Less bleeding by omitting aspirin in non-ST-segment elevation acute coronary syndrome patients: rationale and design of the LEGACY study

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Less bleeding by omitting aspirin in non-ST-segment elevation acute coronary syndrome patients: Rationale and design of the LEGACY study

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Background Early aspirin withdrawal, also known as $P2Y_{12}$-inhibitor monotherapy, following percutaneous coronary intervention (PCI) for non-ST-segment elevation acute coronary syndrome (NSTE-ACS) can reduce bleeding without a trade-off in efficacy. Still the average daily bleeding risk is highest during the first months and it remains unclear if aspirin can be omitted immediately following PCI.

Methods The LEGACY study is an open-label, multicenter randomized controlled trial evaluating the safety and efficacy of immediate $P2Y_{12}$-inhibitor monotherapy versus dual antiplatelet therapy (DAPT) for 12 months in 3,090 patients. Patients are randomized immediately following successful PCI for NSTE-ACS to 75-100 mg aspirin once daily versus no aspirin. The primary hypothesis is that immediately omitting aspirin is superior to DAPT with respect to major or minor bleeding defined as Bleeding Academic Research Consortium type 2, 3, or 5 bleeding, while maintaining noninferiority for the composite of all-cause mortality, myocardial infarction and stroke compared to DAPT.

Conclusions The LEGACY study is the first randomized study that is specifically designed to evaluate the impact of immediately omitting aspirin, and thus treating patients with $P2Y_{12}$-inhibitor monotherapy, as compared to DAPT for 12 months on bleeding and ischemic events within 12 months following PCI for NSTE-ACS. (Am Heart J 2023;265:114–120.)

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Abbreviations: ACS, Acute Coronary Syndrome; BARC, Bleeding Academic Research Consortium; CCS, Chronic Coronary Syndrome; DAPT, Dual AntiPlatelet Therapy; LEGACY, Less Bleeding by Omitting Aspirin in non-ST-segment Elevation Acute Coronary Syndrome Patients; MI, Myocardial Infarction; NSTE-ACS, non-ST-segment Elevation Acute Coronary Syndrome; NSTEMI, non-ST-segment Elevation Myocardial Infarction; PCI, Percutaneous Coronary Intervention.

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Dual antiplatelet therapy (DAPT), consisting of aspirin and a $P2Y_{12}$-inhibitor, reduces the risk of stent-related and spontaneous recurrent ischemic events among patients undergoing percutaneous coronary intervention (PCI) for non-ST-segment elevation acute coronary syndrome (NSTE-ACS).[1] Traditionally, DAPT has been recommended for at least 12 months following first-generation drug-eluting stent implantation due to concerns over (very) late stent thrombosis.[2,3] However, the reduction in ischemic events achieved by DAPT is counterbalanced by an increase in bleeding and contrary to popular belief, these bleeding events are associated with significant morbidity and mortality.[4,5] Combined with improvements in stent technology and pharmacology, better understanding of the prognostic impact of bleeding has led to renewed focus on early de-escalation of antithrombotic therapy.

Historically, novel antithrombotic strategies have been tested on a background of aspirin, but in recent years several randomized controlled trials have demonstrated that early aspirin withdrawal (ie, $P2Y_{12}$-inhibitor monotherapy) significantly reduces bleeding without an increase in ischemic events.[6-11] Still, all previous trials included at least 1 to 3 months of DAPT before stopping aspirin, whereas the average daily bleeding risk is highest during this early period following PCI.[12] So far, immediately omitting aspirin following PCI has only been tested in small, single-arm studies.[13-15] These studies demonstrated the feasibility of immediate aspirin withdrawal, but were not powered to assess the safety and efficacy of this novel strategy. Therefore, we designed the "Less Bleeding by Omitting Aspirin in non-ST-segment Elevation Acute Coronary Syndrome Patients" (LEGACY) study to test the hypothesis that immediately omitting aspirin reduces bleeding and is noninferior with regard to ischemic events compared to DAPT in the 12 months following PCI for NSTE-ACS.

Methods

Study organization and objective

The LEGACY study (ClinicalTrials.gov unique identifier NCT05125276) is an open-label, multicenter randomized controlled trial designed and sponsored by the Amsterdam University Medical Centers. The study is funded through a research grant from the Rational Pharmacotherapy Programme of ZonMw (grant number: 10140022010007) and a research grant from AstraZeneca. The steering committee is solely responsible for the study design, trial execution, data-analysis and reporting of results. The primary objective of our study is to determine the impact of immediately omitting aspirin, and thus treating patients with $P2Y_{12}$-inhibitor monotherapy, as compared to DAPT for 12 months on bleeding and ischemic events within 12 months following PCI for NSTE-ACS (Figure 1). The study has been designed in accordance with the principles of the Declaration of Helsinki, including the requirement for each patient's written informed consent before initiation of any study-specific procedures.

Study population

Patients presenting with acute chest pain (or equivalent symptoms) without persistent ST-segment elevation (ie, NSTE-ACS) who undergo successful PCI are considered eligible for the study, as shown in Table 1. Diagnosis is classified as non-ST-segment elevation myocardial infarction (NSTEMI) or unstable angina based on diagnostic criteria outlined in current European Society of Cardiology (ESC) guidelines.[1] In short, patients are diagnosed with NSTEMI in case of a rise and/or fall pattern of cardiac troponin with at least 1 value above the 99th percentile of the upper reference limit. If patients do not have elevated cardiac troponin levels or no rise and/or fall pattern, they are diagnosed with unstable angina. Patients with an allergy or contraindication for aspirin and/or all commercially available $P2Y_{12}$-inhibitors (ie, ticagrelor, prasugrel or clopidogrel) are excluded as are patients requiring chronic oral anticoagulant therapy. Patients who have an ongoing indication for DAPT or a planned surgical intervention within 12 months of PCI are also excluded. Pregnant or breastfeeding women at time of enrolment are excluded and patients are not permitted to participate in another trial with an investigational drug or device.

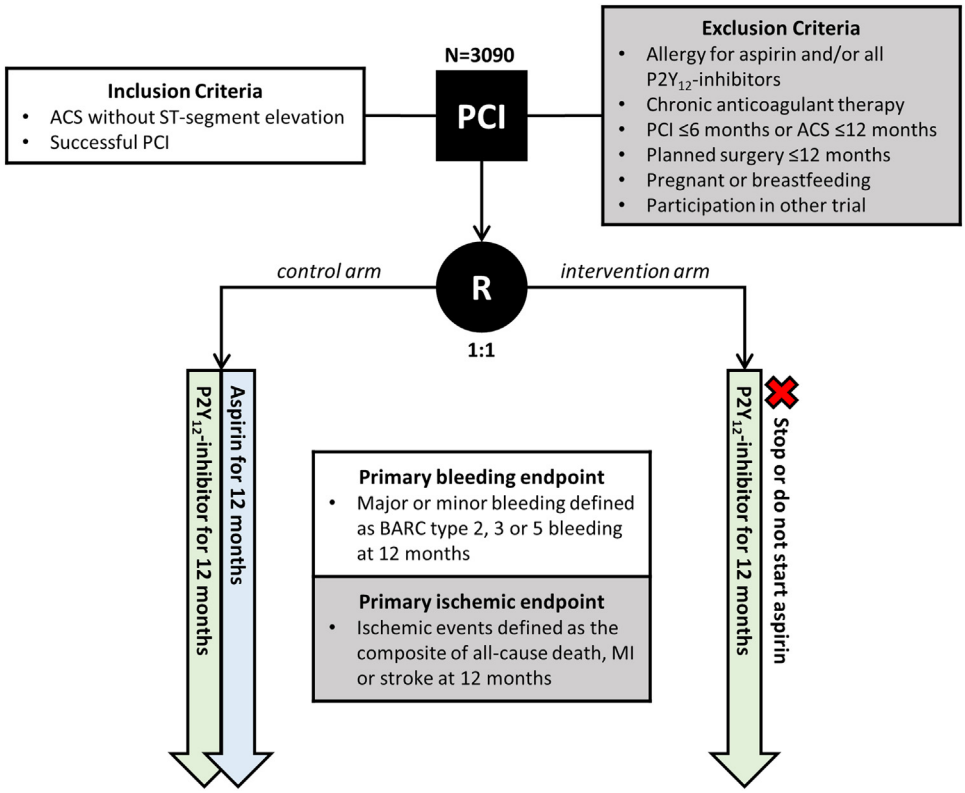
Informed consent and randomization

Patients diagnosed with NSTE-ACS who are scheduled for coronary angiography and possible (ad hoc) PCI are asked to participate. If patients consent before PCI, the in- and exclusion criteria are reassessed after PCI and before randomization. Patients are then randomized in a 1:1 ratio. Randomization occurs in the time window immediately after successful PCI, but no later than the moment of the first planned aspirin administration following PCI (ie, typically the morning after PCI). The allocation sequence is concealed from relevant staff and is computer generated using the Castor randomization website. Randomization is stratified per study site and $P2Y_{12}$-inhibitor of choice and performed using varying block sizes of 4, 6, and 8. The allocated treatment regimen is implemented immediately after randomization.

Study treatment

The investigational antiplatelet regimen is the complete omission of aspirin immediately after PCI. In the control arm, patients receive 75 to 100 mg aspirin once daily in line with current ESC guidelines.[1] Enrolled patients remain on the assigned treatment regimen until 12 months after randomization. Treatment regimens

Figure 1



Study design.
ACS, acute coronary syndrome; BARC; Bleeding Academic Research Consortium; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table I. Inclusion and exclusion criteria

Inclusion criteria
• Clinical diagnosis of non-ST-segment elevation acute coronary syndrome • Successful PCI
Exclusion criteria
• Known allergy or contraindication for aspirin or all commercially available $P2Y_{12}$-inhibitors (ie, ticagrelor, prasugrel, and clopidogrel) • Concurrent use of oral anticoagulants (eg, because of atrial fibrillation) • Ongoing indication for DAPT at admission (eg, due to recent PCI or ACS) • Planned surgical intervention within 12 months of PCI • Pregnant or breastfeeding women at time of enrolment • Participation in another trial with an investigational drug or device

ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

are implemented through regular drug prescription. All patients regardless of randomization receive a $P2Y_{12}$-inhibitor for at least 12 months following PCI. The dose regimen including the administration and timing of a loading dose and choice of a specific $P2Y_{12}$-inhibitor is at the discretion of the treating physician, but should be in line with current ESC guidelines.[1] However, if clopidogrel is chosen as the $P2Y_{12}$-inhibitor of choice, CYP2C19 genotyping and platelet function testing are mandatory.[16] More specifically, carriers of CYP2C19*2

Table II. Study endpoints

Primary endpoints*
Time until the occurrence of: • Primary bleeding endpoint: major or minor bleeding defined as BARC type 2, 3, or 5 bleeding (superiority testing) • Primary ischemic endpoint: ischemic event defined as the composite of all-cause death, MI, or stroke (noninferiority testing)
Secondary endpoints*
Time until the occurrence of: • Net adverse clinical event defined as the composite of all-cause death, MI, stroke or major bleeding defined as BARC type 3 or 5 bleeding • Major bleeding • Individual components of the primary endpoints • Repeat revascularization • ARC defined definite or probable stent thrombosis

ARC, Academic Research Consortium; BARC, Bleeding Academic Research Consortium; MI, myocardial infarction; PCI, percutaneous coronary intervention.
*The primary and secondary endpoints will be tested in hierarchical order to preserve type I error rate.

or CYP2C19*3 loss-of-function alleles should not be treated with clopidogrel as well as patients with high on-treatment platelet reactivity. Patients with agent-specific side-effects are allowed to switch between type of $P2Y_{12}$-inhibitor during follow-up according to the algorithm recommended by the ESC.[17]

If patients develop a new indication for chronic oral anticoagulation therapy after randomization (eg, because of new onset atrial fibrillation), physicians are recommended to follow current ESC guidelines and stop aspirin and/or switch the $P2Y_{12}$-inhibitor of choice if required regardless of randomization.[1] In patients on ticagrelor or prasugrel, ticagrelor or prasugrel is switched to clopidogrel regardless of randomization. In patients on aspirin in the control arm who develop an indication for chronic oral anticoagulation therapy, aspirin should be stopped after a short period (up to 1 week after the acute event) of triple antithrombotic therapy in accordance with current ESC guidelines.[1] All patients regardless of randomization should receive a proton pump inhibitor if indicated according to current ESC guidelines.[1]

Follow-up

Clinical follow-up is performed at 1, 3, 6, and 12 month(s) by telephone contact. As part of follow-up patients are asked to complete the EQ-5D-5L questionnaire, Institute for Medical Technology Assessment (iMTA) Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ) at various time points. Additionally, patients attend in-person visits at the outpatient clinic at regular intervals as part of routine clinical practice. During follow-up, investigators assess the occurrence of any adverse events including the occurrence of the primary bleeding or ischemic endpoint. Furthermore, patient-reported treatment adherence is checked at each follow-up moment and treatment adherence is corroborated by prescription refill data reported by the pharmacy. Any modification to the antiplatelet regimen during follow-up is documented including the date and reason for modification.

Study endpoints

The primary bleeding and ischemic endpoints are shown in Table 2. The primary bleeding outcome is the time till first occurrence of major or minor bleeding defined as Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding within 12 months following PCI.[18] In brief, BARC type 2, 3, or 5 bleeds are defined as clinically overt hemorrhage requiring medical attention (type 2), requiring transfusion, surgical correction or associated with a significant hemoglobin drop (type 3) or fatal events (type 5).[18] BARC type 3 or 5 bleeding are considered major bleeding, while type 2 is considered minor bleeding. Previous studies have shown that BARC type 2 and 3 bleeds are independently associated with increased mortality and reduced health-related quality of life, thereby justifying their inclusion within the primary bleeding endpoint.[5,19] The primary ischemic endpoint is the time till first occurrence of all-cause death, myocardial infarction (MI) or stroke. MI and stroke are included in the primary ischemic endpoint regardless of etiology. MI is classified according to the 4th universal definition of MI which includes stent thrombosis (MI type 4b).[20]

The key secondary endpoints include the time until: (1) net adverse clinical event defined as the composite of all-cause mortality, MI, stroke, or major bleeding, (2) major bleeding, (3) the individual components of the primary endpoints, (4) repeat (urgent) revascularization and (5) Academic Research Consortium (ARC) defined definite or probable stent thrombosis. All primary and secondary endpoints will be adjudicated by an independent clinical event committee. Members of this committee will be blinded to treatment allocation.

Sample size calculations

Our power calculation is based on a superiority comparison for the primary bleeding endpoint and a noninferiority comparison for the primary ischemic endpoint within 12 months after randomization. Based on previous randomized controlled trials evaluating $P2Y_{12}$-inhibitor monotherapy following PCI, the anticipated bleeding rate in the control arm is 5.0% compared to 3.0% in the intervention arm, a relative reduction in bleeding of 40%.[6-10] The anticipated rate of ischemic events is 3.5% in both groups.[6-10] The present trial will require 3,012 and 2,652 patients to detect the projected reduction in bleeding and to rule out an absolute difference in risk of 2.0 percentage points regarding ischemic events with at least 80% power, respectively. To account for a 2.5% loss to follow-up, 3,090 patients will be enrolled. The superiority hypothesis is tested using a 2-sided α of 0.05 and the noninferiority hypothesis is tested using a 1-sided α of 0.025. All other hypotheses tests will be performed using a 2-sided α of 0.05 unless specifically stated otherwise.

Statistical analysis plan

The primary bleeding and ischemic analyses will be conducted using data from all randomized patients according to the intention-to-treat principle. Event rates of the primary bleeding and ischemic endpoints at 12 months after randomization are estimated using the Kaplan-Meier method. In order to preserve type 1 error rate, the superiority hypothesis for the primary bleeding endpoint and the noninferiority hypothesis for the primary ischemic endpoint will be tested in hierarchical order. First, we will test if omitting aspirin is superior to standard DAPT in terms of major or minor bleeding at 12 months. Data from patients who do not meet the primary bleeding endpoint between randomization and 12 months are censored at time of death, time of last contact or at the end of follow-up, whichever comes first. Hazard ratios and 95% confidence intervals (CI) are generated using Cox proportional hazard methods. Absolute differences and 95% CI are calculated with Kaplan-Meier estimates and Greenwood standard errors. For the superiority analysis, we will use a 2-sided α of 0.05. Superiority of completely omitting aspirin will be declared if the 95% CI of the absolute rate differences excludes 0.0% which is equivalent to a *P*-value for the log-rank test below .05. If immediately omitting aspirin is superior to standard DAPT with regards to the primary bleeding endpoint, we will test if omitting aspirin is noninferior to standard DAPT in terms of ischemic events at 12 months. Data from patients who do not meet the primary ischemic endpoint are censored at time of last contact or at the end of follow-up. Noninferiority of completely omitting aspirin is declared if the 95% CI of the rate difference is less than or equal to 2.0%. Both analyses will be repeated in the per protocol cohort to support the primary results. In the per protocol cohort, patients who start (or continue) aspirin in the intervention arm or discontinue aspirin in the control arm after randomization will be censored at time of treatment modification, thus only take into account events that occur while the patient is on the allocated treatment. Data analysts will be blinded to treatment allocation.

Predefined subgroup analyses

Incidence for the primary bleeding and ischemic endpoints at 12 months following PCI will be calculated in the following subgroups: Age $\geq$75 years, female sex, NSTE-ACS subtype, diabetes mellitus, chronic kidney disease (eGFR $<$60 mL/min/1.73m^2), history of prior MI, high mortality risk according to the GRACE risk score, high ischemic risk according to the DAPT score, high bleeding risk according to the PRECISE-DAPT score and ARC-HBR criteria, high PCI complexity according to the criteria set out by Giustino et al.[21], total stent length $\geq$30 mm, minimal stent diameter $<$3.0 mm, presence or absence of multivessel disease and type of $P2Y_{12}$-inhibitor (ticagrelor, prasugrel, or clopidogrel). Subgroup-specific hazard ratios including corresponding 95% CI will be calculated using Cox proportional hazards models. Formal interaction testing will be done using the subgroup by treatment allocation as an interaction term in the model.

Cost-effectiveness and cost-utility analysis

The economic evaluation of omitting aspirin as compared to the current standard-of-care will be composed of both a cost-effectiveness and a cost-utility analysis with a time horizon of 12 months after randomization. The health economic outcomes for the cost-effectiveness analysis will be costs per patient without a primary bleeding endpoint and costs per patient without a primary ischemic endpoint, for the cost-utility analysis the outcome will be costs per quality adjusted life year. Our primary hypothesis is that omitting aspirin reduces bleeding without an effect on ischemic events, thereby improving quality of life and reducing costs.

Safety monitoring

An independent data and safety monitoring board (DSMB) will provide external oversight to ensure the safety of the study patients. DSMB meetings are held on a periodic basis, at least every 6 months, to evaluate the interim results and check reporting and stopping rules specified in the study protocol and DSMB charter. Importantly, the DSMB members are not affiliated with the study sponsor or principal investigator. The interim report provided to the DSMB will include data on enrollment progress, the incidence of the primary endpoints and any serious adverse events. The DSMB can recommend to continue the study as planned, continue the study with modifications to conduct or design, discontinue the study due to clear harm or discontinue the

study because completion of the study is not feasible. All final decisions regarding study modifications are made by the steering committee, although deviation from the DSMB recommendation has to be reported to the institutional review board.

Discussion

The primary hypothesis of LEGACY is that completely omitting aspirin will significantly reduce bleeding complications, while remaining noninferior with regards to ischemic events in the 12 months following PCI for NSTE-ACS compared to standard DAPT. In recent years, several large randomized controlled trials have demonstrated that early aspirin withdrawal after a short course of DAPT significantly reduce bleeding without increasing the number of ischemic events.[6-11] So far, immediately omitting aspirin following PCI has only been tested in smaller, single-arm studies.[13-15] These studies demonstrated that immediately omitting aspirin was feasible and not associated with any overt safety concerns given the absence of stent thrombosis or spontaneous MI during follow-up. However, these studies were not powered to assess the comparative safety and efficacy of immediate aspirin withdrawal and maximized safety by applying stringent patient selection resulting in enrollment of relatively low-risk patients. The ASET (Acetyl Salicylic Elimination Trial) study was the first to examine the feasibility and safety of prasugrel monotherapy immediately following everolimus-eluting stent implantation in patients with chronic coronary syndrome (CCS) and low anatomic complexity.[13] In the ASET study, 201 patients from Brazil were treated with DAPT prior to the index procedure and started prasugrel immediately after PCI. Overall, 98.5% of patients were adherent to prasugrel monotherapy and there were no cases of stent thrombosis or spontaneous MI at 3 months follow-up. One patient (0.5%) suffered from a fatal intracranial bleeding in the days following PCI, although the overall rate of bleeding (BARC type 1-5) was extremely low at 0.5%. The ASET investigators maximized safety by applying stringent patient selection focused on enrolling only low-risk patients. Consequently, patients were possibly not only at low ischemic risk, but also at low bleeding risk. More recent, the ASET-JAPAN investigators included 206 CCS patients with low complex, de-novo coronary lesions who were treated with biodegradable-polymer platinum-chromium everolimus-eluting stent(s) in a follow-up study conducted in 12 centers. Following successful PCI patients received 3 months of low-dose prasugrel (3.75 mg once daily).[14] At 3 months follow-up, none of the patients met the primary ischemic endpoint, which was a composite of cardiac death, spontaneous target-vessel MI, or definite stent thrombosis. Only 1 patient reported minor bleeding (BARC type 2) and 4 patients reported minimal bleeding (BARC type 1). The OPTICA (Optical Coherence Tomography-Guided PCI with Single Antiplatelet Therapy) study was the first to test the feasibility of immediate ticagrelor or prasugrel monotherapy in patients with NSTE-ACS.[15] Importantly, all 75 patients underwent platelet function testing to rule out high on-treatment platelet reactivity and half of all patients underwent OCT-guided PCI, minimizing the risk of recurrent ischemic events during follow-up. Still, $P2Y_{12}$-inhibitor monotherapy was feasible in most patients and more importantly not associated with any overt safety concerns given the absence of stent thrombosis and spontaneous MI within the first 6 months of follow-up. However, the OPTICA study had several important limitations, such as the exclusion of patients undergoing complex PCI.

Thus far, ticagrelor, and clopidogrel have been predominant used in randomized controlled trials evaluating $P2Y_{12}$-inhibitor monotherapy and experience with prasugrel in this setting has been limited.[22] However, treatment modifications in trials evaluating different antithrombotic strategies are common with approximately 10% to 15% of all patients altering treatment during follow-up.[6,10,23] Prasugrel could serve as an alternative in patients not tolerating ticagrelor or clopidogrel.[24,25] Therefore, it is important to test omitting aspirin irrespective of $P2Y_{12}$-inhibitor of choice.

Current status

The first patient was randomized on May 13th 2022 and enrollment is expected to continue until July 2024. At present 16 sites have started enrollment and a total of 738 patients have been randomized so far. The last follow-up visit is expected to occur in July 2025.

Conclusion

The LEGACY study is the first randomized study that is specifically designed to evaluate the impact of immediately omitting aspirin, and thus treating patients with $P2Y_{12}$-inhibitor monotherapy, as compared to DAPT for 12 months on bleeding and ischemic events within 12 months following PCI for NSTE-ACS.

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