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Research paper

# Coronary volume to left ventricular mass ratio in patients with diabetes mellitus

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ABSTRACT

*Background:* Diabetes mellitus is a major risk factor for coronary artery disease (CAD) and may provoke structural and functional changes in coronary vasculature. The coronary volume to left ventricular mass (V/M) ratio is a new anatomical parameter capable of revealing a potential physiological imbalance between coronary vasculature and myocardial mass. The aim of this study was to examine the V/M derived from coronary computed tomography angiography (CCTA) in patients with diabetes.

*Methods:* Patients with clinically suspected CAD enrolled in the ADVANCE (Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care) registry and known diabetic status were included. Coronary artery volume and left ventricular myocardial mass were analyzed from CCTA and the V/M ratio was calculated and compared between patients with and without diabetes.

*Results:* Of the 3053 patients (age 66 ± 10 years; 66% male) with known diabetic status, diabetes was present in 21.9%. Coronary volume was lower in patients with diabetes compared to those without diabetes (2850 ± 940 $mm^3$ vs. 3040 ± 970 $mm^3$, $p < 0.0001$), whereas the myocardial mass was comparable between the 2 groups (122 ± 33 g vs. 122 ± 32 g, $p = 0.70$). The V/M ratio was significantly lower in patients with diabetes (23.9 ± 6.8 $mm^3$/g vs. 25.7 ± 7.5 $mm^3$/g, $p < 0.0001$). Among subjects with obstructive CAD (n = 2191, 24.0% diabetics)

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and non-obstructive CAD (16.7% diabetics), the V/M ratio was significantly lower in patients with diabetes compared to those without (23.4 ± 6.7 $mm^3$/g vs. 25.0 ± 7.3 $mm^3$/g, p < 0.0001 and 25.6 ± 6.9 $mm^3$/g vs. 27.3 ± 7.6 $mm^3$/g, respectively, p = 0.006).

*Conclusion:* The V/M ratio was significantly lower in patients with diabetes compared to non-diabetics, even after correcting for obstructive coronary stenosis. The clinical value of the reduced V/M ratio in diabetic patients needs further investigation.

**List of abbreviations**

| | |
|---|---|
| ADVANCE | Assessing Diagnostic Value of Non-invasive $FFR_{CT}$ in Coronary Care registry |
| CAD | Coronary artery disease |
| CCTA | Coronary computed tomography angiography |
| FFR | Fractional flow reserve |
| $FFR_{CT}$ | CCTA-derived fractional flow reserve |
| LV | Left ventricular |
| V/M | Coronary artery volume to left ventricular myocardial mass |

## 1. Introduction

The ratio of the total epicardial coronary artery lumen volume to left ventricular (LV) myocardial mass (V/M) is a newly available anatomical parameter capable of revealing a potential physiological imbalance between the supply (coronary artery epicardial volume) and demand (myocardial mass).[1,2] Previous studies observed that low V/M ratios derived from coronary computed tomography angiography (CCTA) were related with more advanced CAD, reduced myocardial blood flow and lesion-specific fractional flow reserve (FFR) ≤0.80 suggesting ischemia.[2,3]

Diabetes mellitus is a major risk factor for CAD affecting millions of people worldwide.[4,5] Moreover, diabetes has been associated with increased total coronary artery plaque burden, more advanced coronary atherosclerosis, and increased risk of adverse cardiovascular events.[6–10] In addition, diabetes has been associated with abnormalities in the coronary circulation including microvascular dysfunction and reduced vasodilation capacity.[11]

The high rate of adverse events in diabetic patients with CAD has raised questions about the roles of anatomic and functional characteristics of diabetic coronary arteries. The V/M ratio might provide additional insight into the epicardial vascular characteristics and risk in patients with diabetes. However, data examining the V/M ratio in patients with diabetes are lacking. The aim of this study is to evaluate the association of the V/M ratio with the diabetic status using the data from a large multicenter registry comprising diabetic and non-diabetic subjects with clinically suspected CAD.

## 2. Methods

### 2.1. Study populations

Patients were selected from the *Assessing Diagnostic Value of Non-invasive $FFR_{CT}$ in Coronary Care* (ADVANCE) registry (NCT02499679). ADVANCE is an international multicenter, prospective registry designed to evaluate the utility of CCTA-derived Fractional Flow Reserve ($FFR_{CT}$) in the clinical setting. The design of the study has been described in detail previously.[12] In short, subjects were enrolled in 38 sites across North America, Europe, and Asia between July 2015–October 2017. Patients with clinically suspected CAD >18 years of age with documented atherosclerosis on CCTA and ability to provide written informed consent were included. The patients without CAD on CCTA, insufficient CCTA image quality, life expectancy <1 year and inability to comply with follow-up were excluded. In the present analysis, only patients with a) known diabetic status and b) coronary artery lumen volume and LV myocardial mass analysis were included. The study complied with the Declaration of Helsinki. All subjects provided written informed consent following local Institutional Review Board approval.

### 2.2. CCTA acquisition and image analysis

CCTA was performed in accordance with local and international guidelines using ≥64-row multidetector computed tomography scanners.[13,14] Sublingual nitrates were administered before scanning in all subjects and, if necessary, beta-blockers were administered in order to achieve a heart rate <60 bpm. All coronary arteries ≥2 mm diameter were evaluated for stenosis severity in accordance with current guidelines.[14] The strategy of visual CCTA assessment was left to the discretion of the local investigators of each site. CCTA images were submitted to a central core laboratory for $FFR_{CT}$ and V/M analysis (HeartFlow Inc., Redwood City, California, USA) which has been described previously.[1,12,15–17] In brief, a 3-dimensional model of the coronary tree was derived from the CCTA datasets provided. For $FFR_{CT}$ analysis, the luminal boundaries of all vessels >1 mm diameter were extracted, the total coronary flow was computed and coronary resistance under hyperemia was calculated. For V/M analysis, the total coronary arterial lumen volume and LV myocardial volume were measured.[18] The volume of the extracted myocardium was multiplied by 1.05 g/ml to calculate the myocardial mass. Subsequently, the ratio between the coronary arterial lumen volume and LV myocardial mass was calculated (Fig. 1).

### 2.3. Clinical endpoints

The diagnosis of diabetes was based on the medical history in the electronic case report forms. There was no sub-classification of Type 1 or 2 diabetes. Baseline patient characteristics, including cardiac risk factors and symptom status, and CCTA data were obtained and compared between patients with and without diabetes. In addition, the coronary volume and LV myocardial mass were separately analyzed among subjects with anatomically obstructive and non-obstructive CAD. Obstructive CAD was defined as any atherosclerotic lesion ≥50% diameter stenosis.

### 2.4. Statistical analysis

Continuous variables following a normal distribution are presented as mean ± standard deviation (SD). Continuous variables were compared using a 2-sample *t*-test with Satterthwaite approximation for the degrees of freedom. Categorical variables are presented as absolute numbers and percentages (%) and were compared using the $\chi 2$ test. Analysis of covariance (ANCOVA) models were used to correct for the potential confounding effect of age, body mass index, hypertension, hyperlipidemia, smoking status and the number of vessels with obstructive CAD on the coronary volume and LV myocardial mass as well as V/M ratio, and were used as covariates. The differences in coronary volume, LV myocardial mass and the V/M ratio between patients with and without diabetes in the ANCOVA models are presented as least square (LS) mean difference estimate with 95% confidence intervals (CI). A p-value <0.05 was considered significant. All statistical analysis were performed using SAS version 9.4 (SAS institute, Cary, North Carolina, USA).

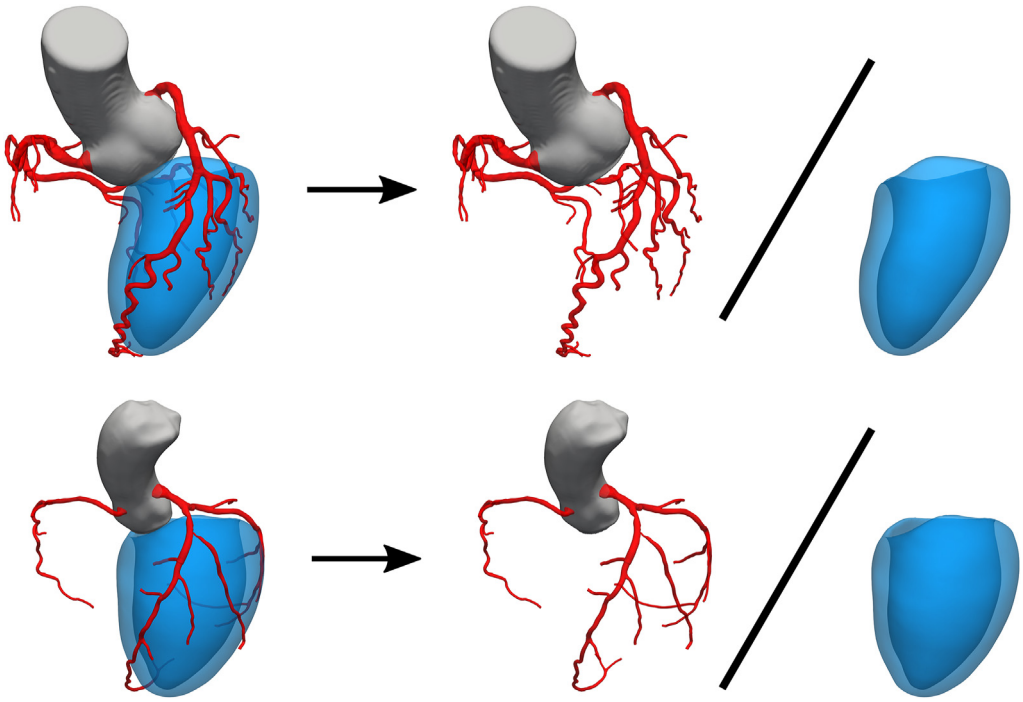

**Figure 1.** Graphical presentation of the coronary artery volume and left ventricular myocardial mass and the coronary volume to left ventricular mass ratio showing the difference between a non-diabetic (top of figure) and a diabetic patient (bottom of figure). Both subjects had non-obstructive coronary artery disease (0–30% diameter stenosis).

## 3. Results

### 3.1. Study population

A total of 5083 patients were enrolled in the ADVANCE registry. Of these, 3053 patients (age 66.4 ± 10.3 years; 66% male) with known diabetic status and measured V/M ratio were included in this analysis. A flowchart of patient enrolment and follow-up is shown in Fig. 2. Comparison of the patients included in the analysis versus those excluded due to missing V/M ratios is shown in the Supplemental Table 1. Diabetes was present in 670 patients (21.9%). Baseline patient demographic and clinical characteristics are summarized in

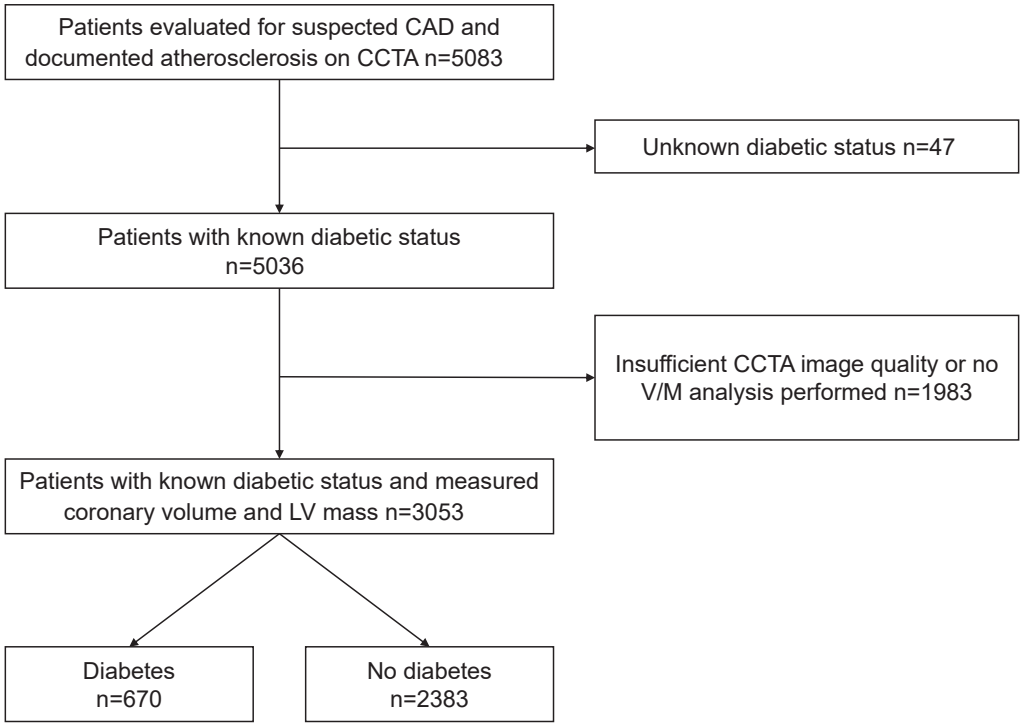


**Figure 2.** Flowchart study population. CAD = coronary artery disease, CCTA = coronary computed tomography angiography, LV = left ventricular, V/M = coronary volume and left ventricular mass.

Table 1. Patients with diabetes had a higher cardiovascular risk profile, were older (67.6 ± 9.8 vs 66.1 ± 10.4 years, p = 0.001), had a higher body mass index (BMI) (27.0 ± 5.2 vs 26.1 ± 4.7 kg/m$^2$, p < 0.0001) and were more likely to be current smokers (p = 0.039) as compared to patients without diabetes. In addition, hypertension and hyperlipidemia were more often present among patients with diabetes (both p < 0.0001).

### 3.2. CCTA parameters and coronary volume to mass ratio in diabetic and non-diabetic patients

The main CCTA characteristics are reported in Table 2. Patients with diabetes had more frequently obstructive CAD and severe stenosis by anatomical CCTA evaluation (both p < 0.0001). In the quantitative analysis, epicardial coronary artery volume was lower in patients with diabetes (2850 ± 940 mm$^3$ vs. 3040 ± 970 mm$^3$, p < 0.0001), whereas the LV myocardial mass was comparable between patients with and without diabetes (122 ± 33 g vs. 122 ± 32 g, p = 0.70). The V/M ratio was significantly lower in patients with diabetes (23.9 ± 6.8 mm$^3$/g vs. 25.7 ± 7.5 mm$^3$/g, p < 0.0001, Fig. 3).

**Table 1**
Baseline patient demographic and clinical characteristics of patients according to diabetic status.

| | Total (n = 3053) | Diabetes (n = 670) | No diabetes (n = 2383) | p-value |
|---|---|---|---|---|
| Age, y | 66.4 ± 10.3 | 67.6 ± 9.8 | 66.1 ± 10.4 | 0.001 |
| Male sex, n (%) | 2021 (66.2) | 453 (67.6) | 1568 (65.8) | 0.38 |
| Body mass index, kg/m$^2$ | 26.3 ± 4.8 | 27.0 ± 5.2 | 26.1 ± 4.7 | <0.0001 |
| Diamond Forrester CAD likelihood | 51 ± 20 | 52 ± 20 | 51 ± 20 | 0.14 |
| Hypertension, n (%) | 1856 (60.8) | 510 (76.1) | 1346 (56.5) | <0.0001 |
| Hyperlipidemia, n (%) | 1851 (60.6) | 482 (71.9) | 1369 (57.4) | <0.0001 |
| Tobacco use, n (%) | | | | |
| Current smoker | 496 (16.2) | 131 (19.6) | 365 (15.3) | 0.039 |
| Ex-Smoker | 1046 (34.3) | 230 (34.3) | 816 (34.2) | |
| Never Smoked | 1291 (42.3) | 269 (40.1) | 1022 (42.9) | |
| Unknown | 220 (7.2) | 40 (6.0) | 180 (7.6) | |
| Angina status, n (%) | | | | |
| Typical | 597 (19.6) | 131 (19.6) | 466 (19.6) | 0.042 |
| Atypical | 1098 (36.0) | 228 (34.0) | 870 (36.5) | |
| Dyspnea | 343 (11.2) | 68 (10.1) | 275 (11.5) | |
| Non-cardiac Pain | 181 (5.9) | 31 (4.6) | 150 (6.3) | |
| None | 811 (26.6) | 206 (30.7) | 605 (25.4) | |
| Unknown | 23 (0.8) | 6 (0.9) | 17 (0.7) | |
| CCS Angina class, n (%) | | | | |
| Grade I | 141/597 (23.6) | 32/131 (24.4) | 109/466 (23.4) | 0.067 |
| Grade II | 334/597 (55.9) | 69/131 (52.7) | 265/466 (56.9) | |
| Grade II | 62/597 (10.4) | 20/131 (15.3) | 42/466 (9.0) | |
| Grade IV | 11/597 (1.8) | 5/131 (3.8) | 6/466 (1.3) | |
| Unknown | 49/597 (8.2) | 5/131 (3.8) | 44/466 (9.4) | |

Data are presented as mean ± SD or n (%). CAD = coronary artery disease; CCS = Canadian Cardiovascular Society.

### 3.3. Clinical and CCTA parameters and coronary volume to mass ratio in patients with obstructive CAD

Obstructive CAD was present in 2191 subjects (71.9%) of which 525 (24.0%) had diabetes. Baseline patient demographic and clinical characteristics for patients with obstructive CAD are shown in Table 3. In subjects with obstructive CAD, patients with diabetes were older (p = 0.03), had a higher BMI (p = 0.0003), had more frequently a history of hypertension and hyperlipidemia (p < 0.0001 for both), and were more likely to be current smokers (p = 0.045).

Coronary volume was significantly lower in patients with diabetes compared to non-diabetic patients who had obstructive coronary

**Table 2**
Coronary computed tomography angiography parameters of patients according to diabetic status.

| | Total (n = 3053) | Diabetes (n = 670) | No diabetes (n = 2383) | p-value |
|---|---|---|---|---|
| CCTA anatomical stenosis, n (%) | | | | |
| Non-obstructive stenosis <50% | 856 (28.0) | 143 (21.3) | 713 (29.9) | <0.0001 |
| Obstructive stenosis ≥50% | 2191 (71.8) | 525 (74.4) | 1666 (69.9) | |
| Unknown | 6 (0.2) | 2 (0.3) | 4 (0.2) | |
| Non-severe stenosis ≤70% | 2069 (67.8) | 388 (57.9) | 1681 (70.5) | <0.0001 |
| Severe stenosis >70% | 978 (32.0) | 280 (41.8) | 698 (29.3) | |
| Unknown | 6 (0.2) | 2 (0.3) | 4 (0.2) | |
| Degree stenosis, n (%) | | | | |
| Normal (0%) | 18 (0.6) | 3 (0.4) | 15 (0.6) | <0.0001 |
| Minimal (0–30%) | 158 (5.2) | 22 (3.3) | 136 (5.7) | |
| Mild (30–50%) | 680 (22.3) | 118 (17.6) | 562 (23.6) | |
| Moderate (50–70%) | 1213 (39.7) | 245 (36.6) | 968 (40.6) | |
| Severe (70–90%) | 687 (22.5) | 194 (29.0) | 493 (20.7) | |
| Sub-total/occluded (≥90%) | 291 (9.5) | 86 (12.8) | 205 (8.6) | |
| Unknown | 6 (0.2) | 2 (0.3) | 4 (0.2) | |
| Number of vessels with anatomically obstructive CAD ≥50% DS, n (%) | | | | |
| 0 | 856 (28.0) | 143 (21.3) | 713 (29.9) | <0.0001 |
| 1 | 1355 (44.4) | 290 (43.3) | 1065 (44.7) | |
| 2 | 557 (18.2) | 137 (20.4) | 420 (17.6) | |
| 3 | 279 (9.1) | 98 (14.6) | 181 (7.6) | |
| 4 | 0 | 0 | 0 | |
| Unknown | 6 (0.2) | 2 (0.3) | 4 (0.2) | |
| Rate of obstructive CAD per vessel, n (%) | | | | |
| LAD stenosis <50% | 1319 (43.2) | 247 (36.9) | 1072 (45.0) | 0.0002 |
| LAD stenosis ≥50% | 1734 (56.8) | 423 (63.1) | 1311 (55.0) | |
| LCX stenosis <50% | 2321 (76.0) | 457 (68.2) | 1864 (78.2) | <0.0001 |
| LCX stenosis ≥50% | 732 (24.0) | 213 (31.8) | 519 (21.8) | |
| RCA stenosis <50% | 2213 (72.5) | 448 (66.9) | 1765 (74.1) | 0.0002 |
| RCA stenosis ≥50% | 840 (27.5) | 222 (33.1) | 618 (25.9) | |
| Coronary volume – myocardial mass | | | | |
| Epicardial coronary artery volume, mm$^3$ | 3000 ± 970 | 2850 ± 940 | 3040 ± 970 | <0.0001 |
| LV myocardial mass, g | 122 ± 32 | 122 ± 33 | 122 ± 32 | 0.70 |
| Coronary volume/mass ratio, mm$^3$/g | 25.3 ± 7.4 | 23.9 ± 6.8 | 25.7 ± 7.5 | <0.0001 |

Data are presented as mean ± SD or n (%). CAD = coronary artery disease; CCTA = coronary computed tomography angiography; DS = diameter stenosis; LAD = left anterior descending artery; LCX = left circumflex artery; LV = left ventricular; RCA = right coronary artery.

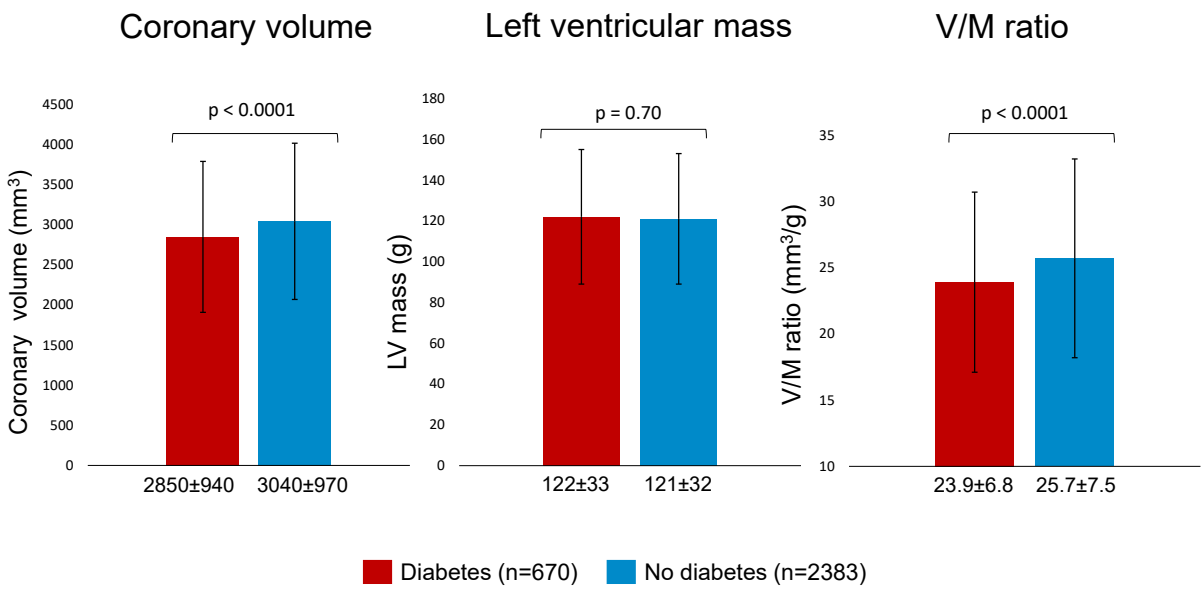


**Figure 3.** Bar chart showing the mean coronary artery volume, LV myocardial mass and V/M ratio for patients with and without diabetes.

disease (2800 ± 920 $mm^3$ vs. 2990 ± 950 $mm^3$, p < 0.0001). LV mass was not significantly different between groups (122 ± 31 g vs. 123 ± 32 g, respectively, p = 0.63). Accordingly, the V/M ratio was significantly lower in patients with diabetes (23.4 ± 6.7 $mm^3$/g vs. 25.0 ± 7.3 $mm^3$/g, p < 0.0001, Fig. 4).

### *3.4. Clinical and CTA parameters and coronary volume to mass ratio in patients with non-obstructive CAD*

Diabetes was present in 143 out of 856 (16.7%) patients with non-obstructive CAD. Patients with diabetes were older (p = 0.02), had a

**Table 3**
Baseline patient demographic and clinical characteristics of patients with anatomically obstructive and non-obstructive CAD according to diabetic status.

| | Obstructive CAD (≥50% DS) | | | | Non-obstructive CAD (<50% DS) | | | |
|---|---|---|---|---|---|---|---|---|
| | Total (n = 2191) | Diabetes (n = 525) | No diabetes (n = 1666) | p-value | Total (n = 856) | Diabetes (n = 143) | No diabetes (n = 713) | p-value |
| Age, y | 66.8 ± 10.1 | 67.7 ± 9.7 | 66.6 ± 10.3 | 0.03 | 65.3 ± 10.6 | 67.2 ± 10.1 | 64.9 ± 10.7 | 0.02 |
| Male sex, n (%) | 1526 (69.6) | 374 (71.2) | 1152 (69.1) | 0.3637 | 492 (57.5) | 78 (54.5) | 414 (58.1) | 0.44 |
| Body mass index, kg/$m^2$ | 26.1 ± 4.6 | 26.8 ± 5.0 | 25.9 ± 4.5 | 0.0003 | 26.7 ± 5.3 | 27.9 ± 5.6 | 26.4 ± 5.2 | 0.005 |
| Diamond Forrester CAD likelihood | 53 ± 20 | 54 ± 20 | 53 ± 20 | 0.37 | 46 ± 19 | 46 ± 19 | 46 ± 19 | 0.95 |
| Hypertension, n (%) | 1365 (62.3) | 397 (75.6) | 968 (58.1) | <0.0001 | 487 (56.9) | 111 (77.6) | 376 (52.7) | <0.0001 |
| Hyperlipidemia, n (%) | 1332 (60.8) | 372 (70.9) | 960 (57.6) | <0.0001 | 514 (60.0) | 108 (75.5) | 406 (56.9) | <0.0001 |
| Tobacco use, n (%) | | | | | | | | |
| Current smoker | 386 (17.6) | 112 (21.3) | 274 (16.4) | 0.045 | 109 (12.7) | 18 (12.6) | 91 (12.8) | 0.99 |
| Ex-Smoker | 758 (34.6) | 182 (34.7) | 576 (34.6) | | 286 (33.4) | 48 (33.6) | 238 (33.4) | |
| Never Smoked | 896 (40.9) | 202 (38.5) | 694 (41.7) | | 393 (45.9) | 67 (46.9) | 326 (45.7) | |
| Unknown | 151 (6.9) | 29 (5.5) | 122 (7.3) | | 68 (7.9) | 10 (7.0) | 58 (8.1) | |
| Angina status, n (%) | | | | | | | | |
| Typical | 500 (22.8) | 118 (22.5) | 382 (22.9) | 0.032 | 96 (11.2) | 13 (9.1) | 83 (11.6) | 0.74 |
| Atypical | 740 (33.8) | 172 (32.8) | 568 (34.1) | | 356 (41.6) | 56 (39.2) | 300 (42.1) | |
| Dyspnea | 222 (10.1) | 45 (8.6) | 177 (10.6) | | 121 (14.1) | 23 (16.1) | 98 (13.7) | |
| Non-cardiac Pain | 120 (5.5) | 20 (3.8) | 100 (6.0) | | 59 (6.9) | 9 (6.3) | 50 (7.0) | |
| None | 594 (27.1) | 166 (31.6) | 428 (25.7) | | 216 (25.2) | 40 (28.0) | 176 (24.7) | |
| Unknown | 15 (0.7) | 4 (0.8) | 11 (0.7) | | 8 (0.9) | 2 (1.4) | 6 (0.8) | |
| CCS Angina class, n (%) | | | | | | | | |
| Grade I | 117/500 (23.4) | 27/118 (22.9) | 90/382 (23.6) | 0.048 | 23/96 (24.0) | 5/13 (38.5) | 18/83 (21.7) | 0.64 |
| Grade II | 284/500 (56.8) | 62/118 (52.5) | 222/382 (58.1) | | 50/96 (52.1) | 7/13 (53.8) | 43/83 (5.8) | |
| Grade III | 58/500 (11.6) | 20/118 (16.9) | 38/382 (9.9) | | 4/96 (4.2) | 0/13 | 4/83 (4.8) | |
| Grade IV | 10/500 (2.0) | 5/118 (4.2) | 5/382 (1.3) | | 1/96 (1.0) | 0/13 | 1/83 (1.2) | |
| Unknown | 31/500 (6.2) | 4/118 (3.4) | 27/382 (7.1) | | 18/96 (18.8) | 1/13 (7.7) | 17/83 (20.5) | |
| Coronary volume – myocardial mass | | | | | | | | |
| Epicardial coronary artery volume, $mm^3$ | 2940 ± 950 | 2800 ± 920 | 2990 ± 950 | <0.0001 | 3150 ± 1010 | 3030 ± 1000 | 3170 ± 1020 | 0.13 |
| LV myocardial mass, g | 123 ± 32 | 122 ± 32 | 123 ± 32 | 0.63 | 120 ± 33 | 122 ± 39 | 119 ± 32 | 0.31 |
| Coronary volume/mass ratio, $mm^3$/g | 24.6 ± 7.2 | 23.4 ± 6.7 | 25.0 ± 7.3 | <0.0001 | 27.0 ± 7.5 | 25.6 ± 6.9 | 27.3 ± 7.6 | 0.006 |

Data are presented as mean ± SD or n (%). CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; LV = left ventricular.

higher BMI (p = 0.005), had more frequently a history of hypertension and hyperlipidemia (p < 0.0001 for both). Smoking status was similar between patients with and without diabetes in subjects with non-obstructive CAD (p = 0.99, Table 3) which was in contrast to those with obstructive coronary disease.

Coronary volume was not significantly different between patients with and without diabetes who did not have obstructive coronary disease (3030 ± 1000 $mm^3$ vs. 3170 ± 1020 $mm^3$, p = 0.13). Moreover, LV mass was comparable between groups (122 ± 39 g vs. 119 ± 32 g, respectively, p = 0.31). Still, the V/M ratio was significantly lower in patients with diabetes (25.6 ± 6.9 $mm^3$/g vs. 27.3 ± 7.6 $mm^3$/g, p = 0.006, Fig. 4).

Similar results were observed when correcting for the differences in baseline and CCTA characteristics between patients with and without diabetes: significantly lower coronary volume and V/M ratio in patients with diabetes versus those without (LS mean difference estimate: −209 (95% CI: −295,-123) $mm^3$, p < 0.001 and −1.4 (95% CI: −2.0, −0.8) $mm^3$/g, p < 0.001, respectively), whereas the myocardial mass was comparable in both groups (LS mean difference estimate: −2.3 (95% CI: −5.0, 0.5) g, p = 0.19).

## 4. Discussion

We examined the coronary V/M ratio in patients with and without diabetes in the multicenter ADVANCE registry comprising subjects with suspected stable CAD. We found that patients with diabetes had a significantly lower V/M ratio compared to those without diabetes. This difference was observed not only in diabetic patients with obstructive CAD but also among those with non-obstructive CAD or when corrected for differences in baseline characteristics.

The principle of the V/M ratio is based on allometric scaling laws and was first described by Gould et al. over 40 years ago.[19] More recently, CCTA proved to be an excellent noninvasive instrument capable to perform coronary volume and myocardial mass analysis. Previous studies including data from the NXT (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps) and PACIFIC (Prospective Comparison of CCTA, SPECT, PET, and Hybrid Imaging for Diagnosis of Ischemic Heart Disease using FFR) trials reported that patients with a low V/M ratio had more extensive atherosclerosis and also reduced myocardial blood flow on positron emission tomography compared to patients with a high V/M ratio.[3] Furthermore, the V/M ratio was independently associated with an FFR ≤0.80.[2]

Diabetes has been linked with increased risk of atherosclerosis but also abnormalities in the coronary circulation including microvascular dysfunction and reduced vasodilation capacity.[11] We observed that the decreased V/M ratio in patients with diabetes was mainly driven by lower coronary artery volume while LV myocardial mass was comparable between the groups. As the presence of atherosclerosis has been linked with reduced coronary volume, we analyzed separately the patients with and without obstructive CAD. The V/M ratio in diabetic patients was found to be reduced in both groups.

The question arises why the V/M ratio is lower in patients with diabetes compared to non-diabetics. Since the LV mass is similar in both groups, the difference in the V/M ratio is explained by the lower coronary volume. There are several potential mechanisms by which the coronary volume - and thus the V/M ratio - is reduced in patients with diabetes. One explanation is that atherosclerosis is more advanced, even in the group without obstructive CAD. Patients with diabetes have shown increased plaque burden and more advanced atherosclerosis compared to non-diabetic patients with a subsequent augmented risk of adverse outcome.[7,20,21] Atherosclerosis may also reduce the coronary volume, not only directly via its lumen narrowing effect, but also as a result of impaired endothelial function with a subsequent reduction of vasodilator capacity.[22]

The vascular complications of diabetes independent of atherosclerosis might provide a second explanation for the lower V/M ratios in diabetic patients. As a result of insulin resistance, chronic hyperglycemia and autonomic dysfunction, diabetes may alter vascular structure and function. High glucose concentrations lead to endothelial dysfunction due to several pathophysiological mechanisms including an imbalance between nitric oxide bioavailability and accumulation of reactive oxygen species.[23] Accordingly, endothelial dysfunction results in reduced vasodilatation after the admission of nitrates. Moreover, this impaired response to hyperemia has been found even in the absence of atherosclerosis.[24]

Microvascular dysfunction has been linked with reduced V/M ratio in a retrospective case-control study by Grover et al.[1] that reported significantly lower V/M ratios in patients who met the criteria for microvascular angina as compared to their matched controls. This difference was mainly driven by lower coronary artery volumes. These results support the hypothesis that a lower V/M ratio could be linked with microvascular dysfunction in patients with diabetes, although no direct evidence for this was provided by the present study.

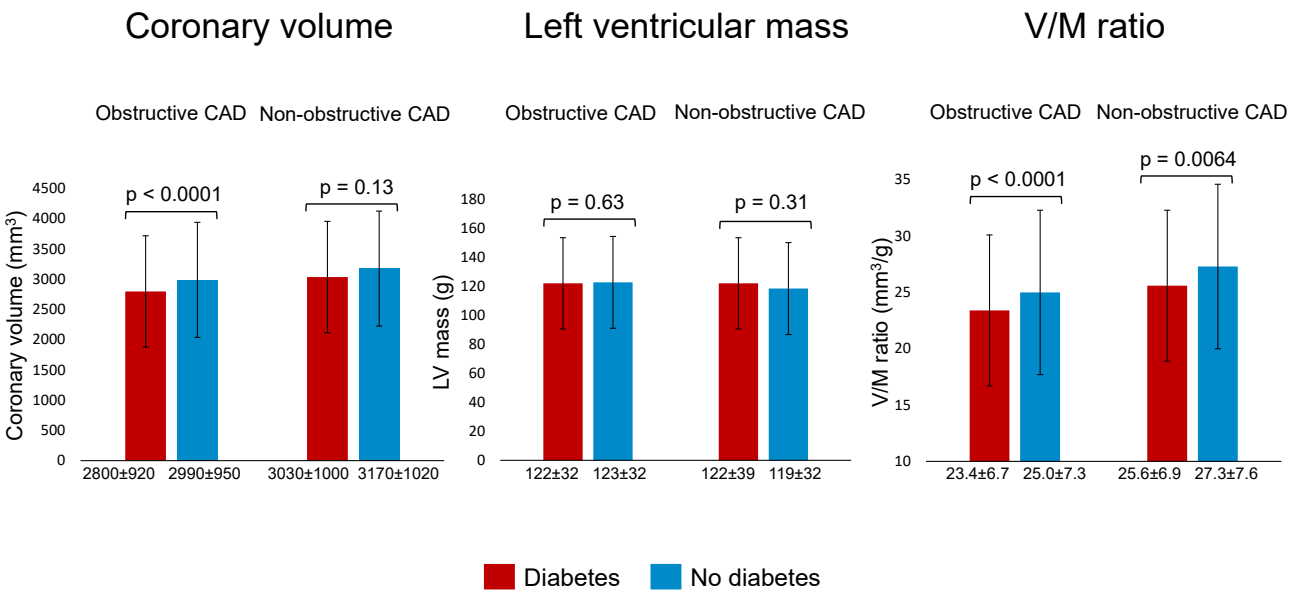


**Figure 4.** Bar chart showing the mean coronary artery volume, LV myocardial mass and V/M ratio for diabetic and non-diabetic patients in subjects with anatomically obstructive and non-obstructive CAD.

### 4.1. Limitations

This study has some limitations. First, the ADVANCE registry, as with all registries, may have been affected by referral bias. Second, of the total of 5083 subjects enrolled in the ADVANCE registry, diabetic status was unknown in 47 patients. In addition, the V/M ratio analysis was performed in only 3053 studies because of software development during the study time period. However, the patient characteristics of the population with measured V/M ratio were comparable with the total population in this registry (Supplemental Table 1). Fourth, this study lacked the ability to further characterize atherosclerosis. In addition, right ventricular mass was not measured in the current analysis. At last, the diagnosis of diabetes was based on medical history and detailed information about the severity and duration as well as type and treatment of the diabetes was lacking.

## 5. Conclusion

The coronary volume to myocardial mass ratio was significantly lower in patients with diabetes compared to non-diabetics, even after correcting for obstructive coronary stenosis and differences in baseline characteristics. Whether this is due to more advanced CAD in diabetics or diabetic-related changes in coronary structure and function remains unclear. These intriguing findings provide interesting data for future studies. The clinical value of the V/M ratio needs also further investigation.

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## Declaration of competing interest

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2022.01.004.

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