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# Chapter 5

## Impact of coronary artery disease on the efficacy of radiofrequency catheter ablation for atrial fibrillation

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## Abstract

Background: Coronary artery disease (CAD) has been associated with the development of atrial fibrillation (AF). However, little is known about the impact of CAD on the outcome treatment of AF. The aim of this study was to investigate the impact of CAD on the efficacy of radiofrequency catheter ablation (RFCA) for AF using multi-detector row computed tomography (MDCT).

Methods: In 125 consecutive patients undergoing RFCA for AF, a pre-procedural MDCT examination (coronary angiography and/or coronary calcium score) was performed to evaluate the presence and severity of CAD. Furthermore all patients underwent a comprehensive echocardiographic evaluation to measure the left atrial size and to rule out structural heart disease. After RFCA all patients were regularly evaluated at the outpatient clinic.

Results: After a mean follow-up of  $12 \pm 3$  months, 78 patients (62%) had maintained stable sinus rhythm and 47 patients (38%) had recurrence of AF. Left atrial volume index was a significant predictor of AF recurrence after RFCA. Presence of CAD on MDCT did not influence the efficacy of RFCA for AF.

Conclusions: The presence of CAD on MDCT is not associated with a higher risk for AF recurrence after RFCA.

## Introduction

Coronary artery disease (CAD) is one of the underlying mechanisms of atrial fibrillation (AF) in Western countries.<sup>1</sup> Coronary artery disease leads to myocardial ischemia, left ventricular dysfunction and elevated left atrial pressures that may induce ultra-structural changes within the atrial myocardium. These changes form the arrhythmogenic substrate for AF.<sup>2</sup>

Radiofrequency catheter ablation (RFCA) is a curative treatment option which is currently reserved for patients with symptomatic drug refractory AF.<sup>3</sup> The cornerstone of most RFCA strategies is pulmonary vein isolation.<sup>3</sup> However, in patients with a high extent of atrial remodeling, in part caused by CAD, elimination of pulmonary vein triggers may not be sufficient to cure AF. Little is known about the impact of CAD on the efficacy of RFCA for AF.<sup>2</sup>

Multi-detector computed tomography (MDCT) is frequently performed prior to RFCA for AF in order to plan and guide the ablation procedure. MDCT provides information about the number and location of pulmonary veins draining into the left atrium and also permits evaluation of CAD.<sup>4,5</sup> Therefore, MDCT provides information on one of the underlying mechanisms related to AF. The aim of this study was to investigate the impact of significant and non-significant CAD on the efficacy of RFCA for AF.

## Methods

### Patient population and evaluation

The population comprised a cohort of consecutive patients undergoing RFCA for symptomatic drug-refractory non-valvular AF. Prior to the ablation, all patients underwent transthoracic echocardiography to assess left atrial size, left ventricular systolic function and to exclude valvular heart disease. Moreover, all patients underwent, according to the clinical protocol, an MDCT

examination in order to obtain anatomical information to guide the ablation procedure and to exclude significant CAD. After RFCA, all patients were regularly evaluated at the outpatient clinic during a 12 months follow-up period. Electrocardiogram (ECG) recordings were acquired each visit and 24-hour ECG Holter registrations were scheduled after 3, 6 and 12 months follow-up. Importantly, all patients were encouraged to immediately obtain an ECG registration when experiencing palpitations. All medications were continued for at least 3 months. Afterwards, anti-arrhythmic drugs were discontinued at the discretion of the physician. After a blanking period of 3 months, recurrence of AF was defined as any recording of AF on ECG or an episode longer than 30 s on 24-hour ECG Holter registration. All clinical, MDCT and echocardiographic data were prospectively collected in the departmental cardiology information system (EPD-Vision®) and echocardiographic database and were retrospectively analysed.

### Echocardiography

Two-dimensional transthoracic echocardiography was performed using a commercially available ultrasound system (Vivid 7 and E9, General Electric Vingmed, Milwaukee, WI), equipped with a 3.5-MHz and 5S transducers. All patients were imaged in left lateral decubitus position. Two-dimensional and color Doppler data were obtained in the parasternal short- and long-axis views and the apical 2- and 4-chamber views, adjusting gain settings and depth. All images were ECG-triggered and stored in cineloop format for off-line analyses (EchoPac 111.0.00, General Electric – Vingmed). Maximum left atrial volume was obtained from the apical 4- and 2-chamber views by disc's method and indexed to body surface area.<sup>6</sup> Left ventricular ejection fraction was calculated from the standard apical 2- and 4-chamber views by Simpson's method, according to the American Society of Echocardiography guidelines.<sup>6</sup>

## Multi-detector row computed tomography

### *Data acquisition*

MDCT scanning was performed using a Toshiba Aquilion ONE system (Toshiba Medical Systems, Otawara, Japan) with 320 detector rows, each 0.50 mm wide. One hour prior to the examination, an oral beta-adrenergic blocking agent (metoprolol 50-100 mg) was administered if the heart rate was above 65 beats per minute, unless contra-indicated. In patients with a heart rate above 65 beats per minute on arrival to the scanner an additional bolus of intravenous beta-blocking agent was administered (metoprolol 2.5-10 mg), unless contra-indicated. Before computed tomography angiography (CTA), a non-enhanced low-dose scan was performed to measure the coronary calcium score (CCS). The CCS-scan was prospectively triggered at 75% of R-R interval using a single-rotation-wide volume acquisition (slices reconstructed to 3 mm) with a gantry rotation time 350 to 500 ms, tube voltage 120 kV, and tube current 200 to 250 mA. In patients with a heart rate above 65 beats per minute the CCS-scan was prospectively triggered at 45% of R-R interval. Next, CTA scanning was performed using prospective ECG triggering, imaging the entire heart in a single volume with a maximum of 16 cm cranio-caudal coverage. Tube voltage was adapted to body mass index (<23 kg/m<sup>2</sup>: 100 kV, 23–35 kg/m<sup>2</sup>: 120 kV, >35 kg/m<sup>2</sup>: 135 kV) and tube current varied between 400–580 mA, depending on body weight. Contrast material was administered in a triple-phase protocol: first a bolus of 60 ml, followed by 30 ml of a 50:50 mixture of contrast and saline, followed by saline flush with a flow rate of 5–6 ml/s (Iomeron 400, Bracco, Milan, Italy). Automatic detection of the contrast bolus in the left ventricle was used to time the start of the scan with a threshold of +180 Hounsfield units. Scanning was performed during inspiratory breath-hold. If the heart rate was stable and <60 beats per minute the phase window was set

at 70–80% of R-R interval, if the heart rate was 60–65 beats per minute the phase window was set at 65–85% of R-R interval and if the heart rate was >65 beats per minute the phase window was set at 30–80% of the R–R interval (using multiple beats). Images were reconstructed in the end-diastolic phase (75% of R–R interval) with a slice thickness of 0.50 mm and a reconstruction interval of 0.25 mm. If motion artefacts were present, multiple phases were reconstructed to obtain maximal diagnostic image quality. Afterwards, all datasets were exported, post-processed and analysed on a dedicated workstation (Vitrea FX 1.0, Vital Images, Minnetonka, MN, USA).

### *Image analyses*

The CCS was calculated using the Agatston method and patients were categorised as CCS=0, CCS=1-400, and CCS>400. Evaluation of the contrast-enhanced CTA datasets for the presence and severity of CAD was performed by 2 experienced investigators. All datasets were assessed as recommended by the Society of Cardiovascular Computed Tomography guidelines for the interpretation and reporting of CTA.<sup>7</sup> The coronary anatomy was determined using a standardized 17-segments model according to a modified American Heart Association (AHA) classification.<sup>8</sup> Each segment was scored as normal (no CAD), non-significant CAD (<50% luminal narrowing), significant CAD (>50% luminal narrowing) or uninterpretable using the axial slices with the assistance of multiplanar and curved multiplanar reconstructed images. Subsequently, vessel-based and patient-based analyses of the CTA were performed. In the vessel-based analysis, the left main was considered part of the left anterior descending coronary artery and the intermediate branch was considered part of the left circumflex coronary artery. If one segment was uninterpretable, an intention-to-diagnose strategy was applied. If more than one segment in a single vessel was uninterpretable, the vessel was considered to be of non-



diagnostic image quality. In the patient-based analysis, each CTA was classified as normal, non-significant CAD (<50% luminal narrowing) and significant CAD (>50% luminal narrowing). Similarly, if one vessel was uninterpretable, an intention-to-diagnose strategy was applied. If more than one vessel was uninterpretable, the entire examination was considered to be non-diagnostic.

### Radiofrequency catheter ablation

Radiofrequency catheter ablation was aimed at pulmonary vein isolation. The procedure was performed using either a non-fluoroscopic electroanatomical mapping system with a 3.5-mm quadripolar open-loop irrigated ablation catheter and a decapolar circular mapping catheter (CARTO XP™, CARTO Merge™, 7.5Fr Navistar, LASSO, Biosense Webster, Diamond Bar, CA, USA) or a non-irrigated multi-electrode catheter with a duty-cycled, unipolar-bipolar radiofrequency generator that allows independent delivery of energy to each of the electrodes (PVAC™, GENius™, Medtronic Ablation Frontiers LLC, Carlsbad, CA, USA). All patients received intravenous heparin to maintain an activated clotting time of 300-400 s. A single or double transseptal puncture was performed to gain entrance to the left atrium. Intracardiac echocardiography was used to safely guide transseptal punctures.

Using the CARTO system, circular lesions were created around the ipsilateral left and right pulmonary vein ostia. Radiofrequency current was applied at 30-35 W with a maximum temperature of 45°C and an irrigation flow of 20 ml/min until a bipolar voltage of <0.1 mV was achieved, with a maximum of 60 s per point. Using the PVAC system, all pulmonary veins were selectively isolated. The RFCA was delivered to the antral side of the pulmonary vein ostia. Special care was taken to avoid energy application inside the pulmonary veins. Radiofrequency current was applied at a maximum power of 8 W using a 4:1 bipolar/unipolar ratio and at 10 W using a 2:1 ratio for 60 seconds per

application. Power settings were automatically adjusted in order to reach a target temperature of 60 °C. The end-point of the procedure was pulmonary vein isolation as confirmed by recording entrance block during sinus rhythm or pacing from inside the coronary sinus.

### Statistical analysis

All variables were tested for a normal distribution with the Kolmogorov-Smirnov test. Continuous variables are presented as mean  $\pm$  SD and were **compared with the Student's t-test** for paired or unpaired data. Categorical variables are presented as number (percentage) and were compared with the chi-square test. The cumulative rate of AF recurrence after RFCA according to the presence or absence of significant CAD and the CCS were evaluated with the Kaplan Meier curves. Comparison of the cumulative event rates was performed using the log-rank test. Univariable Cox proportional hazard analyses were performed to investigate the impact of coronary artery disease and other clinical characteristics on the recurrence of AF after RFCA. All statistical analyses were performed with SPSS software (version 16.0, SPSS Inc., Chicago, IL, USA). A value of  $p < 0.05$  was considered statistically significant.

## Result

### Patient characteristics

A total of 125 patients (96 men [77%], mean age  $58 \pm 9$  years) undergoing a first RFCA procedure for drug refractory paroxysmal AF were included from an ongoing clinical registry.<sup>9</sup> The mean left atrial volume index was  $39.5 \pm 15.5$  ml/m<sup>2</sup> and AF was paroxysmal in 96 patients (77%) and persistent in 29 (23%), according to current guidelines definitions.<sup>10</sup> In 92 patients RFCA was performed using the CARTO-system and in 33 patients the PVAC-system was

used. The procedural end point of PV isolation was reached in all patients and no major procedural complications occurred. A more detailed description of the baseline characteristics is shown in Table 1 and Table 2.

Table 1. Baseline characteristics

	Population (n=125)
<b>Clinical characteristics</b>	
Age (years)	58 ± 9
Male gender, n (%)	96 (77)
Body Surface Area (m <sup>2</sup> )	2.08 ± 0.20
Duration of atrial fibrillation (months)	65 ± 53
Persistent atrial fibrillation, n (%)	29 (23)
Failed anti-arrhythmic drugs (n)	3.0 ± 1.1
Left atrial volume index (ml/m <sup>2</sup> )	39.5 ± 15.5
Left ventricular ejection fraction (%)	58 ± 7
<b>Medication</b>	
Statin, n (%)	39 (31)
Angiotensin-converting enzyme inhibitor, n (%)	18 (14)
Angiotensin II receptor antagonist, n (%)	40 (32)
Class IC anti-arrhythmic drug, n (%)	47 (38)
Class III anti-arrhythmic drug, n (%)	64 (51)

Prevalence of coronary artery disease assessed with multi-detector row computed tomography

Multi-detector row computed tomography coronary angiography was performed in a total of 100 patients. In the remaining 25 patients, CTA was not attempted because of AF with a high ventricular rate unresponsive to beta-adrenergic blocking agent prior to scanning. In 5 patients the CTA examination

was considered non-diagnostic. Significant CAD (>50% luminal narrowing in at least one vessel) was present in 22 patients (23%). A more detailed description of the CTA results is shown in Table 3.

Coronary calcium score was measured in a total of 121 patients. The total CCS was 0 in 52 patients (43%), 1-400 in 56 patients (46%) and >400 in 13 patients (11%).

Table 2. Risk factors coronary artery disease

	Population n=125
Risk factors coronary artery disease	
Smoking, n (%)	41 (33)
Hypertension, n (%)	45 (36)
Hypercholesterolemia, n (%)	36 (29)
Diabetes Mellitus, n (%)	7 (6)
Family history, n (%)	38 (30)
Known coronary artery disease, n (%)	
• Percutaneous coronary intervention, n (%)	5 (4)
• Coronary bypass surgery, n (%)	1 (1)
• Acute myocardial infarction, n (%)	2 (2)

Table 3. Prevalence and extent of coronary artery disease on computed tomography angiography

	Normal	Non-significant	Significant	Non-diagnostic
<b>Vessel-based analysis</b>				
Right	55 (55)	34 (34)	4 (4)	7 (7)
Left anterior descending	45 (45)	41 (41)	11 (11)	3 (3)
Left circumflex	57 (57)	32 (32)	5 (5)	6 (6)
<b>Patient-based analysis</b>	32 (32)	41 (41)	22 (22)	5 (5)

### Coronary artery disease and atrial fibrillation recurrence

After a mean follow-up of  $12 \pm 3$  months, 47 patients (38%) had experienced AF recurrence and 78 patients (62%) had maintained stable sinus rhythm. All patients remained stable and no coronary events were recorded during the follow-up. A repeat RFCA procedure was performed in 40 patients (32%). There was no difference in AF recurrence between patients with or without significant CAD on CTA (Figure 1, panel A). Moreover, the CCS on MDCT was similar in patients with and without AF recurrence (Figure 1, panel B). Figure 2 panel A illustrates the cumulative rates of AF recurrences after RFCA in patients with significant versus non-significant CAD. At 12 months follow-up, the incidence of AF recurrence was 32% in patients with significant CAD compared with 32% in patients without significant CAD (log-rank  $p=0.62$ ). In addition, when the patient population was divided according to the CCS, no differences were observed in the 12 month AF recurrence rate among the three groups of patients: 33%, 39% and 54% for patients with CCS 0, between 1-400 and  $>400$ , respectively (log-rank  $p=0.24$ ) (Figure 2 panel B). Univariable Cox proportional hazards analyses confirmed that there was no prognostic impact of significant CAD and CCS on the risk for AF recurrence after RFCA (Table 4). In contrast, left

atrial volume index was the only characteristic associated with a significantly higher risk for AF recurrence after RFCA (Table 4).

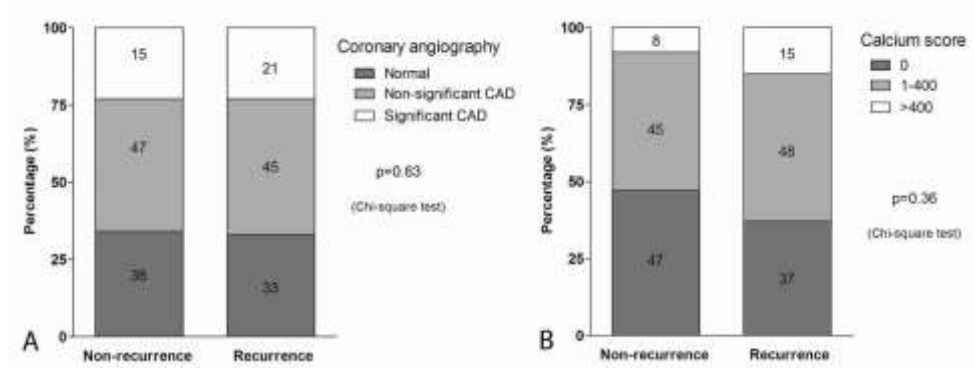


Figure 1. Panel A: Illustration of the distribution of normal findings during coronary angiography on multi-detector row computed tomography, non-significant coronary artery disease (CAD) and significant CAD among patients with recurrence of atrial fibrillation (recurrence) and patients that maintained sinus rhythm after radiofrequency catheter ablation (non-recurrence). Panel B: Illustration of the distribution of coronary calcium score on multi-detector row computed tomography divided into categories among patients with recurrence of atrial fibrillation (recurrence) and patients that maintained sinus rhythm after radiofrequency catheter ablation (non-recurrence).

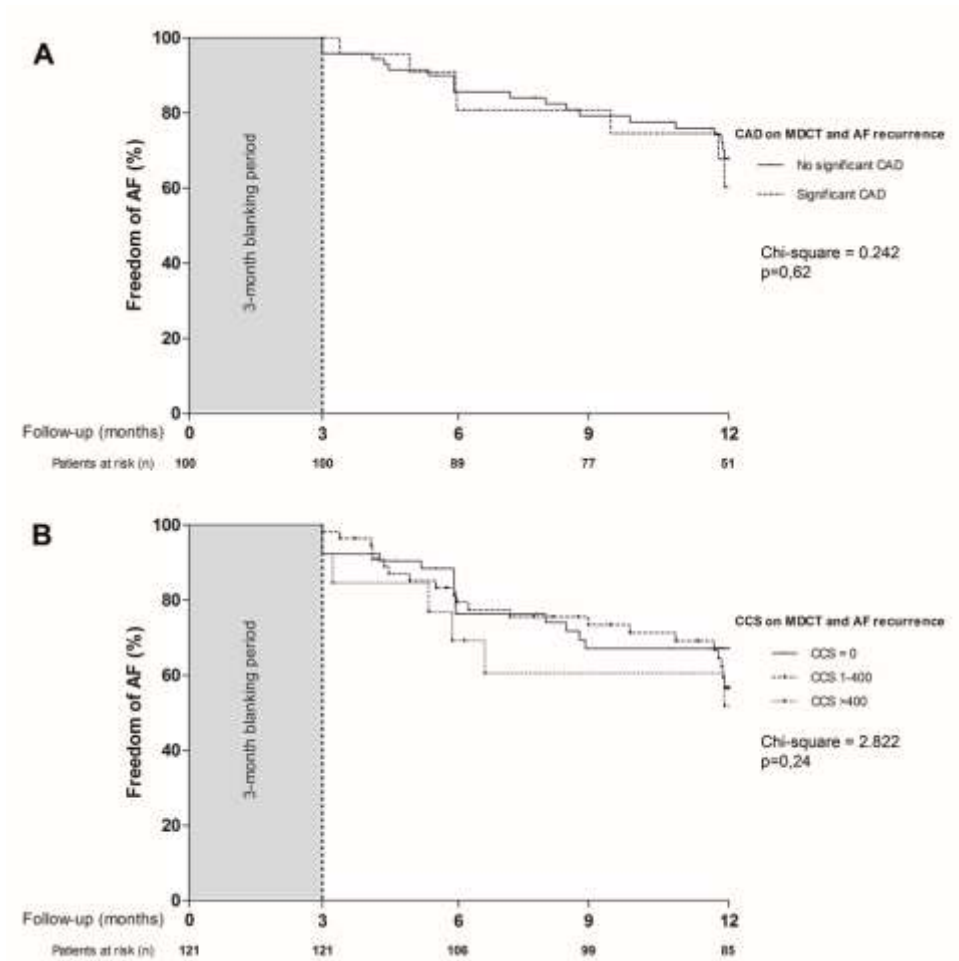


Figure 2. Kaplan Meier curve for freedom of atrial fibrillation (AF) after radiofrequency catheter ablation according to the presence or absence of significant coronary artery disease (CAD)(panel A) and coronary calcium score (CCS) divided in three categories (CCS=0, CCS 1-400 and CCS>400)(panel B).

Table 4. Cox univariable proportional hazard analyses of clinical and computed tomography characteristic to predict atrial fibrillation recurrence after catheter ablation

	HR	95% CI	P-value
Clinical characteristics			
Age (per year)	1.030	0.993-1.069	0.11
Male gender	1.381	0.641-2.973	0.41
Body Surface Area (per m <sup>2</sup> )	1.740	0.379-7.979	0.48
Duration of atrial fibrillation (per month)	1.001	0.943-1.064	0.96
Persistent atrial fibrillation	1.735	0.919-3.275	0.09
Hypertension	1.693	0.935-3.064	0.08
Left atrial volume index (per ml/m <sup>2</sup> )	1.017	1.003-1.032	0.018*
Left ventricular ejection fraction (per %)	1.006	0.964-1.051	0.77
Multi-detector row computed tomography			
• Significant coronary artery disease on angiography	1.238	0.527-2.903	0.62
• Coronary calcium score			
▪ > 0	1.584	0.836-2.999	0.16
▪ > 400	1.663	0.739-3.742	0.22



## Discussion

The present study investigated the impact of CAD on the efficacy of RFCA for AF. The main finding was that the presence of CAD was not a determinant of RFCA outcome. Moreover, there was no relationship between the CCS and the risk for AF recurrence after RFCA.

### Coronary artery disease and atrial fibrillation

Coronary artery disease has frequently been associated with the development of AF.<sup>1,2,5,11-13</sup> Both conditions are commonly present in the same group of patients and many risk factors predisposing for CAD are risk factors to develop AF.<sup>11,12</sup> However, it remains controversial whether there is a causal relationship between CAD and the development of AF.<sup>14</sup> Ischemic left ventricular dysfunction can increase left atrial pressures and eventually cause left atrial wall remodeling providing the substrate for AF.<sup>2</sup> However, the Manitoba follow-up study demonstrated that the impact of symptomatic ischemic heart disease on the development of AF was independent of the presence of congestive heart failure.<sup>13</sup> Importantly, these results imply that CAD can result in AF without causing left ventricular systolic dysfunction. Recently, Nishida et al. demonstrated that chronic occlusion of an atrial coronary branch in a canine model leads to increased atrial ectopy and conduction abnormalities that facilitate reentry.<sup>15</sup> These results imply that chronic atrial ischemia or an atrial infarction can provide the triggers and substrate needed to develop AF. However, the impact of CAD on the outcome of rhythm control therapies has not been elucidated so far.

## Coronary artery disease and the efficacy of radiofrequency catheter ablation

Radiofrequency catheter ablation is a curative treatment option for AF and is currently performed in an increasing number of patients.<sup>3,16</sup> The cornerstone of most ablation strategies is electrical isolation of the pulmonary vein region thereby preventing the ectopic beats originating from that area to trigger AF.<sup>3</sup> However, pulmonary vein isolation seems to be less effective in patients with a high degree of atrial disease (e.g. patients with a large left atrial volume and/or a high extent of atrial fibrosis).<sup>17-19</sup> In the presence of extensive atrial disease, pulmonary vein triggers seem to be less important in the initiation and perpetuation of AF than in patients with relatively healthy atria.

Coronary artery disease can cause myocardial ischemia, resulting in an impaired relaxation of the left ventricle and leading to higher pressures in the left atrium. High left atrial pressures cause ultrastructural and electrical changes in the atrial tissue, potentially limiting the efficacy of RFCA for AF. In the present study no relationship was observed between the presence of CAD and the risk for AF recurrence after RFCA and therefore, the presence of CAD does not limit the efficacy of RFCA for AF. Most likely, in patients without symptomatic CAD, other pathophysiological factors such as age and hypertension may contribute to left atrial structural remodelling and limit the efficacy of RFCA. To our best knowledge this is the first study to investigate the impact of CAD on the efficacy of RFCA for AF.

## Limitations

Some limitations of the present study should be acknowledged. First, MDCT provides anatomical information of the coronary arteries. However, MDCT does not provide information about the presence or absence of myocardial ischemia. Second, the present study included patients with symptomatic AF

but without complaints of chest pain. Therefore, the present study population comprised a low risk population for significant CAD.

## Conclusion

The presence of significant or non-significant CAD on MDCT is not associated with a higher risk for AF recurrence after RFCA.

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