

# Prone-position computed tomography in the late phase for detecting intracardiac thrombi in the left atrial appendage before catheter ablation for atrial fibrillation

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## Abstract

**Background:** Contrast computed tomography (CT) is a useful tool for the detection of intracardiac thrombi. We aimed to assess the accuracy of the late-phase prone-position contrast CT (late-pCT) for thrombus detection in patients with persistent or long-standing persistent atrial fibrillation (AF). **Methods:** Early and late-phase pCT were performed in 300 patients with persistent or long-standing AF. If late-pCT did not show an intracardiac contrast defect (CD), catheter ablation (CA) was performed. Immediately prior to CA, intracardiac echocardiography (ICE) from the left atrium was performed to confirm thrombus absence and the estimation of the blood velocity of the left atrial appendage (LAA). For patients with CDs on late-pCT, CA performance was delayed, and late-pCT was performed again after several months following oral anticoagulant alterations or dosage increases. **Results:** Of the 40 patients who exhibited CDs in the early phase of pCT, six showed persistent CDs on late-pCT. In the remaining 294 patients without CDs on late-pCT, the absence of a thrombus was confirmed by ICE during CA. In all six patients with CD-positivity on late-pCT, the CDs vanished under the same CT conditions after subsequent anticoagulation therapy, and CA was successfully performed. Furthermore, the presence of residual contrast medium in the LAA on late-pCT suggested a decreased blood velocity in the LAA ([?] 15 cm/s) (sensitivity = 0.900 and specificity = 0.621). **Conclusions:** Late-pCT is a valuable tool for the assessment of intracardiac thrombi and LAA dysfunction in patients with persistent or long-standing persistent AF before CA.

## Introduction

Atrial fibrillation (AF) is among the major risk factors for intracardiac thrombi that can lead to cerebral or systemic embolism.<sup>1</sup> The majority of intracardiac thrombi are formed inside the left atrial appendage (LAA) due to turbulence and lower blood flow rates, particularly during AF.<sup>2,3</sup> Meanwhile, catheter ablation (CA) has become the first AF treatment choice in the last few decades. Prior to CA, when a thrombus is present in the LAA, safety evaluations must be performed, particularly in patients with persistent or long-standing

persistent AF. Although the gold standard for the detection of intracardiac thrombi is transesophageal echocardiography (TEE), this method is associated with occasional technical and appraisal difficulties.

Contrast computed tomography (CT) is another standard method used for the detection of intracardiac thrombi and has the potential to replace TEE. Compared to TEE, CT is easier to perform and is related to lower levels of discomfort among physicians. Additionally, the level of difference observed in the evaluation of CT images is much lower than that in TEE. However, similar to TEE, CT can still show false-positive results under conditions of low blood flow or stasis in the LAA. In these situations, the contrast medium hardly fills the whole LAA, particularly the edge of LAA, at the time of CT. Some reports have shown that CT performed in the prone position is more useful in the differentiation of thrombi from stasis than scans performed in the supine position, as gravity can increase the spread of contrast dye into the top area of the LAA.<sup>4,5</sup> It has been suggested that contrast CT conducted in the delayed or late phase yields improved accuracy in the detection of thrombi than that performed in the early phase.<sup>6-8</sup> However, neither method is completely exclusive of false-positive results, and there is currently no known method that combines late-phase contrast CT and prone-position contrast CT (late-pCT) in this setting.

Therefore, with the aim of minimizing the rate of false-positive results, we sought to investigate the diagnostic accuracy of late-pCT in the detection of thrombi in the LAA among patients with persistent or long-standing persistent AF prior to CA and re-evaluated the LAA by intracardiac echocardiography (ICE) during CA.

## Methods

### *Study population*

Patients with persistent or long-standing persistent AF who were scheduled for CA and enrolled at the Japan Red Cross Yokohama City Bay Hospital from January 2018 to July 2020 were included in this study. Patients were excluded if they had an allergy to the contrast agent, renal dysfunction, or severe mitral valve disease, or were intolerant to oral anticoagulants. All patients were prescribed oral anticoagulants for at least 4 weeks prior to the CA procedure. The study protocol was approved by the ethics committee of the Japan Red Cross Yokohama City Bay Hospital, and written informed consent was obtained from all the participants before study initiation.

### *CT protocols and image analysis*

CT was performed within the 3 weeks before CA. Early and late-phase cardiac CT was conducted in the prone position using a 128-section helical CT scanner (Somatom Definition AS, Siemens Healthcare GmbH, Erlangen, Germany). Contrast material (Iopamiro®, 370 mg of iodine/ml, Bracco Imaging, Milan, Italy) was injected intravenously at a dose of 25.9 mg/kg body weight/s for 12-14 s. Early-phase prone-position CT (early-pCT) was initiated 5 s after the region of interest in the ascending aorta reached 160 Hounsfield units. Late-pCT was started 30 s later. Once the contrast was visualized, a breath-hold instruction was provided to the patient, and CT was initiated. After CT, the patients were observed for at least 15 min for the detection of any contrast medium-related side effects, such as a rash, nausea, or abnormal blood pressure. Three-dimensional CT images were reconstructed for the left atrium (LA) and LAA. All CT images were reviewed by two experienced cardiologists and one radiologist.

If no contrast defect (CD) was observed in the LAA by late-pCT, CA was performed as planned. If CDs were detected only during early-pCT but not late-pCT, CA was performed on schedule. The performance of CA was postponed in patients with CDs who were found on late-pCT; in these patients, we changed or increased the anticoagulant dose and performed a careful follow-up at our outpatient clinic. CT angiography was repeated after several months of altered anticoagulation therapy. If the subsequent late-pCT revealed the absence of CDs in the LAA, CA was performed.

### *CA and ICE*

All the patients were administered oral anticoagulants more than 3 weeks before CA. Novel oral anticoagulants other than dabigatran were changed to dabigatran on the day of surgery and the day following CA. If

the anticoagulants used were dabigatran or warfarin, their intake was continued throughout the perioperative period. CA was performed under general anesthesia. Activated clotting time (ACT) was measured using blood samples obtained venously every 15-30 min during the procedure; this value was maintained at 300-350 s using unfractionated heparin. An ICE probe (ViewFlex Xtra ICE catheter, Abbott Laboratories, Illinois, USA or ACUSON AcuNav, Johnson and Johnson, New Jersey, USA) was inserted from the right or left femoral vein through a long sheath (SL0, Abbott Laboratories, Illinois, USA). After the transseptal approach, we placed the ICE probe in the LA, and the probe was turned to scan the entire LA and LAA before CA performance in the LA. The LAA was visualized from the body of the LA. If there was no thrombus in the LAA, CA was performed. Meanwhile, if a thrombus was suspected on ICE, CA in the LA was abandoned. The thrombi evaluated by ICE were defined as circumscribed and uniformly echo-dense intra-cavity masses distinct from the underlying endocardium and pectinate muscles.

Using the ICE probe, the velocity of blood flow was estimated inside the LAA. These data were obtained using pulse-Doppler imaging. Sample volumes were positioned within 1 cm of the orifice of the LAA and the velocities were assessed during AF. The peak emptying velocities of the LAA were averaged over a minimum of five consecutive cardiac cycles (with each R-R interval).<sup>9</sup>

Three-dimensional CT (3DCT) of the LA was made of images of early-pCT for LA reconstruction. These LA images were merged with a 3D mapping system during CA.

We also assessed the presence of symptomatic stroke events during the perioperative period.

#### *Analysis of parameters*

Data on the following parameters were analyzed: baseline clinical characteristics, the type of oral anticoagulants used, congestive heart failure, hypertension, diabetes, previous stroke/transient ischemic attack-vascular disease, age, sex, and the CHA<sub>2</sub>DS<sub>2</sub>-VASc score. The morphology of the LAA obtained from 3DCT was classified into the following four types: cactus, cauliflower, chicken-wing, and windsock, as previously reported.<sup>10</sup>

#### *Statistical analysis*

Data are presented as mean  $\pm$  standard deviation. The two-tailed Welch's *t*-test was used for the comparison of non-parametric variables between the groups. Fisher's exact test was used to evaluate the differences in the categorical variables between the groups. A P-value  $< 0.05$  was considered significant.

### **Results**

During the study period, 300 patients with persistent or long-standing persistent AF were enrolled. Table 1 presents their baseline characteristics.

#### *Computed tomography and CA*

CT was performed during the AF rhythm and ICE was used to visualize the LAA in all the patients. No CD was found in both the early and late phases in 260 patients (86%). Of the 40 patients who exhibited CDs on early-pCT, 34 (11%) did not have them during the late phase (Figure 1). The average dose length product was  $2166.22 \pm 224.27$  mGycm, which of those only in the early phase was  $1084.88 \pm 114.25$  mGycm and those in the late phase was  $1031.34 \pm 133.46$  mGycm. The total contrast medium which used for CT scanning was  $1810.46 \pm 384.95$  mg of Iopamiro.

Among the 294 patients without a CD on late-pCT, CA was performed on schedule. The absence of thrombus was reconfirmed using ICE performed from the LA (Table 2). In one patient, the LAA could not be visualized clearly from the body of the LA. The ICE was inserted into the left superior pulmonary vein, which enabled to observe the whole LAA.

CDs existed in both the early and late phases of pCT in the remaining six patients (2%, Figures 2A and 2B). None of the patients showed CDs only on late-pCT. There CDs were located at the entrance of the LAA in 1, outer edge in 2, inner edge in 2 and the residual LAA portion after LAA clipping in 1. In these six patients, CA was cancelled, and the type of anticoagulant was changed or the dose was increased in the case of warfarin

use. Follow-up CT was performed after 3-7 months. We observed CD disappearance on subsequent late-pCT under the same CT conditions (Figure 2C); following this, CA was performed. The absence of thrombi was confirmed using ICE in all six patients. Among them, four patients were also performed TEE after the CT scanning, and thrombi were observed in all patients. One of six patient with CDs in both the early and late phases required two changes in the anticoagulant used for CD disappearance (Figure 3); in the remaining five patients, the anticoagulant type was altered once.

In the whole population, six patients had also undergone CT in the supine position (sCT) within 3 days before pCT and CD presence was suspected. These CDs disappeared on late-pCT in three patients (Figure 4) and no thrombus was detected on ICE during CA, as mentioned previously.

ICE imaging was performed during the AF rhythm in all patients. The average duration between first CT scanning to catheter ablation was  $9.4 \pm 7.5$  days. The first subsequent CT in patients with CDs was performed in median 68 (38-131) days, and for one patient, another CT was needed for the disappearance of a contrast defect 58 days after second CT scanning (Figure 3D). None of the patients had complications related to CT, and no symptomatic stroke events were observed during the perioperative period of CA.

#### *Residual contrast material in the LAA*

Of the 300 patients, 48 (16%) showed residual contrast medium in the LAA during late-pCT (Figures 1B, 2B, and 2C). Table 3 presents the results of the comparison of the clinical features of the patients with and without residual contrast material in the LAA during late-pCT. There was no significant difference in the distribution of the LAA morphology types between the groups. The presence of residual contrast was significantly associated with a higher CHAD<sub>2</sub>S<sub>2</sub>-VASc score, an enlarged left atrial diameter, a decreased left ventricular ejection fraction, an increased brain natriuretic peptide level, and the presence of CDs, as detected on early or late-pCT. In addition, the blood velocity in the LAA during AF was much lower in the group with residual contrast medium.

Figure 4 shows the receiver operating characteristic (ROC) curve analysis of the LAA emptying velocity and its influence on residual contrast medium in the LAA. The presence of residual contrast medium in the LAA suggested a reduced blood velocity [?] 15.0 cm/s in the LAA, as estimated on ICE performed from the LA.

### **Discussion**

In the present study conducted among patients with persistent or long-standing persistent AF: 1) the negative predictive value for thrombi using late-pCT was 100% as a reference of ICE, 2) all the CDs detected by late-pCT disappeared on subsequent late-pCT after several months under an altered anticoagulation therapy regime, and 3) the presence of residual contrast medium in the LAA on late-pCT was suggested to lower the blood velocity in the LAA to a value lower than 15cm/s.

In our study, CDs were observed on late-pCT in 2% of the patients, and despite the presence of CDs on early-pCT, 85% of the patients showed CD disappearance on late-pCT. In the patients without CDs on late-pCT, thrombus absence was confirmed on ICE performed from the LA. All the CDs observed on late-pCT vanished after the administration of altered anticoagulant therapy for several months under the same CT conditions.

#### *CDs observed on late-pCT*

For many years, TEE was the first choice for the detection of thrombi in the LAA; the technique shows a high sensitivity of 93.3-100% and specificity of 99-100%.<sup>11,12</sup> However, the performance of TEE can prove difficult or may be impossible in some patients, such as those who experience pain on probe insertion even under anesthesia or those with anatomical abnormalities. The overall TEE complication rate is 0.18-2.8%, inclusive of a mortality value of 0.01-0.02%, laryngospasm rate of 0.14%, dysphagia rate of 1.8%, hoarseness rate of 12%, and dental injury rate of 0.1%.<sup>13</sup> In addition, patients who have experienced difficulties in association with TEE may be unwilling to undergo the procedure again. Moreover, TEE has been shown to be associated with a heightened risk of severe acute respiratory syndrome coronavirus 2 transmission

during the ongoing novel coronavirus disease pandemic. Therefore, there is a need for another detection tool with a high accuracy. Cardiac CT performed in the delayed phase has been established as a reliable alternative to TEE in the detection of thrombi, with a sensitivity of 96% and specificity of 92%.<sup>6</sup> In the absence of contraindications to the contrast medium used, CT is non-invasive and associated with a lower level of differences in the evaluation of results and rarely leaves a bad impression on patients.

Although the detection of thrombi using contrast CT exhibits excellent negative predictive values (99-100%), the positive predictive value is still low, at 13-31%.<sup>14-16</sup> This may be attributed predominantly to difficulties in distinguishing real thrombi from circulatory stasis in the LAA, particularly at a low blood velocity. The discrimination between thrombi and circulatory stasis is more crucial in patients with persistent or long-standing AF than in those with paroxysmal AF; in the former population, 28% of patients showed CDs on sCT in the early phase and as a reference of TEE or ICE, the positive and negative predictive values were 40.7% and 100%, respectively.<sup>17</sup> On the other hand, in patients with paroxysmal AF, the assessment of thrombi using either TEE or CT is not difficult, owing to a high blood flow rate during the sinus rhythm and lower degree of LAA dysfunction. Although delayed or late-phase CT reportedly improves the accuracy of the detection of thrombi and significantly increases the positive predictive value to up to 92% from 41%,<sup>8</sup> the value is still <100%. Several case reports have shown that a shift from the supine to the prone position allows for successful thrombus classification.<sup>18, 19</sup> Notably, Kantarci et al. reported that pCT was associated with a positive and negative predictive value of 100%.<sup>4</sup> Nevertheless, in the present study, early-pCT did not exclude all thrombi, and in some persistent or long-standing AF patients, a CD detected on early-pCT scan disappeared on late-pCT. In three of our participants, only late-pCT showed CD absence, unlike in the case of sCT or early-pCT, and thrombus absence was confirmed by ICE. In minimizing or nullifying the false-positive rate, the performance of late-pCT is the most ideal. Among patients with a CD on late-pCT, we did not perform TEE simultaneously for thrombus confirmation; therefore, we could not determine the presence of true thrombi. Regarding the resolution of CDs on CT, Gottlieb et al suggested that a patient with atrial fibrillation and newly stroke showed CDs on CT and diagnosed as thrombi on TEE.<sup>20</sup> After several months with warfarin controlled with higher INR, CDs were disappeared on CT and no thrombus was confirmed on TEE. Likewise, all the CDs in this study disappeared or changed the shape of that following anticoagulant type alterations or increases in doses, indicating that the CD was most likely a thrombus. Notably, CDs detected by late-pCT were diagnosed as thrombi in all 4 patients who could be performed TEE.

Kawaji et al. presented some data on the effectiveness of late-pCT in thrombus detection.<sup>5</sup> They performed late-pCT only in patients with incomplete filling of the contrast medium in the LAA or a filling defect, as observed on early sCT. It was necessary for the radiographers to perform prompt screening to assess the need for additional late-phase CT. Furthermore, additional CT was performed in patients in both the supine and prone positions, pointing to substantial exposure to radiation. However, in our study, we performed early and late-phase contrast CT only in the prone position, which required as much radiation exposure as the previous study of patients without a detectable CD in the early phase, although there was no requirement for stationed physicians for the quick determination of CD presence in the LAA. Moreover, the protocol of pCT scanning was simpler and there was no timing shift due to re-positioning.

In this study, ICE was used as a reference for the detection of thrombi in patients without CDs on late-pCT. For these days, ICE has been proved to be a valid tool for the diagnosis of intracardiac thrombi and sometime been superior to the TEE. Anter et al showed that TEE and ICE were performed simultaneously in 71 patients and 4 thrombi were detected.<sup>21</sup> Among them, all were visualized on ICE but 1 on TEE. The difference of visibility between TEE and ICE was also argued by Sriram et al that clear definition and complete visualization of the LAA were achieved in 99 and 100% using TEE and ICE in 122 patients with AF.<sup>22</sup> ICE identified a thrombus in 7 patients with a previous negative TEE, and in 2 patients, TEE could not rule out a thrombus within the LAA due to spontaneous echo contrast. Which was subsequently shown to be pectinate muscles, not a thrombus, on ICE. Furthermore, Ikegami et al exhibited that four of 97 patients with persistent or long-standing persistent AF who did not exhibit thrombi on TEE revealed a thrombus on ICE; following this, the CA procedure was cancelled.<sup>17</sup> From these points, the efficacy of ICE was deemed as being superior to that of TEE in thrombus detection.

However, the LAA could be observed using ICE from the right atrium in only 71% of the 970 patients.<sup>23</sup> To achieve the clear visualization of the LAA, it is a key to place the ICE probe close to the LAA as possible. Although the utility of ICE from the PA was reported compared to the RA or right ventricular outflow tract (RVOT), it is sometimes difficult to advance the ICE probe to the RVOT and above PA and a risk for pericardial effusion.<sup>24</sup> Therefore, we inserted the ICE probe into the LA closer to the LAA. In one patient, the LAA could not be clearly described from the body of the LA and we moved the ICE probe to the left superior pulmonary vein. As a result, the LAA could be clearly described in all 300 of our patients.

### *Residual contrast medium in the LAA*

The prone position tends to lead to the congestion of contrast medium due to the influence of gravity. Therefore, in patients with impaired LAA function, the contrast agent may not be completely removed from the LAA even in the late phase of contrast CT. The presence of residual contrast medium in the LAA during late-pCT indicated the presence of LAA dysfunction. Patients with AF and an LAA blood flow velocity <20 cm/s, as estimated by TEE, have 2.6 times the risk of ischemic stroke compared to those with a higher LAA velocity.<sup>25</sup> Moreover, the presence of spontaneous echo contrast (SEC) in the LA or LAA on TEE is related to thrombus formation and LAA velocities < 20–25 cm/s.<sup>25,26</sup> Although CT cannot aid in the measurement of the exact LAA velocity or SEC in the LA or LAA, our study suggested that the presence of residual contrast medium in the LAA during late-pCT was associated with a LAA velocity [?] 15 cm/s. This cutoff value was lower than that for TEE. Therefore, the presence of residual contrast medium on late-pCT implies a higher risk for thrombotic events.

### **Study limitations**

Our study has several limitations that should be noted. First, it did not have a randomized, single-center design. Second, CT and ICE were not performed on the same day; therefore, the presence of changes in the thrombus or blood circulation status cannot be ruled out. Third, ICE could be performed only in patients without CDs on late-pCT. In addition, further examination of thrombi using TEE was performed in 4 of 6 patients with CDs. Forth, the 3DCT model from the CA procedure was reconstructed from CT images obtained in the prone position. Although 3DCT did not cause any issues throughout the CA procedure, there may be differences in the 3DCT images of the LA between those obtained in the prone and supine positions.

### **Conclusions**

Late-pCT was highly useful in the assessment of intracardiac thrombi in patients with persistent or long-standing AF before CA. Compared to TEE, CT was noninvasive and reproducible, and associated with a significantly lower degree of differences in the evaluation performed by physicians. The presence of residual contrast medium in the LAA, as detected on late-pCT, is indicative of a low blood velocity.

### **Conflict of interests**

None.

### **Data availability statement**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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**Table 1.** Patients' baseline characteristics

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AF, atrial fibrillation; BNP, brain natriuretic peptide; LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

**Table 2.** Inspection flow of CT and ICE during catheter ablation

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In total, 263 patients exhibited no contrast defect (CD) by prone-position contrast computed tomography (pCT), and catheter ablation for atrial fibrillation was subsequently performed. At that time, no intracardiac thrombus was found on intracardiac echocardiography (ICE). A CD observed only during pCT in the early phase was found in 34 patients, but not during pCT in the late one; these patients showed no thrombi due to ICE during ablation. The remaining six patients had CD in both the early and late phases of pCT. They did not undergo catheter ablation, and pCT was conducted after several months of altered or increased oral anticoagulation (OAC) therapy. Thereafter, all six patients showed no CD on pCT in the late phase, and no thrombus was observed using ICE.

**Table 3.** Clinical characteristics of patients with and without residual contrast medium in the left atrial appendage

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CD, contrast defect; early-pCT, early-phase prone-position contrast CT; late-pCT, late-phase prone-position contrast CT; BNP, brain natriuretic peptide; LAA, left atrial appendage LAD, left atrial diameter; LVEF, left ventricular ejection fraction.

#### Figure Legends

**Figure 1.** Difference in the contrast defects (CDs) on computed tomography between the early and late phases.

A CD (arrow) was seen on top of the left atrial appendage in the early phase (A), which was replaced with contrast medium in the late phase (D, arrowhead).



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**Figure 2.** Change in contrast defects (CDs) by altered oral anticoagulant therapy.

Contrast computed tomography (CT) in the prone position was performed in the early (A) and late phases (B). Both images showed CDs. We changed the oral anticoagulant from edoxaban to rivaroxaban, and three months later, subsequent CT showed the disappearance of the CD, and residual contrast was observed along the margin of the left atrial appendage under the same CT conditions (C). Arrows show CDs, and arrowheads show residual contrast.

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**Figure 3.** Contrast defect (CD) after left atrial appendage (LAA) closure.

The patients had undergone clipping of LAA during coronary artery bypass graft surgery. There remained an LAA portion between the site of the LAA clipping and entrance of the LAA after the surgery. CDs were observed with contrast computed tomography (CT) in both the early (A) and late phases (B) at the left atrial side of the LAA closure. The anticoagulant was switched from rivaroxaban to dabigatran, and 38 days later, the subsequent late-phase prone-position contrast CT (late-pCT) showed a much larger CD in the same area as the LAA (C). Then, we changed the agent to warfarin, and finally, the CD vanished on late-pCT 58days after second CT scanning (D). Arrows show CDs.

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**Figure 4.** Contrast defect (CD) changes in association with the CT position and scanning phase.

This patient was administered apixaban for more than 3 months for persistent atrial fibrillation. Contrast computed tomography (CT) in the supine position was performed, and a CD was detected in both the early and late phases (A, B). The patient was intolerant to transesophageal echocardiogram due to difficulties in swallowing the echo probe. A week from CT performed in the supine position, CT in the prone position was performed under the same anticoagulant type and dose conditions. A CD was only detected using CT in the early phase (C), but not in the late phase (D). Arrows show CDs, and arrowheads show residual contrast.

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**Figure 5.** Receiver operating characteristic curve analysis of the left atrial appendage (LAA) blood velocity depending on the presence of residual contrast medium in the LAA.

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The cutoff value of residual contrast medium in the LAA during late-phase contrast computed tomography in the prone position was 15.0 cm/s. The sensitivity and specificity were 0.900 and 0.621, respectively. AUC, area under the curve.

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