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Implementation and extended use of computed tomography coronary angiography

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Aortic valve calcification volumes and chronic brain infarctions in patients undergoing transcatheter aortic valve implantation

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ABSTRACT

Background: Chronic silent brain infarctions, detected as new white matter hyperintensities on magnetic resonance imaging (MRI) following transcatheter aortic valve implantation (TAVI), are associated with long-term cognitive deterioration. This is the first study to investigate to which extent the calcification volume of the native aortic valve measured with cardiac computed tomography angiography (CTA) predicts the increase in chronic white matter hyperintensity volume after TAVI.

Methods and Results: A total of 36 patients (79±5 years, median EuroSCORE II 1.9 %, Q1-Q3: 1.5-3.4%) with severe aortic valve (AV) stenosis underwent fluid attenuation inversion recovery (FLAIR) MRI <24 hours prior to TAVI and at 3 months follow-up for assessment of cerebral white matter hyperintensity volume (mL). Calcification volumes (mm3) of the AV, aortic arch, landing zone and left ventricle were measured on the CTA pre-TAVI. The largest calcification volumes were found in the AV (median 692mm3) and aortic arch (median 633mm3), with a large variation between patients (Q1-Q3: 482-1297mm3 and Q1-Q3: 213-1727mm3, respectively). The white matter hyperintensity volume increased in 72% of the patients. In these patients the median volume increase was of 1.1mL (Q1-Q3: 0.3-4.6mL), corresponding with a 27% increase from baseline (Q1-Q3: 7-104%). The calcification volume in the AV predicted the increase of white matter hyperintensity volume (Δ %), with a 35% increase of white matter hyperintensity volume, per 100mm3 of AV calcification volume (SE: 8.5, p<0.001). The calcification volumes in the aortic arch, landing zone and left ventricle were not associated with the increase in white matter hyperintensity volume.

Conclusions: In 72% of the patients new chronic white matter hyperintensities developed 3 months after TAVI, with a median increase of 27%. A higher calcification volume in the AV was associated with a larger increase in the white matter hyperintensity volume. These findings show the potential for automated aortic valve calcium screening as an imaging biomarker to predict chronic silent brain infarctions.

BACKGROUND

Transcatheter aortic valve implantation (TAVI) has been established as an effective treatment of severe aortic valve stenosis, reducing both clinical symptoms and mortality. Nevertheless, one of the most feared complications, namely the occurrence of stroke, is still observed in 2.4% of the patients undergoing TAVI (1). This complication is observed despite the expansion to low-risk populations, the increase in operator experience and the development of improved valve-systems (2). The cerebral emboli during TAVI are attributed to the dislodgement of aortic arch calcifications during the advancement of the catheter through the orifice and the expansion of the implanted valve crushing the calcified native valve (3). Our previous research showed that stroke after TAVI is associated with poor outcomes, including a six-fold increase of procedural mortality (1). Nevertheless, clinically overt strokes are only the tip of the iceberg, since shortly after TAVI acute silent cerebral infarctions are visible with diffusion-weighted magnetic resonance imaging (DW-MRI) in up to 78% of the patients (4). Unfortunately, currently the majority of the TAVI-induced cerebral emboli remains unpredictable.

Cardiac computed tomography angiography (CTA) scans are part of the routine pre-TAVI work-up and may be used to measure the local calcification burden in the area of the aortic valve and arch (5). This is confirmed by a previous study that showed that a large plaque volume in the aortic valve prior to TAVI predicted the occurrence of acute silent brain infarctions several days after TAVI (6). Despite a high increase of acute silent brain infarctions, these lesions have as yet not been related to long-term cognitive deterioration (7). Previous research showed that only a proportion of the acute silent brain infarctions, as detected with DW-MRI several days after TAVI, proceeded into chronic loco-regional remnants, which can be identified as white matter hyperintensities on fluid attenuation inversion recovery (FLAIR) MRI sequence, several months after TAVI (7).

In contrast to acute silent brain infarctions, chronic white matter hyperintensities that emerged after the procedural phase were associated with a decrease in cognitive functioning during long-term follow-up (7). Moreover, in the general elderly population white matter hyperintensities are associated with cognitive impairment, a two-fold higher risk of dementia and a three-fold higher risk of stroke (8). TAVI has been developed to improve quality of life, however the increase in TAVI-associated white matter hyperintensities may evoke cognitive deterioration and subsequently compromise self-reliance and increase healthcare costs. If it could be predicted which patients are at risk for developing chronic white matter hyperintensities after TAVI, these high-risk patients could be protected by using additional procedural protective methods, such as cerebral protections devices.

We investigated for the first time to which extent the calcification volume of the native aortic valve, aortic arch, landing zone and left ventricle measured with cardiac computed tomography angiography (CTA), can be used to predict the increase in chronic white matter hyperintensities after TAVI, indicating new chronic brain infarctions.

METHODS

Study population and trial design
The current study is a single centre, prospective trial, initiated and managed by the Heart Centre of the Amsterdam University Medical Centre (UMC), a high volume tertiary cardiac care and TAVI centre. Patients with severe aortic valve stenosis planned to undergo TAVI of a native valve were eligible for inclusion in the trial. Exclusion criteria for trial participation were known structural brain disease (including a history of stroke or transient ischemic attacks) or presence of an MRI contra-indication. The decision for TAVI treatment was made by our multidisciplinary TAVI team consisting of a cardiac surgeon, an interventional-cardiologist, a radiologist, a geriatric internist and a dedicated nurse-practitioner. Moreover, the dedicated multidisciplinary TAVI-team selected the access route and the valve size, all according to the most recent guidelines (5). The transfemoral approach was the default access option, alternatively, in patients with severe peripheral artery disease the transaortic route was used. The study protocol was approved by the Institutional Review Boards of the Academic Medical Centre and all participants provided written informed consent. The current study is registered at the Netherlands Trial Register (NL7495).

Endpoints
The main objectives of the study were to determine the distribution of calcification volumes (mm3) using CTA in four prespecified sections of the heart and aortic arch of patients undergoing TAVI (Figure 1) and to determine whether an association exists between the prespecified regional calcification volumes (mm3) and the increase in FLAIR-MRI determined cerebral white matter hyperintensity volume (Δ% from baseline mL), 3 months after TAVI. This relative increase (Δ%) rather than the actual increase (ΔmL) was chosen since we expected large variations in baseline white matter hyperintensity volumes between patients and baseline white matter hyperintensity volume is known to predict the actual increase in volume over time (ΔmL) (9). Hence, by selecting the relative increase (Δ%) we investigated the influence of the TAVI-procedure rather than the baseline patient risk. The secondary objective was to determine clinical (patient) predictors of both the calcification volume (mm3) and of actual increase in new white matter hyperintensities (mL).

Cerebral MRI and Cardiac CTA acquisition and image analyses

A detailed description of the image acquisition and analyses is provided as supplementary text with corresponding table and figure (Figure 1, Supplementary text 1 and Table 1). In brief, the included patients underwent cerebral MRI evaluation of white matter hyperintensities using a FLAIR sequence at a 3-tesla MRI scanner at baseline (<24 hours prior to the TAVI procedure) and 3 months after the TAVI. The FLAIR sequence was used because of its sensitivity to measure white matter hyperintensities, appearing as lesions with increased brightness. White matter hyperintensities were quantified using an automated segmentation method. CTA scans were acquired in all patients as part of the routine pre-TAVI work-up and used to measure the calcification volumes in the selected segments (Figure 2). In these CTA scans, patient-specific cut-off values for calcifications were automatically detected to minimize differences in calcification volume measurements between patients with different CTA setting (tube voltage (kV) and different contrast delivery protocol. These cut-off values were based on the distribution of the amount of pixels with pixel-values, corresponding with the primary components of the segments (calcifications, contrast material and soft-tissue) (Figure 1).

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Figure 1

Methodology of calcification segmentation

1) Aortic valve segments   **2)** Calcification cut-off value determination   **3)** Segmented calcification
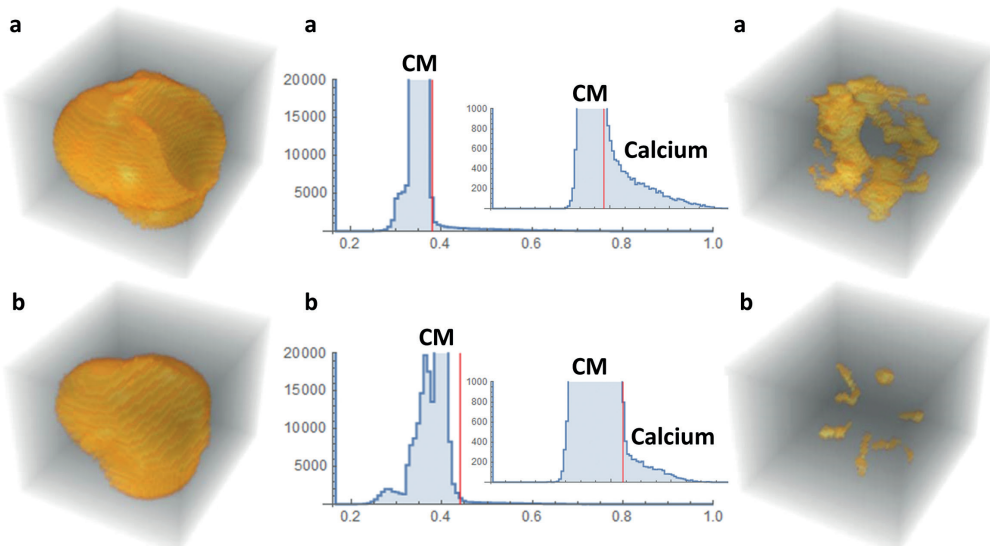
1) Segments of the aortic valve of two patients with either high (**a**) and low calcification volume (**b**) are visualized in 3D. **2)** A patient specific cut-off value was automatically selected (red lines in the histograms) to create binary masks. **3)** Binary masks are used to segment the calcifications from the aortic valve segments in 3D. Note the visual difference in the calcification volume between the patients a and b.

Table 1. Baseline patient and procedural characteristics

|	Study population (n=36)
Demographics	
Age (years)	78.7±4.5
Female gender	22 (61%)
Body mass index (kg/m^2)	29.8 ± 7.4
Medical history	
Previous myocardial infarction	6 (17%)
Previous PCI	10 (28%)
Previous CABG	3 (8%)
Diabetes mellitus	10 (28%)
Hypertension	21 (58%)
Dyslipidemia	6 (17%)
History of coronary artery disease	14 (39%)
Atrial fibrillation	16 (44%)
Glomerular filtration rate < 30 ml/min/1.73m^2	3 (8%)
NT-proBNP (ng/L)	882 (361-2775)
New York Heart Association (NYHA) class III or IV	22 (61%)
Risk scores	
EuroSCORE II (%)	1.9 (1.5-3.4)
STS-PROM mortality (%)	2.8 (1.9-3.7)
Echocardiographic characteristics	
Aortic max gradient (mmHg)	68 ± 24
Aortic mean gradient (mmHg)	43 ± 17
Aortic valve area (cm^2)	0.74 ± 0.16
Procedural details	
Transfemoral access	33 (92%)
Transaortic access	3 (8%)
Edwards SAPIEN 3	35 (97%)
Direct Flow	1 (3%)
Medication at discharge	
Single antiplatelet therapy	1 (3%)
Dual antiplatelet therapy	18 (50%)
Single antiplatelet therapy + Anticoagulation therapy (VKA/NOAC)	12 (33%)
Anticoagulation therapy only (VKA/NOAC)	5 (14%)
Statin	24 (67%)

Values are mean (± SD), n (%) or median (interquartile range). VKA= vitamin K antagonist, NOAC = novel oral anticoagulant.

Statistical analysis

Continuous values of patient and MRI characteristics, including calcification volumes per segment and white matter hyperintensity volumes were tested for normal distribution and are reported as mean ± SD or median with interquartile ranges (Q1-Q3, 25th-75th percentile) where appropriate. Accordingly, depending on the distribution of the data, either the independent t-test or Mann-Whitney U test determined differences between groups. Categorical variables are presented as frequencies and percentages, differences between groups were tested with chi-square. Moreover, the calcification volumes per segment (mm3) were explored as predictors of the relative increase of white matter hyperintensities (Δ%) using linear regression. In a secondary analysis, to correct for inter-individual variance in intracranial volumes, the white matter

Figure 2

Segments of the heart and aortic arch used for calcification volume determination
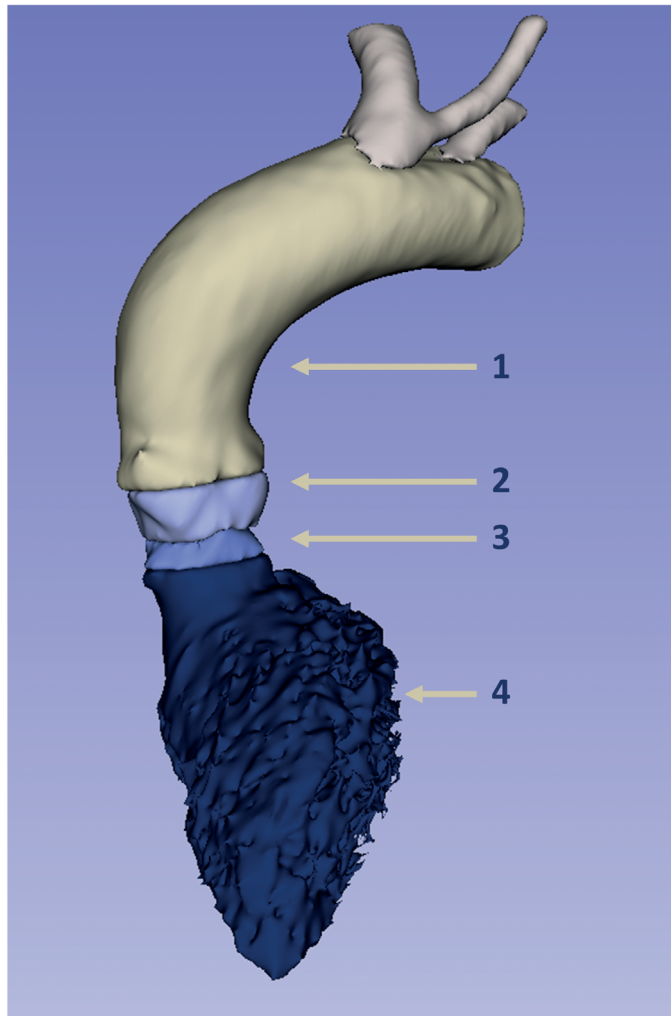
1) aortic arch, starting at the offspring of the left subclavian artery, ending at the distal level of the coronary ostia; **2)** aortic valve; **3)** landing zone, starting immediately below the level of the aortic valve leaflets and including the larger part of the left ventricular outflow tract. This section includes all calcifications adherent to but below the level of the aortic valve; **4)** left ventricle, starting below the landing zone and including the mitral valve.

hyperintensity volume (mL) was normalized for intracranial volume (mL). Moreover, baseline patient characteristics were explored by linear regression as predictors of either the baseline calcification volume per segment (mm3) or the increase of white matter hyperintensities (ΔmL). Potential clinical predictors were tested in a univariate model, and if $p < 0.05$, simultaneously entered to create a multiple regression model. The results of all regression models are reported as beta coefficients (B) and standard errors (SE). All statistical tests were two-tailed, and a value of $p < 0.05$ was considered to indicate a statistically significant difference. Calculations were generated using SPSS software (version 25.0 for Windows, SPSS, Inc., Chicago, Illinois).
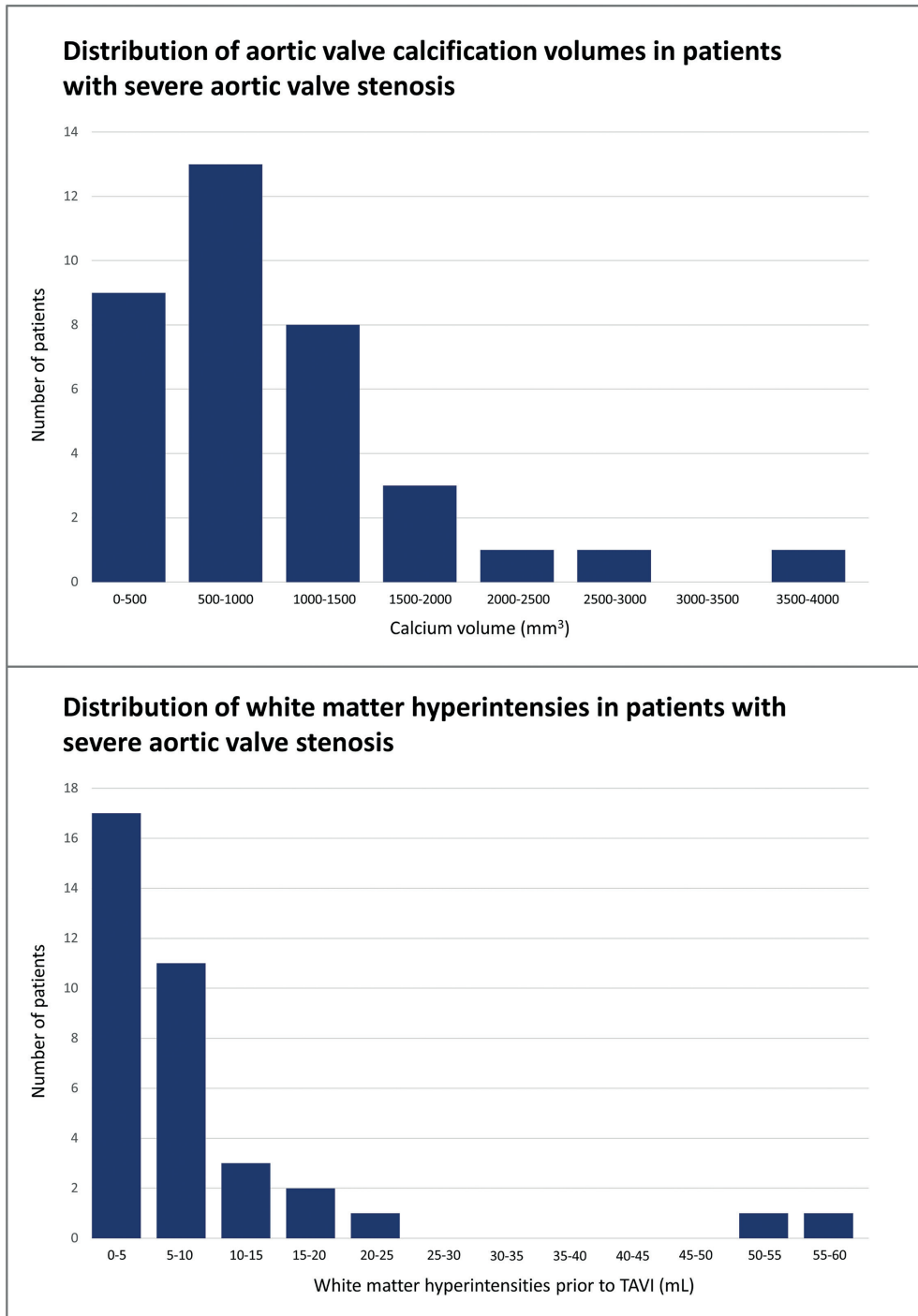
RESULTS

Baseline patient characteristics

Between June 2016 and November 2017, a total of 48 patients with severe aortic valve stenosis in the work-up for TAVI underwent baseline assessment of white matter hyperintensity volume. Twelve patients (25%) did not undergo follow-up cerebral MRI 3 months after the procedure related to either post-TAVI pacemaker implantation (n=6) or refusal of MRI follow-up (n=6). Accordingly, the final study population included 36 TAVI patients with complete MRI follow-up. Baseline demographic and clinical characteristics of the patients are provided in Table 1. Mean age was 78.7 ± 4.5 years with the majority (61%) female. The Society of Thoracic Surgeons (STS) median score of 2.8% (Q1-Q3: 1.9-3.7%) indicated this was a low-risk TAVI population. Nevertheless, many patients had comorbidities including diabetes (28%), atrial fibrillation (44%) and a history of coronary artery disease (39%). The majority of the patients underwent transfemoral TAVI (92%) with a balloon-expandable Edwards SAPIEN 3 valve (97%). Following TAVI, 50% of the patients were treated with dual antiplatelet therapy (DAPT) and 33% received single antiplatelet therapy (SAPT) in combination with anticoagulant therapy. Patients not undergoing MRI follow-up had a higher median EuroSCORE II (3.4%, Q1-Q3: 2.0-4.6%, vs 1.9%, Q1-Q3: 1.5-3.5%, p=0.03) and a larger aortic valve area (0.91 ± 0.18 cm2 vs 0.74 ± 0.16 cm2 vs, p=0.004) prior to TAVI (Supplementary Table 2).

Cardiac and aortic calcification volumes

Out of the four prespecified segments median calcification volumes were the highest in the aortic valve (692mm3, Q1-Q3: 482-1297mm3) and the aortic arch (633mm3, Q1-Q3: 213-1727mm3). The distribution of the calcification volumes in the aortic valve are displayed in Figure 3. A CTA example of a low versus a high calcification volume of the aortic valve is shown in Figure 4. In multiple regression analysis, aortic valve calcification volumes were larger in patients with a larger (CT-determined) annular area, with a 3.8 mm3 (SE: 1.2, p=0.004) increase of aortic valve calcification volume per

Figure 3

Distribution of aortic valve calcification volumes in patients with severe aortic valve stenosis

Distribution of white matter hyperintensies in patients with severe aortic valve stenosis
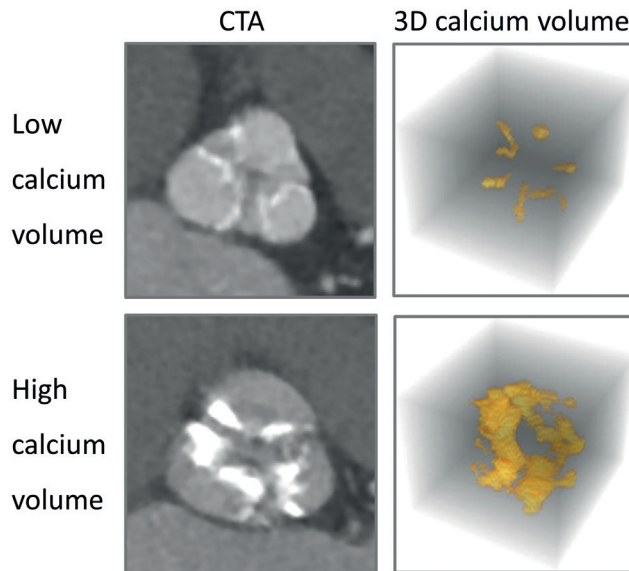
The lower bound of each category of calcification volumes or white matter hyperintensity volume includes the integer number

Figure 4

Cardiac Computed Tomography Angiography (CTA)

Aortic valve calcification volumes

every additional mm2 of annular area (Supplemental table 3). Moreover, patients with a higher mean gradient had higher aortic valve calcification volumes, with a 15.9 mm3 (SE: 4.9, p=0.003) increase per every additional mmHg mean gradient increase. The majority of patients with severe aortic valve stenosis (82%) also had some calcifications in the left ventricle. These calcifications were generally located around the mitral valve and had a lower volume than the aortic valve and arch (164mm3, Q1-Q3: 19-1332mm3). Finally, 63% of the patients had calcifications in the landing zone, with a relatively low calcification volume compared with the other segments (16mm3, Q1-Q3: 0-68mm3).

Cerebral white matter hyperintensity volume

All patients with severe aortic valve stenosis had white matter hyperintensities prior to TAVI, with a median volume of 5.1mL (Q1-Q3: 2.1-8.9mL), this was 0.4% of the total intracranial volume (Q1-Q3: 0.2-0.7%). The volume of baseline white matter hyperintensities varied considerably between patients, the distribution is given in Figure 3. Figure 5 shows two patients with few versus widespread white matter hyperintensities. Patients with vs. without pre-existing atrial fibrillation had a more than two-fold higher baseline white matter hyperintensity volume (8.6 mL, Q1-Q3: 4.2-
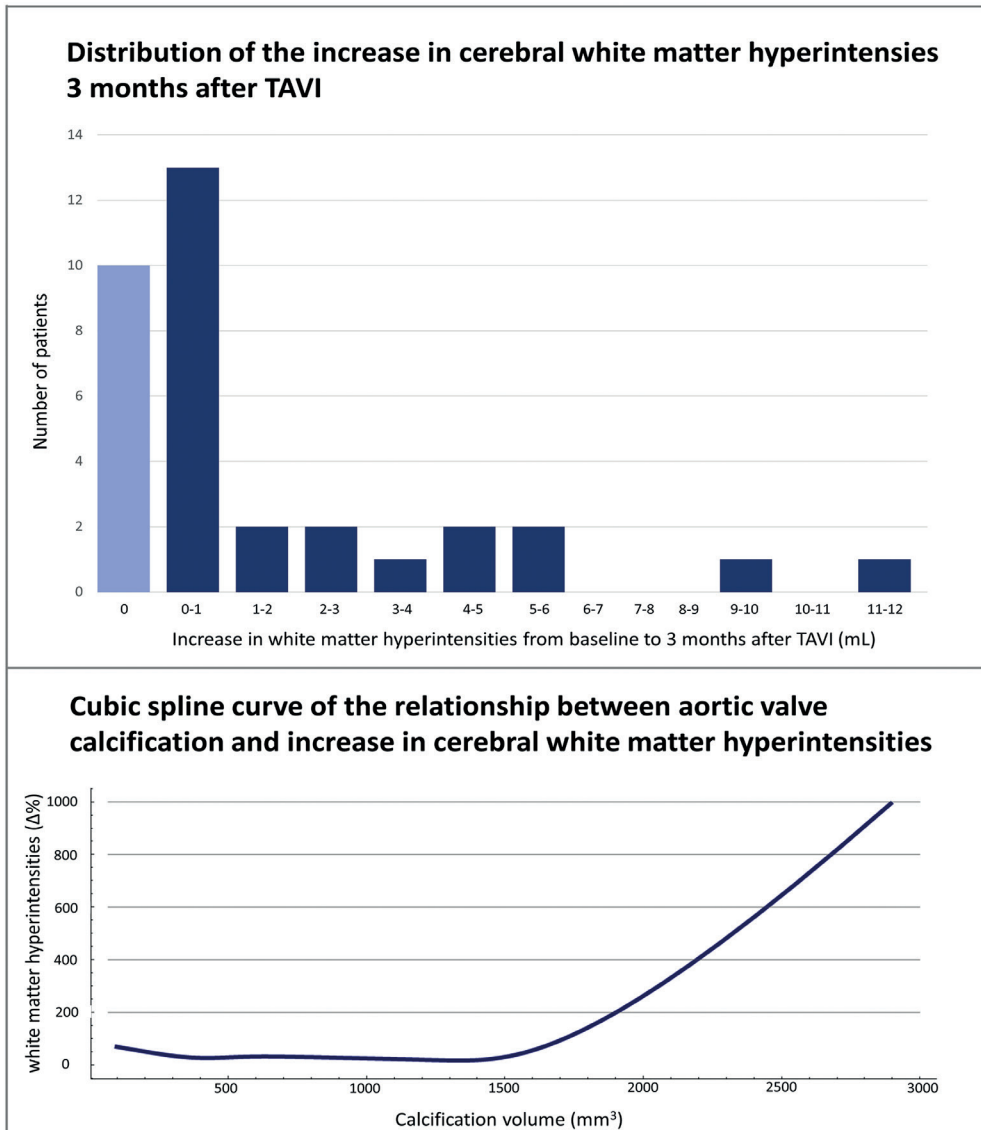
Figure 5

Fluid-Attenuated Inversion Recovery (FLAIR)

Cerebral white matter hyperintensities
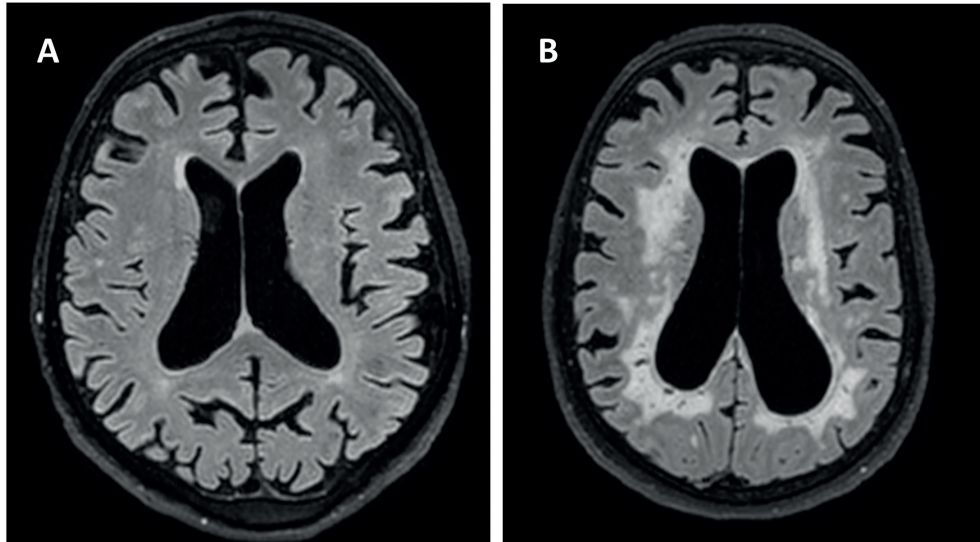
A) Patient with few white matter hyperintensities (Fazekas 1)

B) Patient with widespread white matter hyperintensities (Fazekas 3)

13.9mL vs. 3.7mL, Q1-Q3: 1.4-6.0mL, p=0.03). None of the patients experienced clinical overt stroke during the follow-up period. Nevertheless, in 26 patients (72%) the white matter hyperintensity volume increased 3 months after TAVI. The median increase in these patients was 1.1mL (Q1-Q3: 0.3-4.6mL), corresponding with a 27% increase from baseline (Q1-Q3: 7-104%), the distribution of the increase in white matter hyperintensity volume is shown in Figure 6. The calcification volume of the aortic valve predicted the relative increase of white matter hyperintensity volume at follow-up (Δ%), with a 35.2% increase per 100 mm3 of native aortic valve calcification volume (SE: 8.5, p<0.001). The relationship between aortic valve calcification volume and the increase in white matter hyperintensities is displayed in Figure 6. In contrast, the calcification volume of the aortic valve was not associated with the volume of baseline white matter hyperintensities (B: 0.0, SE: 0.0, p=0.87). Furthermore, the calcification volume in the aortic arch (B: 3.0%, SE: 3.7, p=0.42), landing zone (B: -31.9%, SE: 79.5, p=0.69) and left ventricle (B: -3.9%, SE: 6.5, p=0.55) did not predict the relative increase in cerebral white matter hyperintensity volume. There was a considerable variation in intracranial volumes between patients, with a median volume of 1352 mL (Q1-Q3: 1205-1468 mL) at baseline. Correction for intracranial volumes resulted in similar outcomes, with the aortic valve calcification

Figure 6

Distribution of the increase in cerebral white matter hyperintensies 3 months after TAVI

Number of patients (y-axis, 0 to 14)

Increase in white matter hyperintensies from baseline to 3 months after TAVI (mL)

Cubic spline curve of the relationship between aortic valve calcification and increase in cerebral white matter hyperintensies

white matter hyperintensities (Δ%) (y-axis, 0 to 1000)

Calcification volume (mm^3)

The lower bound of each category of increase in white matter hyperintensity volume includes the integer number

volume remaining a significant predictor of the relative increase in white matter hyperintensity volume (p<0.001). In multiple regression analysis, no clinical factors other than the calcification burden of the aortic valve predicted the increase of white matter hyperintensity volume (Supplemental table 4).

DISCUSSION

Main findings

This is the first study to address the relationship between calcification volumes of the heart and aortic arch prior to TAVI and chronic brain infarctions following TAVI. The main findings were that in patients with severe aortic valve stenosis a large variation exists in CTA assessed calcification volumes of the aortic valve. Likewise, the variation in baseline white matter hyperintensity volumes is considerable, with a two-fold higher volume in patients with history of atrial fibrillation. Cerebral white matter hyperintensity volume increased in the majority of patients (72%) during follow-up. A higher volume of aortic valve calcification volume pre-TAVI was associated with a larger increase of white matter hyperintensity volume during follow-up, indicating chronic brain infarctions. Altogether, these findings show the potential for automated aortic valve calcium screening as an imaging biomarker to predict chronic silent brain infarctions in patients undergoing TAVI.

Whiter matter hyperintensities after TAVI

The findings of the current study emphasize that the TAVI procedure induces a chronic cerebral embolic burden in an already frail population. In the current low-risk TAVI population, 7 out of 10 patients undergoing TAVI had an increase in white matter hyperintensity volume, with a median increase of 1.1mL (Q1-Q3: 0.3-4.6 mL) in the course of 3 months. In comparison, the mean white matter hyperintensity volume increased with the same volume (1.1±1.8 mL) in the course of 4 years in a population-based study in healthy subjects with a comparable mean age of 79 years (10). Further emphasizing the embolic burden in a portion of the patients, we found that half of the patients had an increase of new white matter hyperintensities <1mL, whereas the other half had an increase of 2-12mL. In population based studies, white matter hyperintensities were related to impaired neuropsychological functioning across all domains including memory, verbal fluency and mental slowing (11).

Similar to findings of the current study, a previous study found that the calcification volume of the aortic valve, measured with the Agatston calcium score, predicted the number of solid cerebral emboli during the TAVI procedure measured with transcranial Doppler (12). The highest number of cerebral embolizations takes place during the phase

of the valve positioning, indicating that calcifications dislocate during valve placement. Similarly, the current results showed that the aortic valve volume predicted the relative increase in white matter hyperintensity volume, rather than the calcification volume in the aortic arch, landing zone and left ventricle. This is despite the fact that large sized catheters are approached through the aortic arch with substantial calcification volumes in almost all patients. This significant role of aortic valve calcifications in cerebral embolizations during the TAVI procedure is underlined by clinical studies indicating that patients with a smaller aortic valve area, higher pre-TAVI aortic valve gradient, increased aortic arch atheroma and/or severe aortic calcification, all indicating a higher calcification burden, are more likely to experience early post-procedural cerebrovascular events (1, 17-20). Moreover, not the calcification volume itself, but the plaque volume in the aortic valve of a lower density than calcifications (50-130HU), matching fibrous tissue, was shown to be associated with the occurrence of new DW-MRI lesions short after TAVI (6). However, studies in TAVI populations did not find a relationship between occurrence of these new DW-MRI lesions after TAVI and (long-term) neurocognitive decline (13). A mismatch between the presence of acute ischemic lesions detected with DW-MRI and the absence of chronic white matter hyperintensities detected with FLAIR, can be applied to identify salvageable brain areas (14). In contrast to acute DW-MRI lesions, there is an association between long-term white matter hyperintensities in TAVI patients and a clear trend of cognitive decline, indicating that not all acute silent infarctions continue to be chronic brain infarctions (7). Accordingly, in contrast to the DW-MRI study, the findings of the current study highlight the relationship between calcification volume in patients with aortic valve stenosis and the increased risk of new white matter hyperintensities after TAVI, which will potentially induce long-term cognitive deterioration.

The risk of atrial fibrillation in TAVI patients

The reported prevalence of pre-existing atrial fibrillation in TAVI patients ranges from 16% to 51% (15). An interesting finding of the current study was that patients with a history of atrial fibrillation had a more than two-fold higher volume of baseline white matter hyperintensity volume before TAVI compared without pre-existing atrial fibrillation. This finding is in accordance with data from a large population-based study (16). Patients with atrial fibrillation are at heightened risk of cognitive decline and dementia, even in the absence of a medical history of past stroke (17). Moreover, compared with healthy control subjects, patients with atrial fibrillation have a lower cerebral perfusion and impaired cerebrovascular reactivity indicative of a limited cerebral vascular reserve (18). These findings emphasize the risk of atrial fibrillation on cognitive functioning in patients with aortic valve stenosis.

Reduction of new white matter hyperintensities after TAVI

Unfortunately, reliable clinical characteristics that predict the risk of (silent) brain infarctions after TAVI are lacking in the existing literature. We believe the findings from the current study, at the background of previous studies, indicate that the routinely performed CTA during pre-TAVI work-up could identify patients at risk for TAVI induced chronic silent brain infarctions. Identification of significant ascending aortic atheroma, using preoperative CT, in patients undergoing cardiac surgery, followed by tailored alternative operative strategies led to a three-fold lower stroke rate compared with patients who did not undergo aortic atheroma identification with CT (p=0.05)(19). In a similar way, the aortic valve calcification volume, measured with automated algorithms in CTA's during the pre-TAVI work-up could assess the risk of cerebral embolization during TAVI and identify patients that could benefit from expensive cerebral protection devices (20).

Limitations

The current study did not include a control population that did not undergo TAVI. Moreover, the current study included a low-risk population, whereas the calcification burden may be even higher in intermediate and high-risk populations. Subsequently, a higher calcification burden may be associated with a higher volume of new white matter hyperintensities after TAVI. Similarly, the current study included only balloon-expandable valves, even though self-expandable valves have been associated with a higher stroke rate (21). Balloon-expandable valves are implanted rather rapidly, in contrast, self-expandable valves are implanted stepwise and slowly and allow repositioning before the final implantation. Therefore, we cannot exclude a relation between the calcification volume in the ascending aorta or left ventricular outflow trajectory and new white matter hyperintensities in patients treated with self-expandable valves. Furthermore, were not able to use the commonly used Agatston calcium score as this has not been validated in contrast enhanced cardiac CTA scans. Non-contrast CT scans of the heart were not part of the TAVI work-up. Moreover, white matter hyperintensities not only include chronic brain infarctions but also regions of small vessel disease. The former is characterized by a rather acute increase of volume, whereas the latter is characterized by a slow gradual increase. Therefore, we believe that by selecting the relative increase (Δ%) over the course of a short period of 3 months as the endpoint, the measured outcome mainly detects new infarctions rather than small vessel disease. Finally, cognitive functioning tests were not performed in the current study and relationships between the aortic valve calcification volume, the volume of new white matter hyperintensities and cognitive functioning cannot be confirmed. Even though various studies reported a relationship between the increase in white matter hyperintensities and neuropsychological functioning, there is currently limited evidence reporting an increase in white matter hyperintensity volumes is associated with neurocognitive impairment (22, 23).

CONCLUSIONS

In a low-risk population with severe aortic valve stenosis, all patients had valve calcifications prior to TAVI, with a large variation in calcification volumes between patients. The majority of the patients (72%) had new cerebral white matter hyperintensities 3 months after TAV, with a median increase of 27%. A larger calcification volume in the aortic valve, but not in the aortic wall, landing zone and left ventricle prior to TAVI was associated with a higher increase in cerebral white matter hyperintensity volume after TAVI, indicating new chronic brain infarctions.

Conflict of Interest
Dr. Baan receives an unrestricted research grant from Edwards Lifesciences. The remaining authors have no relevant disclosures.

Ethical approval
All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical approval
Informed consent was obtained from all individual participants included in the study.

SUPPLEMENTARY TEXT 1

Coronary computed tomographic image acquisition and analysis

Cardiac CTA acquisition was performed on a third-generation dual-source CT scanner in the majority of the patients (SOMATOM Force, Siemens Healthcare, Erlangen, Germany) and in the minority of patients on a second generation dual-source CT scanner (SOMATOM Definition AS, Siemens Healthcare, Erlangen, Germany) or a single source CT scanner (Phillips iCT 256 Brilliance, Phillips Healthcare, Best, Netherlands). Technical specifications are listed in **Supplementary table 1**. Retrospective ECG-gated acquisition was performed in all patients. Tube voltage ranged from 70-140 kV and tube current was adjusted according to individual body habitus. During cardiac CTA acquisition, 80-110ml (4.5-5.5 ml/s) iodinated contrast (Ultravist 300: iopromide 300 mg I/ml, Bayer Healthcare Pharmaceuticals, Whippany, USA) was injected into an antecubital vein and followed by a 40 ml saline flush (5 ml/s). The images were reconstructed with a slice thickness of 1.5 mm and an increment of 1.5 mm using iterative reconstruction.

Supplementary table 1 Supplemental table 1. CT-scanner specifications and image acquisition with contrast delivery details

	Number of patients	Detector rows (slices)	Rot. Time (ms/rot)	Tube voltage settings (kV)	Tube charge settings (mAs)	Contrast conc. (mg I/ml)	Contrast volume (ml)
Siemens SOMATOM Force	31	2 x 96 (2 x 192)	250	70-120	75-330	300	80
Siemens SOMATOM Definition AS+	3	64 (128)	300	100	75-175	300	110
Phillips iCT 256 Brilliance	2	128 (256)	270	100-140	130-600	300	80-100

The cardiac and aortic regions were manually labelled using version 4.8.1 of 3D slicer (1,2).

The labelled regions were: 1) aortic arch, starting at the offspring of the left subclavian artery, ending at the distal level of the coronary ostia; 2) aortic valve: 3) landing zone, starting immediately below the level of the aortic valve leaflets and including the larger part of the left ventricular outflow tract. This section included all calcifications adherent to but below the level of the aortic valve leaflets; 4) left ventricle, starting below the landing zone and including the mitral valve. Wolfram Mathematica (Version 11.3; Wolfram Research, Inc., Champaign, Il, USA) was used for segmentation and post processing.

Since intravascular attenuation and the attenuation of calcium in cardiac CTA are susceptible to changes in contrast delivery and tube voltage settings, we were not able to select a single cut-off value for the semi-automatic segmentation of calcium. To overcome this problem, pixel value mapping was applied per patient in the combined

segmented 3D volumes to identify the main components (contrast material and calcium). A patient specific cut-off value was automatically selected, based on these main components and used to create binary masks. These masks, containing all pixels with a pixel value higher than the selected cut-off value (a pixel value higher than contrast material), were used to segment the calcium from each individual segment. Calcium volume was calculated by multiplying the pixels by the pixel dimensions. **Figure 1** in the manuscript shows a systematical representation of the described method for two aortic valve segments of patient with low and high calcium volume.

White matter hyperintensity volume measurement

Brain MRI scans were obtained at baseline (within 24 hours prior to TAVI) and at 3 months follow-up. Participants were all scanned on the same 3-Tesla Philips Ingenia MRI-scanner (Best, the Netherlands) both during baseline and at follow-up (C.B.L.M). The scan quality was reviewed visually by a neuroradiologist. White matter hyperintensities were automatically segmented from the fluid attenuation inversion recovery (FLAIR) scans using a method based on (3). In addition, an automated brain segmentation method was applied to the T1-weighted scans. Both segmentation methods were developed by Quantib B.V. From these segmentations, we computed the intracranial volume and the volume of white matter hyperintensities (mL). White matter fraction was computed by dividing a patient's white matter volume by their intracranial volume. The primary endpoint was the relative increase (Δ%) in white matter hyperintensities per patient from baseline to follow-up.

Chapter 7

Supplementary table 2. Baseline patient and procedural characteristics in study population vs lost to follow-up patients

	Total population (N=48)	Study population (n=36)	No follow-up (n=12)	p-value (*)
Demographics				
Age (years)	79.2 ± 5.0	78.7 ± 4.5	80.7 ± 6.1	0.24
Female gender	26 (54%)	22 (61%)	4 (33%)	0.09
Body mass index (kg/m²)	28.8 ± 6.8	29.8 ± 7.4	25.9 ± 3.8	0.09
Medical history				
Previous myocardial infarction	8 (17%)	6 (17%)	2 (17%)	1.00
Previous PCI	12 (25%)	10 (28%)	2 (17%)	0.44
Previous CABG	4 (8%)	3 (8%)	1 (8%)	1.00
Diabetes mellitus	13 (27%)	10 (28%)	3 (25%)	0.85
Hypertension	27 (56%)	21 (58%)	6 (50%)	0.61
Dyslipidemia	11 (23%)	6 (17%)	5 (42%)	0.07
History of coronary artery disease	18 (38%)	14 (39%)	4 (33%)	0.73
Atrial fibrillation	21 (44%)	16 (44%)	5 (42%)	0.87
GFR < 30 ml/min/1.73m²	4 (8%)	3 (8%)	1 (8%)	1.00
NT-proBNP	1065 (440-2775)	882 (361-2775)	1088 (627-4118)	0.18
NYHA class III or IV	27 (56%)	22 (61%)	5 (42%)	0.24
Risk scores				
EuroSCORE II (%)	2.2 (1.6-3.5)	1.9 (1.5-3.4)	3.4 (2.0-4.7)	0.03
STS-PROM mortality (%)	2.8 (1.9-3.7)	2.8 (1.9-3.7)	2.7 (1.9-4.1)	0.71
Echocardiographic characteristics				
Aortic max gradient (mmHg)	65 ± 24	68 ± 24	56 ± 23	0.11
Aortic mean gradient (mmHg)	41 ± 16	43 ± 17	34 ± 12	0.07
Aortic valve area (cm²)	0.78 ± 0.18	0.74 ± 0.16	0.91 ± 0.18	0.004
Procedural details				
Transfemoral access	44 (92%)	33 (92%)	11 (92%)	0.30
Transaortic access	3 (6%)	3 (8%)	0 (-)	0.30
Transapical access	1 (2%)	0 (-)	1 (8%)	0.08
Edwards SAPIEN 3	47 (98%)	35 (97%)	12 (100%)	0.56
Direct Flow	1 (2%)	1 (3%)	0 (-)	0.56
Medication at discharge				
SAPT	4 (8%)	1 (3%)	3 (25%)	0.02
DAPT	21 (44%)	18 (50%)	3 (25%)	0.13
SAPT + VKA/NOAC	17 (35%)	12 (33%)	5 (42%)	0.60
VKA/NOAC	6 (13%)	5 (14%)	1 (8%)	0.61
Statin	33 (69%)	24 (67%)	9 (75%)	0.59

Values are mean (± SD), n (%) or median (interquartile range). PCI = percutaneous coronary intervention, CABG = coronary artery bypass grafting, GFR = glomerular filtration rate, NT-ProBNP = N-terminal prohormone of brain natriuretic peptide, NYHA = New-York Heart Association, EuroSCORE = European System for Cardiac Operative Risk Evaluation, STS-PROM = Society of Thoracic Surgeons Predicted Risk of Mortality, SAPT= single anti-platelet therapy, DAPT= double anti-platelet therapy, VKA= vitamin K antagonist, NOAC=platelet

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Supplementary table 3. Univariate and multiple regression of calcium volume in the aortic valve

	Univariate, B (SE)	P-Value	Multiple, B (SE)	P-Value
Demographics				
Age (per year increase)	3.32 (29.39)	0.91	-	-
Male gender	991.29 (208.25)	<0.001	658.76 (245.11)	0.01
Body mass index (per kg/m^2 increase)	7.40 (17.96)	0.68	-	-
Length (per cm increase)	62.14 (13.15)	<0.001	32.12 (15.67)	0.049
Medical history				-
Previous myocardial infarction	-180.80 (350.28)	0.61	-	-
Previous PCI	-327.46 (287.15)	0.26	-	-
Previous CABG	-104.36 (473.83)	0.83	-	-
Diabetes mellitus	-263.63 (289.08)	0.37	-	-
Hypertension	74.74 (265.51)	0.78	-	-
Dyslipidemia	-238.60 (349.26)	0.50	-	-
History of coronary artery disease	126.35 (267.95)	0.64	-	-
Atrial fibrillation	230.29 (260.76)	0.38	-	-
GFR < 30 ml/min/1.73m^2	307.64 (471.22)	0.52	-	-
(NYHA) class III or IV	171.12 (267.22)	0.53	-	-
Number of stents during pre-TAVI PCI (per stent)	541.00 (218.33)	0.13	-	-
Risk scores				
EuroSCORE II (per % increase)	-63.50 (86.97)	0.47	-	-
STS-PROM mortality (per % increase)	-60.14 (73.77)	0.42	-	-
Echocardiographic characteristics				
Aortic max gradient (per mmHg increase)	12.61 (5.18)	0.02	-	-
Aortic mean gradient (per mmHg increase)	18.29 (7.58)	0.02	15.35 (5.5)	0.01
Aortic valve area (per 0.1 cm^2 increase)	-89.57 (80.41)	0.27	-	-

B = the increase of aortic valve calcium volume (in mm^3 with 95% with standard error. The max gradient was not used in the multiple regression prediction model since this is directly related to the mean gradient.

Supplementary table 4. Univariate regression analysis of increase in cerebral white matter hyperintensities

	Univariate, B (SE)	P-Value
Demographics		
Age (per year increase)	-0.05 (0.11)	0.63
Male gender	-0.28 (1.00)	0.78
Body mass index (per kg/m^2 increase)	0.04 (0.07)	0.59
Medical history		
Previous myocardial infarction	-0.05 (1.31)	0.97
Previous PCI	-0.18 (1.09)	0.87
Previous CABG	0.84 (1.75)	0.64
Diabetes mellitus	1.55 (1.05)	0.15
Hypertension	1.44 (0.96)	0.14
Dyslipidemia	0.24 (1.30)	0.86
Current smoking	-0.10 (1.56)	0.95
History of coronary artery disease	-0.46 (1.00)	0.65
Atrial fibrillation	0.90 (0.97)	0.36
GFR < 30 ml/min/1.73m^2	-0.37 (1.76)	0.84
(NYHA) class III or IV	-1.17 (0.98)	0.24
Risk scores		
EuroSCORE II (per % increase)	0.22 (0.32)	0.50
STS-PROM mortality (per % increase)	-0.12 (0.28)	0.66
Echocardiographic characteristics		
Aortic max gradient (per mmHg increase)	-0.02 (0.02)	0.38
Aortic mean gradient (per mmHg increase)	-0.03 (0.03)	0.36
Aortic valve area (per 0.1 cm^2 increase)	-0.59 (0.29)	0.049

B = the increase of cerebral white matter hyperintensities (in mL with standard error)

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