Sex-Based Differences in Left Atrial anatomical characteristics: Impact on Atrial Fibrillation Ablation Outcomes – A Retrospective Multicenter Analysis

TRIAL IDENTIFIER: *Sex-Tailored BY-LAWT AF-Ablation*

PROTOCOL VERSION 1.0 (August 7, 2025)

Protocol Version	Date of change	Description and comments	Control
1.0	Aug 07, 2025	First version	RM, DT, GF

0. Study Investigators and participating centers

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0.1 Coordinating clinical investigator

This will be the principal investigator of the study and the person who will take the decision to submit the report for publication, and will have ultimate authority over all the activities:

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0.2 Responsibilities of the coordinating center

Heart Institute, Teknon Medical Center is the coordinating center that will manage the data and perform statistical analysis.

1. INTRODUCTION

Pulmonary vein isolation (PVI) is a well-established therapeutic strategy for managing both paroxysmal atrial fibrillation (PAF) and persistent atrial fibrillation (PeAF) (1). While generally effective, long-term outcomes remain heterogeneous across patients. Technological innovations, such as the use of electroanatomical mapping systems, have further improved the efficacy, efficiency, and safety of PVI(2).

The goal of PVI is to create continuous, transmural, and permanent lesions. Non-transmural ablation is a major determinant of post-ablation AF recurrence. In fact, pulmonary vein (PV) reconnection is often attributed to insufficient lesion depth. (3)

Personalizing ablation based radiofrequency titration according to patient-specific anatomical features—such as left atrial wall thickness (LAWT) assessed by pre-procedural multidetector computed tomography (MDCT)—has proven feasible, effective, and safe(4). In such a tailored approach, anatomical sex differences, particularly in left atrial volume (LAV), LAWT, and intramyocardial fat (inFAT) volume and distribution, may impact procedural characteristics and long-term arrhythmia-free survival(5) (6, 7)

The aim of our study is to assess sex-related differences in patients who underwent a first ablation procedure for paroxysmal or persistent AF, guided by the personalized ablation strategy of the BY-LAWT protocol. Specifically, we aim to compare anatomical characteristics, procedural parameters, and clinical outcomes between sexes.(8, 9)

2. OBJECTIVES

2.1 Research Hypothesis

We hypothesize that, among patients undergoing a first catheter ablation for PAF or PeAF,

women exhibit significantly lower LAWT, LAV, and inFAT compared to men. These anatomical differences may lead to procedural variability, particularly a lower average ablation index (AI) required in women to achieve comparable clinical outcomes.

This study aims to evaluate whether such sex-related anatomical differences translate into different ablation strategies, potentially supporting the development of individualized, sex-specific ablation protocols.

In addition, we aim to assess whether long-term clinical outcomes differ between sexes.

2.2 Study Objectives

2.2.1 Primary Objective:

To compare long-term clinical outcomes of LAWT-guided atrial fibrillation ablation between male and female patients.

2.2.2 Secondary Objectives:

- To retrospectively compare mean LAWT, LAV, and inFAT between male and female patients undergoing their first ablation for PAF or PeAF.
- To assess whether there are sex-based differences in the AI values used during AF ablation performed according to the BY-LAWT protocol.
- To analyze the impact of sex on procedural parameters, including procedure time, total radiofrequency time, number of RF applications, early PV reconnection rates, and peri-procedural complications.
- To evaluate the correlation between LAWT, LAV, inFAT, and the occurrence of procedural complications (particularly cardiac perforation/tamponade and PV

stenosis), stratified by sex.

- To determine whether baseline differences in LAWT, LAV, and inFAT between sexes are independent predictors of long-term ablation success.

3. METHODS

3.1 STUDY DESIGN

This is a retrospective, multicentric study, based on the analysis of already collected clinical and procedural data.

3.2 STUDY SETTING

The study will be conducted at Teknon Medical Center and at Pilar Medical Center., centers with proven experience in performing atrial fibrillation ablation. Electronic records of patients who underwent AF ablation will be reviewed.

3.3 ELIGIBILITY CRITERIA

Consecutive patients who underwent a first ablation procedure for paroxysmal or persistent atrial fibrillation at Teknon Medical Center and at El Pilar Hospital, starting from 01/01/2019 to 31/03/2025.

3.3.1 Inclusion Criteria:

- Patients who underwent a first ablation procedure for atrial fibrillation (paroxysmal or persistent).
- Availability of an adequate pre-procedural cardiac CT scan for LAWT, LAV and inFAT analysis.

- Availability of complete procedural data, including ablation index (AI) values recorded using the SmartTouch catheter (Biosense Webster).
- Availability of 12-month follow-up data for efficacy and safety endpoint evaluation.
- Ablation performed according to the by-LAWT protocol

3.3.2 Exclusion Criteria:

- Age < 18 years.
- Previous cardiac ablation (including AF ablation or other arrhythmias).
- Incomplete data regarding procedural parameters, or follow-up.
- Poor quality pre-procedural cardiac MDCT
- Ablation not performed according to the BY-LAWT protocol.
- Structural heart disease (e.g., dilated cardiomyopathy, valvular heart disease with surgical indication) that could substantially influence atrial dimensions or ablation response.

3.4 RETROSPECTIVE DATA COLLECTION

Data will be extracted from electronic medical records of patients. All information will be anonymized before analysis.

3.4.1 Pre-procedure CT scan (Existing data)

Pre-procedural multidetector computed tomography (MDCT) images, previously acquired and already analyzed as per the inclusion criteria of the BY-LAWT protocol, will be retrieved from the institutional archive.

3.4.2 Image Processing (Existing Data and New Analysis)

MDCT images will be analyzed (or re-analyzed, if necessary for uniformity) using ADAS-3D™ (Galgo Medical, Barcelona, Spain) to obtain 3D left atrial wall thickness maps and calculate left atrial volume. The analysis methodology will be consistent with what is described for a prospective study, ensuring the derivation of:

- The endocardial layer defined by semi-automatic segmentation.
- The epicardial layer defined by manual delineation with interpolation.
- Calculation of wall thickness at each endocardial point as the distance between each endocardial point and its projection to the epicardial shell.
- 3D thickness map with a color scale. The color map uses a color scale to depict a range of thickness, as follows (*right image*):
    - **< 1 mm: Red**
    - **1-2.5 mm: Yellow**
    - **2.5-3 mm: Green**
    - **3-4 mm: Blu**
    - **> 4 mm: Purple**
- 3D inFAT maps using a threshold-based segmentation of the volume between the endocardial and the epicardial LA shells previously obtained for 3D LAWT maps. InFAT will be defined as a tissue with reduced radiodensity, in the range of −194 Hounsfield Units (HU) to −5 HU. Two specific inFAT subranges will be explored, the former between −194 HU and −50 HU (dense inFAT) and the latter between −50 HU and −5 HU (fat-myocardium admixture)
- Calculation of left atrial volume (LAV) using ADAS-3D™ or standardized software.

3.5 STUDY ENDPOINTS

Efficacy Correlation:

The primary efficacy endpoint will be freedom from any atrial arrhythmia (AF, atrial tachycardia [AT], or atrial flutter [AFL]) at the 12-month follow-up. The following definitions apply:

- AF recurrence will be considered only after the 3-month blanking period (see below), and defined as:
    - Patient-reported symptoms clearly suggestive of recurrence (e.g., rapid, recurrent palpitations with sudden onset and termination, lasting for several minutes or hours),
    - or AF documented on a 12-lead ECG,
    - or AF detected on a Holter monitor or device recording lasting >30 seconds.
- The blanking period is defined as the first 3 months following the PVI procedure, during which a transient increase in atrial tachyarrhythmias may occur due to proarrhythmogenic inflammatory changes related to RF lesion formation.

Sex-based differences in the primary endpoint will be analyzed.

3.5.2 Secondary Endpoints

- LAWT, inFAT, and LAV Differences:

  Comparison of mean left atrial wall thickness (LAWT), intramyocardial fat (inFAT) volumes and distribution, and left atrial volume (LAV) between male and female patients.

- Procedural Outcomes:

  Sex-based comparison of procedural characteristics, including delivered ablation index (AI), total procedure time, cumulative RF application time, number of RF applications, fluoroscopy time, first-pass pulmonary vein isolation rates, and incidence of early pulmonary vein reconnection.

- **Periprocedural Complications:**

Incidence of the following complications, extracted from patient records:

  - Death
  - Myocardial infarction
  - Diaphragmatic paralysis
  - Stroke or transient ischemic attack (TIA)
  - Other thromboembolic events
  - Cardiac perforation or tamponade
  - Vascular complications
  - Prolonged or repeated hospitalization
  - Heart block
  - Pulmonary vein (PV) stenosis >70% (as assessed by follow-up cardiac CT, if available)
  - Atrioesophageal fistula
  - Pericarditis requiring intervention
  - Pneumothorax

- Pulmonary edema

3.6 VARIABLES TO BE COLLECTED

Data will be collected retrospectively from clinical records and medical images.

3.6.1 Baseline Data (at original patient enrollment)

- Demographic data (age, sex, weight, height, BMI).
- Medical and cardiovascular history (type of AF: paroxysmal/persistent, AF duration, cardiovascular risk factors, comorbidities, NYHA functional class, medications).
- Transthoracic echocardiography (LA diameter, LVEF).
- PV anatomy (anatomical variants).

3.6.2 Procedural Data

- Ablation catheter used (confirmation of SmartTouch Biosense).
- Ablation parameters (RF power, mean and minimum contact force, mean ablation index (AI) per lesion, duration of RF applications).
- Number of RF applications (total/per PVI RF line/per segment).
- RF time (s), procedure time, fluoroscopy time.
- First-pass isolation rates (and which veins).
- Acute reconnections (and which veins/sites).
- Acute peri-procedural complications.

3.6.3 MDCT Variables of Wall Thickness and Atrial Volume (derived from re-analysis or valid original analysis)

- Mean total LAWT (mm).
- Mean total, dense inFAT and fat-myocardial admixture volumes (mL)
- Mean LAWT of the PVI RF line (mm).
- Mean total, dense inFAT and fat-myocardial admixture of the PVI RF line (mL)
- Normalized LAWT of the PVI RF line (segment by segment, if possible).
- Normalized total, dense inFAT and fat-myocardial admixture of the PVI RF line (segment by segment, if possible).
- Left Atrial Volume (LAV) (ml).
- Coefficient of variation of wall thickness in each segment (CV-WT) (segment by segment): standard deviation of wall thickness/mean LAWT.
- Gaussian curvature (to get an idea of tissue heterogeneity).
- Mean LAWT of reconnection points/segments (if identified).

3.7 TIMELINE AND RECRUITMENT

Given the retrospective nature of the study, no real-time patient recruitment will be performed. Data will be extracted from a pre-existing patient archive, covering the period from 01/01/2019 to 31/03/2025.

3.8 FOLLOW UP

All patients routinely underwent clinical follow-up at 1, 3, 6, and 12 months after the index AF ablation. Therefore, follow-up data will be collected from clinical records, specifically assessing arrhythmia recurrence and the occurrence of late complications

3.9 DATA MANAGEMENT

Data will be extracted anonymously into a secure electronic database, compliant with data privacy regulations (e.g., GDPR, if applicable). Access to data will be password-restricted to authorized investigators. Original paper medical records will remain in the center's archives.

3.10 SAMPLE SIZE CALCULATION

Given the retrospective design and the use of existing data, the sample size will be determined by the number of eligible patients identified in the medical records during the study period, from January 1, 2019, to May 31, 2025.

3.11 STATISTICAL METHODS

All analyses will be two-sided and performed using a significance level of 5% (α=0.05).

- Continuous variables will be expressed as mean ± standard deviation (SD) or median (interquartile range) depending on their distribution (Shapiro-Wilk test). They will be compared using Student’s t-test or Mann-Whitney U test.
- Categorical variables will be expressed as number (percentage) and compared with the chi-square test or Fisher’s exact test.
- To compare LAWT, LAV and inFAT between men and women, appropriate statistical tests (e.g., independent t-test or ANOVA) will be used.
- The efficacy endpoint (freedom from atrial arrhythmia at 12 months) will be analyzed using the Kaplan-Meier method, and curves will be compared with the log-rank test.

- Logistic or Cox proportional hazards regression models (for freedom from arrhythmia) will be used to identify independent predictors of ablation success, including sex, LAWT, LAV, inFAT and AI.

3.11 PROTOCOL DEVIATIONS

In a retrospective study, "protocol deviations" refer to cases where available data do not align with the inclusion/exclusion criteria or the planned data collection. Such cases will be documented and justified.

3.12 HARMS

There are no direct risks to patients associated with a retrospective study based on data review. Risks associated with the ablation procedure itself were addressed at the time of the original procedure

4. ETHICS AND DISSEMINATION

4.1 RESEARCH ETHICS APPROVAL

This protocol must be reviewed and approved by the institutional review board (IRB) of Teknon Medical Center before data collection begins. A waiver of informed consent for retrospective collection of anonymized data will be requested, as patients will not be contacted directly.

Should the ethics committee require retrospective informed consent for data use, it will be obtained.

4.2 CONFIDENTIALITY

All study-related information will be stored securely at the study site. All participant data will be anonymized using a unique study ID number. Records containing personal identifiers will be kept separate from anonymized study data. All electronic databases will be password-protected. Data confidentiality will be managed in compliance with applicable data privacy regulations.

4.3 ACCESS TO DATA

The principal investigators of the project will have direct access to the anonymized datasets. To ensure confidentiality, data distributed to project team members will be stripped of any participant identifying information.

4.4 DISSEMINATION POLICY

Study results will be disseminated through presentations at scientific conferences and publications in peer-reviewed journals. Results will be communicated in a way that does not permit the identification of individual patients.

APPENDIX 1: Data collection sheet for the byLAWT study

Name: ……. Medical Record No.: …….

Date of Birth: …… Study Code: …… Center: …….

1. PATIENT DATA (AT THE TIME OF PROCEDURE):

FIRST OPERATOR …… Anesthesiologist …… EVALUATING OPERATOR ……

PROCEDURE DATE ..... /..... /.....

AF Type: Paroxysmal // Persistent

First AF diagnosis date: ..... /..... /.....

Longest AF episode: <3 months / 3-6 months / 6-12 months / > 12 months

Procedure: First AF Ablation (confirm)

Age: ..... Sex: Male // Female CHA2DS2-VASc = ... HAS-BLED: … Weight ..... Kg Height: ..... m

CVRF: none // HBP // Dyslipidemia // DM-2 // Smoker // OSA // Sport (>4 h/week x 10 years)

Underlying Heart Disease: none // Hypertensive // Ischemic // HOCM // Valvular // Other .....

Conduction Disturbances: none // LBBB // RBBB // LAHB // LPHB // Other: .....

Pharmacological Treatment (pre-ablation): ..... OAC: .....

Transthoracic Echocardiographic Data (most recent before procedure): LA Dimension (mm): ..... LVEF: ..... Mitral Annulus: …….. cm Other: ……

PV Anatomy (from CT/mapping report): 4 independent // Common left. // Common right // Accessory veins: .....

2. PROCEDURAL DATA:

Ablation Catheter Used (confirm SmartTouch Biosense): YES // NO (if NO, exclude patient)

Ablation Lines Adapted to "Fingerprinted" Esophagus: YES // NO (reason if NO: ……..)

Catheter Curve (Smarttouch): Blue // Orange // Black

Procedure Time: ..... min FAM + Merge Time: …… min Transseptal Time: ……. min

Transseptal Puncture Technique: Fluoroscopy // Fluid // TEE // Radiofrequency

Fluoro Time: ..... sec Fluoro Dose: …… mGy Fluoro Dose (index): ……..Gy/cm2

RF Power: anterior wall ..... W // posterior wall ..... W

RF Time: Right PV ..... s // Left PV ..... s

Number of RF Points: Left PVs …… Right PVs……

First Pass Isolation (which veins): RSPV // RIPV // LSPV // LIPV

Acute Reconnection after min 10' waiting (which veins): RSPV // RIPV // LSPV // LIPV

Intra-procedural Electrical Cardioversion: Yes // No

Acute Peri-procedural Complications: …….

Was the procedure evaluated for the absence of gaps by the 2nd operator?: YES // NO

3. MDCT VARIABLES OF WALL THICKNESS AND ATRIAL VOLUME (FROM ADAS-3D™ ANALYSIS):

CT Date: ..... /..... /.....

Mean Total LAWT (mm): ……

Mean total, dense inFAT and fat-myocardial admixture volumes (mL): ……

Mean LAWT of PVI RF Line (mm): ……

Mean total, dense inFAT and fat-myocardial admixture volumes of PVI RF Line (mL): ……

Normalized LAWT of PVI RF Line (segment by segment, if possible): ……

Normalized total, dense inFAT and fat-myocardial admixture of the PVI RF line (segment by segment, if possible): ……

Left Atrial Volume (LAV) (ml): ……

Coefficient of Variation of Wall Thickness in Each Segment (CV-WT) (segment by segment): ……

Gaussian Curvature (mean for ablation areas): ……

Mean LAWT of Reconnection Points/Segments (if identified): ……

4. 12-MONTH FOLLOW-UP DATA (FROM PROCEDURE DATE):

Last Follow-up Date: ..... /..... /.....

Reported Arrhythmia Symptoms (at 3, 6, 12 months): Yes // No

12-Lead ECG at 12 months: Sinus Rhythm // AF // AT // Atrial Flutter // Other: …….

24-Hour Holter at 12 months: Sinus Rhythm // AF (>30s) // AT (>30s) // Atrial Flutter (>30s) // Other: …….

Freedom from Any Atrial Arrhythmia at 12 Months (after blanking period): YES // NO

Antiarrhythmic Medications (at 12th month): .....

Late Complications (e.g., PV stenosis >70% from subsequent CT, if performed): ……

Subsequent Re-ablation? Yes // No (Date and Reason: ……)

Other: …….

APPENDIX 2: Informed consent material

1) PATIENT INFORMATION SHEET FOR A RESEARCH STUDY

Study Title: Sex-Based Differences in Left Atrial anatomical characteristics: Impact on Atrial Fibrillation Ablation Outcomes – A Retrospective Multicenter Analysis

Principal Investigator: Dr. Antonio Berruezo

Research Center Address: Centro Médico Teknon

Contact Phone Number: 932 90 62 00

You are being asked to participate in a research study. First, we want you to know that your participation is completely **voluntary**. This consent document contains important information about the research study. Please read it carefully before deciding whether to participate. No one can force you to participate, and you can withdraw from the study at any time. If you agree to participate, you must sign this informed consent document. You will receive a signed copy for your records. This study has been reviewed and approved by the Hospital's Clinical Research Ethics Committee.

1. WHAT IS THE PURPOSE OF THE STUDY?

You are being asked to participate in this study because you have an abnormal heart rhythm called **atrial fibrillation (AF)**. Radiofrequency ablation for AF is a procedure that uses a catheter to apply radiofrequency energy to the areas where the pulmonary veins connect to the left atrium. This electrically isolates these veins from the left atrium. This approach has been used for more than 20 years, since the origin of this arrhythmia was first described at the opening of the pulmonary veins into the left atrium. The efficacy of a single ablation procedure is approximately 75-80% at one year. In some cases, a second ablation procedure is required to isolate a point that may have reconnected one of the pulmonary veins to the atrium.

The main objective of this study is to determine if procedures for effective electrical isolation of the pulmonary veins using the PeAF-by-LAWT protocol with the Thermocool SmartTouch® catheter (Biosense Webster, Inc., Irvine, CA, USA) show sex-based differences, considering existing anatomical characteristics, and whether they are at least as clinically effective (measured by atrial arrhythmia-free survival at 3, 6, and 12 months).

2. WHAT ARE THE COMPLICATION RISKS OF THE STUDY?

Since this is a **retrospective study** that analyzes existing data, there are no additional direct risks to you from your participation. All risks associated with your ablation procedure were explained to you and accepted at the time of your intervention.

3. HOW IS THE STUDY DESIGNED?

This is a **retrospective study**. This means we will analyze existing information from your medical records and medical images (such as cardiac CT) related to your atrial fibrillation ablation. Your data will be **anonymized** to protect your privacy.

4. WHAT ARE THE ALTERNATIVES TO PARTICIPATING IN THIS STUDY?

Your decision to participate or not participate in this retrospective study will **not affect your current or future medical care** in any way.

5. WHAT ARE THE POSSIBLE BENEFITS OF PARTICIPATING IN THIS STUDY?

Although there are no direct benefits to you, your participation (through the anonymous use of your data) will contribute to the scientific understanding of sex-based anatomical differences in the left atrium and how these may influence the practice of atrial fibrillation ablation. This could lead to more personalized and safer treatments for future patients.

6. IS PARTICIPATION IN THIS STUDY VOLUNTARY?

Yes. Participation in this research study is voluntary. You may decide not to participate, and you can also change your mind later and **withdraw from the study at any time** without it affecting your clinical care.

I, _____(Name and Surname)

Have spoken with:

_____

I have received sufficient information about why I am being asked to participate in the study. I have been able to ask questions about the study. I understand that my participation is voluntary. I understand that I can withdraw from the study at any time, without having to provide an explanation, and without it affecting my medical care. I consent to the collection and processing of my personal and medical data according to the specified conditions. And I have expressed my agreement to participate.

PARTICIPANT:

_____ _____ _____

Participant's Signature Date Time

INVESTIGATOR:

_____ _____

Investigator's Signature Date Time

2) PATIENT INFORMATION SHEET FOR THE RESEARCH STUDY

Study Title: Sex-Based Differences in Left Atrial anatomical characteristics: Impact on Atrial Fibrillation Ablation Outcomes – A Retrospective Multicenter Analysis

Principal Investigator: Dr. Antonio Berruezo

Research Center Address: Centro Médico Teknon

Contact Phone Number: 932 90 62 00

1. IF I PARTICIPATE IN THIS RESEARCH STUDY, HOW WILL MY PRIVACY BE PROTECTED?

Access to your medical history and data from the procedure: The doctors, nurses, and other staff at the center involved in this study will need to access your medical history, including medical records and previous results, for the purposes of this study. By signing this consent form, you authorize this access and, if necessary, allow them to contact your general practitioner or other healthcare professionals to access your medical history during the study. In accordance with current data protection regulations, you expressly consent to the inclusion of your clinical data, as well as the data resulting from your participation in the study, in a personal data file under the responsibility of the Center. Access to your personal information will be restricted to the study doctor and their collaborators, health authorities, and the Research Ethics Committee. By signing this consent, you agree to the use of your anonymized data from the CT scan performed before the ablation. This data will be used to optimize the software for image post-processing (ADAS-3DTM) and to develop a platform for the automation and standardization of this post-processing. Likewise, you consent to the use of anonymized data from the CARTO3TM navigation system and your clinical information by both the investigators at Centro Médico Teknon and the collaborating institutions (ADAS 3D Medical SL, Biosense Webster).

Confidentiality of your health information: Your health information related to the trial will be included in a database, but you will not be identified by name in any report or publication.

Withdrawal from the study: If you decide to withdraw from the study, please inform your study doctor. In this case, the study staff will not collect any new information about you. However, the information already collected may continue to be used as previously described. If you have any questions about this, we recommend that you speak with your study doctor.

Compliance with current legislation on the confidentiality of your health information: The research team is committed to ensuring compliance with the principles established in Law 14/2007 on Biomedical Research and Organic Law 3/2018, of December 5, on Personal Data Protection and Guarantee of Digital Rights. Furthermore, the research team is committed to facilitating your right to access, rectify, cancel, and oppose the use of your data, as provided for in Organic Law 3/2018 on Personal Data Protection and Guarantee of Digital Rights. The processing, communication, and transfer of participants' personal data will comply with the provisions of the European Data Protection Regulation (EU 2016/679). For any questions about the management of your data, you should contact the Centro Médico Teknon in Barcelona at C/Vilana, 12. 08022 Barcelona. In addition to the rights you are already aware of (access, modification, opposition, and cancellation of data), you can now also limit the processing of

data that is incorrect, request a copy, or have the data you provided for the study transferred to a third party (portability). To exercise your rights, please contact the principal investigator of the study. We remind you that data cannot be deleted, even if you stop participating in the study, to ensure the validity of the research and to comply with legal obligations and drug authorization requirements. You also have the right to contact the Data Protection Agency if you are not satisfied.

2. WHO SHOULD I TALK TO ABOUT MY RIGHTS OR TO ASK QUESTIONS?

Before signing this document, you should ask about anything you do not understand. The study team will answer your questions before, during, and after the study. If you feel your question has not been fully answered or if you do not understand the response, please keep asking until you are satisfied. If you have any concerns or complaints about this study or the way it is being conducted, please feel free to discuss them with the study team. The phone numbers to contact the study team are on the first page of this document.

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