Official Title
Dual Antiplatelet Therapy Versus Antiplatelet Monotherapy Plus Anticoagulation in Patients With Acute Coronary Syndrome and Coronary Artery Ectasia: A Multicenter Randomized

Brief Title
Multicenter Trial of Antithrombotic Strategies in Acute Coronary Syndrome With Coronary Artery Ectasia

Acronym
OVER-TIME II

Study Type
Interventional

Study ID and Approval Number
26-1556

Principal Investigator
Diego Araiza-Garaygordobil

Investigator Official Title
Attending Cardiologist at the Coronary Care Unit and Emergency Department

Investigator Affiliation
Instituto Nacional de Cardiologia Ignacio Chavez

Document Date
March 30th, 2026

This document includes: Study Protocol and Statistical Analysis Plan

Brief Summary
Coronary artery ectasia (CAE) is a condition in which a coronary artery becomes abnormally dilated, measuring at least 50% larger than the adjacent normal segment. Although relatively uncommon, CAE is clinically important because it can lead to abnormal blood flow and increase the risk of blood clot formation. Patients with CAE are at higher risk of angina, myocardial infarction, and complications during coronary interventions. Despite these risks, the optimal antithrombotic treatment for patients with acute coronary syndrome (ACS) and CAE remains uncertain.Dual antiplatelet therapy (aspirin plus clopidogrel) is currently the most commonly used treatment. However, the abnormal blood flow patterns observed in CAE may promote clot formation through mechanisms that could potentially be better addressed with anticoagulant therapy.The OVER-TIME II trial is a multicenter randomized clinical trial designed to compare two antithrombotic strategies in patients with ACS and CAE: standard dual antiplatelet therapy versus antiplatelet monotherapy combined with anticoagulation. The study aims to determine whether the addition of anticoagulation reduces major cardiovascular events without significantly increasing bleeding risk.

Introduction

Coronary artery ectasia (CAE) is defined as an abnormal dilation of the coronary artery in which the length of the dilated segment is ≥50% greater than the adjacent diameter (1,2). CAE is an uncommon but clinically relevant entity, and its therapeutic management remains controversial. The reported prevalence of CAE ranges from 0.3% to 4.9% across different international series (1, 3–9). However, a study conducted by our research group showed that in a consecutive series of angiograms in patients with ST-elevation myocardial infarction (STEMI), the prevalence of CAE was 10.3%, a figure notably higher than previously described (10), highlighting the heterogeneity of its distribution and the importance of studying it in the Mexican population.

The most common etiology of CAE is atherosclerosis, accounting for approximately 50% of cases (11). Other causes include connective tissue diseases, coronary trauma (including iatrogenic injury during percutaneous coronary interventions), infectious arteritis, Kawasaki syndrome, and congenital forms (12).

From a pathophysiological standpoint, CAE promotes thrombosis due to alterations in coronary hemodynamics characterized by slow flow or blood stasis (13). Elevated levels of prothrombotic and inflammatory biomarkers (such as P-selectin, platelet factor 4, D-dimer, and fibrinogen) have been described in patients with CAE compared to controls (14–16). Additionally, these patients exhibit changes in the expression of genes involved in the inflammatory response, as well as in microRNA-mediated regulation of transcription and subsequent translation of factors associated with angiogenesis and vascular remodeling. These findings suggest the involvement of genetic and molecular mechanisms in the pathophysiology of the disease (17, 18).

Currently, evidence regarding the optimal treatment of acute coronary syndrome (ACS) in patients with CAE is limited, and there are no guidelines defining a clear therapeutic strategy. Management is often left to the discretion of the treating team, with dual antiplatelet therapy (DAPT: acetylsalicylic acid 100 mg and clopidogrel 75 mg) being the routinely recommended regimen (6–9). However, given the previously described prothrombotic pathophysiology and the presence of marked dilation and slow flow, anticoagulants have been proposed as a strategy to improve outcomes. A retrospective Japanese study in patients with CAE and acute myocardial infarction showed that those treated with warfarin and maintaining therapeutic INR >60% of the time had fewer cardiac events compared to those without adequate anticoagulation (0% vs 33%, p = 0.03) (19). Likewise, a systematic review of cases found that recurrences were concentrated among patients treated with DAPT, whereas those receiving anticoagulation (8/13) had better outcomes, even though most were only receiving a single concomitant antiplatelet agent (20). Even the use of potent P2Y12 inhibitors has not satisfactorily prevented thrombosis in this group (7).

In this context, the OVER-TIME study was conducted at our Institute, an exploratory clinical trial led by the principal investigator of the present proposal (21). This study compared the use of SAPT+DOAC (clopidogrel 75 mg + rivaroxaban 15 mg) versus standard DAPT in patients with ACS and CAE. Despite its exploratory nature and limitations related to sample size, the results were clinically relevant: the SAPT+DOAC group showed a numerical reduction in major cardiovascular events, a lower rate of ischemic recurrence, and a favorable safety trend, without a significant increase in bleeding events. Additionally, a significant reduction in clot lysis time was

observed in patients receiving SAPT+DOAC, suggesting improved fibrinolytic activity and providing mechanistic evidence for the potential benefit of anticoagulation in this setting.

However, it remains unknown whether, beyond the effects on hemostasis, treatment response is associated with genetic, post-transcriptional, or translational modifications, an aspect that warrants further investigation. The findings generated at our center support the hypothesis that anticoagulation may play a key role in these patients. OVER-TIME thus represents the strongest available preliminary evidence and the ideal platform to propose a larger-scale trial with 12-month follow-up aimed at definitively confirming these findings and establishing evidence-based therapeutic recommendations. Furthermore, this project will explore the genetic and molecular profile of these patients to assess potential changes during disease progression or in response to treatment, consolidating a unique and necessary line of translational research in this field.

Arms and Interventions

Active Comparator: Dual Antiplatelet Therapy

Description: Participants receive standard dual antiplatelet therapy consisting of aspirin 100 mg once daily plus clopidogrel 75 mg once daily.

Experimental: Antiplatelet Monotherapy Plus Anticoagulation

Description: Participants receive antiplatelet monotherapy with clopidogrel 75 mg once daily combined with oral anticoagulation using rivaroxaban 15 mg once daily.

Outcomes

Primary Outcomes

1. Time to First Major Adverse Cardiovascular Event (MACE)
Time to first occurrence of the composite of cardiovascular death, non-fatal myocardial infarction, or repeat coronary revascularization in patients with coronary artery ectasia following acute coronary syndrome, according to the assigned antithrombotic treatment strategy (dual antiplatelet therapy versus clopidogrel plus rivaroxaban).

2. Time to First Bleeding Event According to the BARC Classification
Time to first occurrence of a composite of major or minor bleeding events defined according to the Bleeding Academic Research Consortium (BARC) classification in patients with coronary artery ectasia following acute coronary syndrome, according to the assigned antithrombotic treatment strategy (dual antiplatelet therapy versus clopidogrel plus rivaroxaban).

Secondary Outcomes

1. Individual Components of the Major Adverse Cardiovascular Event Composite
Incidence of each individual component of the primary efficacy composite endpoint (cardiovascular death, non-fatal myocardial infarction, and repeat coronary revascularization) in

patients with coronary artery ectasia following acute coronary syndrome, according to the assigned antithrombotic treatment strategy.

2. Individual Bleeding Events According to the BARC Classification
Incidence of individual bleeding events according to the Bleeding Academic Research Consortium (BARC) classification in patients with coronary artery ectasia following acute coronary syndrome, according to the assigned antithrombotic treatment strategy.

Exploratory Outcomes

1. Genetic Variants and Gene Expression Profiles Associated With Coronary Artery Ectasia and Treatment Response

Analysis of genetic variants and gene expression profiles, including DNA, RNA and circulating microRNA obtained from peripheral blood samples collected at randomization and at 12 months of follow-up. These analyses aim to identify molecular signatures associated with susceptibility to coronary artery ectasia, disease progression, and differential response to antithrombotic therapy. This exploratory analysis will be performed in an approximately 30% subset of the study population.

Methodology

Study design
Randomized, multicentric, open-label clinical trial

Description of the study population
- Target population
Patients with coronary artery ectasia and acute coronary syndrome.
- Eligible population
Patients with coronary artery ectasia and acute coronary syndrome presenting to the National Institute of Cardiology for care, without any other indication for concomitant anticoagulation.

Inclusion criteria
Patients with coronary artery ectasia:

1. Patients of both sexes, aged 18–80 years, hospitalized for acute coronary syndrome with or without ST-segment elevation. Operational criteria include ALL of the following:
   A. Acute coronary syndrome within 7 days prior to recruitment, with or without persistent ST-segment elevation; with high-sensitivity cardiac troponin above the 99th percentile.
   B. Coronary ectasia in the infarct-related artery and one- or two-vessel coronary artery disease. Definitions of ectasia include:
   a. **Theoretical definition:** coronary ectasia is defined as dilation >1.5 times the diameter of an adjacent normal coronary segment or the expected normal diameter according to sex-based distribution.
   b. **Operational definition:** after review by two expert observers (interventional cardiologists), supported by quantitative coronary angiography (QCA), the presence of coronary ectasia is determined unanimously. In case of disagreement, a third observer

(interventional cardiologist) will adjudicate.
c. The infarct-related artery is defined as the artery corresponding to the affected electrocardiographic territory (in cases with ST elevation) or showing signs of an atherothrombotic event such as thrombus (TIMI I–V) or reduced flow on coronary angiography.

2. Hospital admission lasting >24 hours.
3. Percutaneous revascularization or medical treatment, as deemed appropriate by the treating team. Intracoronary interventions such as stent angioplasty, balloon angioplasty, or thrombus aspiration are allowed.
4. Signed informed consent and willingness to participate voluntarily.

Exclusion criteria

1. Pregnant women.
2. Patients with any indication for temporary or permanent anticoagulation at recruitment.
3. Chronic kidney disease KDIGO stage IV or higher (eGFR <30 ml/min/1.73 m²).
4. eGFR at hospital discharge <30 ml/min/1.73 m².
5. History of major bleeding (upper gastrointestinal bleeding, intracranial hemorrhage, etc.) or high bleeding risk determined by the treating physician.
6. Advanced heart failure defined as LVEF <30% plus one of the following:
I. More than two hospitalizations or unplanned ER visits in the past year and/or
II. NYHA class III or higher despite optimal medical therapy at recruitment or within the past 3 months.

Elimination criteria

1. Discharge diagnosis other than acute coronary syndrome with or without ST elevation.
2. Failure to provide or withdrawal of informed consent.

Sample size

Based on the exploratory OVER-TIME trial (Araiza-Garaygordobil et al., 2025), sample size was calculated with 80% power, alpha 0.05, 5% crossover, event rate of 87.5% in the DAPT group and 96.7% in the anticoagulation + SAPT group. A total of 326 patients (163 per arm).

Of these, 126 patients are expected to be recruited at our Institute, based on recruitment patterns observed in the OVER-TIME study (2021–2025). The study will begin as single-center and later expand to a multicenter design including:

- Hospital Juárez de México
- Centro de Estudios Clínicos de Querétaro S.C.

Specification of variables

Independent variable: treatment group

- DAPT group: aspirin 100 mg + clopidogrel 75 mg
- SAPT+DOAC group: rivaroxaban 15 mg + clopidogrel 75 mg

Dependent variable: primary composite endpoint of major cardiovascular events

- Defined as: composite of cardiovascular death, nonfatal recurrent myocardial infarction, and repeat revascularization/repeat coronary angiography (per international definitions for RCTs).

Dependent variable: co-primary bleeding endpoint

- Defined as: composite of minor and major bleeding events according to the Bleeding Academic Research Consortium (BARC) scale.

Dependent variable: gene expression profiles in patients with CAE and ACS

- Defined as total DNA and RNA extracted from peripheral blood, including differentially expressed genes, gene signatures, and microRNA profiles.

Data collection methods

Patients will be recruited from the Emergency Department and Coronary Care Unit of the National Institute of Cardiology. After eligibility confirmation, they will be randomized 1:1 to DAPT vs. SAPT+DOAC. Treatment will continue for 12 months.

Follow-up visits will occur at 30 (±3) days and 12 months, with telephone follow-up at months 3 and 6. Clinical data, outcomes, and objective documentation of events will be recorded, and peripheral blood samples will be collected for analysis at the INMEGEN Cardiovascular Diseases Laboratory.

Case Report Form (CRF)

A standardized CRF will ensure uniform data collection across centers, including:

1. Demographics and baseline characteristics
2. ACS clinical data
3. Angiographic characteristics
4. Treatment allocation and adherence
5. Major cardiovascular events
6. Bleeding events (BARC classification)
7. Clinical follow-up data
8. Biological samples (DNA/RNA)
9. Exclusion/elimination during follow-up

<u>Statistical analysis plan</u>

All statistical analyses will be performed using Stata version 14.1 (StataCorp, College Station, TX, USA). A two-sided p-value <0.05 will be considered statistically significant.

Analysis populations

- The intention-to-treat (ITT) population will be the primary analysis set and will include all randomized patients, analyzed according to their assigned treatment group.
- A per-protocol (PP) analysis will also be conducted as a sensitivity analysis, including patients with adequate adherence and no major protocol deviations.
- A safety population will include all patients who received at least one dose of the assigned treatment.

Descriptive analysis
Baseline characteristics will be summarized by treatment group. Continuous variables will be reported as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on distribution (assessed using the Shapiro–Wilk test). Categorical variables will be expressed as frequencies and percentages.

Between-group comparisons at baseline will be performed using:

- Student's t-test or Wilcoxon rank-sum test for continuous variables
- Chi-square test or Fisher's exact test for categorical variables

No formal statistical testing of baseline differences will be used to guide adjustments.

Primary efficacy endpoint
The primary endpoint is a composite of cardiovascular death, nonfatal recurrent myocardial infarction, and repeat revascularization/repeat coronary angiography.

- Time-to-event will be defined from randomization to first occurrence of any component of the composite endpoint.
- Patients without events will be censored at the time of last follow-up.
- Event-free survival will be estimated using Kaplan–Meier curves and compared using the log-rank test.
- Cox proportional hazards regression models will be used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).
- The proportional hazards assumption will be assessed using Schoenfeld residuals and graphical methods.

Adjusted analyses will be performed including clinically relevant covariates (e.g., age, sex, diabetes, baseline renal function, Killip class) if imbalance is observed or pre-specified.

Co-primary safety endpoint (bleeding)
The co-primary endpoint is a composite of major and minor bleeding events according to the BARC classification.

- Time-to-first bleeding event will be analyzed using Kaplan–Meier methods and Cox regression.
- Additionally, bleeding incidence rates will be compared using chi-square tests.
- A net clinical benefit analysis (composite of ischemic and major bleeding events) may be performed as an exploratory endpoint.

Secondary analyses

- Individual components of the primary endpoint will be analyzed separately using time-to-event methods.
- Recurrent events may be analyzed using Andersen–Gill models or negative binomial regression, if applicable.
- Subgroup analyses will be performed for predefined groups (e.g., STEMI vs NSTEMI, presence of multivessel disease, sex, diabetes), including interaction testing.

Biomarker and genetic analysis

- Differential gene expression analyses will be performed using appropriate normalization methods (e.g., DESeq2/edgeR pipeline if RNA-seq is used).
- Associations between gene expression profiles and clinical outcomes will be explored using multivariable regression models.

Handling of missing data

- Efforts will be made to minimize missing data through active follow-up.
- Missing baseline covariates may be imputed using **multiple imputation by chained equations (MICE)** if missingness exceeds 5%.
- For time-to-event analyses, censoring will be applied at last known follow-up.
- Sensitivity analyses will be conducted to assess the impact of missing data.

References

1. P.S. Swaye, L.D. Fisher, P. Litwin, et al., Aneurysmal coronary artery disease, Circulation 67 (1) (1983) 134–138.
2. Markis JE, Joffe CD, Cohn PF, Feen DJ, Herman MV, Gorlin R. Clinical significance of coronary arterial ectasia. Am J Cardiol (1976) 37(2):217–22.
3. Hartnell GG, Parnell BM, Pridie RB. Coronary artery ectasia: its prevalence and clinical significance in 4993 patients. Br Heart J (1985) 54:392–5.
4. Yip HK, Chen MC, Wu CJ, Hang CL, Hsieh KY, Fang CY, Yeh KH, Fu M. Clinical features and outcome of coronary artery aneurysm in patients with acute myocardial infarction undergoing a primary percutaneous coronary intervention. Cardiology. 2002;98(3):132-40.
5. Erden I, Erden EC, Ozhan H, Karabulut A, Ordu S, Yazici M. Outcome of primary percutaneous intervention in patients with infarct-related coronary artery ectasia. Angiology. 2010 Aug;61(6):574-9.
6. Bogana Shanmugam V, Psaltis PJ, T L Wong D, T Meredith I, Malaiapan Y, Ahmar W. Outcomes After Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction Caused by Ectatic Infarct Related Arteries. Heart Lung Circ. 2017 Oct;26(10):1059-1068.
7. Iannopollo G, Ferlini M, Koziński M, Ormezzano MF, Crimi G, Lanfranchi L, Camporotondo R, Visconti LO, De Ferrari GM, De Servi S. Patient Outcomes With STEMI Caused by Aneurysmal Coronary Artery Disease and Treated With Primary PCI. J Am Coll Cardiol. 2017 Jun 20;69(24):3006-3007.
8. Gunasekaran P, Stanojevic D, Drees T, Fritzlen J, Haghnegahdar M, McCullough M, Barua R, Mehta A, Hockstad E, Wiley M, Earnest M, Tadros P, Genton R, Gupta K. Prognostic significance, angiographic characteristics and impact of antithrombotic and anticoagulant therapy on outcomes in high versus low grade coronary artery ectasia: A long-term follow-up study. Catheter Cardiovasc Interv. 2019 Jun 1;93(7):1219-1227.
9. Núñez-Gil IJ, Cerrato E, Bollati M, Nombela-Franco L, et al. Coronary artery aneurysms, insights from the international coronary artery aneurysm registry (CAAR). Int J Cardiol. 2020 Jan 15;299:49-55.
10. Gonzalez-Gutiérrez JC, Araiza-Garaygordobil D et al. Submitted for publication.
11. Cohen P, O'Gara PT. Coronary artery aneurysms. A review of the natural history, pathophysiology, and management. Cardiol Rev (2008) 16(6):301–4.

12. Boyer N, Gupta R, Schevchuck A, Hindnavis V, Maliske S, Sheldon M, Drachman D, Yeghiazarians Y. Coronary artery aneurysms in acute coronary syndrome: case series, review, and proposed management strategy. J Invasive Cardiol. 2014 Jun;26(6):283-90.
13. Swanton HR, Thomas ML, Coltart DJ, et al. Coronary artery ectasia: a variant of occlusive coronary arteriosclerosis. Br Heart J. 1978;40(4):393-400.
14. Yasar AS, Erbay AR, Ayaz S, et al. Increased platelet activity in patients with isolated coronary artery ectasia. Coron Artery Dis. 2007;18:451-454.
15. Dogan A, Tunc B, Ergene O, Ozaydin M, Nazli C, Altinbas A, Gedikli O. Evaluation of overall fibrinolytic activity in patients with coronary artery ectasia: global fibrinolytic capacity. Int J Cardiovasc Imaging. 2003 Dec;19(6):465-71.
16. Liang S, Zhang Y, Gao X, Zhao H, Di B, Sheng Q, Liu R. Is Coronary Artery Ectasia a Thrombotic Disease? Angiology. 2019 Jan;70(1):62-68.
17. Lu TP, Chuang NC, Cheng CY, et al. Genome-wide methylation profiles in coronary artery ectasia. Clin Sci (Lond). 2017;131(7):583-594. doi:10.1042/CS20160821
18. Iwańczyk S., Lehmann T., Cieślewicz A., Malesza K., Woźniak P., Hertel A., Krupka G., Jagodziński P.P., Grygier M., Lesiak M., et al. Circulating miRNA-451a and miRNA-328-3p as Potential Markers of Coronary Artery Aneurysmal Disease. Int. J. Mol. Sci. 2023;24:5817. doi: 10.3390/ijms24065817.
19. Doi T, Kataoka Y, Noguchi T, Shibata T, Nakashima T, Kawakami S, Nakao K, Fujino M, Nagai T, Kanaya T, Tahara Y, Asaumi Y, Tsuda E, Nakai M, Nishimura K, Anzai T, Kusano K, Shimokawa H, Goto Y, Yasuda S. Coronary Artery Ectasia Predicts Future Cardiac Events in Patients With Acute Myocardial Infarction. Arterioscler Thromb Vasc Biol. 2017 Dec;37(12):2350-2355.
20. Pranata R, Yonas E, Chintya V, Alkatiri AA. Is Anticoagulant Necessary in Patients with Coronary Artery Ectasia Presenting with Acute Coronary Syndrome? A Systematic Review of Case Reports. Int J Angiol. 2019 Dec;28(4):231-236.19-21|
21. Araiza-Garaygordobil D, Gopar-Nieto R, Sierra-Lara Martínez JD, et al. A randomized trial of antithrombotic therapy in patients with acute coronary syndrome and coronary ectasia. Am Heart J. 2025;281:103-111. doi:10.1016/j.ahj.2024.11.012
22. Bosco, E., Hsueh, L., McConeghy, K. W., Gravenstein, S., & Saade, E. (2021). Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. BMC Medical Research Methodology, 21(1), 1-13. https://doi.org/10.1186/s12874-021-01440-5