*Intergenic*	rs6664786	1
Other Processes	*CHD2*	rs7164668	15
Other Processes	*CHD2*	rs7173103	15
Other Processes	*ICT1*	rs902726	17
Other Processes	*Intergenic*	rs9289423	3
Other Processes	*CHD2*	rs961233	15
Other Processes	*CELSR1*	rs9615978	22
Other Processes	*Intergenic*	rs9644872	9
Other Processes	*Intergenic*	rs9819617	3
Other Processes	*Intergenic*	rs9824398	3
Other Processes	*FTO*	rs9939609	16

Supplemental Table II

Clinical and demographic variables. Categorical variables.	**Frequency (n)**
Clinical variables at enrollment	
Female	37.9% (565)
Tobacco use	51.8% (743)
Alcohol intake	30% (415)
Low physical activity	34.8% (355)
Presence of Hypertension	60.5% (886)
Presence of Dyslipidemia	37.6% (546)
Presence of Diabetes Mellitus	27.5% (401)
Previous Angina Pectoris	8.1% (119)
Previous Myocardial Infarction (MI)	6.4% (94)
Previous Atrial Fibrillation	15.8% (234)
Previous Carotid Stenosis (>50%)	1.3% (15)
Previous Leukoaraiosis	11.7% (133)
Previous Deep Venous Thrombosis	2.5% (37)
Previous Diabetic Nephropathy	3.9% (57)
Previous Dementia	2.6% (38)
Previous Migraine	3.1% (45)
Previous Sleep Apnea Syndrome	4.1% (59)
Familial History of Stroke	24.5% (321)
Familial History of MI or Angina Pectoris	13.3% (172)
Familial History of Dementia	8.3% (107)
Clinical variables after recruitment	
Inclusion TIA	7.9% (117)
Carotid revascularization	5.7% (76)
Presence of intracraneal stenosis	16% (148)
Administration of rt-PA	18.7% (270)
Vascular Recurrence	10.2% (137)
Ischemic Stroke Recurrence	6.7% (90)
TOAST	
Large Vessel Stroke	20.6% (299)
Cardioembolism	26.8% (389)
Small Vessel Disease	14.4% (209)
Undetermined >2 causes	3.2% (47)
Undetermined (study completed)	8.3% (120)
Undetermined (uncompleted study)	22.8% (330)
Clopidogrel administration	21.2% (297)
Diuretics administration	18.1% (253)
B-blockers administration	12.4% (174)
Oral antidiabetic drugs administration	15.9% (223)
Clinical and demographic variables. Continuous variables.	
Clinical variables at enrollment	
Age, years (mean, median)	68 years (24-98 years), 71years
Weight (kilograms, median)	73 Kg
Height (cm, median)	165 cm
Red blood cells (count, median)	4510000 /mm^3
Hemoglobin (median)	14.2 g/dL
Platelets (count, median)	215700 /mm^3
Leukocytes (count, median)	7770 /mm^3

Cholesterol (median)	182 mg/dl
HDL (median)	43 mg/dl
LDL (median)	111 mg/dl
Triglycerides (median)	121 mg/dl
Glucose levels (median)	101 mg/dl
Fibrinogen (median)	6.7 mg/dl
Homocysteine (median)	12.2 μmol/L
Proteinuria (median)	110.2 mg/24h
Baseline NIHSS (median)	5
NIHSS at discharge (median)	1
Baseline mRS (median)	1
mRS at discharge (median)	1

Supplemental Table III. SNPs associated with ischemic stroke recurrence under a dominant-recessive model in the Discovery cohort A; SNPs associated with vascular recurrence under a dominant-recessive model in the Discovery cohort A; SNPs associated with vascular recurrence under an additive model.

			Ischemic Stroke Recurrence Dom/Rec model. % Recurrence. Discovery cohort (n=1.494)			
NEARBY GENE	**SNP**	**RG**	**RG in cases**	**RG in controls**	**HZ**	**Pvalue**
NOTCH2	rs10923931	T carriers> GG	8.4	3.4	2.641	0.013
SMAD3	rs17228212	CC> T carriers	9.5	4	2.519	0.04
SERPINE1	rs1799768	GG> - carriers	8	2.8	3	0.001
LEPR	rs1137101	AA> G carriers	6.7	3.1	2.275	0.042
HMGCR	rs12654264	AA> T carriers	6.6	3.2	2.157	0.026
CDKN2B-AS1	rs1333049	GG> C carriers	10	2.2	5	0.022
APOB	rs1367117	AA> G carriers	9.4	3.6	2.76	0.04
ADIPOQ	rs1501299	AA> C carriers	10.3	3.9	2.863	0.017
PROC	rs1799810	T carriers> AA	6.5	1.3	5.221	0.003
LRP1	rs1800168	CC> T carriers	9.1	3.9	2.479	0.045
NOS3	rs1800779	G carriers> AA	5.6	2.2	2.609	0.043
NOS3	rs2257090	AA> G carriers	9.8	3.8	2.79	0.039
MMP12	rs2276109	GG> A carriers	16.7	4.2	4.613	0.03
NOS3	rs310586	GG> A carriers	7.1	3.1	2.396	0.028
APOB	rs7575840	TT> G carriers	11.5	3.8	3.317	0.009
CHD2	rs961233	AA> G carriers	9.4	0.8	12.396	0.005
CNTN3	rs9808232	GG/ T carriers	6	1.6	3.982	0.017
			Vascular Recurrence Dom/Rec model. % Vascular Recurrence. Discovery cohort A (n=1.494)			
NEARBY GENE	**SNP**	**RG**	**RG in cases**	**RG in controls**	**OR**	**Pvalue**
ALOX5AP	rs10507391	AA>T carriers	12.5	6.5	2.056	0.03
VWF	rs1063856	AA> G carriers	10.2	5.6	1.931	0.033
IL1B	rs1143634	TT> C carriers	22.2	6.9	3.841	0.004
SMAD3	rs17228212	CC> T carriers	14.3	6.9	2.243	0.026
SERPINE1	rs1799768	GG> - carriers	11.4	5.4	2.251	0.003
PPARGC1	rs8192678	G carriers >AA	8.1	2.1	4.036	0.039
ADIPOQ	rs1501299	AA> C carriers	13.8	6.7	2.213	0.038
IL1A	rs1800587	TT> C carriers	17.5	7.1	2.763	0.02
NOS3	rs1800779	G carriers> AA	8.9	4	2.315	0.022
APOC3	rs2854117	AA> G carriers	15.9	6.4	2.755	0.018
APOB	rs7575840	TT> G carriers	17.3	6.8	2.848	0.006
CHD2	rs961233	AA> G carriers	11.3	3.3	3.702	0.041
CNTN3	rs9819617	CC> T carriers	22.2	4.4	6.163	0.003
			Vascular Recurrence additive model. % Recurrence. Discovery cohort A (n=1.494)			
NEARBY GENE	**SNP**	**RA**	**RA in cases**	**RA in controls**	**HZ**	**P (K-Meyer)**
THBD	rs1042579	T	16.7	15.3	1.108	0.006
ENPP1	rs1044498	C	6.4	6.1	1.05	0.005
P2RY1	rs1065776	T	9.4	6.6	1.469	0.003
NOTCH2	rs10923931	T	7.6	6.5	1.178	0.001
IL1B	rs1143634	T	7.2	6.2	1.176	1.09E-04
PDE4D	rs1396476	T	6.5	5.2	1.283	0.030

FGF2	rs1449683	T	6.9	6	1.154	0.008
GSTP1	rs1695	A	6.6	6.3	1.048	0.017
APOB	rs1713222	C	6.7	5.9	1.157	0.024
MC4R	rs17782313	T	7	5.3	1.353	0.022
SERPINE1	rs1799768	G	7.3	5.1	1.471	5.50E-06
PROC	rs1799810	A	6.9	5.9	1.18	0.026
LRP1	rs1800127	T	12.5	6.5	2.044	0.021
IL1A	rs1800587	T	7.1	6.6	1.076	0.001
LIPC	rs1800588	C	6.5	5.4	1.215	0.013
FGB	rs1800790	G	6.8	4.9	1.422	0.012
MGP	rs1800801	G	6.1	5.9	1.04	0.010
IL10	rs1800896	A	6.8	6.1	1.114	0.033
MTHFR	rs1801131	A	6.4	5.7	1.131	0.029
A2M	rs1805651	G	5.8	5	1.176	0.040
PLAT	rs2020918	C	6.6	6.1	1.092	0.025
IL9	rs2069885	T	8.2	6.1	1.377	1.23E-04
MMP9	rs2236416	A	6.2	5.9	1.051	0.018
ADIPOQ	rs2241766	T	7.1	5.6	1.302	0.043
NOS3	rs2243428	A	6.4	5.3	1.209	0.035
MMP13	rs2252070	G	7.2	6.2	1.181	0.001
NOS3	rs2257073	C	6.5	5.4	1.207	0.021
MMP9	rs2274755	T	6.7	6.3	1.054	0.004
MMP12	rs2276109	G	7.1	6.1	1.175	1.78E-04
IL5RA	rs2290608	G	6.4	5.5	1.184	0.009
VKORC1	rs2359612	G	6.8	5.9	1.159	0.005
NOS3	rs2435608	A	6.7	5.1	1.336	0.036
PDE4D	rs2910829	T	6.8	6.4	1.066	0.012
NOS3	rs310586	G	7	5.6	1.273	0.001
GST	rs3211206	C	6.5	4.6	1.453	0.001
CX3CR1	rs3732379	C	6.4	6	1.061	0.007
APOE	rs405509	C	6.9	6.5	1.066	0.017
IGFBP2	rs4402960	T	7.1	6	1.21	2.13E-04
ANP	rs5065	A	6.6	5	1.36	0.037
AGTR1	rs5186	A	6.3	5.8	1.094	0.033
SELE	rs5355	T	9.4	6.5	1.486	0.001
SELE	rs5361	C	7.9	6.2	1.298	0.002
EDN1	rs5370	G	6.2	5.1	1.228	0.047
APOB	rs563280	T	9.1	4.5	2.12	0.002
FGA	rs6050	G	6.7	6.1	1.104	0.001
CDKAL1	rs6931514	G	4.7	3.8	1.244	9.00E-03
CHD2	rs7164668	T	7.4	4	1.909	0.027
CHD2	rs7173103	T	7.4	4	1.909	0.027
APOE	rs7412	T	7.4	6.6	1.13	0.026
PON2	rs7493	G	6.8	6.4	1.068	0.005
IMPA2	rs7506045	T	7	6.7	1.05	0.006
APOB	rs7575840	T	8.1	6.2	1.332	6.17E-04
PPARGC1	rs8192678	G	6.5	6.1	1.055	0.013

Supplemental Table IV. SNPs associated with ischemic stroke recurrence under an additive model in the Discovery cohort A.

			% Recurrence. Discovery cohort (n=989)			
NEARBY GENE	**SNP**	**RA**	**% RA in cases**	**% RA in controls**	**HZ**	**Pvalue**
S100B	rs1051169	C	4	3.9	1.207	0.046
ITGA2	rs1126643	T	4.8	4.4	1.118	0.026
CRP	rs1130864	T	4.3	4.2	1.017	0.04
LDLR	rs11668477	G	4.7	4.5	1.027	0.042
CRP	rs1205	T	4.6	4.1	1.136	0.007
LRP1	rs12307379	T	5.1	4	1.297	0.037
GCKR	rs1260326	T	4.5	3.7	1.217	0.01
CDKN2B	rs1333049	G	6.6	1.9	3.568	0.011
PDE4D	rs1396476	T	4.8	2.8	1.736	0.024
MC4R	rs17782313	T	4.7	3.1	1.559	0.044
SERPINE1	rs1799768	G	5.6	2.8	2.070	4.36E-06
PROC	rs1799810	T	5.1	4.5	1.127	0.012
CYP11B2	rs1799998	T	5.3	3.4	1.573	0.002
PPARA	rs1800206	G	4.8	4	1.213	0.033
LIPC	rs1800588	T	5.4	4	1.362	0.001
NOS3	rs1800779	G	5.6	3.9	1.460	3.35E-04
FGB	rs1800790	G	4.7	3.1	1.541	0.039
MGP	rs1800801	G	4.6	3.5	1.334	0.009
MTHFR	rs1801131	C	5.2	4	1.300	0.004
Intergenic	rs180117	T	4.7	3.7	1.291	0.023
NEUROD1	rs1801262	G	5.2	3.5	1.526	0.007
CD40	rs1883832	T	4.8	4	1.207	0.006
IL9	rs2069885	T	5.1	4.1	1.251	0.021
PITX2.ENPEP	rs2200733	T	6.4	4	1.614	0.003
PLAU	rs2227564	C	3.2	0.9	3.584	0.005
MMP9	rs2236416	G	5	4	1.252	0.019
MMP13	rs2252070	G	5.2	3.6	1.465	0.003
MMP9	rs2274755	T	5.7	4	1.456	0.003
MMP12	rs2276109	G	8.5	3.7	2.394	2.24E-08
HIF1AN	rs2295778	G	6.8	3.7	1.917	7.31E-06
VKORC1	rs2359612	G	4.6	3.9	1.173	0.043
CD14	rs2569190	G	4.3	3.8	1.148	0.037
PDE4D	rs2910829	T	4.7	4.2	1.138	0.042
VEGFA	rs3024994	T	6.4	4.3	1.512	0.018
VEGFA	rs3025000	T	5	4	1.262	0.012
VEGFA	rs3025010	T	4.6	4	1.165	0.047
VEGFA	rs3025033	G	7.2	4.2	1.758	0.001
NOS3	rs310586	G	5.3	3.3	1.674	0.001
GST	rs3211206	C	4.2	3.4	1.250	0.021
IGFBP2	rs4402960	T	5.2	4.1	1.280	0.004
ADD1	rs4961	T	5.1	3.9	1.327	0.009
ANP	rs5065	G	5	4.2	1.185	0.01
AGTR1	rs5186	C	5.3	3.8	1.389	0.003
SELE	rs5355	T	6.3	4.5	1.421	0.038
APOB	rs576203	G	5	3.4	1.494	0.038
PROS1	rs6123	G	4.6	4.4	1.060	0.037
A2M	rs669	G	5	4	1.279	0.005

APOB	rs693	T	5.9	3.7	1.632	0.001
CDKAL1	rs6931514	A	2.9	2.7	1.100	0.006
PDE4D	rs702553	A	3.9	3.8	1.035	0.038
CHD2	rs7164668	T	6.1	2.4	2.597	0.041
CHD2	rs7173103	T	6.1	2.4	2.597	0.042
SERPINE1	rs7242	T	4.4	3.4	1.317	0.011
LRP1	rs7398375	G	5	3.6	1.399	0.002
PON2	rs7493	G	5	4.4	1.144	0.025
IMPA2	rs7506045	T	7	4.4	1.642	0.002
APOB	rs7575840	T	7.2	3.5	2.135	2.01E-06
TCF7L2	rs7903146	T	5	4.4	1.084	0.035
TSPAN8. LGR5	rs7961581	T	4.8	3.7	1.307	0.026
PPARGC1	rs8192678	G	4.5	3.7	1.241	0.025

Supplemental Table V. Clinical and demographic variables for the VISP cohort.

Categorical variables and continuous variables.

Clinical and demographic variables. Categorical variables.	**Frequency (n)**
Clinical variables at enrollment	
Female	36.4% (765)
Tobacco use	N/A
Current Smokers	15.6% (328)
Alcohol intake	59.8% (1256)
Low physical activity	N/A
Presence of Hypertension	72.1% (1515)
Presence of Dyslipidemia	N/A
Presence of Diabetes Mellitus	27.1% (570)
Previous Angina Pectoris	N/A
Previous Myocardial Infarction (MI)	N/A
Previous Atrial Fibrillation	N/A
Previous Carotid Stenosis (>50%)	N/A
Previous Leukoaraiosis	N/A
Previous Deep Venous Thrombosis	N/A
Previous Diabetic Nephropathy	N/A
Previous Dementia	N/A
Previous Migraine	N/A
Previous Sleep Apnea Syndrome	N/A
Familial Antecedents of Stroke	23.2% (488)
Familial Antecedents of MI or Angina Pectoris	N/A
Familial Antecedents of Dementia	N/A
Clinical variables after recruitment	N/A
Inclusion TIA	N/A
Carotid revascularization	N/A
Presence of intracraneal stenosis	N/A
Administration of rt-PA	N/A
Vascular Recurrence	N/A
Ischemic Stroke Recurrence	8.7% (182)
TOAST	N/A
Cardioembolic	N/A
Aterothrombotic	N/A
Lacunar	N/A
Undetermined	N/A
Clopidogrel administration	N/A
Diuretics administration	N/A
B-blockers administration	N/A
Oral antidiabetic drugs administration	N/A
Clinical and demographic variables. Continuous variables.	
Clinical variables at enrollment	
Number of Individuals (EA/AA/other)	2100 (1725/258/117)
Age (yrs) Mean ± S.D. Median	 67.2 ± 10.8 68

range	35-89
Weight (kilograms, median)	79.37
Height (cm, median)	170.18
Red blood cells (count)	N/A
Hemoglobin (mean)	N/A
Platelets (count)	N/A
Leukocytes (count)	N/A
Cholesterol (median)	200 mg/dl
HDL (median)	43 mg/dl
LDL (median)	120 mg/dl
Triglycerides (median)	150 mg/dl
Glucose levels (mean)	N/A
Fibrinogen (median)	400 mg/dL
Homocysteine (median)	12.2 (umol/L)
Proteinuria	N/A
Baseline NIHSS (median)	1
NIHSS at discharge (median)	N/A
Baseline mRS (median)	1
mRS at discharge (median)	N/A

Supplemental Table VI. Clinical and demographic description variables Replication cohorts

B+C. Categorical variables and continuous variables.

Clinical and demographic variables. Categorical variables.	**Frequency (n)**
Clinical variables atenrollment	
Female	34% (453)
Tobacco use	28.3% (370)
Alcohol intake	NA
Low physical activity	NA
Presence of Hypertension	60.6% (791)
Presence of Dyslipidemia	30.3% (396)
Presence of Diabetes Mellitus	23.5% (307)
Previous Angina Pectoris	NA
Previous Myocardial Infarction (MI)	NA
Previous Atrial Fibrillation	30.8% (403)
Previous Carotid Stenosis (>50%)	NA
Previous Leukoaraiosis	NA
Previous Deep Venous Thrombosis	NA
Previous Diabetic Nephropathy	NA
Previous Dementia	NA
Previous Migraine	NA
Previous Sleep Apnea Syndrome	NA
Familial History of Stroke	NA
Familial History of MI or Angina Pectoris	NA
Familial History of Dementia	NA
Clinical variables after recruitment	
Inclusion TIA	NA
Carotid revascularization	NA
Presence of intracraneal stenosis	NA
Administration of rt-PA	100% (1305)
Vascular Recurrence	25.5% (334)
Ischemic Stroke Recurrence	14.5% (190)
TOAST	
Large Vessel Stroke	23.3% (304)
Cardioembolism	45.2% (590)
Small Vessel Disease	12.7% (166)
Undetermined	20.7% (271)
Undetermined >2 causes	NA
Undetermined (study completed)	NA
Undetermined (uncompleted study)	NA
Clopidogrel administration	NA
Diuretics administration	NA
B-blockers administration	NA
Oral antidiabetic drugs administration	NA
Clinical and demographic variables. Continuous variables.	
Clinical variables at enrollment	
Age, years (mean)	71 years (17-97 years) median 73
Weight (kilograms, mean)	NA
Height (cm)	NA

Red blood cells (count)	NA
Hemoglobin (mean)	NA
Platelets (count)	NA
Leukocytes (count)	NA
Cholesterol (mean)	NA
HDL (mean)	NA
LDL (mean)	NA
Triglycerides (mean)	NA
Glucose levels (mean)	135.54 mg/dl (median 123)
Fibrinogen (mean)	NA
Homocysteine (mean)	NA
Proteinuria	NA
Baseline NIHSS (median)	15
NIHSS at discharge (median)	5
Baseline mRS (median)	NA
mRS at discharge (median)	NA

Supplemental Figure I. Hospitals that participated in the GRECOS study.