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Small whole heart volume predicts cardiovascular events in patients with stable chest pain: insights from the PROMISE trial

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Abstract

Objectives The size of the heart may predict major cardiovascular events (MACE) in patients with stable chest pain. We aimed to evaluate the prognostic value of 3D whole heart volume (WHV) derived from non-contrast cardiac computed tomography (CT).

Methods Among participants randomized to the CT arm of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE), we used deep learning to extract WHV, defined as the volume of the pericardial sac. We compared the WHV across categories of cardiovascular risk factors and coronary artery disease (CAD) characteristics and determined the association of WHV with MACE (all-cause death, myocardial infarction, unstable angina; median follow-up: 26 months).

Results In the 3798 included patients (60.5 ± 8.2 years; 51.5% women), the WHV was 351.9 ± 57.6 cm^3/m^2. We found smaller WHV in no- or non-obstructive CAD, women, people with diabetes, sedentary lifestyle, and metabolic syndrome. Larger WHV was found in obstructive CAD, men, and increased atherosclerosis cardiovascular disease (ASCVD) risk score ($p < 0.05$). In a time-to-event analysis, small WHV was associated with over 4.4-fold risk of MACE (HR (per one standard deviation) = 0.221; 95% CI: 0.068–0.721; $p = 0.012$) independent of ASCVD risk score and CT-derived CAD characteristics. In patients with non-obstructive CAD, but not in those with no- or obstructive CAD, WHV increased the discriminatory capacity of ASCVD and CT-derived CAD characteristics significantly.

Conclusions Small WHV may represent a novel imaging marker of MACE in stable chest pain. In particular, WHV may improve risk stratification in patients with non-obstructive CAD, a cohort with an unmet need for better risk stratification.

Key Points

- *Heart volume is easily assessable from non-contrast cardiac computed tomography.*
- *Small heart volume may be an imaging marker of major adverse cardiac events independent and incremental to traditional cardiovascular risk factors and established CT measures of CAD.*
- *Heart volume may improve cardiovascular risk stratification in patients with non-obstructive CAD.*

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Keywords Multidetector computed tomography · Cardiac volume · Heart failure · Coronary disease

Abbreviations

ASCVD	Atherosclerosis cardiovascular disease
AUC	Area under the curve
BSA	Body surface area
CAC	Coronary artery calcium
CAD	Coronary artery disease
CI	Confidence interval
CT	Computed tomography
CTA	Computed tomography angiography
CV	Cardiovascular
DL	Deep learning
HR	Hazard ratio
HRPF	High-risk plaque features
IQR	Interquartile range
MACE	Major adverse cardiac events
MI	Myocardial infarction
ROC	Receiver operator characteristic
SD	Standard deviation
UA	Unstable angina
WHV	Whole heart volume

Introduction

Cardiac computed tomography (CT) is increasingly used to exclude obstructive coronary artery disease in patients presenting with stable chest pain. According to the most recent European Society of Cardiology Guidelines, cardiac CT represents a first-line diagnostic method to assess cardiovascular (CV) risk in patients with chronic coronary syndromes, including those with stable chest pain [1]. While cardiac CT is a reliable method to exclude coronary artery disease (CAD) (negative predictive value ~99%) and to detect obstructive CAD, assessment of CV risk remains challenging, especially in those with non-obstructive disease [2]. Symptomatic patients with non-obstructive CAD, however, account for the majority of future CV events [3, 4], require advanced risk stratification, and are frequently referred to further testing.

CT-derived measures beyond stenosis assessment have revealed an additional prognostic value. For instance, elevated coronary artery calcium (CAC) or presence of high-risk plaque features (HRPF) on CT angiograms have been associated with increased risk of major adverse CV events (MACE) [3, 5, 6]. In addition to showing coronary arteries, cardiac CT has an advantage to image adjacent anatomical structures. Advanced CAD phenotyping, incorporating these structures, may leverage additional information and improve risk stratification. For example, epicardial adipose tissue, size of individual cardiac chambers, or CT-derived cardiac function has been related to adverse CV events beyond coronary stenosis and clinical risk factors [7–10].

Regarding heart morphology, the diameter of the heart on X-ray, and its proportion to thorax size (i.e., cardiothoracic ratio), is established measures of CV risk [11–14]. However, the prognostic value of CT-derived whole heart volume (WHV), a detailed 3D measure of heart size available in all cardiac CT scans, has not been evaluated yet. Thus, this study's primary aim was to determine the association of WHV with MACE, adjusting for traditional measures of CV risk (i.e., atherosclerotic cardiovascular disease [ASCVD] risk score) and CAD characteristics on CT. In a final step, we performed a subgroup analysis across CAD categories (i.e., no-, non-obstructive, and obstructive CAD) and determined whether WHV had discriminatory capacity incremental to ASCVD risk score and CT-derived CAD characteristics.

Methods

Study population and clinical characteristics

In this sub-study of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, we included patients who were randomized to anatomical testing and received non-contrast cardiac CT and contrast-enhanced coronary CT angiography (CTA). As per the PROMISE trial inclusion criteria, patients with known CAD or heart failure were not included. We excluded patients who received the first test other than CTA, did not undergo testing, received non-contrast CT only, or those with unavailable or non-diagnostic image data (Consort diagram Fig. 1). Demographics and traditional CV risk factors were assessed with standard methods at the time of enrollment to the PROMISE trial [15]. Local and central institutional review boards approved the study, and all patients provided written informed consent.

Follow-up and the endpoints

All patients were followed for a median of 2 years. The primary endpoint was MACE, defined as a composite of all-cause mortality (CV + non-CV death), non-fatal myocardial infarction (MI), and hospitalization for unstable angina (UA), as adjudicated by an independent committee [15].

WHV—definition and measurements

WHV (cm^3) was defined as the volume of the pericardial sac, including all chambers (i.e., ventricles and atria), walls, and

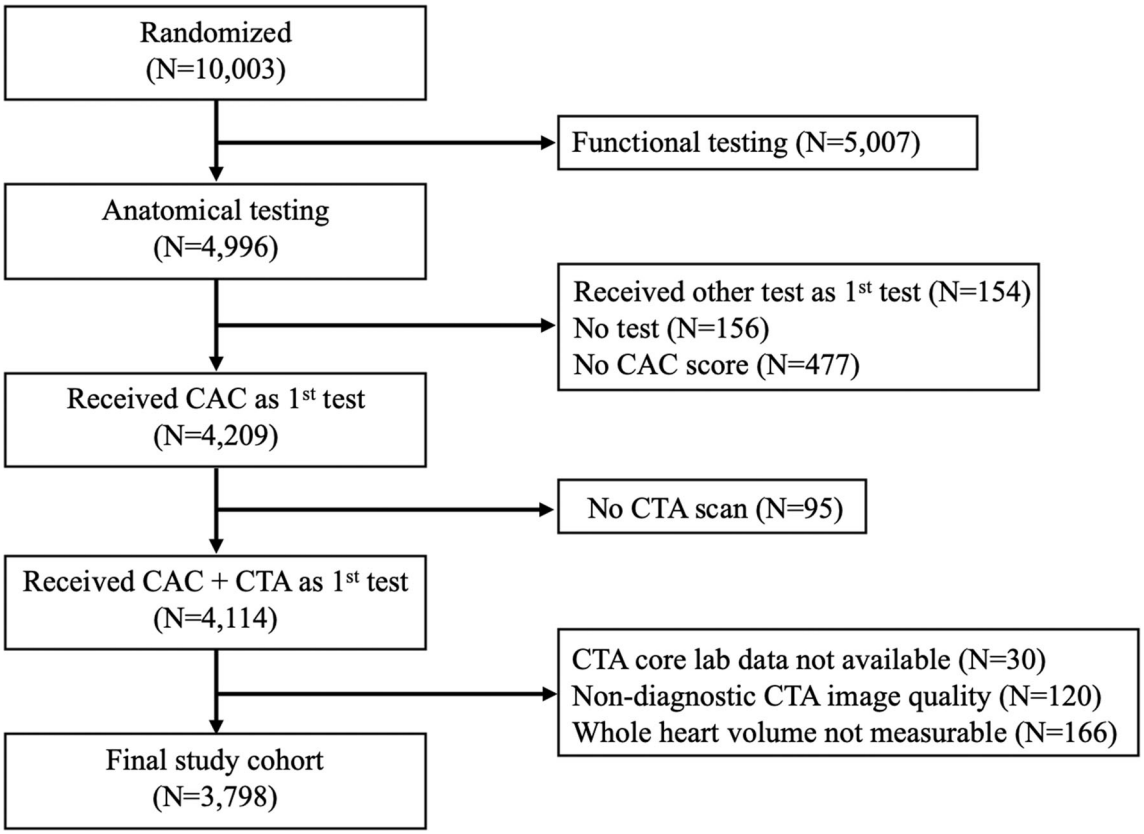

Fig. 1 Consort diagram. *CAC*, coronary artery calcium; *CTA*, computed tomography angiography

coronary arteries, but excluding epicardial fat (tissue ≤ -45 HU). The cranial border was the axial slice at the level of the right mid pulmonary artery (Fig. 2). To adjust for individual body size differences, we indexed the WHV by body surface area (BSA) (cm^3/m^2) [16].

To decrease segmentation time, increase clinical feasibility, and standardize the measurement of WHV, we used a deep learning system for the segmentation. The system consisted of two consecutive deep learning networks of the U-Net architecture, to (1) localize and (2) segment the heart. The code was written in Python (v2.7) [17] using Tensorflow-GPU (v1.14) [18], Keras (v2.3.1) [19] with NVIDIA CUDA (v10.2) [20].

To ensure generalizability of the system, the training and tuning cohorts included 858 multicenter and multi-vendor CT scans from the Framingham Heart Study (FHS n = 628), the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE, n = 130), and the National Lung Screening Trial (NLST, n = 100). Three experienced readers (B.F., P.E., J.E.S.) provided manually segmented hearts for the training (i.e., supervised learning). Here, the readers traced pericardial contours in axial images at 15-mm intervals and interpolated the space between the images using 3D Slicer (v.4.10) [21].

To further increase the segmentation accuracy, we automatically removed possibly incorrectly segmented lung tissue by excluding outer voxels with an attenuation < - 400 HU. There was no manual correction of the automatic segmentations. The system accuracy was determined on an independent external validation dataset of 1010 manually segmented hearts in PROMISE, revealing an excellent agreement (Dice coefficient: 0.94 ± 0.02).

CT-derived CAD characteristics

Experienced core lab readers measured CAC on non-contrast cardiac CT using the standard Agatston method [22]. Moreover, our core lab assessed all coronary arteries for the presence of CAD (non-obstructive: 1–69% and obstructive ≥ 70% maximal luminal narrowing in any coronary artery or ≥ 50% in the left main coronary artery) as well as the presence of HRPF as described elsewhere [5]. To determine CAD extent, accounting for plaque location and morphology, we calculated the Leaman score, an established tool to quantify total coronary atherosclerotic burden with information regarding localization, type of plaque, and degree of stenosis [23].

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range (IQR)) and categorical variables as frequencies and percentages. Differences of WHV across clinical characteristics were tested with the

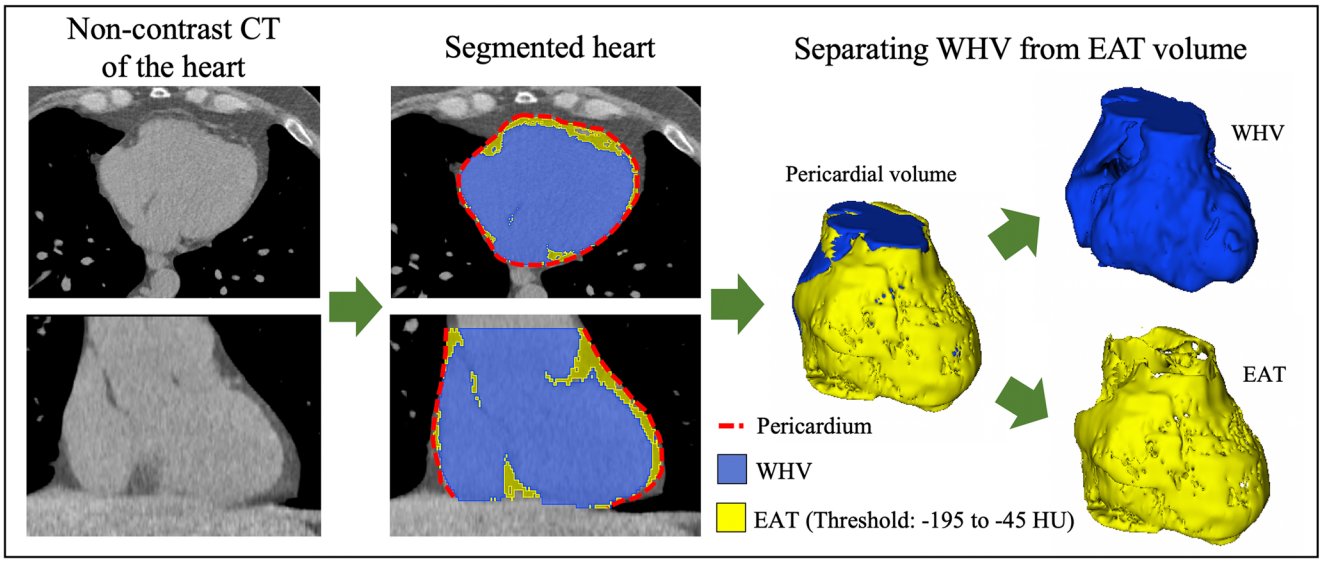

Fig. 2 Measurements of WHV on non-contrast CT. Segmented hearts were derived from non-contrast cardiac CT images. The natural border was the pericardial sac (red-dotted line), and the segmentation ranged from the mid-right pulmonary artery (PA) to the most caudal part of the pericardial sac. To render WHV (blue), we subtracted the EAT volume (yellow), defined as fatty tissue with density thresholds of - 195 to - 45 HU. *CT*, computed tomography; *EAT*, epicardial adipose tissue; *HU*, Hounsfield units; *WHV*, whole heart volume

Wilcoxon rank-sum test, while differences between categorical variables were tested with Fisher's exact test.

Univariate and multivariate Cox regressions were used to estimate the association of WHV with MACE. Results were reported as hazard ratios (HR) and 95% confidence intervals (CI). All regressions were stepwise adjusted for age, sex, ASCVD risk score, and Leaman score. Standard Kaplan-Meier survival curves incl. log-rank tests showed the differences in event-free survival across quintiles of WHV.

To test the incremental value of WHV, we evaluated whether the model fit increases significantly by adding WHV to the ASCVD risk and Leaman scores using the likelihood-ratio test for nested models. We also calculated receiver operator characteristic (ROC) curves to determine the area under the curve (AUC) and estimate the increase of discriminatory capacity.

All analyses were performed in Stata 15.0, and two-sided p values < 0.05 were considered statistically significant.

Results

Study population

Out of the 4996 PROMISE patients randomized to anatomical testing, 3798 fulfilled the inclusion criteria (Fig. 1). The analytic cohort consisted of middle-aged (60.5 ± 8.2 years), mostly overweight (median BMI: 30.3 ± 5.8 kg/m^2), and predominantly male patients (58.5%) with intermediate CV risk (mean 10-year ASCVD risk score: 14.3 ± 11.4%) (Table 1). On coronary CTA, the mean Leaman score was 5.0 ± 5.1, and HRPFs were present in 582/3798 (15.3%) patients. Over a median follow-up of 26.1 (18.0–34.4) months, 116/3,798 (3.1%) patients experienced MACE (MI: 21/116 (18.1%); death: 53/116 (45.7%); CV death: 30/116 (25.9%); UA: 46/116 (39.7%)).

Differences of WHV across categories of CV risk factors and CAD characteristics

The mean WHV was 351.9 ± 57.6 cm^3/m^2 (range 100.6–746.1 cm^3/m^2). In general, men and those with increased ASCVD risk (≥ 7.5%) and advanced CAD (i.e., obstructive CAD, higher CAC score, HRPF present) presented with larger hearts ($p < 0.001$ for all). On the other hand, women, patients with no- or non-obstructive CAD, obese patients, and those with metabolic syndrome, and sedentary lifestyle presented with significantly smaller hearts ($p < 0.05$ for all). Separated by median age (59.7 years), WHV did not differ between younger and older patients ($p = 0.397$). Individual WHV across categories of CV risk factors and CAD characteristics on CT are shown in Fig. 3.

Association of WHV with MACE

Patients who experienced MACE had smaller WHV compared to those without MACE (346.0 ± 55.4 vs. 352.1 ± 57.6 cm^3/m^2; $p = 0.005$). In an age- and sex-adjusted time-to-event analysis, we found that a decrease of WHV by one standard deviation was associated with over 4.4 times higher hazard of MACE (HR (per one standard deviation increase) = 0.225, 95% CI: 0.066–0.769, $p = 0.017$). This association remained significant and at a similar magnitude after adjusting

Table 1 Baseline characteristics

Mean ± SD or *n* (%)	All (*N* = 3798)	No MACE (*N* = 3682)	MACE (*N* = 116)	*p*
Demographics				
Age, years	60.5 ± 8.2	60.4 ± 8.2	63.0 ± 9.1	0.003
Women	1955 (51.5)	1905 (51.7)	50 (43.1)	0.073
Cardiovascular risk factors				
Hypertension	2441 (64.3)	2361 (64.1)	80 (69.0)	0.325
Diabetes mellitus	773 (20.4)	744 (20.1)	29 (25.0)	0.200
Dyslipidemia	2562 (67.5)	2486 (67.5)	76 (65.5)	0.687
BMI, kg/m^2	30.3 ± 5.8	30.3 ± 5.8	29.7 ± 5.7	0.255
Current or past smoker	1954 (51.5)	1878 (51.0)	76 (65.5)	0.002
Family history of premature (< 55 years) CAD	1258 (33.2)	1222 (33.3)	36 (31.0)	0.689
Any PAD	193 (5.1)	185 (5.0)	8 (6.9)	0.385
Metabolic syndrome	1379 (36.3)	1334 (36.2)	45 (38.8)	0.624
Sedentary lifestyle	1819 (48.0)	1747 (47.5)	72 (62.1)	0.002
Cardiovascular risk, %				
ASCVD risk score	14.3 ± 11.4	14.2 ± 11.3	20.2 ± 13.7	< 0.001
Relevant medication				
Beta-blocker	904 (24.8)	878 (24.8)	31 (27.4)	0.508
ACE inhibitor or ARB	1579 (43.4)	1529 (43.4)	50 (44.3)	0.848
Statin	1659 (45.6)	1611 (45.7)	48 (42.5)	0.565
Aspirin	1639 (45.0)	1589 (45.1)	50 (44.3)	0.924
Left ventricular EF*, %	64.6 ± 9.0	64.6 ± 8.9	65.2 ± 10.8	0.648
CAD on cardiac CT				
Coronary calcium score	20.2 (0.0–159.3)	18.2 (0.0–150.2)	146.4 (19.6–405.0)	< 0.001
Leaman score	3.7 (0.0–8.6)	3.7 (0.0–8.4)	8.0 (4.6–13.1)	< 0.001
No CAD	1297 (34.2)	1286 (34.9)	11 (9.5)	< 0.001
Non-obstructive CAD (1–69%)	2268 (59.7)	2192 (59.5)	76 (65.5)	
Obstructive CAD (≥ 70%)	233 (6.1)	204 (5.5)	29 (25.0)	

ACE, angiotensin-converting enzyme; *ARB*, angiotensin receptor blocker; *ASCVD*, atherosclerotic cardiovascular disease; *BMI*, body mass index; *CAD*, coronary artery disease; *CT*, computed tomography; *MACE*, major adverse cardiac events; *PAD*, peripheral arterial disease. *Available in a subgroup of 1815 patients. Values expressed as mean ± SD, median (IQR) or *N* (%)

for the clinical ASCVD risk and Leaman score (adjusted HR = 0.221, 95% CI: 0.068–0.721, $p = 0.012$). Additional results for raw WHV (i.e., not BSA-indexed) revealed similar results and are shown in Table 2. In a supplemental analysis, WHV remained significantly associated with MACE in a combined model adjusting for ASCVD, Leaman score, and CAC (BSA-indexed and ln-transformed WHV: HR = 0.21, 95% CI: 0.066–0.710, $p = 0.011$).

WHV across subgroups of CAD

On coronary CTA, 1297 (34.2%), 2268 (59.7%), and 233 (6.1%) patients presented with no-, non-obstructive, and obstructive CAD, respectively. Event rates differed significantly between patients without CAD and those with non-obstructive and obstructive disease (0.9% vs. 3.4% vs. 12.5%, respectively; log-rank test, $p < 0.001$). In patients with non-obstructive CAD, a decrease in WHV by one standard deviation was associated with 16.7 times higher hazard of MACE independent of ASCVD risk and Leaman score (adjusted HR = 0.06, 95% CI: 0.013–0.269, $p < 0.001$). However, there was no significant association between WHV and MACE in those with no- or obstructive CAD ($p = 0.146$–0.853). Table 3 provides the results for raw WHV and BSA-adjusted WHV, which have shown similar results as the standardized WHV.

Non-obstructive CAD and WHV

In our cohort, the majority ($n = 76/116$; 66%) of incident events occurred in the 2268 patients with non-obstructive CAD. Among these, women presented with a slightly higher event rate compared to men (3.7% vs. 3.1%). Across quintiles of WHV, the MACE rate ranged between 2.3 and 5.4%, being nearly twice as high in the lowest quintile of WHV compared to Q2–5 (5.4% vs. 2.3–3.3%). In a time-to-event analysis, the

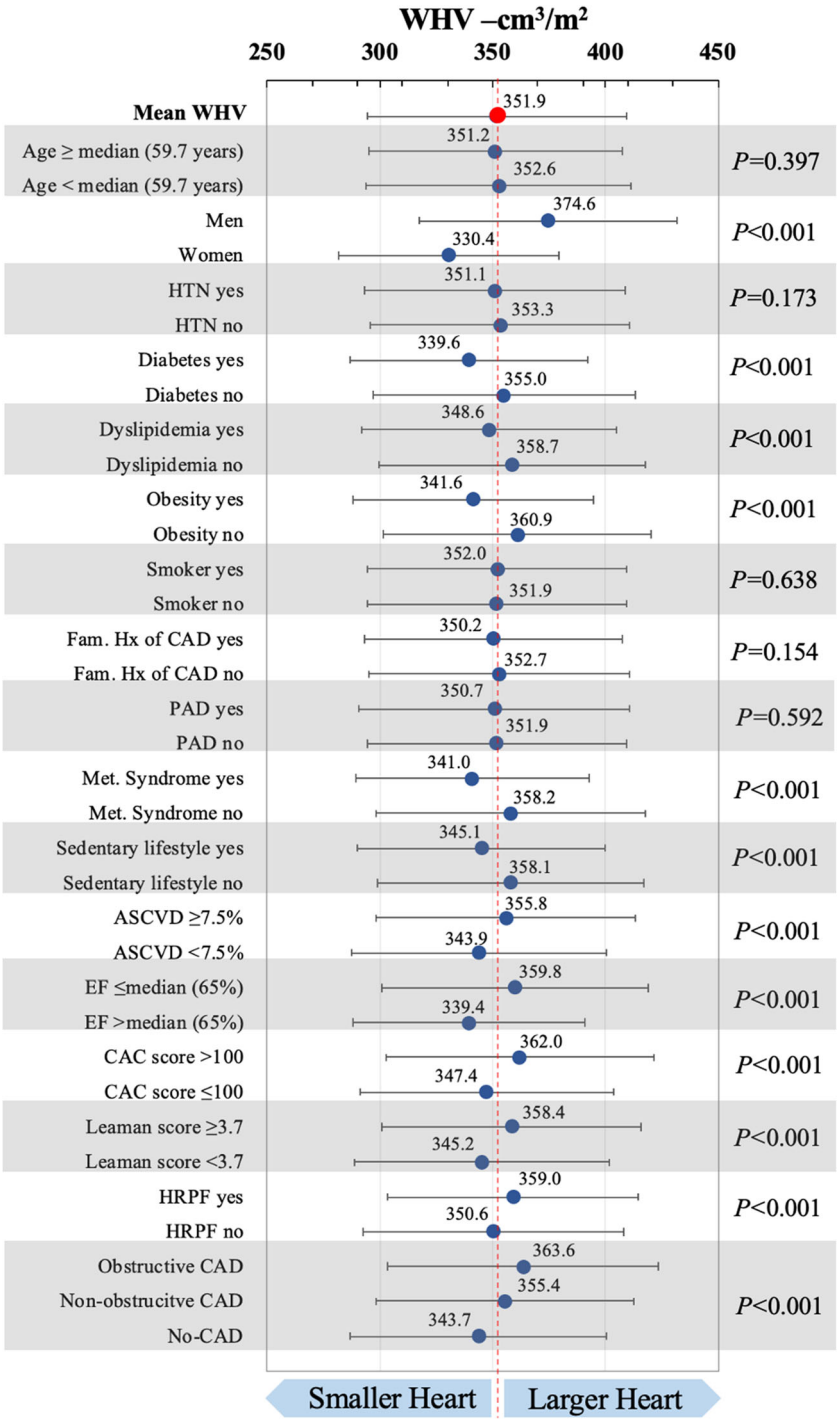

Fig. 3 Whole heart volume, cardiovascular risk factors, and CAD on CT. Red-dotted line marks the mean WHV as reference (351.9 cm^3/m^2). Bracketed lines represent standard deviations. ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CAD, coronary artery disease; EF, ejection fraction; HRPF, high-risk plaque features; HTN, arterial hypertension; WHV, whole heart volume; PAD, peripheral arterial disease

lowest event-free survival was found in those with the lowest quintile of WHV (log-rank Q1 vs. Q2–5: $p < 0.001$; Fig. 4). This association was further reflected in over twofold higher hazard of MACE even after adjustment for ASCVD risk and Leaman score (adjusted HR (Q1 vs. Q2–5) =2.13; 95% CI: 1.29–3.51; $p = 0.003$). In a sex-stratified analysis of patients with non-obstructive CAD, WHV showed an independent association with MACE in both women and men, being slightly stronger in men compared to women (men: HR = 0.064, 95% CI: 0.007–0.613, $p = 0.017$ vs. women: HR = 0.080, 95% CI: 0.001–0.781, $p = 0.030$ for BSA-indexed and ln-transformed WHV; Supplemental Table S1).

Regarding event types, patients with small WHV experienced rather unspecific events, such as non-CV death or hospitalization for unstable angina, while those with larger hearts (Q2–5 of WHV) presented with more specific CV events, such as CV death or non-fatal myocardial infarction (Fig. 5).

Table 2 Association of WHV with MACE in all patients with stable chest pain ($N = 3798$; MACE: $N = 116$)

	Adjusted for age and sex			Adjusted for ASCVD and Leaman score		
	HR	95% CI	*p*	HR	95% CI	*p*
WHV (absolute), mm^3	0.998	0.997–1.000	0.035	0.999	0.997–1.000	0.024
WHV (BSA-indexed), cm^3/m^2	0.996	0.992–0.999	0.022	0.996	0.992–0.999	0.018
WHV (BSA-indexed + *ln*-transformed)	0.225	0.066–0.769	0.017	0.221	0.068–0.721	0.012

Association of WHV with MACE (death, MI, or hospitalization for unstable angina). *ASCVD*, atherosclerotic cardiovascular disease; *BSA*, body surface area; *MACE*, major adverse cardiac events; *WHV*, whole heart volume

Incremental value of WHV in non-obstructive CAD

In patients with stable chest pain and non-obstructive CAD, clinical parameters (i.e., ASCVD risk score), the CT-derived Leaman score, and WHV reached only a fair discriminatory capacity (AUC = 0.627, 0.599, and 0.589, respectively). While adding Leaman score to the ASCVD risk score did not lead to relevant changes of the AUC (0.627 vs. 0.627), the addition of WHV to the model resulted in a statistically significant improvement of model fit (likelihood-ratio test (3 degrees of freedom): X^2=17.9; $p < 0.001$). Correspondingly, the AUC increased by 4.6% reaching an AUC of 0.673 (Fig. 6). We did not test for incremental value of WHV in patients with no- or obstructive CAD, since the initial tests (i.e., regressions) were negative.

Discussion

The primary finding of this study is that small WHV is an independent prognostic imaging marker of MACE among stable chest pain patients. This association is the strongest in those with non-obstructive CAD, a group of patients with the highest need for enhanced risk stratification. Moreover, in this group, WHV improves the discriminatory capacity of the traditional clinical CV risk factors and CTA-derived CAD characteristics.

Small hearts and MACE

Because our finding of an association of small WHV with MACE, especially in those with non-obstructive CAD, was independent of traditional CV risk factors and CAD burden, and that patients with small WHV experienced predominantly unspecific events, we suggest that the mechanism relating small WHV with MACE may not be directly linked to epicardial coronary atherosclerosis.

A clue, elucidating the potential pathophysiological/mechanistic link between small WHV and MACE, may be found in that small WHV was more frequent in women, people with diabetes, obese patients with metabolic syndrome, and sedentary lifestyle. This constellation, especially in the presence of non-obstructive CAD, has been described in the early stages of heart failure with preserved ejection fraction (HFpEF) [24–26]. Here, despite normal cardiac function, a combination of cardiometabolic disorder and non-obstructive CAD promotes myocardial fibrosis with concentric LV-remodeling [27, 28] and ultimately increased risk for

Table 3 Association of WHV with MACE stratified by CAD status on CTA

Adjustment	Age and sex			ASCVD and Leaman score		
	HR	95%CI	*P*	HR	95%CI	*P*
No CAD: 0% stenosis ($N = 1297$; MACE: $N = 11$)						
WHV (absolute), cm^3	1.002	0.998–1.007	0.327	1.002	0.999–1.006	0.255
WHV (BSA-indexed), cm^3/m^2	1.006	0.996–1.015	0.272	1.006	0.997–1.015	0.184
WHV (BSA-indexed + *ln*-transformed)	10.91	0.25–468.10	0.213	13.02	0.41–415.72	0.146
Non-obstructive CAD: 1–69% stenosis ($N = 2268$; MACE: $N = 76$)						
WHV (absolute), cm^3	0.997	0.995–0.999	0.003	0.997	0.996–0.999	0.001
WHV (BSA-indexed), cm^3/m^2	0.992	0.988–0.997	0.002	0.993	0.989–0.997	0.002
WHV (BSA-indexed + *ln*-transformed)	0.064	0.013–0.317	0.001	0.060	0.013–0.269	< 0.001
Obstructive CAD: ≥ 70% stenosis ($N = 233$; MACE: $N = 29$)						
WHV (absolute), cm^3	0.999	0.997–1.002	0.671	1.000	0.998–1.003	0.899
WHV (BSA-indexed), cm^3/m^2	0.998	0.991–1.005	0.623	0.999	0.993–1.006	0.803
WHV (BSA-indexed + *ln*-transformed)	0.55	0.04–7.01	0.648	0.80	0.08–8.14	0.853

Association of WHV with MACE (death, MI, or hospitalization for unstable angina) was driven by those with non-obstructive CAD. *ASCVD*, atherosclerotic cardiovascular disease; *BSA*, body surface area; *CAD*, coronary artery disease; *ln*, natural log; *MACE*, major adverse cardiac events; *WHV*, whole heart volume

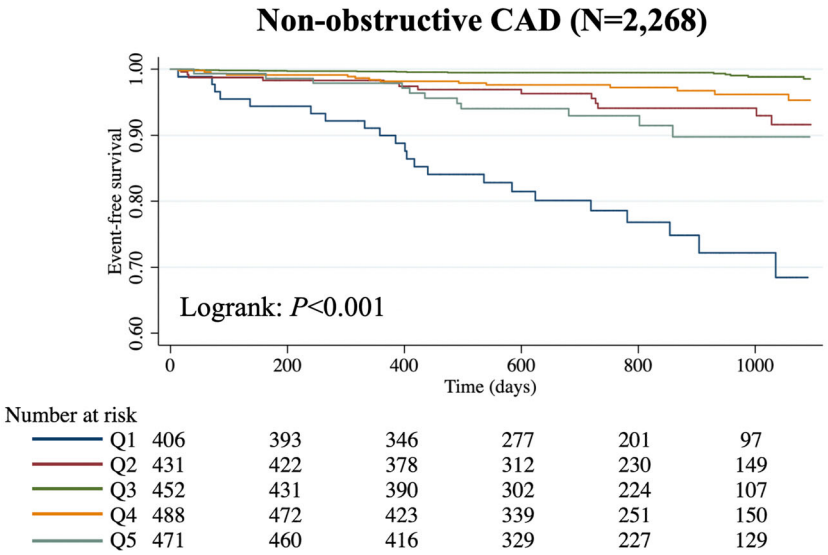

Fig. 4 Quintiles of WHV and MACE in non-obstructive CAD. Significantly reduced event-free survival in patients with WHV in the first quintile (Q1) as compared to Q2–5 (log-rank results displayed as Q1 vs. Q2–5). All KM-curves were adjusted for ASCVD and Leaman score. *Q1–Q5*= quintiles of WHV. Kaplan-Meier curves for WHV in no- and obstructive CAD did not show significant results and are shown in Supplemental Figure S1

MACE [27, 29]. PROMISE patients with small WHV had normal cardiac function based on prior definitions [30], including those with MACE.

Moreover, coronary microvascular dysfunction (CMD) and HFpEF are closely related, and a recent study found that 70–80% of patients with HFpEF also have CMD [31]. CMD and HFpEF also share clinical risk factors such as hypertension, diabetes, smoking, obesity, and chronic inflammatory disorders [32, 33], the majority of risk factors found in those with small WHV in our study. Our results add to the growing body of evidence, suggesting that CMD may be associated with non-obstructive CAD [32–35] and, thus, may represent a potential link between non-obstructive CAD and HFpEF.

Given that PROMISE did not include patients with heart failure or known CAD (i.e., groups with often enlarged hearts), we hypothesize that the association between small WHV and MACE may represent the left segment of a J-shaped relationship between WHV and MACE. This phenomenon has been described for other markers of CV risk, such as obesity [36]. However, this suggestion is hypothesis-generating and requires further investigation.

Large hearts and MACE

In our cohort, patients with more advanced CAD on cardiac CT (e.g., elevated CAC or Leaman score, obstructive CAD, or HRPF present) or, in general, elevated CV risk (i.e., ASCVD risk score ≥7.5%) presented with larger hearts. As expected, patients with larger hearts presented with rather typical CV events, such as CV death or non-fatal myocardial infarction. To some degree, these findings corroborate well-known associations of pathologically enlarged hearts, for example, those with clinical heart failure, dilatated or ischemic cardiomyopathy, and MACE [9, 14, 37–41]. It is crucial to understand that the PROMISE trial excluded patients with clinical signs of

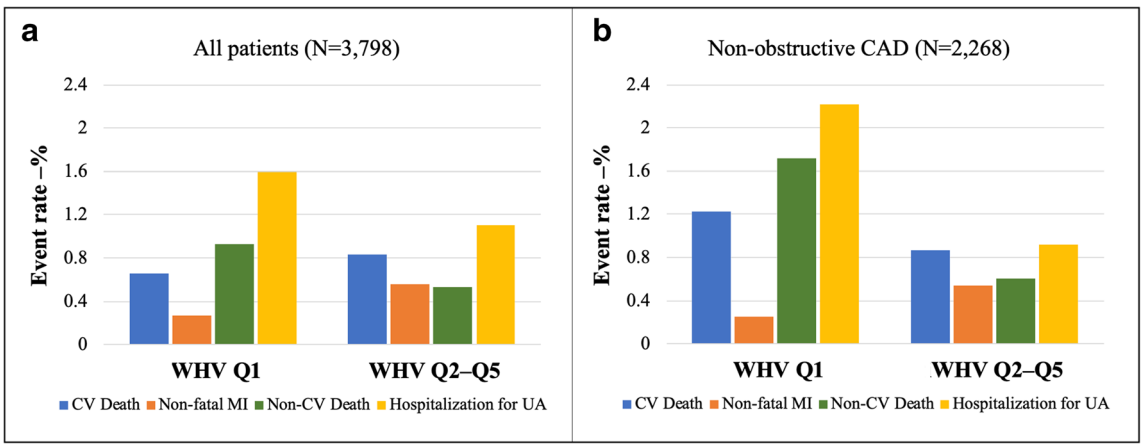

Fig. 5 Event types and WHV. Patients with small WHV (Q1) presented with rather unspecific event types while those with higher WHV presented more frequently with specific cardiovascular events, an observation particularly seen in non-obstructive CAD. CAD, coronary artery disease; CV, cardiovascular; MI, myocardial infarction; Q1–Q5, quintiles of WHV; UA, unstable angina; WHV, whole heart volume

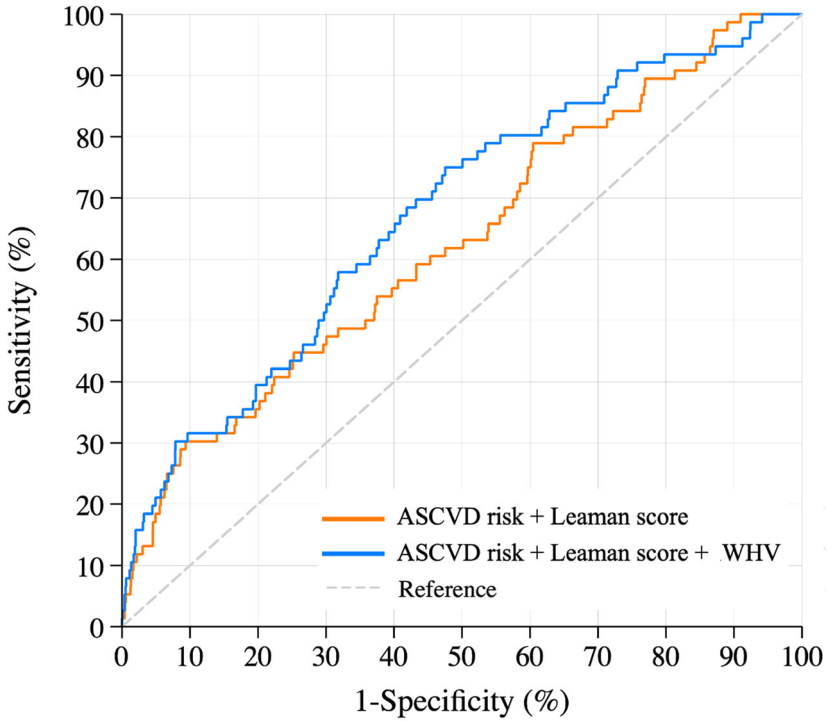

Fig. 6 Incremental value of WHV in non-obstructive CAD. Addition of WHV to clinical risk factors and CT-derived CAD characteristics increased the discriminatory capacity significantly by 4.6%. Addition of WHV to the model resulted in a statistically significant improvement of model fit (X^2=17.9; $p < 0.001$). AUC, area under the receiver operator characteristic curve; ASCVD, atherosclerotic cardiovascular disease; WHV, body surface area-indexed whole heart volume. To maintain readability, only curves for the composites are displayed here. Individual curves are available in Supplemental Figure S2

Parameter	AUC	95% CI
ASCVD risk score	0.627	0.561–0.692
Leaman score	0.599	0.530–0.667
WHV	0.589	0.521–0.656
ASCVD risk + Leaman score	0.627	0.560–0.693
ASCVD risk + Leaman score + WHV	0.673	0.610–0.735

heart failure or known CAD, an aspect of selection that may explain why there was not a clear association between large hearts and MACE in our cohort.

Future perspectives

Future studies adding markers of structural and functional alterations of the heart (e.g., myocardial stiffness, interstitial collagen content, diastolic dysfunction, and strain), as well as CMD measures, are needed to test our hypothesis that small WHV relates to CMD and HFpEF in non-obstructive CAD. Moreover, studies of WHV in community-based populations, including those with enlarged hearts/heart failure, are needed to investigate the J-shaped relationship between WHV and MACE.

Clinical relevance

Our group and others have shown that non-obstructive CAD is related to an increased risk of MACE [3, 4]. In the PROMISE trial, non-obstructive CAD was associated with a threefold increased risk for MACE compared to no CAD and accounted for the majority of events [3]. Thus, there is an unmet need for further risk stratification. Our study delivers a novel imaging marker that may improve risk stratification in this cohort at increased CV risk.

Limitations

Our study is a retrospective secondary analysis of a large randomized trial. Accordingly, our results are hypothesis-generating rather than confirmatory and need validation in large prospective cohorts. A comparison of WHV between patients with chest pain and normal WHV values was not possible since normal WHV has not been defined yet. Normal range of WHV will need to be derived from populations free of clinical symptoms. Despite the large scale of the PROMISE trial, the number of events is limited to provide reliable results in patient subgroups (e.g., quintiles of WHV in women and men with non-obstructive disease).

Conclusion

In stable chest pain patients, smaller WHV is an independent prognostic marker of MACE. Particularly in patients with non-obstructive CAD, small WHV may help to stratify CV risk beyond the traditional CV risk factors and CT measures of CAD and may help to guide clinical management.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Dr. Borek Foldyna.

Conflict of interest The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Statistics and biometry One of the authors (Prof. Thomas Mayrhofer) has significant statistical expertise and no complex statistical methods were necessary for this paper.

Informed consent Local and central institutional review boards approved the study, and all patients provided written informed consent.

Ethical approval Local and central institutional review boards approved the study.

Study subjects or cohorts overlap This investigation is a sub-study of the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial.

Methodology
- Secondary analysis
- Multicenter randomized controlled trial

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