Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Detailed Methodology

Subject characteristics in the Bruneck Study: The study protocol included a clinical examination and standardized questionnaires on medical history, life-style behaviours and vascular risk factors[1-5]. Subjects were coded as current smokers or non-smokers (including former smokers). The number of pack-years was noted for each smoker and former smoker. Alcohol consumption was quantified in grams per day. Body mass index was calculated as weight (kg) divided by height $(m)^2$. Systolic and diastolic blood pressures were means of three independent measurements, each of which was taken after the participant had been sitting for 10 minutes. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or the use of antihypertensive drugs. Diabetes mellitus was determined as fasting plasma glucose level ≥126 mg/dL (≥7.0 mmol/L) or the use of anti-diabetic medication. Glomerular filtration rate was estimated using the CKD-EPI equation. Socioeconomic status was defined according to a 3-category scale (low, medium, high) based on information about occupational status and educational level of the person with the highest income in the household. High socioeconomic status was assumed if the participant had ≥12 years of education or an occupation with an average monthly income ≥$2,000 (baseline salary before tax). Low socioeconomic status was defined by ≤8 years of education or an average monthly income ≤$1,000. Atherosclerosis was assessed by carotid duplex ultrasound according to a standardized protocol, as described previously[5]. The present study uses a contrast of 0 (no plaque) versus 1 (presence of one or more plaque in one of the 8 segments of the right and left carotid arteries). PR interval (in milliseconds), corrected QT interval (in milliseconds) and P axis (in degrees) were determined automatically from resting 12-lead ECGs (Hewlett Packard M1700A). P-wave terminal force, defined as the product of the duration of the negative P-wave deflection (in

milliseconds) in lead V1 multiplied by the absolute value of its amplitude (μV), was an average of three consecutive cardiac cycles measured manually by two observers. Prolonged PR interval and corrected QT interval, P wave axis <30° and high values of P-wave terminal force have been associated with atrial abnormality in previous studies[6-9]. Myocardial infarction was deemed confirmed when World Health Organization criteria for definite disease status were met[10]. Symptoms suggestive of heart failure were classified using the New York Heart Association classification[11]. Ischemic stroke and transient ischemic attack (TIA) were classified according to the criteria of the National Survey of Stroke[12]. The situation in Bruneck is unique in that medical care is primarily provided in the Bruneck hospital to which residents of Bruneck usually are referred by general practitioners for diagnostic tests. Additionally, population mobility in this area has been low over the past 20 years. Given the shared pathomechanisms and risk factors, TIAs were included in the ischemic stroke endpoint if the diagnosis was made with high accuracy (medical record-confirmed TIA).

Assessment of laboratory parameters in the Bruneck Study: Measurement of sVCAM-1 was performed in samples stored at -70°C for 11 years without any cycle of thawing and refreezing. Comparison of this assessment with sVCAM-1 levels measured in 1993 after only 2.5 years after sampling (n=84) yielded strong evidence of a high stability of sVCAM-1 under the storage conditions applied (mean sVCAM-1 in the 1993 and 2001 assessment, 679.5 and 724.6 ng/mL, difference [95%CI] 45.1 [-9.8 to 100.0], P=0.11).

Laboratory parameters were measured in baseline samples using standard procedures, as described previously [1-5]. High-sensitivity cardiac troponin T (hs-cTnT) was assessed using highly sensitive reagents on an Elecsys® 2010 analyser (Roche Diagnostics, Burgess Hill, UK)[13]. Values of hs-cTnT were categorized into groups of

undetectable and tertiles of detectable hs-cTnT levels according to a recent publication of the Cardiovascular Health Study[14]. Other markers of inflammation, immune activation, or endothelial dysfunction were determined in samples collected during the 2000 follow-up by Proximity Extension Assay (PEA)[15], using Proseek Multiplex CVD I^{96x96} and Proseek Multiplex Inflammation I^{96x96} reagents kits (Olink Bioscience, Uppsala, Sweden). Each of these assays yielded 92 protein measurements. Of 26 proteins that were measured in both assays only measurements from the Inflammation assay were considered, 3 proteins were discarded because they had already been measured in 1990, and 23 proteins were discarded because they had more than 50% nondetects. This resulted in 132 candidate proteins, from which proteins potentially relevant to inflammation, immune activation, or endothelial dysfunction were selected as those annotated with GO terms that were partially matched by any of the character strings "inflamm", "immun", or "endothel", for a final set of 75 proteins measured in 2000. All variables were $\log_e$-transformed and standardised to unit variance.

Methodological details of the SAPHIR Study: At baseline and during the follow-up visit, all participants underwent a comprehensive clinical assessment including patient history, physical examination, 12-lead standard ECG, and laboratory tests[16,17]. Definitions of hypertension, body mass index, diabetes, smoking, atherosclerosis and ECG variables (PR interval, corrected QT interval) were the very same as used in the Bruneck Study. Alcohol consumption was quantified as the number of standard drinks per week (10-12 g of alcohol per drink). Information on AF was available in 1629 participants (92%) as of September 2013 and ascertained by 1) ECGs recorded at baseline and during the follow-up study visit, 2) ECGs recorded during interim hospitalizations and outpatient visits to the hospital, 3) self-report of physician-diagnosed AF in follow-up questionnaires, and 4) reviewing all medical records for a diagnosis of

AF. Laboratory parameters were assessed by standard methods. Measurement of sVCAM-1 were performed in samples stored at -70° C for a mean of 15 years (baseline examination) and 10 years (follow-up examination) without any cycle of thawing and refreezing and using the same enzyme-linked immunosorbent assay as in the Bruneck Study. Absolute values of sVCAM-1 in the baseline and follow-up samples of the same individuals were similar (mean difference [95% CI] 29.5 [-2.4 to 61.4] P=0.072) and highly correlated (r=0.60).

In SAPHIR, we used a nested case-control design for replication purposes. After excluding individuals with AF at baseline, 60 subjects with new-onset AF formed the case group (all detected by medical records). To each case we matched two controls free of AF with identical age (± 1 year) and sex. For cases with AF manifestation between baseline and the follow-up examination and the respective controls we used levels of sVCAM-1 measured from baseline samples while for cases with AF manifestation after the follow-up examination and the respective controls we used levels of sVCAM-1 measured from follow-up samples. The quantity of frozen blood was insufficient in 6 control individuals, thus 60 cases and 114 controls were finally analysed. The association between baseline characteristics and incident AF was analysed with conditional logistic regression analysis.

eTable 1. Associations Between 75 Markers of Inflammation, Immune Activation, or Endothelial Dysfunction and Incident Atrial Fibrillation in the Bruneck Study.

		Unadjusted			Adjusted for age and sex		
Protein	**Full name**	**Hazard ratio (95% CI)**	**P value**	**[a]P value**	**Hazard ratio (95% CI)**	**P value**	**[a]P value**
IL-6	Interleukin-6	1.33 (1.16-1.51)	<0.001	0.003	1.19 (0.98-1.45)	0.08	>0.99
TNF-R2	Tumor necrosis factor receptor 2	1.53 (1.23-1.91)	<0.001	0.02	1.16 (0.91-1.48)	0.23	>0.99
FABP4	Fatty acid-binding protein, adipocyte	1.50 (1.19-1.90)	<0.001	0.06	1.41 (1.07-1.87)	0.02	>0.99
ADA	Adenosine Deaminase	0.65 (0.50-0.84)	<0.001	0.05	0.80 (0.61-1.04)	0.09	>0.99
IL27-A	Interleukin-27 subunit alpha	1.48 (1.16-1.88)	0.002	0.15	1.24 (0.97-1.58)	0.08	>0.99
TNF-R1	Tumor necrosis factor receptor 1	1.44 (1.14-1.82)	0.002	0.15	1.06 (0.83-1.34)	0.67	>0.99
LOX-1	Lectin-like oxidized LDL receptor 1	1.38 (1.12-1.71)	0.003	0.23	1.25 (1.00-1.58)	0.05	>0.99
OSM	Oncostatin-M	1.35 (1.10-1.65)	0.004	0.30	1.30 (1.05-1.62)	0.02	>0.99
PlGF	Placenta growth factor	1.36 (1.09-1.70)	0.007	0.53	1.11 (0.87-1.41)	0.41	>0.99
EN-RAGE	Protein S100-A12	1.33 (1.07-		0.68	1.23 (0.99-	0.06	>0.9

		1.65)	0.009		1.53)		9
FGF-19	Fibroblast growth factor 19	0.74 (0.58-0.94)	0.02	>0.99	0.82 (0.64-1.05)	0.11	>0.99
CXCL10	C-X-C motif chemokine 10	1.30 (1.05-1.62)	0.02	>0.99	0.96 (0.75-1.24)	0.78	>0.99
ST2	ST2 protein	1.34 (1.07-1.67)	0.01	0.83	1.19 (0.94-1.50)	0.14	>0.99
CXCL9	C-X-C motif chemokine 9	1.31 (1.06-1.62)	0.01	0.98	0.88 (0.68-1.14)	0.33	>0.99
CHI3L1	Chitinase-3-like protein 1	1.26 (1.02-1.57)	0.04	>0.99	0.97 (0.76-1.25)	0.84	>0.99
IL-12B	Interleukin-12 subunit beta	1.27 (1.00-1.61)	0.05	>0.99	1.27 (0.99-1.64)	0.06	>0.99
CD40	CD40L receptor	0.78 (0.60-1.00)	0.05	>0.99	0.88 (0.68-1.15)	0.35	>0.99
ECP	Eosinophil cationic protein	1.26 (0.98-1.61)	0.07	>0.99	1.13 (0.88-1.44)	0.33	>0.99
TRAIL	TNF-related apoptosis-inducing ligand	0.80 (0.63-1.02)	0.07	>0.99	1.07 (0.82-1.39)	0.64	>0.99
CCL23	C-C motif chemokine 23	1.24 (0.97-1.59)	0.08	>0.99	1.16 (0.91-1.48)	0.22	>0.99
PECAM-1	Platelet endothelial cell adhesion molecule	1.21 (0.97-1.52)	0.10	>0.99	1.06 (0.83-1.34)	0.65	>0.99
GAL	Galanin peptides	0.82 (0.65-1.04)	0.11	>0.99	0.95 (0.75-1.21)	0.68	>0.99
LAP TGF-Î²-1	Latency-associated peptide transforming growth factor beta 1	0.81 (0.62-1.06)	0.12	>0.99	0.90 (0.68-1.18)	0.44	>0.99
MCP-4	Monocyte chemotactic protein 4	0.83 (0.65-1.06)	0.13	>0.99	0.84 (0.65-1.07)	0.15	>0.99
BDNF	Brain-derived neurotrophic factor	0.82 (0.64-	0.13	>0.99	0.95 (0.74-	0.68	>0.9

		1.06)			1.22)		9
TF	Tissue factor	1.20 (0.95-1.52)	0.13	>0.99	1.00 (0.78-1.27)	0.97	>0.99
CTSL1	Cathepsin L1	1.19 (0.94-1.49)	0.14	>0.99	1.09 (0.86-1.39)	0.47	>0.99
IL-16	Interleukin-16	1.19 (0.94-1.51)	0.15	>0.99	1.14 (0.89-1.46)	0.31	>0.99
EGF	Epidermal growth factor	1.18 (0.94-1.49)	0.15	>0.99	1.05 (0.83-1.34)	0.67	>0.99
TNFB	TNF-beta	0.85 (0.67-1.07)	0.16	>0.99	1.02 (0.78-1.32)	0.91	>0.99
CXCL11	C-X-C motif chemokine 11	1.17 (0.94-1.45)	0.17	>0.99	1.04 (0.82-1.34)	0.73	>0.99
IL-1ra	Interleukin-1 receptor antagonist protein	1.16 (0.93-1.44)	0.18	>0.99	1.16 (0.93-1.45)	0.20	>0.99
MCP-2	Monocyte chemotactic protein 2	1.16 (0.93-1.43)	0.18	>0.99	1.00 (0.79-1.26)	0.99	>0.99
CCL3	C-C motif chemokine 3	1.12 (0.93-1.36)	0.23	>0.99	0.95 (0.75-1.20)	0.66	>0.99
CD40-L	CD40 ligand	1.14 (0.91-1.43)	0.25	>0.99	1.06 (0.84-1.35)	0.60	>0.99
TNFSF14	Tumor necrosis factor ligand superfamily member 14	0.85 (0.65-1.12)	0.25	>0.99	0.94 (0.70-1.24)	0.65	>0.99
CCL20	C-C motif chemokine 20	1.13 (0.91-1.41)	0.26	>0.99	1.11 (0.88-1.40)	0.40	>0.99
Î²-NGF	Beta-nerve growth factor	1.11 (0.93-1.33)	0.26	>0.99	0.96 (0.73-1.25)	0.76	>0.99
CXCL6	C-X-C motif chemokine 6	0.87 (0.68-1.12)	0.27	>0.99	0.96 (0.74-1.23)	0.73	>0.99
MCP-3	Monocyte chemotactic protein 3	1.14 (0.90-	0.28	>0.99	0.88 (0.67-	0.36	>0.9

		1.43)			1.16)		9
IL-18R1	Interleukin-18 receptor 1	0.88 (0.69-1.12)	0.29	>0.99	1.05 (0.82-1.36)	0.69	>0.99
VEGF-A	Vascular endothelial growth factor A	1.12 (0.89-1.41)	0.34	>0.99	1.01 (0.79-1.28)	0.95	>0.99
SCF	Stem cell factor	1.13 (0.87-1.45)	0.37	>0.99	1.22 (0.93-1.58)	0.15	>0.99
HSP 27	Heat shock 27 kDa protein	1.11 (0.88-1.39)	0.39	>0.99	1.04 (0.81-1.32)	0.77	>0.99
FAS	Tumor necrosis factor receptor superfamily member 6	1.09 (0.88-1.35)	0.41	>0.99	1.01 (0.79-1.28)	0.96	>0.99
CCL28	C-C motif chemokine 28	1.10 (0.87-1.39)	0.43	>0.99	0.91 (0.69-1.20)	0.49	>0.99
SIRT2	SIR2-like protein 2	0.91 (0.71-1.16)	0.43	>0.99	0.94 (0.72-1.23)	0.66	>0.99
NEMO	NF-kappa-B essential modulator	1.10 (0.87-1.39)	0.44	>0.99	0.94 (0.74-1.21)	0.64	>0.99
FGF-23	Fibroblast growth factor 23	1.09 (0.86-1.39)	0.48	>0.99	1.04 (0.80-1.36)	0.75	>0.99
IL-17C	Interleukin-17C	1.08 (0.86-1.35)	0.50	>0.99	0.99 (0.78-1.26)	0.93	>0.99
IL-8	Interleukin-8	1.07 (0.86-1.35)	0.54	>0.99	0.86 (0.65-1.15)	0.30	>0.99
CCL4	C-C motif chemokine 4	1.07 (0.85-1.34)	0.56	>0.99	0.96 (0.76-1.20)	0.69	>0.99
CXCL1	C-X-C motif chemokine 1	0.93 (0.74-1.18)	0.56	>0.99	0.98 (0.76-1.27)	0.89	>0.99
IL-18	Interleukin-18	1.07 (0.85-1.35)	0.56	>0.99	1.01 (0.80-1.28)	0.92	>0.99
SRC	Proto-oncogene tyrosine-protein kinase Src	1.07 (0.84-	0.58	>0.99	1.05 (0.82-	0.69	>0.9

		1.37)			1.36)		9
CCL19	C-C motif chemokine 19	0.94 (0.73-1.21)	0.63	>0.99	0.96 (0.75-1.22)	0.71	>0.99
CCL25	C-C motif chemokine 25	0.95 (0.75-1.20)	0.65	>0.99	0.91 (0.72-1.15)	0.43	>0.99
TIE2	Angiopoietin-1 receptor	0.95 (0.75-1.20)	0.67	>0.99	1.12 (0.89-1.41)	0.32	>0.99
HB-EGF	Heparin-binding EGF-like growth factor	1.05 (0.83-1.32)	0.70	>0.99	0.96 (0.74-1.24)	0.75	>0.99
VEGF-D	Vascular endothelial growth factor D	0.96 (0.77-1.21)	0.75	>0.99	1.06 (0.84-1.36)	0.61	>0.99
IL-6RA	Interleukin-6 receptor subunit alpha	1.04 (0.82-1.32)	0.75	>0.99	1.05 (0.84-1.33)	0.66	>0.99
RAGE	Receptor for advanced glycosylation end products	0.97 (0.76-1.23)	0.78	>0.99	1.15 (0.90-1.47)	0.27	>0.99
TWEAK	Tumor necrosis factor superfamily, member 12	0.97 (0.76-1.23)	0.81	>0.99	0.94 (0.74-1.18)	0.58	>0.99
IL-7	Interleukin-7	0.98 (0.77-1.24)	0.84	>0.99	0.93 (0.70-1.23)	0.60	>0.99
PDGF Subunit B	Platelet-derived growth factor subunit B	1.02 (0.81-1.30)	0.85	>0.99	1.01 (0.80-1.29)	0.91	>0.99
MIP-1A	Macrophage inflammatory protein 1-alpha	1.02 (0.81-1.29)	0.86	>0.99	0.85 (0.65-1.11)	0.24	>0.99
CASP-8	Caspase 8	0.98 (0.77-1.24)	0.86	>0.99	0.92 (0.71-1.20)	0.55	>0.99
CX3CL1	Fractalkine	1.02 (0.80-1.30)	0.86	>0.99	0.97 (0.75-1.24)	0.80	>0.99
CSF-1	Macrophage colony-stimulating factor 1	1.02 (0.80-1.29)	0.89	>0.99	1.09 (0.85-1.40)	0.51	>0.99
IL-10	Interleukin-10	0.98 (0.78-	0.89	>0.99	1.00 (0.78-	0.98	>0.9

		1.25)			1.29)		9
PAR-1	Proteinase-activated receptor 1	0.99 (0.78-1.25)	0.91	>0.99	0.90 (0.69-1.16)	0.40	>0.99
IL-10RB	Interleukin-10 receptor subunit beta	1.01 (0.79-1.29)	0.93	>0.99	0.96 (0.75-1.23)	0.76	>0.99
CXCL5	C-X-C motif chemokine 5	1.01 (0.80-1.27)	0.95	>0.99	1.05 (0.80-1.36)	0.74	>0.99
CCL11	Eotaxin-1	0.99 (0.78-1.27)	0.96	>0.99	0.91 (0.71-1.17)	0.48	>0.99
Gal-3	Galectin-3	1.00 (0.79-1.26)	0.99	>0.99	0.96 (0.75-1.23)	0.76	>0.99

Markers were assessed recently from samples collected in 2000 with 10 years of follow-up (2000-2010). Numbers of events and total subjects were 69 and 637. Markers are $\log_e$-transformed for analysis und hazard ratios are given for a 1-SD higher concentration in each marker. Protein order is arranged by descending significance in unadjusted models.

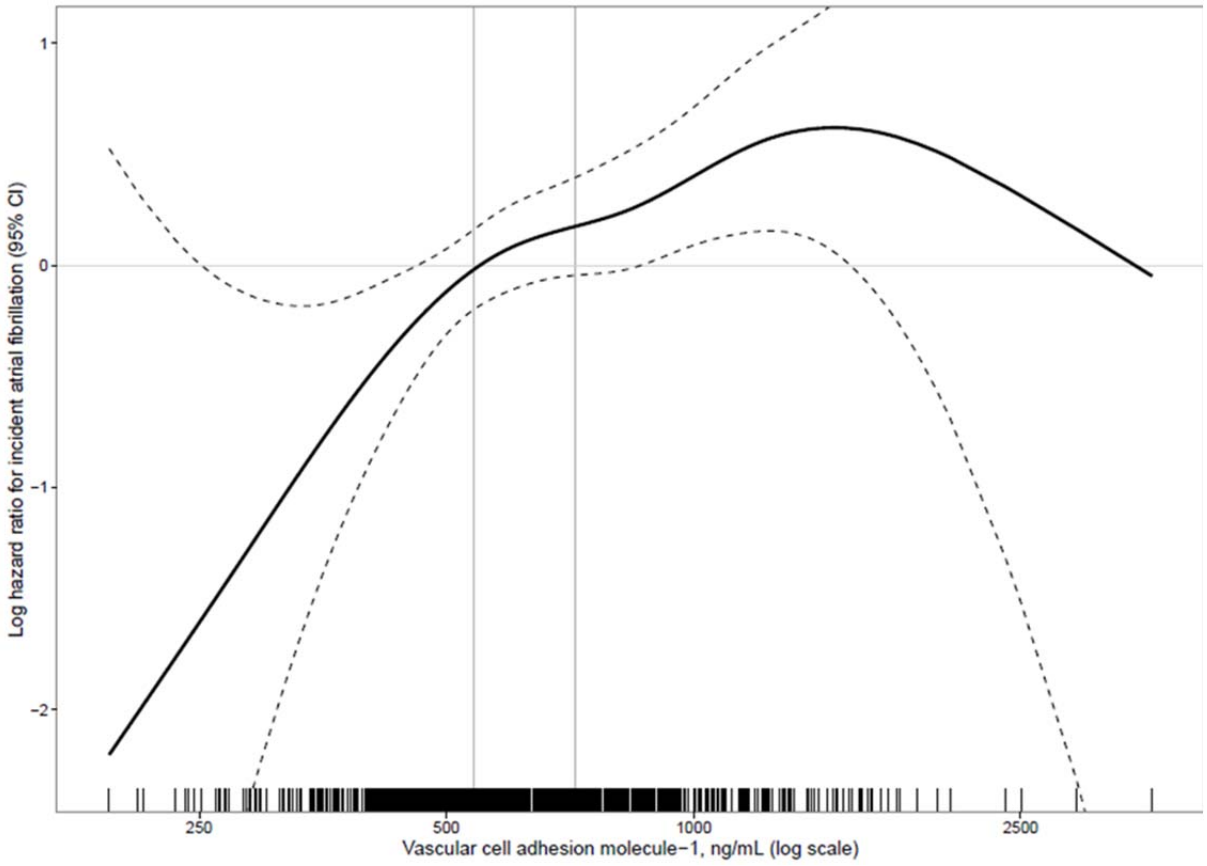
[a]Bonferroni-corrected P value.

eTable 2. Baseline Characteristics in the SAPHIR Study.

Characteristics	Cases (n=60)	Controls (n=114)	P Value[a]
Age, years	54.3±5.2	54.2±5.1	Matched
Female sex, n (%)	24 (40.0)	45 (39.5)	Matched
Diabetes mellitus, n (%)	1 (1.7)	4 (3.5)	0.98
Hypertension, n (%)	43 (71.7)	61 (53.5)	0.02
Body mass index, kg/m^2	26.9±4.8	27.0±4.1	0.97
Smoking, n (%)	7 (11.7)	18 (15.8)	0.27
Alcohol, drinks/week	5.0±6.4	4.3±5.7	0.44
Atherosclerosis, n (%)	15 (25.0)	21 (18.4)	0.26
High-sensitivity CRP, mg/L	1.5 (0.7, 3.1)[b]	1.3 (0.8, 2.8)[b]	0.76
GFR, mL/min	93.7±12.0	92.8±11.2	0.57
PR interval, ms	163.7±22.0	164.9±24.7	0.74
cQT interval, ms	406.2±27.8	406.9±27.1	0.87

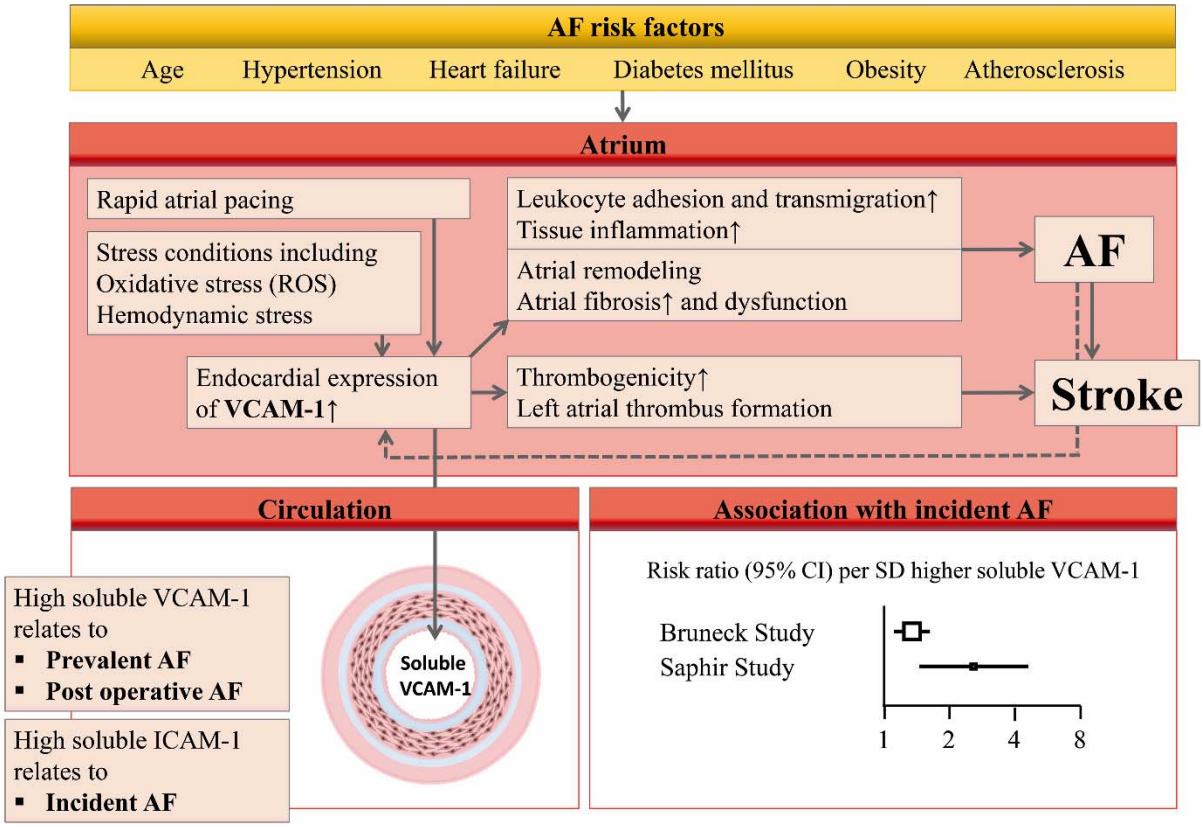
Data presented are mean±SD or n (%).
Abbreviations: cQT interval, corrected QT interval; CRP, C-reactive protein; GFR, glomerular filtration rate.
SI conversion factors: To convert CRP to nmol/L, multiply by 9.542.
[a]P value adjusted for age and sex.
[b]Median (interquartile range) is given for highly skewed variables.

eFigure 1. Penalized Spline Fit of the Association Between Soluble Vascular Cell Adhesion Molecule 1 and Incident Atrial Fibrillation in the Bruneck Study (adjusted for age and sex). There is an adequate fit of a linear dose-response relationship (P=0.004) without evidence of an additional nonlinear component (P=0.230).



eFigure 2. Mechanisms and Epidemiological Evidence Linking Vascular Cell Adhesion Molecule 1 to Atrial Fibrillation.

Abbreviations: ICAM-1, intercellular adhesion molecule 1; ROS, reactive oxygen species.



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