

# Subclinical coronary atherosclerosis identified by coronary computed tomographic angiography in asymptomatic morbidly obese patients

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## Abstract

Obesity is a common public health problem and obese individuals in particular have a disproportionate incidence of acute coronary events. This study was undertaken to identify coronary artery lesions as well as associated clinical features, risk factors and demographics in patients with a body mass index (BMI) >40 kg/m<sup>2</sup> without known coronary artery disease (CAD). Morbidly obese subjects were prospectively recruited to undergo coronary computed tomographic angiography (CCTA) using a dual-source computed tomography (CT) system. CAD was defined as the presence of any atherosclerotic lesion in any one coronary artery segment. The presence, location, and severity of atherosclerosis were related to patient characteristics. Forty-one patients (28 women, mean age, 50.4±10.0 years, mean BMI, 43.8±4.8 kg/m<sup>2</sup>) served as the study population. Of these, 25 patients (61%) had at least one coronary stenosis. All but 2 patients within the CAD cohort had coronary artery cal-

cium (CAC) scores >0, and most plaques identified (75.4%) were non-calcified. There was a predilection of calcified and non-calcified atherosclerosis involving the left anterior descending (LAD) coronary artery compared with other coronary segments. Univariate predictors of CAD included older age, dyslipidemia, and diabetes. In this preliminary study of young morbidly obese patients, CCTA detected a high prevalence of calcified and non-calcified CAD, although the later predominated.

## Introduction

Obesity is a common public health problem reaching epidemic proportions in recent decades. In the United States, 66% of adults are overweight and nearly half of these are obese defined as having a body mass index (BMI) >30 kg/m<sup>2</sup>.<sup>1</sup> Obesity is now classified as an independent modifiable risk factor for the development of coronary artery disease (CAD) and morbidly obese individuals (BMI >40 kg/m<sup>2</sup>) in particular have a disproportionate incidence of acute coronary events.<sup>2,3</sup> In a large retrospective analysis of 111,847 patients in the CRUSADE registry, we reported that BMI >40 kg/m<sup>2</sup> is the strongest determinant of first non-ST-segment elevation myocardial infarction occurring prematurely, exceeding the impact of smoking and family history.<sup>4</sup> Because obesity accelerates the progression of coronary atherosclerosis in young cohorts<sup>5</sup> and significant cardiac events may be asymptomatic,<sup>6</sup> early detection and treatment of those with an increased BMI may yield significant reductions in cardiovascular morbidity and mortality.

Increased abdominal adiposity is associated with the development of metabolic syndrome<sup>7</sup> which now affects over 47 million Americans.<sup>8</sup> In addition, an increased waist to hip ratio has been associated with a heightened risk of acute myocardial infarction.<sup>9</sup> Increased BMI imposes a pro-inflammatory state, releasing factors such as high sensitivity-C reactive pro-

tein which is strongly associated with plaque rupture and acute cardiovascular events.<sup>4</sup> Since traditional risk factors alone may underestimate the extent of subclinical CAD in young cohorts,<sup>10</sup> a non-invasive imaging technique to accurately assess coronary atherosclerosis may provide independent and additive information in risk stratifying this escalating patient subset.

Few data are available regarding the extent and severity of CAD using coronary computed tomographic angiography (CCTA) in morbidly obese individuals. Previously, we have demonstrated that using a novel half-scan reconstruction on a dual-source CT system optimizes image quality with acceptable signal-to-noise and contrast-to-noise ratios which leads to diagnostic images in >90% of morbidly obese patients.<sup>11</sup> The present study was conducted to describe coronary artery morphology as well as associated obstructive and non-obstructive lesions, risk factors and demographics in patients with a BMI >40 kg/m<sup>2</sup> without known CAD.

## Materials and Methods

### Study population

Morbidly obese subjects (BMI >40 kg/m<sup>2</sup>) were prospectively recruited for the BMI-40 trial, using the outpatient facilities associated with William Beaumont Hospital, Royal Oak, Michigan, USA (Clinical Trials.gov Identifier: NCT00468195). Recruitment advertisements were delivered to healthcare providers and various referral centers within the hospital network. A total of 47 patients completed CCTA on a dual-source CT scanner (Somatom Definition, Siemens Medical Systems, Forchheim, Germany). Image reconstructions were performed with a standard quarter scan mode (temporal resolution of 82 milliseconds) and image quality was compared to images reconstructed using a novel half-scan mode (temporal resolution of 165 milliseconds). Diagnostic CCTA images were obtained using

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standardized methodology as previously described, and the average calculated radiation exposure for each patient was  $22 \pm 4.4$  mSv.<sup>11</sup>

Eligibility criteria for inclusion were: (1) BMI  $>40$  kg/m<sup>2</sup>; and (2) absence of pre-existing CAD. Those with an iodinated contrast allergy, markedly irregular heart rhythm, pregnancy, renal insufficiency and inability to tolerate beta-blocking drugs were excluded from study participation. The study was approved by the Human Investigation Committee at William Beaumont Hospital and all patients provided written informed consent.

## Data collection

Baseline clinical characteristics included age, sex, BMI, weight, waist and chest circumference, hypertension, diabetes mellitus, cigarette smoking, hyperlipidemia, use of lipid lowering medications, and a positive family history of cardiovascular disease.

## Angiographic analyses and coronary artery calcification measurement

CCTA was performed using a dual source CT scanner (Somatom Definition, Siemens Medical Systems, Forchheim, Germany). CCTA scans were analyzed according to previously published methodology<sup>12</sup> by a single experienced reader blinded to other findings (KC). Image interpretation and calcium scoring was performed on Somaris/7 Syngo 2007C (Siemens Medical Systems, Forchheim, Germany) and an offline workstation (Aquarius 3D Workstation, TeraRecon Inc., San Mateo, CA, USA). Coronary artery calcium (CAC) was measured using the Agatston scoring method and reported in Hounsfield units (HU). Angiographic analysis was performed employing a previously described 17-segment model of the coronary tree.<sup>13</sup> Lesions were classified by the maximal luminal diameter stenosis according to a qualitative severity scale: 0 = no stenosis, 1 = 1% to 25%, 2 = 26% to 50%, 3 = 51% to 70%, 4 = 71% to 99%, 5 = total occlusion. Identified atherosclerotic plaques were classified as calcified or non-calcified. A calcified plaque was defined as having  $\geq 100$  HU, whereas, a non-calcified plaque had  $\leq 99$  HU. Low-attenuation plaques were identified as having  $\leq 30$  HU. For comparative purposes, the study population was divided into two cohorts: those with and without CAD. Coronary disease was defined as the presence of any atherosclerotic lesion ( $>1\%$  stenosis) in one or more coronary artery segments. Stenosis was further classified as mild (1%-25%), moderate (26%-50%) and obstructive ( $>50\%$ ) in the population with CAD.

## Statistical analysis

This was a convenience sample and no power calculations were formed. Baseline characteristics were expressed as mean  $\pm$  standard deviation or counts with proportions as appropriate. Statistical analysis was performed using Statistica 6.0 (StatSoft Inc, Oklahoma). All data were expressed as mean  $\pm$  standard deviation for continuous variables and counts with proportions for dichotomous variables. Clinical characteristics in the two groups were compared using 2-sided independent-sample t-tests to detect statistical significance.  $P < 0.05$  were considered significant.

## Results

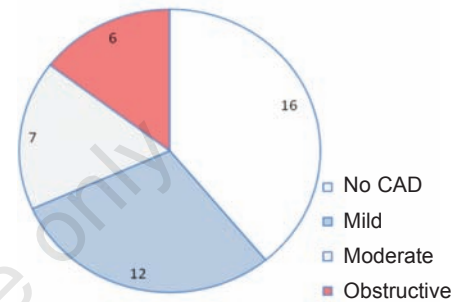
### Patient characteristics

Of the 47 patients enrolled, 6 (12.8 %) were excluded from the analysis because of incomplete or non-diagnostic CCTA studies. Of the remaining 41 patients, 25 (61%) had CAD and 16 (39%) had normal coronary arteries. Baseline characteristics of those patients with and without CAD are shown in Table 1. In the CAD group, history of diabetes, age and the prevalence of hyperlipidemia were significantly greater.

### Coronary angiography

Of the total study population ( $n=41$ ), 25 patients (61%) had at least one coronary

stenosis indicating subclinical CAD. The remaining 16 patients (39%) had normal coronary arteries with no evidence of atherosclerotic lesions. In the CAD group, 12 patients (48%) had mild disease, 7 patients (28%) had moderate disease and 6 patients (24%) had an obstructive coronary artery lesion. Figure 1 shows the prevalence of CAD in this population. Of the 25 patients with CAD, 10 (40%) had single vessel disease, 11 (44%) had double vessel disease and 4 (16%) had triple vessel disease. Coronary stenoses involving the LAD were present in 22 of the CAD patients (88%) and observed in 8 (80%), 10 (45%) and 4 (31%)



**Figure 1. Prevalence of CAD among morbidly obese subjects. Mild was defined as 1% to 25% stenosis. Moderate was defined as 26% to 50% stenosis. Obstructive was defined as  $>50\%$  narrowing in any segment of the coronary artery tree. CAD, coronary artery disease.**

**Table 1. Patient characteristics.**

Mean $\pm$ SD (95% C.I.)	Total	CAD group	Non-CAD group	P
Subjects	N=41	N=25	N=16	
Age (years)	50.4 $\pm$ 10.0 (47.4-53.5)	52.8 $\pm$ 9.4 (49.2-56.5)	46.7 $\pm$ 10.1 (41.8-51.6)	0.054
BMI (kg/m <sup>2</sup> )	43.8 $\pm$ 4.8 (42.3-45.2)	43.8 $\pm$ 4.9 (41.9-45.7)	43.6 $\pm$ 4.7 (41.3-46.0)	0.889
Weight (lb)	272.4 $\pm$ 46.9 (258.0-286.7)	274.8 $\pm$ 52.9 (254.1-295.5)	268.6 $\pm$ 36.9 (250.5-286.6)	0.682
Waist circumference (in.)	51.6 $\pm$ 5.3 (50.0-53.3)	52.1 $\pm$ 5.9 (49.8-54.4)	50.9 $\pm$ 4.2 (48.9-53.0)	0.491
Chest circumference (in.)	51.8 $\pm$ 4.5 (50.4-53.2)	51.9 $\pm$ 4.5 (50.2-53.7)	51.6 $\pm$ 4.5 (49.4-53.8)	0.800
Hypertension	33 (80%)	22 (88%)	11 (69%)	0.136
Diabetes mellitus	12 (29%)	11 (44%)	1 (6%)	0.009
Hyperlipidemia	23 (56%)	17 (68%)	6 (38%)	0.057
Lipid medications	15 (37%)	11 (44%)	4 (25%)	0.228
Cigarette smoking	16 (39%)	12 (48%)	4 (25%)	0.148
Male	13 (32%)	9 (36%)	4 (25%)	0.489
Family history	22 (54%)	14 (56%)	8 (50%)	0.715

Hypertension was defined as systolic blood pressure  $>140$  mm Hg and/or a diastolic blood pressure  $>90$  mm Hg, or treatment with antihypertensive medications. Diabetes mellitus was defined as existing diagnosis of diabetes or current use of oral hypoglycemics or insulin therapy. Hyperlipidemia was defined as a total cholesterol  $>200$  mg/dL or current use of cholesterol lowering therapy. Family history of coronary disease was defined as reported history of coronary artery disease or of a myocardial infarction in a sibling or parent before the age of 55. BMI, body mass index.

patients with 1, 2 and 3 vessel disease, respectively. Of the 22 patients with LAD lesions, 11 (48%), 6 (30%) and 5 (22%) patients had mild, moderate and obstructive disease, respectively. Twelve patients had right coronary artery (RCA) lesions; of these, 7 (58%), 4 (33%) and 1 (8%) patient had mild, moderate and obstructive disease. Of the 7 patients with left circumflex artery (LCx) lesions, 3 had mild and 4 had moderate disease. Lastly, only 4 patients had mild-to-moderate lesions involving the left main (LM) coronary artery. Figure 2 describes the location and degree of coronary lesions in the LM, LAD, RCA and LCx within the CAD cohort.

### Plaque morphology

In the cohort with CAD, 69 coronary plaques were identified within the 425 coronary segments evaluated. Of these lesions, 17 (24.6%) were calcified and 52 (75.4%) were non-calcified. Of the non-calcified plaques, 32 (61.5%) were low-attenuation plaques. Ten (58.8%) of the calcified plaques were found in the LAD, 6 (35.3%) were located in the RCA, and only 1 calcified plaque was identified in the LCx. Of the non-calcified plaques, 31 (59.6%) were found in the LAD and most were low-attenuation plaques. Non-calcified plaques were also present in the RCA 10 (19.2%), LM 4 (7.7%) and LCx 7 (13.5%), respectively. Figure 3 illustrates a CCTA image of a non-calcified plaque causing moderate stenosis at the ostium of the LAD in a morbidly obese subject.

### Coronary artery calcium

Coronary artery calcium was absent in all 16 patients (39%) without CAD and 2 patients (5%) with CAD. The remaining 23 patients (56%) with CAD all had coronary calcium >0. Of the patients with CAD, 7 patients (28%) had a CAC <10 HU, 9 (36%) had a CAC between 10 and 100 HU, 5 (20%) had a CAC between 101 and 400 HU and 4 (16%) had a CAC score >400 HU. Overall, the artery with the highest total calcium score of 1311 HU was the LAD. This was followed by the RCA, LCx and LM with a total CAC score of 1142, 362 and 98 HU, respectively. Of the two patients with CAD and a CAC=0, one had mild disease and the other obstructive disease. Six patients (86%) with CAD and a CAC <10 HU had only mild stenosis on CCTA. Among those patients with CAC ranging between 10 and 100 HU, 5 (56%) had mild stenosis and 3 (33%) had moderate stenosis. When the CAC score was between 101 and 400 HU, an equal number of patients had moderate disease (n=2; 40%) and obstructive disease (n=2; 40%). Lastly, when the CAC score was >400 HU, 2 patients (50%) had moderate disease and 2 patients (50%) had obstructive disease. Figure 4 depicts the distribution of CAD per CAC score. Increasing calcium scores were associated with a greater

prevalence of moderate and obstructive disease in each coronary vessel.

## Discussion

Subclinical atherosclerosis is common in the general population. The Framingham study reported atherosclerosis in approximately one-third of normal weight individuals; moreover, 40% of overweight participants and up to 50% of obese individuals demonstrated subclinical atherosclerotic disease.<sup>14</sup> Our data extend these observations in that 61% of morbidly obese individuals had evidence of CAD by CCTA.

Subclinical atherosclerosis has been shown to predict the development of ischemic cardiovascular events.<sup>15</sup> Moreover, excess adiposity is strongly related to acute coronary syndromes occurring prematurely. A nationwide registry of 111,847 patients with acute coronary syndromes found that the first non-ST-elevation myocardial infarction occurred, on average, 12 years earlier in patients with BMI >40 kg/m<sup>2</sup> as compared with their normal weight counterparts. Multivariate analysis confirmed that a BMI >40 kg/m<sup>2</sup> was more predictive of acute myocardial infarction than any other variable including smoking or family history.<sup>4</sup> Interestingly, the patients in the above study who had a BMI >40 kg/m<sup>2</sup> were generally in their fifties, as were the subjects in our study.

Abdominal obesity and/or an elevated BMI are associated with an increased prevalence of CAC and progression of subclinical coronary atherosclerosis.<sup>16,17</sup> In turn, the CAC burden is widely considered to be a marker of atherosclerosis and a risk factor for the development of future cardiac events.<sup>18</sup> Specifically, patients with CAC of 1-100, 101-300 and >300 HU were 3.6, 7.73 and 9.67 times more likely to suffer from a major cardiac event compared to patients with a CAC=0.<sup>19</sup> In our study, most patients had a CAC score >0, placing this young population at high risk.

Traditional risk factors such as family history, diabetes mellitus, older age, cigarette smoking, hypercholesterolemia and hypertension are harbingers for the development of CAC and the progression of atherosclerotic heart disease.<sup>20</sup> However, these risk factors alone may be insufficient to identify subclinical disease and patients at risk.<sup>15</sup> Detrano *et al.* reported that CAC scoring strengthened the prediction of cardiac events when used in conjunction with these traditional risk factors.<sup>19</sup> Moreover, recent guidelines recommend screening asymptomatic patients using CAC with an intermediate risk (between 10-20%, 10 year estimated risk of coronary events) in order to reclassify patients to a higher risk group.<sup>21</sup>

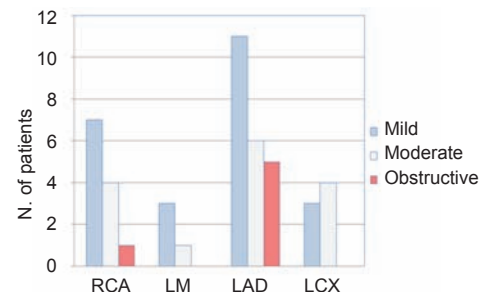


Figure 2. Distribution and severity of lesions in each coronary artery. Mild was defined as 1% to 25% stenosis. Moderate was defined as 26% to 50% stenosis. Obstructive was defined as >50% narrowing in any segment of the coronary artery tree. CAD, coronary artery disease; LAD, left anterior descending; LCx, left circumflex; LM, left main; RCA, right coronary artery.



Figure 3. Non-calcified plaque identified in the LAD. CCTA image of a non-calcified plaque causing moderate stenosis at the ostium of the LAD in a morbidly obese subject. CCTA, coronary computed tomographic angiography; LAD, left anterior descending.

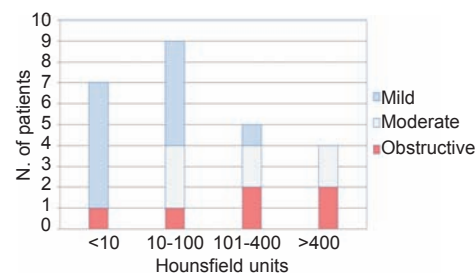


Figure 4. Severity of lesions according to overall calcium score. Mild was defined as 1% to 25% stenosis. Moderate was defined as 26% to 50% stenosis. Obstructive was defined as >50% narrowing in any segment of the coronary artery tree. CAC, coronary artery calcium; CAD, coronary artery disease.

Given most of our patients with CAD had several risk factors and a CAC >0, they could potentially be reclassified to this higher risk group leading to a more aggressive preventive treatment regimen.

Studies have also shown that asymptomatic individuals with a CAC score of zero have a 10 year event rate of 1%, suggesting an excellent survival.<sup>22</sup> However, these data are limited to low risk asymptomatic individuals since recent reports indicate that CAC scoring alone may fail to reveal obstructive disease in symptomatic patients.<sup>21</sup> In our study, we observed one patient with obstructive disease and another with mild disease on CCTA even though CAC=0. Therefore, in selected low risk asymptomatic individuals CAC scoring may be used to rule out CAD and avoid further testing. Accordingly, we essentially ruled out CAD in one third of our subjects; however 2 patients (8%) would have been missed using CAC scoring alone.

In a community based sample of 740 asymptomatic adults, men had significantly more CAC than women in each arterial location.<sup>23</sup> In women, the CAC was greatest in both the LAD and RCA compared with the LCx. Among men, the greatest CAC burden occurred in the LAD followed by the RCA and LCx. In the present study, we found a similar distribution of CAC as detailed above; however, there was no significant difference in the calcium burden between men and women.

Hadamitzky *et al.*<sup>24</sup> studied patients with suspected CAD using CCTA and found that patients having obstructive lesions were three times more likely to suffer from a severe cardiac event compared to those with non-obstructive disease (1.8% vs. 0.6%). Moreover, Min and colleagues reported that predictors of all-cause mortality were directly related to the number of coronary plaques, severity of stenosis and the number of vessels involved, especially the LAD.<sup>25</sup> In contrast, patients with non-obstructive disease had an overall survival of 99.7%. Given that 24% of patients with CAD in our study had obstructive disease and most had double or triple vessel disease affecting the LAD, this may place the morbidly obese population at increased risk for future cardiac events.

Coronary computed tomographic angiography may also be used in conjunction with Framingham risk stratification to intensify therapy to potentially prevent clinical disease. Hadamitzky *et al.*<sup>24</sup> reported that the event rate was significantly lower in patients with non-obstructive disease and higher in obstructive disease compared to the predicted Framingham risk scores. Although CCTA is promising and currently utilized in symptomatic patients, contemporary guidelines do not recommend screening asymptomatic patients.<sup>26</sup>

Diabetes has been shown to be significantly related to an increased CAC burden in both men and women. Moreover, previous studies have shown that diabetes is an independent risk factor for higher CAC scores as well as its progression.<sup>27</sup> Using CCTA, Iwasaki *et al.* reported increased coronary plaques and overall stenosis in asymptomatic diabetic patients compared with their non-diabetics counterparts.<sup>28</sup> These observations are in agreement with our findings. However, since 11 patients in the CAD group (44%) had diabetes compared to only 1 patient in the non-CAD group (6%), we cannot exclude the confounding effect of diabetes on our patient population.

Plaque morphology has also been proposed as an important determinant of subclinical CAD<sup>29</sup> and a predictor of acute coronary syndromes.<sup>30</sup> Hausleiter *et al.* observed that 29.8% of their patient population (mean BMI 26.3 kg/m<sup>2</sup>, mean age 61 yrs, 14.8% diabetic) had non-calcified plaques and that these subjects had higher levels of total cholesterol, low-density lipoprotein and C-reactive protein levels.<sup>29</sup> Of those patients with CAD in our study, 75.4% had non-calcified plaques and most had hyperlipidemia (68%) as well. Motoyama *et al.* studied the plaque composition of 1,059 subjects who underwent CTA<sup>30</sup> and reported that low-attenuation non-calcified plaques ( $\leq 30$  HU) and vascular remodeling were predictors of acute coronary syndromes. Although we did not calculate a remodeling index, we noted that almost half (46.5%) of the plaques identified in the CAD cohort were low-attenuation and non-calcified. Identification of such low-attenuation non-calcified plaques may place this population at higher risk for future cardiac events. Although this is an emerging feature of CCTA, no consensus has been reached with regards to plaque characterization using CCTA since additional data are required.<sup>26</sup>

To our knowledge, this is the first study to describe the extent and severity of CAD using CCTA in young morbidly obese individuals with subclinical disease. Previous CCTA studies have evaluated the extent of coronary stenosis in non-obese patients<sup>31</sup> or in those with diabetes.<sup>28</sup> Choi *et al.* recruited 1,000 asymptomatic middle aged subjects (BMI 24.1 $\pm$ 2.7 kg/m<sup>2</sup>, age 50 $\pm$ 9 yrs, 7.3% diabetic, 14.1% hyperlipidemia) who underwent CCTA as a general screening evaluation and reported that 215 patients (22%) had coronary plaques and only 5% had obstructive disease.<sup>31</sup> Moreover, most patients (73%) had single vessel disease and a CAC=0 (82.5%). Although we cannot directly compare these findings with our own, morbidly obese subjects in our study had almost three times greater CAD identified, and up to five times more obstructive disease. In addition, most morbidly obese subjects in our study had multi-vessel disease and a CAC>0. However, our population had a higher preva-

lence of diabetes (29% vs. 7%).

Although CTA is an attractive non-invasive method for screening patients for subclinical CAD, it cannot be recommended until standardized techniques for image acquisition are defined which allow an acceptable radiation profile in this population. In the current study, patients received a relatively high radiation dose (average 22 $\pm$ 4.4 mSv) which may be an underestimation, given recent studies.<sup>32</sup> However, employing advanced scanning techniques such as voltage modulation,<sup>33</sup> prospective gating<sup>34</sup> and volume scanning<sup>32</sup> the effective radiation dose can be potentially reduced without compromising coronary assessment and diagnostic accuracy. Whether these techniques will be applicable to the morbidly obese population is still to be determined given that increased weight is an independent factor for increasing dose length product or DLP.<sup>35</sup>

### Study limitations

The primary limitations of this study are the small sample size and the lack of a control group of normal weight participants. Despite the high accuracy of CCTA in both normal weight and moderately obese patients, comparison of CCTA in morbidly obese individuals with conventional coronary angiography is required.

### Conclusions

The main finding of this preliminary study was that CCTA identified 61% of morbidly obese patients as having CAD and most individuals had a CAC >0. Of the coronary segments studied, the LAD was the most common artery affected, as well as the site of greatest stenosis and CAC burden. Although most patients had non-obstructive CAD, 24% of these patients had at least one obstructive coronary artery lesion. An increasing calcium score also correlated with a greater severity of disease in each coronary vessel. Lastly, the LAD contained the majority of both calcified and non-calcified plaques, although the latter predominated.

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