Early versus delayed invasive strategy for intermediate- and high-risk acute coronary syndromes managed without P2Y12 receptor inhibitor pretreatment: Design and rationale of the EARLY randomized trial

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WILEY **CLINICAL CARDIOLOGY**

TRIAL DESIGNS

Early versus delayed invasive strategy for intermediate- and high-risk acute coronary syndromes managed without P2Y$_{12}$ receptor inhibitor pretreatment: Design and rationale of the EARLY randomized trial

Gilles Lemesle[1] | Marc Laine[2,3] | Mathieu Pankert[3,4] | Etienne Puymirat[5] |

Thomas Cuisset[6] | Ziad Boueri[7] | Luc Maillard[3,8] | Sébastien Armero[3,9] | Guillaume Cayla[10] |

Laurent Bali[3,11] | Pascal Motreff[12] | Jean-Pascal Peyre[13] | Franck Paganelli[2] |

François Kerbaul[14] | Antoine Roch[15] | Pierre Michelet[16] | Karine Baumstarck[17] |

Laurent Bonello[2,3]

[1]USIC et Centre Hémodynamique, Institut Cœur Poumon, Centre Hospitalier Régional et Universitaire de Lille; Faculté de Médecine de l'Université de Lille; Institut Pasteur de Lille, Unité INSERM UMR 1011; and FACT (French Alliance for Cardiovascular Trials), Lille, F-59000, France

[2]Aix-Marseille Université, AP-HM, Unité INSERM 1076, Unité de Soins Intensifs Cardiologiques, Department of Cardiology, Hôpital Nord, Marseille, France

[3]Mediterranean Association for Research and Studies in Cardiology (MARS Cardio), France

[4]Department of Cardiology, Centre Hospitalier Henri Duffaut, Avignon, France

[5]Département de Cardiologie, Hôpital Européen Georges Pompidou, Assistance Publique des Hôpitaux de Paris, Paris, France; Université Paris Descartes, INSERM U-970, Paris, France

[6]Aix-Marseille Université, AP-HM, Unité INSERM 1062, Unité de Soins Intensifs Cardiologiques, Department of Cardiology, Hôpital Nord, Marseille, France

[7]Department of Cardiology, Centre Hospitalier de Bastia, France

[8]Department of Cardiology, Clinique Axium, Aix-en-Provence, France

[9]Department of Cardiology, Hôpital Européen, Marseille, France

[10]Department of Cardiology, Centre Hospitalier Universitaire de Nîmes, Université de Montpellier, Nîmes, France

[11]Department of Cardiology, Centre Hospitalier de Cannes, France

[12]Department of Cardiology, Centre Hospitalier Universitaire Gabriel Montpied, Clermont-Ferrand, France

[13]Department of Cardiology, Hôpital Privé Beauregard, Marseille, France

[14]Pole RUSH, Assistance-Publique Hôpitaux de Marseille, Marseille, France

[15]Emergency Department, Hôpital Nord, Marseille, France

[16]Emergency Department, Hôpital Timone, Marseille, France

[17]Unité d'Aide Méthodologique à la Recherche Clinique, EA 3279, Laboratoire de Santé Publique, Aix-Marseille Université, Marseille, France

Correspondence
Gilles Lemesle, MD, PhD, Service USIC et Centre Hémodynamique, Institut Cœur Poumon, Boulevard du Professeur Jules Leclercq, Centre Hospitalier Régional et Universitaire de Lille, 59037 Lille Cedex, France
Email: gilles_lemesle@yahoo.fr

According to recent literature, pretreatment with a P2Y$_{12}$ ADP receptor antagonist before coronary angiography appears no longer suitable in non–ST-segment elevation acute coronary syndrome (NSTE-ACS) due to an unfavorable risk–benefit ratio. Optimal delay of the invasive strategy in this specific context is unknown. We hypothesize that without P2Y$_{12}$ ADP receptor antagonist pretreatment, a very early invasive strategy may be beneficial. The EARLY trial (Early or Delayed Revascularization for Intermediate- and High-Risk Non–ST-Segment Elevation Acute Coronary Syndromes?) is a prospective, multicenter, randomized, controlled, open-label, 2-parallel-group study that plans to enroll 740 patients. Patients are eligible if the diagnosis of intermediate- or high-risk NSTE-ACS is made and an invasive strategy intended. Patients are randomized in a 1:1 ratio. In the control group, a delayed strategy is adopted, with the coronary angiography taking place between 12 and 72 hours after randomization. In the experimental

group, a very early invasive strategy is performed within 2 hours. A loading dose of a $P2Y_{12}$ ADP receptor antagonist is given at the time of intervention in both groups. Recruitment began in September 2016 (n = 558 patients as of October 2017). The primary endpoint is the composite of cardiovascular death and recurrent ischemic events at 1 month. The EARLY trial aims to demonstrate the superiority of a very early invasive strategy compared with a delayed strategy in intermediate- and high-risk NSTE-ACS patients managed without $P2Y_{12}$ ADP receptor antagonist pretreatment.

KEYWORDS

Acute Coronary Syndrome, Antiplatelet Therapy, Invasive Strategy, Percutaneous Coronary Intervention, Randomized Controlled Trial

1 | INTRODUCTION

Revascularization of the culprit lesion in acute coronary syndrome (ACS) is required to prevent coronary-artery occlusion and restore coronary flow.[1–3] Indeed, revascularization with percutaneous coronary intervention (PCI) was found to be superior, associated with reduced death and recurrent myocardial infarction (MI) rates, to conservative management in ACS in a large meta-analysis.[4]

However, 2 strategies have been extensively discussed in the management of non–ST-segment elevation ACS (NSTE-ACS): an early invasive strategy aiming to treat the culprit lesion as soon as possible, and a delayed invasive strategy that aims to stabilize the athero-thrombotic process through medical therapy prior to PCI. Several trials have compared the 2 strategies but have shown no clear benefit of the early over the delayed strategy on hard endpoints. The largest study was the Early vs Delayed Timing of Intervention in Patients With Acute Coronary Syndromes (TIMACS) trial (n = 3031 patients), which showed no significant differences between the 2 strategies on the composite primary endpoint (death, MI, stroke) at 6 months.[5] However, this study was terminated early because of slow enrollment. In addition, a post hoc analysis suggested a reduction of recurrent ischemic events (secondary endpoint) in the early group (<24 hours) compared with the delayed group (36 hours). In a meta-analysis of 10 randomized trials comparing an early and a delayed invasive strategy, we observed the lack of difference in mortality.[6] However, among the 7 studies that recorded ischemic recurrences or refractory angina, an early strategy was shown to be superior to a delayed strategy (odds ratio: 0.54, 95% confidence interval: 0.40-0.74) in preventing these events.

Importantly, the 2 strategies were always compared in patients receiving pretreatment with a $P2Y_{12}$ adenosine diphosphate (ADP) receptor antagonist in the past, but things have recently changed. Pretreatment with a loading dose (LD) of a $P2Y_{12}$ ADP receptor antagonist in the setting of NSTE-ACS was questioned because newer, more potent, and fast-acting drugs (compared with clopidogrel) are now available.[7,8] In a meta-analysis, Bellemain-Appaix et al. suggested that despite its theoretical benefit, pretreatment could lead to a significant bleeding hazard.[9] A Comparison of Prasugrel at PCI or Time of Diagnosis of Non–ST-Elevation Myocardial

Infarction (ACCOAST) confirmed that pretreatment using prasugrel before coronary angiography (CA) may be detrimental due to increased bleeding risk and lack of benefit for ischemic events.[10,11] Furthermore, pretreatment also recently has been questioned in the context of ST-segment elevation MI regarding the results of the 30-Day Study to Evaluate Efficacy and Safety of Pre-Hospital vs In-Hospital Initiation of Ticagrelor Therapy in STEMI Patients Planned for Percutaneous Coronary Intervention (ATLANTIC) and those of the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) presented in 2017 at the European Society of Cardiology (ESC) Congress.[12,13]

In case of the absence of pretreatment, patients will no longer be "protected" pending the invasive procedure and may experience recurrent ischemic events and/or complications. We therefore hypothesize that without pretreatment with a $P2Y_{12}$ ADP receptor antagonist, a very early strategy may be even more beneficial than a delayed strategy. Accordingly, we designed the EARLY trial to randomly compare cardiovascular (CV) death and recurrent ischemic events at 1 month in a very early invasive strategy group (<2 hours) and a delayed strategy group (12–72 hours) in intermediate- and high-risk NSTE-ACS without the use of $P2Y_{12}$ ADP-receptor antagonist pretreatment.

2 | METHODS

2.1 | Study design

The EARLY trial (Early or Delayed Revascularization for Intermediate- and High-Risk Non–ST-Segment Elevation Acute Coronary Syndromes?) is a prospective, multicenter, randomized, controlled, open-label, 2-parallel-group study. The study is registered at http://www.clinicaltrials.gov (NCT02750579). The overall study design is shown in the Figure 1.

Patients are included after informed consent is obtained and then randomized in a 1:1 ratio. In the control group, a delayed strategy is implemented, with CA performed between 12 and 72 hours post-randomization. In the experimental group, a very early invasive strategy is implemented, with CA performed within 2 hours after randomization (for additional details on EARLY study methods, study
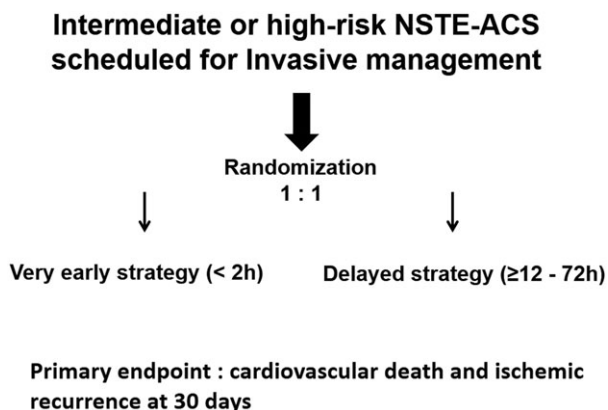
Intermediate or high-risk NSTE-ACS scheduled for Invasive management

↓

Randomization
1 : 1

↓　　　　　　　　　　↓

Very early strategy (< 2h)　　　**Delayed strategy (≥12 - 72h)**

Primary endpoint : cardiovascular death and ischemic recurrence at 30 days

FIGURE 1　Design of the EARLY study. Abbreviations: EARLY, Early or Delayed Revascularization for Intermediate- and High-Risk Non–ST-Segment Elevation Acute Coronary Syndromes?; NSTE-ACS, non–ST-segment elevation acute coronary syndrome

organization, and major committees involved, see Supporting Information, Appendix 1, in the online version of this article). The starting time is designated as the time of randomization to calculate the timing of intervention. It is recommended to all participating centers to randomize patients as soon as possible after the diagnosis of ACS is suspected and an invasive strategy is intended. Randomization in off-hour periods is also promoted. The only difference between the 2 groups of patients included in the study is the timing of the invasive procedure, which will help to limit potential confounders and interactions that could skew the results. In the control group, CA and PCI may be performed before the scheduled time if clinically required based on the physician's decision (based on the occurrence of recurrent ischemic events). In those cases, patients can receive immediate intervention according to the established guidelines.[2,3] The reason for intervention is recorded, and the case is considered as urgent revascularization related to recurrent ischemia.

The study is being performed in accordance with ethical principles consistent with the Declaration of Helsinki. The final study protocol and informed consent have been reviewed and approved by the corresponding health authorities and institutional review boards for all participating sites.

2.2 | Participants

The inclusion criteria for the EARLY trial were designed to enroll a representative population of patients with an intermediate- or high-risk NSTE-ACS (as defined by ESC guidelines)[3] and are summarized in Table 1. Study patients must present with suspected NSTE-ACS defined by the presence of ≥2 of the following criteria: (1) symptoms of myocardial ischemia (prolonged chest pain at rest and/or new-onset chest pain suggestive of angina); (2) electrocardiographic (ECG) ST-segment abnormalities (depression or transient elevation of ≥0.1 mV) or T-wave inversion in ≥2 contiguous leads; or (3) an elevated cardiac troponin (Tn) value (>upper limit of normal). Patients must also require CA according to physician's judgment.

Key exclusion criteria are summarized in Table 1. Pretreatment with an LD of a P2Y$_{12}$ ADP receptor antagonist is not allowed before

CA. The LD of a P2Y$_{12}$ ADP receptor antagonist is given at the time of PCI in both groups.

Recruitment to the EARLY trial began in September 2016, and 558 patients have been recruited so far (October 29, 2017). The primary baseline characteristics that will be collected in this trial are shown in Supporting Information, Table 1, in the online version of this article.

2.3 | Treatment protocol and interventions

Medical care will be performed according to the ESC guidelines.[1,3] Patients will be monitored in the intensive care unit.

2.3.1 | Concomitant antithrombotic therapies

Patients will receive aspirin and anticoagulant therapy as soon as the diagnosis is made and the invasive strategy is intended. The use of these therapies and the doses will be recorded in the electronic case report form. An intravenous LD of 250 mg followed by a daily oral maintenance therapy of 75 to 160 mg of aspirin is encouraged. The choice and dose of the anticoagulant should also reflect the current standard practices. Intravenous or subcutaneous anticoagulant can be started as soon as the diagnosis is reached and should be discontinued at the conclusion of the PCI procedure (with the exception of bivalirudin, which may be continued for up to 4 hours after the PCI). Any upstream use (before the CA) of a glycoprotein (GP) IIb/IIIa inhibitor is not allowed. The use of GPIIb/IIIa inhibitors immediately before and/or after PCI is, however, permitted. The ultimate decision regarding antithrombotic dose and administration regimen is left to the investigator's discretion.

2.3.2 | Coronary revascularization

The decision regarding the need for any coronary revascularizations or to pursue medical therapy alone is left to the investigator's discretion. Optimal medical therapies are encouraged in all cases according to guidelines. Patients can be managed with medical therapy alone or medical therapy combined with coronary revascularization using PCI, coronary artery bypass grafting (CABG), or a combination of both, according to the physician's decision.

When PCI is considered to be appropriate, investigators are required to treat the culprit vessel in the same setting. In cases of multivessel disease, nonculprit vessels could be treated in the same setting or in a staged fashion, according to the investigator's preferences. A LD of a P2Y$_{12}$ ADP receptor antagonist is given at the time of PCI in both groups. The choice of the P2Y$_{12}$ ADP receptor antagonist (clopidogrel, prasugrel, or ticagrelor) is left to the physician's discretion. The use of new P2Y$_{12}$ ADP receptor inhibitors (prasugrel or ticagrelor) is promoted unless contraindicated. The anticoagulant used during PCI and the use of GPIIb/IIIa inhibitors (among the drugs listed in the guidelines) will be left at the physician's discretion. The use of drug-eluting stents and other state-of-the-art interventions is encouraged in both groups.

Based on the physician's judgment, patients may be scheduled for CABG. In these cases, arterial grafts (especially the use of internal mammary arteries) and complete revascularization will be promoted whenever possible.

TABLE 1 Inclusion and exclusion criteria of the EARLY study

Inclusion criteria

Male or female, age ≥ 18 y. Females must not be of childbearing potential (1 year postmenopausal, using contraceptives, or surgically sterile).

Subjects with NSTE-ACS defined by the presence of ≥2 of the following criteria: (1) symptoms of myocardial ischemia; (2) on ECG, ST-segment abnormalities (depression or transient elevation of ≥0.1 mV) or T-wave inversion in ≥2 contiguous leads; (3) elevated cardiac Tn value (>ULN)

Subjects requiring intervention according to physician's judgment, including the following criteria (risk factor defining intermediate- and high-risk ACS): DM, kidney failure, reduced LVEF, CHF, early post-infarction angina, recent PCI, prior CABG, or GRACE risk score > 109

Must be enrolled at a hospital with a cardiac catheterization laboratory

Must be affiliated to or beneficiary of a social security system

Must have signed written informed consent

Exclusion criteria

Minors and pregnant or breastfeeding females

Subjects with stable CAD

Subjects with low-risk ACS

Subjects with very high-risk ACS, as follows: (1) refractory angina, life-threatening ventricular arrhythmias, and hemodynamic instability requiring immediate intervention; or (2) cardiogenic shock (SBP <90 mmHg associated with clinical evidence of end-organ hypoperfusion or subjects requiring vasopressors to maintain SBP >90 mmHg and associated with clinical evidence of end-organ hypoperfusion)

Subjects with STEMI at the time of entry or randomization into the study, defined as a history of chest discomfort or ischemic symptoms of >20 minutes' duration at rest ≤14 days prior to entry into the study with 1 of the following present on ≥1 ECG prior to randomization:

ST-segment elevation ≥1 mm in ≥2 contiguous ECG leads

New or presumably new LBBB

ST-segment depression ≥1 mm in 2 anterior precordial leads (V_1 through V_4) with clinical history and evidence suggestive of true posterior infarction

Subjects with bleeding diathesis

Subjects with upstream pretreatment with any LD of $P2Y_{12}$ receptor antagonists

Subjects with upstream treatment by a GPIIb/IIIa inhibitor

Subjects on chronic anticoagulant therapy

Subjects with thrombolytic therapy during the preceding 24 hours

Subjects with contraindication to $P2Y_{12}$ receptor antagonists (clopidogrel, ticagrelor, and prasugrel)

Subjects not agreeing to participate and/or participating in another research protocol

Subjects wishing to interrupt their participation during the study

Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; DM, diabetes mellitus; EARLY, Early or Delayed Revascularization for Intermediate- and High-Risk Non–ST-Segment Elevation Acute Coronary Syndromes?; ECG, electrocardiogram; GP, glycoprotein; GRACE, Global Registry of Acute Cardiac Events; LBBB, left bundle branch block; LD, loading dose; LVEF, left ventricular ejection fraction; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; Tn, troponin; ULN, upper limit of normal.

2.3.3 | Other care management

Electrocardiographic monitoring and biomarker measurement are performed according to the usual guidelines. Tn must be measured every 6 hours until the peak has been reached and daily thereafter until discharge. ECG and blood samplings are to be performed in addition to Tn measurement during each recurrent chest pain event during the hospital stay to detect ongoing necrosis and periprocedural MI. The patients are monitored for recurrent myocardial ischemia with ECG monitoring and daily clinical examinations until discharge.

2.4 | Follow-up and study outcomes

Randomized patients will return for study visits at discharge and at 1 and 12 months. During the follow-up visits, the patients will be assessed for any adverse or potential endpoint events. A subject will be considered lost to follow-up if he or she fails to return or is unable to be contacted by the site for the scheduled visit at 1 month. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit.

All events will be adjudicated by an independent Clinical Endpoints Committee, including all deaths, recurrent ischemic events, MI, stroke, and Bleeding Academic Research Consortium (BARC) bleeds according to usual definitions.[14–17]

The primary endpoint is defined as the rate of CV death and recurrent ischemic events at the 1-month follow-up. CV death is defined as death attributable to CV disease, sudden death, or death not clearly attributable to non-CV causes (for a detailed definition, see Supporting Information, Appendix 1, in the online version of this article). Recurrent ischemic events are defined by the occurrence of ≥1 of the following events:

- Symptoms of ischemia, including chest pain, increasing dyspnea, and/or epigastric pain (as mentioned in the ESC guidelines) with one of the following conditions: (1) no alternate etiology, lasting >10 minutes, nitro-resistant, and requiring emergent angiography; (2) the presence of dynamic ECG changes; and/or (3) Tn elevation (20% increase) compared with the previous levels.
- Ventricular arrhythmias, including ventricular fibrillation and sustained ventricular tachycardia.

- Acute pulmonary edema requiring oxygen therapy.
- Cardiogenic shock, as defined by systolic arterial pressure of <90 mmHg for >30 minutes or the need for catecholamine therapy to maintain the systolic arterial pressure > 90 mmHg plus signs of pulmonary congestion and impaired end-organ perfusion.

Secondary efficacy and safety endpoints are summarized in Table 2. The date of the occurrence will be collected. The delay will be calculated from the randomization day to the date of the occurrence.

2.5 | Sample size

The sample-size calculation was performed on the hypothesis formulated regarding the primary endpoint (ie, the rate of CV death and recurrent ischemic events). The most recent literature (at time of our study conception) describing the timing of intervention in the clinical setting is the Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndrome (ABOARD) trial.[18] This publication reported a rate of recurrent ischemia (secondary endpoint) of 18.6% in the delayed intervention group within the first month. In addition, they observed a 40% reduction in recurrent ischemia with early intervention compared with a delayed strategy. Based on these data, we made the following assumptions: The estimated rate of the composite of CV death and recurrent ischemia at 1 month will be 20% in the control group (delayed intervention) and 12% in the experimental group (immediate intervention). With an α risk of 5%, an 80% power, and considering a 5% potential loss-to-follow-up rate at 1 month, a total of 370 subjects per group will be required (total of 740 subjects). Calculations were made using Power Analysis and Sample Size (PASS)

software, version 2008 (NCSS, Kaysville, UT). According to the annual number of eligible patients in the participating centers, we estimate that a 24-month inclusion period will be necessary.

2.6 | Randomization

Computer-generated randomized lists have been drawn up using a permuted block design (stratified on center). Each center has a specific list.

2.7 | Statistical analysis

Statistical analysis of this study will be carried out in a blinded manner. The data will be analyzed using SPSS version 17.0 software (SPSS Inc., Chicago, IL). Statistical significance is defined as $P < 0.05$. The methodology will be based on the Consolidated Standards of Reporting Trials statement (CONSORT, http://www.consort-statement.org/consort-statement/).[19] The full analysis population (including all subjects who will be randomized and be evaluated at baseline) will be used in the primary analysis (intention-to-treat analysis). The per-protocol population (including all subjects who will be randomized without major protocol deviations) will be used in the secondary analysis to assess the robustness of the results. No interim analysis is planned. The demographic and baseline characteristics will be summarized and compared between the 2 groups using the χ^2 test for qualitative variables and Student t test for continuous variables. The rates of CV death and recurrent ischemic events at 1 month (primary endpoint) will be estimated in both groups using the Kaplan–Meier method. The analysis of the primary endpoint will be based on the intention-to-treat principle using the Cox proportional hazard

TABLE 2 Secondary endpoints of the EARLY study

Secondary efficacy endpoints

The rate of CV death and recurrent ischemic events at the other evaluation times (at discharge and at 12 months post-randomization)
The rate of CV death and recurrent ischemic events in the subgroup of patients who had PCI during the index hospitalization at discharge and at 1 and 12 months
The rate of CV death and recurrent ischemic events in the subgroups of patients who were and those who were not under a chronic maintenance dose of any P2Y$_{12}$ ADP receptor antagonist before randomization at discharge and at 1 and 12 months
The rate of CV death and recurrent ischemic events in the subgroups of patients based on the GRACE score (<140 vs ≥140)
The occurrence of MACE at discharge, and at 1 and 12 months post-randomization. MACE will be defined by the occurrence of ≥1 of the following criteria: CV death (as defined above), nonfatal MI (defined as any recurrent myocardial necrosis occurring either spontaneously or in the setting of revascularization according to the universal definition), urgent revascularization (any revascularization either by PCI or CABG that was not planned), and recurrent ischemic events (as defined above). MI, included as efficacy endpoints, must be distinct from the qualifying MI event.
All-cause death at discharge and at 1 and 12 months
Probable and definite stent thrombosis (ARC definition) at discharge and at 1 and 12 months
Rate of hospital readmission at 1 and 12 months
Overall length of stay in hospital, which is defined as the no. of days between admission and discharge from the index hospitalization
Urgent revascularization prior to the planned coronary angiogram (PCI or CABG surgery) that is driven by symptoms of ischemia that worsened while waiting for the initially scheduled coronary angiography. PCI that, in the investigator's opinion, requires catheterization prior to the planned time of the procedure at discharge and at 1 and 12 months.
AUC of Tn as a measure of infarct size for the index event

Secondary safety endpoints

The occurrence of bleeding using the BARC classification ≥3 at discharge and at 1 and 12 months

Abbreviations: ADP, adenosine diphosphate; ARC, Academic Research Consortium; AUC, area under the curve; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; CV, cardiovascular; EARLY, Early or Delayed Revascularization for Intermediate- and High-Risk Non–ST-Segment Elevation Acute Coronary Syndromes?; GRACE, Global Registry of Acute Cardiac Events; MACE, major adverse cardiac events; MI, myocardial infarction; PCI, percutaneous coronary intervention.

model and log-rank test with a factor for the treatment group. The hazard ratios for immediate vs delayed intervention will be presented with 95% confidence intervals. The primary endpoint analysis and all other key efficacy and safety analyses will be conducted using the 2-sided log-rank test from a time-to-first event analysis, unless otherwise specified. Time-to-event is defined as the time from randomization to the onset of the endpoint. Rates of secondary endpoints will be compared between the 2 groups using the same procedure, except that the hospitalization length of stay will be compared between the 2 groups using the Student t test. Planned post-hoc analyses and substudies are detailed in Supporting Information, Appendix 1, in the online version of this article).

3 | DISCUSSION

Despite the fact that several randomized trials[18,20–24] have been performed to assess the optimal delay for performing CA in patients with intermediate- or high-risk NSTE-ACS, this matter remains largely unresolved. This issue is even more pertinent because, until recently, a delayed strategy was preferred with the following assumptions: first, antithrombotic and slow-acting antiplatelet therapies were initiated to prepare the culprit atherothrombotic lesion for subsequent revascularization (thus limiting periprocedural complications); and second, this strategy would be relatively safe because the patients were under the "protection" of antithrombotic therapy (thus avoiding recurrent ischemic events pending the CA). However, because pretreatment using a LD of a $P2Y_{12}$ ADP receptor antagonist failed to demonstrate any clinical benefit in NSTE-ACS patients,[9–11] these theories are no longer scientifically based.

The reason for the lack of benefit of pretreatment by a $P2Y_{12}$ ADP receptor antagonist is multifactorial. First, according to recent registries, up to 25% of the patients presenting with suspected NSTE-ACS do not undergo PCI after the assessment of coronary anatomy because of coronary lesions requiring CABG surgery, coronary lesions requiring optimal medical treatment only, or even because of an incorrect diagnosis.[4,25,26] In these latter cases, the benefit of pretreatment with a $P2Y_{12}$ ADP receptor inhibitor may be reduced, whereas the risk of bleeding persists. In addition, this cohort of patients who do not require PCI may even be larger in modern practice because new hypersensitive Tn assessments are being used, which certainly increases sensitivity but also decreases specificity.[27] Second, because new more potent and fast-acting drugs (compared with clopidogrel) are available, some experts have therefore suggested waiting for the coronary anatomy assessment before $P2Y_{12}$ ADP receptor inhibitor administration.[9] A recent meta-analysis[9] suggested that pretreatment is not associated with an improved clinical outcome and could lead to an increase in bleeding events. The ACCOAST trial confirmed that pretreatment using prasugrel may be detrimental due to the increased bleeding risk with no benefit for ischemic events.[10,11] However, several considerations should be highlighted. The delay between the diagnosis of NSTE-ACS and the CA was very short in the ACCOAST trial (mean of 4 hours), which limits the extrapolation of the trial results to current practice. Moreover, if we look back to the Clopidogrel in Unstable Angina to

Prevent Recurrent Events (CURE) trial results, focusing on the period between the diagnosis of NSTE-ACS and the CA, it is important to note that this delay was much longer than the one observed in the ACCOAST trial (approximately 10 days) and that the rate of the composite endpoint, MI and refractory ischemia, was significantly higher in the placebo group than in the clopidogrel group (15.3% vs 12.1%).[28] We therefore hypothesize that without $P2Y_{12}$ ADP receptor antagonist pretreatment, a very early strategy may be more beneficial than a delayed strategy to prevent events in intermediate- and high-risk NSTE-ACS.

The exclusion criteria have been carefully chosen to select only patients with intermediate- or high-risk NSTE-ACS, which is the patient population in which the question of the optimal delay of coronary anatomy assessment is relevant. In addition, patients who received any LD of a $P2Y_{12}$ ADP receptor inhibitor as pretreatment or upstream GPIIb/IIIa inhibitor treatment will be excluded from the present study. However, our goal was also to include a broad and representative population of NSTE-ACS patients that matches the patients seen in clinical practice. For that purpose, patients under a chronic maintenance dose of a $P2Y_{12}$ ADP receptor antagonist (especially clopidogrel at 75 mg daily) will not be excluded from our study. In previous studies, the use of an additional LD of a $P2Y_{12}$ ADP receptor antagonist in patients under chronic therapy and suffering a recurrent ACS has been shown to be beneficial for ischemic events.[29,30] Therefore, in our opinion, the question largely pertains to this subgroup. In addition, a prespecified analysis of this subgroup of patients is already scheduled to better comprehend the impact of chronic $P2Y_{12}$ ADP receptor antagonist treatment on our results (see Supporting Information, Appendix 1, in the online version of this article).

Finally, we defined our primary endpoint as the rate of CV death and recurrent ischemic events (including recurrent ACS) at the 1-month follow-up (composite criteria). Such a composite event was, in fact, the one that has been shown to benefit from implementing an early strategy in previous trials such as TIMACS (although it was defined as a secondary endpoint in that specific study).[5] In addition, in a recent meta-analysis that focused on the impact of a very early invasive strategy on the outcomes in NSTE-ACS patients, we observed differences in recurrent ischemic events and the length of hospital stay, which were both significantly lower in the group of patients managed with an early invasive strategy.[6] Therefore, the composite endpoint that was chosen for the present study seems appropriate to test our hypothesis. Recurrent ischemic events have been defined using a broad definition to prevent underestimation and include clinically relevant events.

3.1 | Challenges and limitations of the study design

We acknowledge that the open nature of our study could be a limitation, as it was the case in similar previous trials. It is, however, the only possible way to conduct such a trial. This limitation is reduced when you select a hard endpoint (eg, death, MI, or stroke), as in TIMACS, for example, or when you select a blinded uncontrollable endpoint (eg, Tn peak level, as in ABOARD).[5,18] Here, we made the choice to select a "soft" composite primary endpoint (eg, CV death and recurrent ischemia), which was, in fact, the one that has shown benefit of an early

strategy in previous trials (although defined as a secondary end-point).[5,31] In a recent meta-analysis (including 10 studies and 6397 patients), we did not observe any difference between groups on hard endpoints (CV mortality or MI), but only on recurrent ischemic events.[6] Therefore, the composite endpoint that we have chosen looks appropriate to test our hypothesis and is of clinical interest because it reflects how patients are managed in current practice. Such a "soft" endpoint may, however, expose the trial to potential bias in judgment by investigators, and we acknowledge that the independent Clinical Endpoints Committee cannot change this, as they will validate the decision of CA and subsequent PCI previously made by investigators. However, we would highlight that only suggestive symptoms that require an emergent coronary angiography be performed will be classified as "recurrent ischemia." More important, if angiography shows no culprit lesion, then the endpoint would not be met. Finally, hard endpoints (all-cause death, CV death, MI), as well as Tn value, will also be collected and analyzed as secondary endpoints in our study.

We also acknowledge that our study is not an event-driven trial. Subsequently, the power could be lower than expected if the event rate is substantially below 20% in the "delayed" group as anticipated. Our sample size was derived from the results of ABOARD, which was the most recent study reporting data on recurrent ischemia at 30 days at the time of our study conception. In ABOARD, the rate of recurrent ischemia at 30 days was 18.6% in the "delayed" group and 12% in the "early" group ($P = 0.08$).[18] We therefore anticipated a rate of CV death and recurrent ischemia of 20% in the "delayed intervention" group within the first month and a 40% reduction in this composite endpoint in the "early intervention" group. We plan to enroll twice as many patients as compared with the ABOARD trial. In addition, it should be underlined that the "early" group in our study is similar to the "immediate" strategy of the European guidelines, thus reducing to the minimum the potential for recurrent ischemia pending the CA in this group. It is important to notice that the results of the recent Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients (RIDDLE-NSTEMI) study, published in 2016 after our study conception, are very concordant and support our power calculation.[31] Indeed, in that study the rate of recurrent ischemia was 15.5% in the "delayed" group, vs 3.7% in the "early" group ($P = 0.001$). A recent meta-analysis focusing on this specific endpoint also supports our sample-size calculation.[6]

Another point that should be highlighted is that the timing for setting the invasive procedure will start at randomization in both groups, and there is unfortunately no possibility to do it in a different manner in regard to ethics. It is, however, recommended that randomization occur as soon as possible after the diagnosis of ACS is suspected and an invasive strategy is intended. Randomization in off-hour periods is also promoted in all participating centers. Previous trials in the field have managed this way.

Finally, we recommend the use of ticagrelor or prasugrel (over clopidogrel) anytime it is possible. We acknowledge that chewing/crushing these drugs may further shorten the delay of action, but such data were not available at the time of study conception and this strategy is therefore not recommended in our trial. The use of cangrelor is also not recommended, as it is not available in France at the current time.

4 | CONCLUSION

The EARLY trial aims to compare CV death and recurrent ischemic events at 1 month in a very early invasive strategy group (<2 hours) compared with a delayed strategy group (12–72 hours) in intermediate- or high-risk NSTE-ACS patients managed without P2Y$_{12}$ ADP receptor antagonist pretreatment.

Conflicts of interest

G.L. reports receiving lecture and/or consulting fees from Amgen, AstraZeneca, Bayer, Biopharma, Bristol-Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, Merck Sharp & Dohme, Novartis, Pfizer, Sanofi-Aventis, Servier, and The Medicines Company. The authors declare no other potential conflicts of interest.

ORCID

Gilles Lemesle https://orcid.org/0000-0002-2917-9273

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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