Title: A cluster of blood-based protein biomarkers reflecting coagulation relates to the burden of cerebral small vessel disease

Supplemental Table 1. List of 92 biomarkers involved in the OLINK cardiovascular III panel

Biomarker (abbreviation)
Aminopeptidase N (APN)
Azurocidin (AZU1)
Bleomycin hydrolase (BLMH)
C-C motif chemokine 15 (CCL15)
C-C motif chemokine 16 (CCL16)
C-C motif chemokine 22 (CCL22)
C-C motif chemokine 24 (CCL24)
C-X-C motif chemokine 16 (CXCL16)
Cadherin-5 (CDH5)
Carboxypeptidase A1(CPA1)
Carboxypeptidase B (CPB1)
Caspase 3 (CASP-3)
Cathepsin D (CTSD)
Cathepsin Z (CTSZ)
CD166 antigen (ALCAM)
Chitinase-3-like protein 1 (CHI3L1)
Chitotriosidase (CHIT1)
Collagen alpha-1(I) chain (COL1A1)
Complement component C1q receptor (CD93)
Contactin-1 (CNTN1)
Cystatin-B (CSTB)
E-selectin (SELE)
Ephrin type-B receptor 4 (EPHB4)
Epidermal growth factor receptor (EGFR)
Epithelial cell adhesion molecule (Ep-CAM)
Fatty acid-binding protein; adipocyte (FABP4)
Galectin-3 (Gal-3)
Galectin-4 (Gal-4)
Granulins (GRN)
Growth/differentiation factor 15 (GDF-15)
Insulin-like growth factor binding protein 1(IGFBP-1)

Insulin-like growth factor binding protein 2 (IGFBP-2)

Insulin-like growth factor-binding protein 7 (IGFBP-7)

Integrin beta-2 (ITGB2)

Intercellular adhesion molecule 2 (ICAM-2)

Interleukin-1 receptor type 1 (IL-1RT1)

Interleukin-1 receptor type 2 (IL-1RT2)

Interleukin-17 receptor A (IL-17RA)

Interleukin-18-binding protein (IL-18BP)

Interleukin-2 receptor subunit alpha (IL2-RA)

Interleukin-6 receptor subunit alpha (IL6-RA)

Junctional adhesion molecule A (JAM-A)

Kallikrein-6 (KLK6)

Low-density lipoprotein receptor (LDLR)

Lymphotoxin-beta receptor (LTBR)

Matrix extracellular phosphoglycoprotein (MEPE)

Matrix metalloproteinase-2 (MMP-2)

Matrix metalloproteinase-3 (MMP-3)

Matrix metalloproteinase-9 (MMP-9)

Metalloproteinase inhibitor 4 (TIMP4)

Monocyte chemotactic protein 1 (MCP-1)

Myeloblastin (PRTN3)

Myeloperoxidase (MPO)

Myoglobin (MB)

N-terminal prohormone brain natriuretic peptide (NT-proBNP)

Neurogenic locus notch homolog protein 3 (Notch 3)

Osteopontin (OPN)

Osteoprotegerin (OPG)

P-selectin (SELP)

Paraoxonase 3 (PON3)

Peptidase inhibitor 3 (PI3)

Peptidoglycan recognition protein 1(PGLYRP1)

Perlecan (PLC)

Plasminogen activator inhibitor 1 (PAI)

Platelet endothelial cell adhesion molecule (PECAM-1)

Platelet-derived growth factor subunit A (PDGFA)

Proprotein convertase subtilisin/kexin type 9 (PCSK9)

Protein delta homolog 1(DLK-1)

Proteolysis

Pulmonary surfactant-associated protein D (PSP-D)

Resistin (RETN)

Retinoic acid receptor responder protein 2 (RARRES2)

Scavenger receptor cysteine-rich type 1 protein M130 (CD163)

Secretoglobin family 3A member 2 (SCGB3A2)

Spondin-1 (SPON1)

ST2 protein (ST2)

Tartrate-resistant acid phosphatase type 5 (TRAP)

Tissue factor pathway inhibitor (TFPI)

Tissue-type plasminogen activator (t-PA)

Transferrin receptor protein 1 (TR)

Trefoil factor 3 (TFF3)

Trem-like transcript 2 protein (TLT-2)

Tumor necrosis factor ligand superfamily member 13B (TNFSF13B)

Tumor necrosis factor receptor 1 (TNF-R1)

Tumor necrosis factor receptor 2 (TNF-R2)

Tumor necrosis factor receptor superfamily member 10C (TNFRSF10C)

Tumor necrosis factor receptor superfamily member 14 (TNFRSF14)

Tumor necrosis factor receptor superfamily member 6 (FAS)

Tyrosine-protein kinase receptor UFO (AXL)

Tyrosine-protein phosphatase non-receptor type substrate 1(SHPS-1)

Urokinase plasminogen activator surface receptor (U-PAR)

Urokinase-type plasminogen activator (uPA)

von Willebrand factor (vWF)

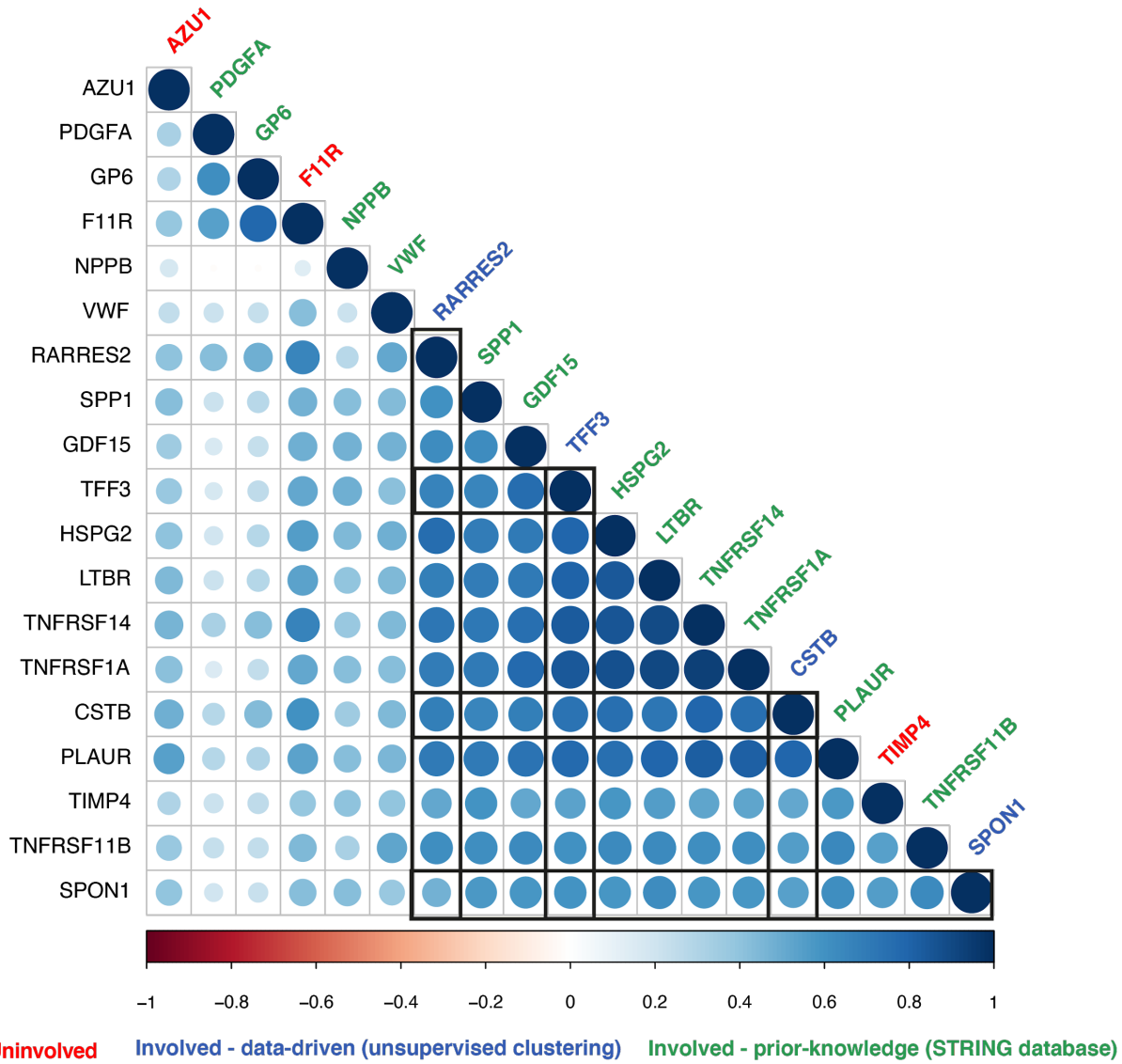
Supplemental Table 2. Enriched pathways reflected in the complete OLINK cardiovascular III panel

Pathway name	No. of biomarkers found/No. of total biomarkers	p-value	FDR
Inflammation pathway			
Signaling by Interleukins	28/647	<0.001	<0.001
Cytokine Signaling in Immune system	31/1108	< 0.001	< 0.001
Interleukin-4 and Interleukin-13 signaling	14/216	< 0.001	< 0.001
Immune System	48/2713	< 0.001	< 0.001
Neutrophil degranulation	17/480	< 0.001	< 0.001
Interleukin-10 signaling	8/86	< 0.001	< 0.001
TNFs bind their physiological receptors	4/30	< 0.001	0.006
Interleukin-1 family signaling	7/165	< 0.001	0.016
Interleukin-33 signaling	2/4	< 0.001	0.018
ECM organization pathway			
Extracellular matrix organization	13/330	< 0.001	< 0.001
Integrin cell surface interactions	6/87	< 0.001	0.005
Degradation of the extracellular matrix	7/48	< 0.001	0.010
Collagen degradation	5/69	< 0.001	0.011
Cell organization pathway			
Regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	6/127	< 0.001	0.020

Abbreviations: FDR, false discovery rate; TNF, tumour necrosis factor; No., number; ECM, extracellular matrix organization.

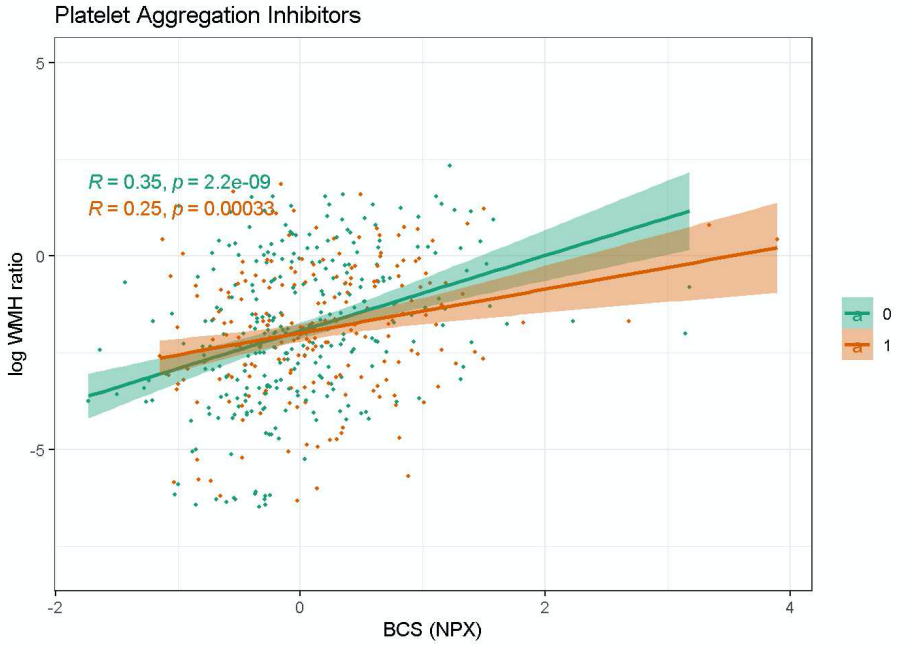
Data are presented as the number of biomarkers found per pathway (expressed as percentage of the total number of biomarkers known to be involved per pathway) with corresponding p-values and FDRs. A statistically significant p-value implies that the number of biomarkers identified within a pathway is higher than would be expected by chance.

Supplemental Figure 1. Correlations between 19 biomarkers associated with white matter hyperintensity volume

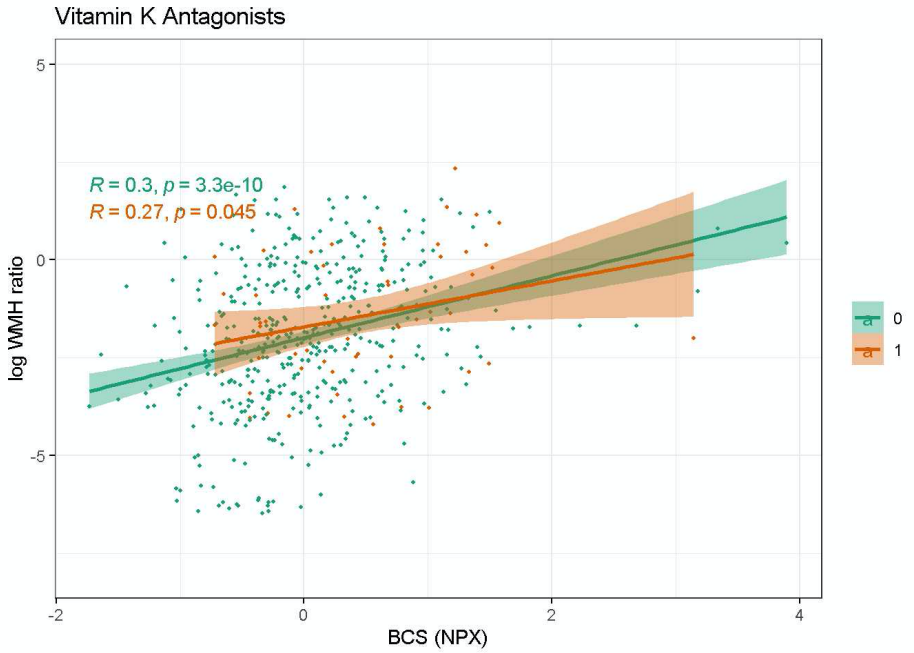


Visualization of correlation coefficients between biomarkers associated with white matter hyperintensity volume (expressed as percentage of total brain volume), where larger and darker circles correspond to higher positive correlations. Names of biomarkers that are involved in the unsupervised data-driven cluster, in the STRING-cluster and uninvolved in both clusters are shown in blue, green and red respectively. Interrelations between the blue-colored and green-colored biomarkers are not yet established in the STRING-database. However, the correlation coefficients suggest strong positive correlations ($r > 0.8$) with biomarkers involved in the STRING-cluster, therefore, we added the blue-colored biomarkers to our cluster of interest.

Supplemental Figure 2. Correlation between the Biomarker Compound Score and white matter hyperintensity volume, stratified by medication use



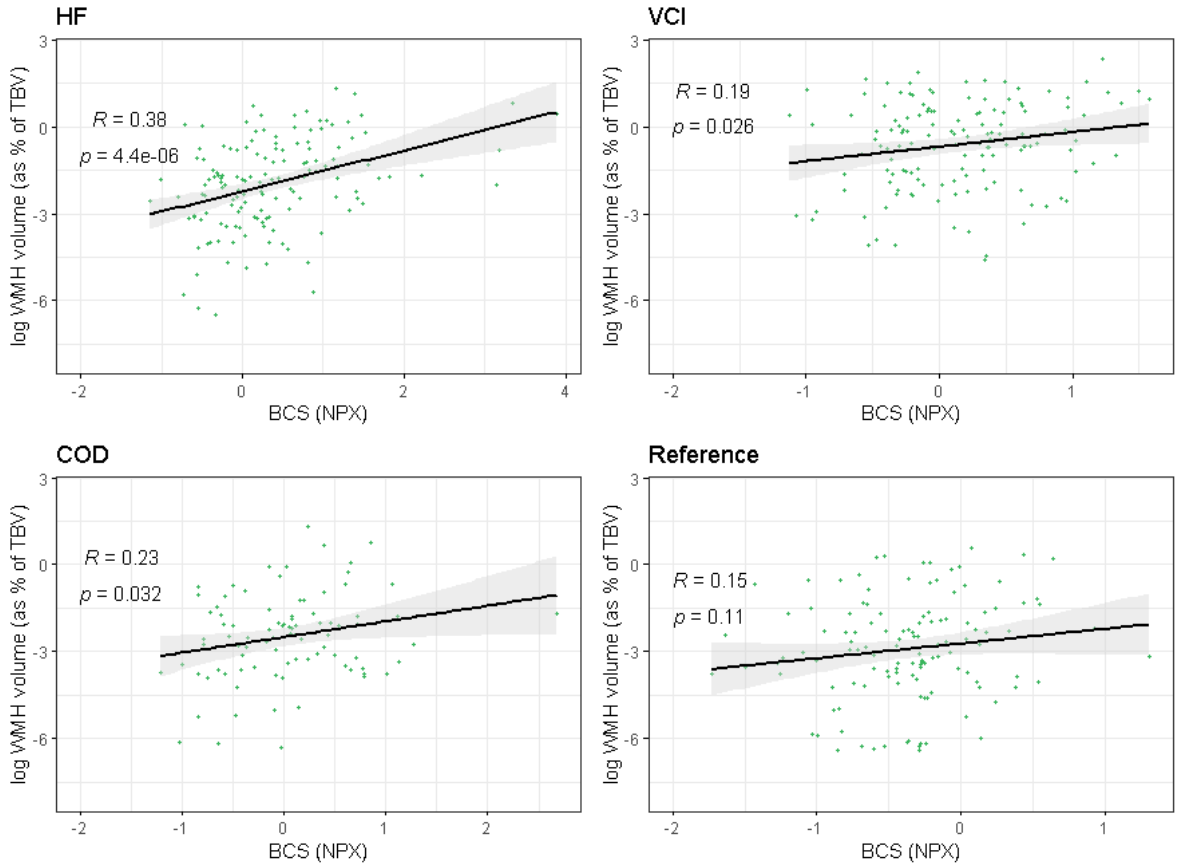
A



B

Correlation plots showing the correlation between the Biomarker Compound Score (BCS) and white matter hyperintensity volume, stratified by use of platelet aggregation inhibitors (panel A) and vitamin K antagonists (panel B). The BCS was expressed as Normalized Protein eXpression (NPX) and the natural log of white matter hyperintensity (WMH) volume was expressed as percentage of total brain volume (TBV).

Supplemental Figure 3. Correlation between the BCS and white matter hyperintensity volume in four participant groups



This figure shows the correlation between the Biomarker Compound Score (BCS) expressed as Normalized Protein eXpression (NPX) and the natural logarithm of white matter hyperintensity (WMH) volume expressed as percentage of total brain volume (TBV) in participants with heart failure (HF), vascular cognitive impairment (VCI), carotid occlusive disease (COD) and reference participants. Correlations are unadjusted (see the methods section).