Comparison of one-month versus twelve-month dual antiplatelet therapy after implantation of drug-eluting stents guided by either intravascular ultrasound or angiography in patients with acute coronary syndrome: rationale and design of prospective, multicenter, randomized, controlled IVUS-ACS and ULTIMATE-DAPT trial

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Background Current guidelines recommend administering dual antiplatelet therapy (DAPT) for 12 months to patients with acute coronary syndromes (ACS) and without contraindications after drug-eluting stent (DES) implantation. A recent study reported that 3 months of DAPT followed by ticagrelor monotherapy is effective and safe in ACS patients undergoing DES implantation compared with the standard duration of DAPT. However, it is unclear whether antiplatelet monotherapy with ticagrelor alone versus ticagrelor plus aspirin reduces the incidence of clinically relevant bleeding without increasing the risk of major adverse cardiovascular and cerebrovascular events (MACCEs) in ACS patients undergoing percutaneous coronary intervention (PCI) with DES implantation guided by either intravascular ultrasound (IVUS) or angiography who have completed a 1-month course of DAPT with aspirin plus ticagrelor.

Methods The IVUS-ACS and ULTIMATE-DAPT is a prospective, multicenter, randomized, controlled trial designed to determine (1) whether IVUS-guided versus angiography-guided DES implantation in patients with ACS reduces the risk of target vessel failure (TVF) at 12 months and (2) whether ticagrelor alone versus ticagrelor plus aspirin reduces the risk of clinically relevant bleeding without increasing the risk of MACCE 1–12 months after the index PCI in ACS patients undergoing DES implantation guided by either IVUS or angiography. This study will enroll 3486 ACS patients eligible for DES implantation, as confirmed by angiographic studies. The patients who meet the inclusion criteria and none of the exclusion criteria will be randomly assigned in a 1:1 fashion to the IVUS- or angiography-guided group (*first randomization*). All enrolled

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patients will complete a 1-month course of DAPT with aspirin plus ticagrelor after the index PCI. Patients with no MACCEs or major bleeding (≥Bleeding Academic Research Consortium (BARC) 3b) within 30 days will be randomized in a 1:1 fashion to either the ticagrelor plus matching placebo (SAPT)group or ticagrelor plus aspirin (DAPT)group for an additional 11 months (*second randomization*). The primary endpoint of the IVUS-ACS trial is TVF at 12 months, including cardiac death, target vessel myocardial infarction (TVMI), or clinically driven target vessel revascularization (CD-TVR). The primary superiority endpoint of the ULTIMATE-DAPT trial is clinically relevant bleeding, defined as BARC Types 2, 3, or 5 bleeding, and the primary non-inferiority endpoint of the ULTIMATE-DAPT trial is MACCE, defined as cardiac death, myocardial infarction, ischemic stroke, CD-TVR, or definite stent thrombosis occurring 1–12 months in the second randomized population.

Conclusion The IVUS-ACS and ULTIMATE-DAPT trial is designed to test the efficacy and safety of 2 different antiplatelet strategies in ACS patients undergoing PCI with DES implantation guided by either IVUS or angiography. This study will provide novel insights into the optimal DAPT duration in ACS patients undergoing PCI and provide evidence on the clinical benefits of IVUS-guided PCI in ACS patients. (Am Heart J 2021;236:49–58.)

Background

The current standard antiplatelet therapy after percutaneous coronary intervention (PCI) with drug-eluting stents (DES) is dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ receptor inhibitor.[1,2] The latest guidelines recommend at least 12 months of DAPT in patients with acute coronary syndromes (ACS) and without contraindications after DES implantation.[1,2] Prolonged administration of DAPT is associated with a low risk of ischemic events at the cost of increased bleeding risk.[3,4] Accordingly, the paradigm of DAPT is shifting to a short duration of DAPT or even antiplatelet monotherapy. Recently, several studies have shown that a 1 to 3-month course of DAPT followed by antiplatelet monotherapy is associated with significant reductions in bleeding events without increasing the risk of ischemic events compared with DAPT for 12 months or longer.[5-8] Analysis of the Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT)-ACS subgroup analysis also showed the efficacy and safety of 3-month DAPT followed by ticagrelor monotherapy versus standard DAPT in ACS patients undergoing DES implantation.[9]

Intravascular ultrasound (IVUS) is a useful tool for PCI. Previous studies have reported that IVUS-guided DES implantation significantly improves clinical outcomes in all-comers or complex PCI,[10-12] in particular, for patients with PCI optimized with IVUS-defined criteria as opposed to those with angiography guidance. The ADAPT-DES registry showed that IVUS-guided DES implantation is associated with a low risk of stent thrombosis (ST) and myocardial infarction (MI) within 1 year, especially with the greatest benefits in ACS patients and complex lesions.[13] However, to date, no randomized controlled trial (RCT) has been performed to determine whether IVUS-guided DES implantation improves clinical outcomes in patients with ACS as compared with angiography guidance.

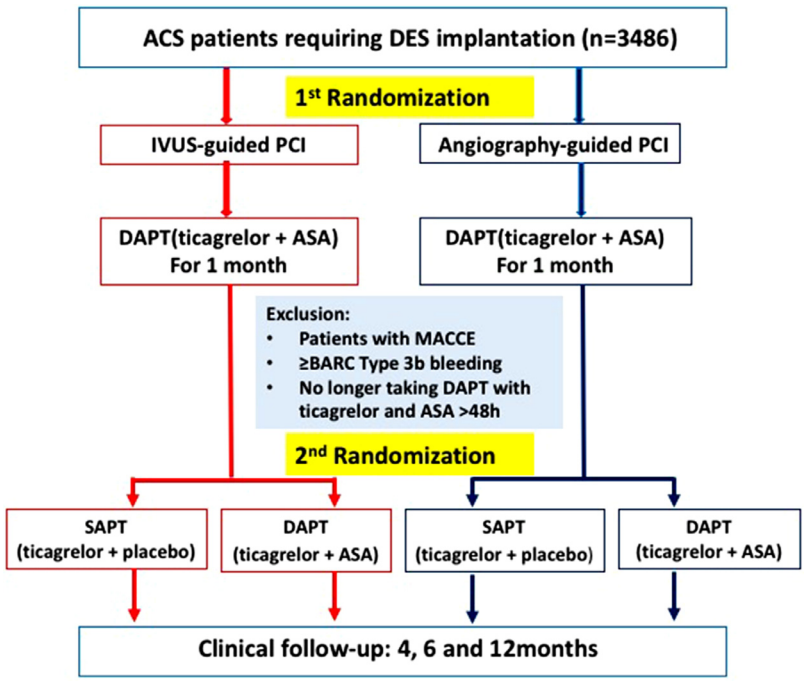
Contemporary PCI is characterized by a new generation of DESs, potent $P2Y_{12}$ inhibitors,[14,15] and optimal PCI procedures under intracoronary imaging,[8] which have potential roles in further shortening DAPT duration and antiplatelet monotherapy for patients undergoing DES implantation. In the STOPDAPT-2 study, >98% of the patients underwent PCI under intracoronary imaging, and the patients who underwent DES implantation with 1-month DAPT followed by antiplatelet monotherapy achieved similar clinical outcomes with conventional DAPT.[8] To date, it is unclear whether a 1-month course of ticagrelor plus aspirin followed by ticagrelor monotherapy for an additional 11 months is superior to conventional DAPT with respect to clinically relevant bleeding while maintaining efficacy of ischemic events in ACS patients undergoing DES implantation guided by IVUS.

Methods

Study hypothesis

The current study hypothesizes that ticagrelor alone versus ticagrelor plus aspirin for an additional 11 months will be superior in reducing clinically relevant bleeding and will be noninferior with respect to major adverse cardiovascular and cerebrovascular events (MACCEs) in ACS patients undergoing an optimization PCI with IVUS-guided DES implantation who have completed a 1-month course of DAPT with ticagrelor plus aspirin. This hypothesis will be tested with the following specific aims: (1) to determine the effect of IVUS-guided DES implantation versus angiography-guided implantation on target vessel failure (TVF) at 12 months in patients with ACS, (2) to determine the efficacy of ticagrelor alone versus ticagrelor plus aspirin in reducing clinically relevant bleeding, and (3) to determine the safety of ticagrelor alone versus ticagrelor plus aspirin with respect to MACCEs 1 to 12 months after the index PCI. The study is funded by Jiangsu Provincial Special Program of Medical Science

Figure 1



Study flowchart. ACS, acute coronary syndrome; ASA, aspirin; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention; MACCE, major adverse cardiovascular and cerebrovascular events; SAPT, single antiplatelet therapy.

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Study design

The IVUS-ACS and ULTIMATE-DAPT (ClinicalTrial.gov unique identifier NCT 03971500) is a prospective, multicenter, randomized, controlled trial designed to test the efficacy and safety of two different antiplatelet strategies in ACS patients undergoing either IVUS-guided or angiography-guided PCI with DES implantation. The study flowchart is shown in Figure 1**.** The IVUS-ACS and ULTIMATE-DAPT consists of two trials: the IVUS-ACS and the ULTIMATE-DAPT. The subpopulation of the IVUS-ACS is enrolled to the ULTIMATE-DAPT Figure 2.

Study population

The current study will enroll 3,486 ACS patients, aged ≥18 years, eligible for DES implantation, as confirmed by angiography. Patients who meet the inclusion criteria and none of the exclusion criteria (Table 1) will be randomized in a 1:1 fashion to the IVUS- or angiography-guided group (*first randomization*). Patients enrolled will have to complete a 1-month course of DAPT with aspirin plus ticagrelor after the index PCI. Patients with no MACCEs or major bleeding (≥ Bleeding Academic Research Consortium (BARC) 3b) within 30 days and who are on continued aspirin and ticagrelor for 30 days without interruption for >48 hours will be randomized in a 1:1 fashion to either ticagrelor plus matching placebo (SAPT group) or ticagrelor plus aspirin (DAPT group) for an additional 11 months (*second randomization*). The study will comply with the Declaration of Helsinki regarding investigations in humans and will seek approval from the institutional ethics committees at each participating center. Each subject enrolled in the current study will be asked to provide written informed consent prior to undergoing any study-related procedure.

Study treatment, PCI procedures, and medications

All procedures will be performed according to contemporary PCI guidelines and local practices. The use of unfractionated heparin or a direct thrombin inhibitor (such as Bivalirudin) is mandatory during PCI procedures; the activated clotting time (ACT) will be maintained at >280 s if the former is used. A loading dose of aspirin (300 mg) and clopidogrel (300 or 600 mg) or ticagrelor (180 mg) is recommended for all patients before PCI.

Patients with ACS who are eligible for DES implantation confirmed by angiography will be randomized to

Table 1. Inclusion and exclusion criteria

Inclusion criteria

- Subject or a legally authorized representative must provide written informed consent prior to undergoing any study-related procedure
- Men and women 18 years and older
- Established indication to percutaneous coronary intervention according to contemporary guidelines
- Enrollment into the study will require meeting at least one of these clinical diagnosis:
    - Unstable angina, defined as rest pain for 5-30 minutes or deteriorative exertional angina with either (a) transient ST segment depression or elevation, or (b) angiography showing a visually estimated diameter stenosis ≥90% or a ruptured plaque or thrombotic lesion
    - Non-ST-elevation myocardial infarction
    - ST-elevation myocardial infarction

Exclusion criteria

- Unable or unwilling to provide written informed consent
- Stroke within 3 months or any permanent neurologic deficit, prior intracranial bleed, or any intracranial disease such as aneurysm or fistula
- Previous coronary artery bypass graft
- Any planned surgery within 12 months
- Any reason why any antiplatelet therapy might need to be discontinued within 12 months
- Severe chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73 m^2
- Need for chronic oral anticoagulation (warfarin/coumadin or direct oral anticoagulants)
- Platelet count <100,000 mm^3
- Contraindication to aspirin
- Contraindication to ticagrelor
- Liver cirrhosis
- Women of child-bearing potential
- Life expectancy <1 year
- Any condition likely to interfere with study processes including medication compliance or follow-up visits (eg, dementia, alcohol abuse, severe frailty, long distance to travel for follow-up visits, etc.)

Table 2. Second randomization ineligibility criteria at 1 month

- Refusal of randomization by subject or treating physician
- Withdrawal of consent
- Lost to follow-up
- Death
- Major bleeding (BARC Types 3b or greater)
- Occurrence of an ischemic event after PCI such as MI, definite or probable stent thrombosis, ischemic stroke, TVR
- No longer taking DAPT with aspirin and ticagrelor >48 h
- Non physician-guided cessation of aspirin or ticagrelor of 5 consecutive days or greater
- Women of child-bearing potential
- Renal failure requiring dialysis
- Current indication for oral anticoagulation or high dose aspirin

BARC, bleeding academic research consortium; DAPT, dual antiplatelet therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; TVR, target vessel revascularization.

the IVUS- or angiography-guided group (*first randomization*). New generation drug-eluting stent will be recommended to use. In the angiography-guided group, angiographic success will be defined as thrombolysis in myocardial infarction (TIMI) flow grade 3, residual stenosis <20%, and absence of ≥type B dissection. In the IVUS-guided group, the optimal stent deployment criteria will include the following: (1) the minimum lumen area (MLA) in the stented segment >5.0 mm^2 or >90% of the MLA at the distal reference segments, (2) plaque burden 5 mm proximal or distal to the stent edge is <55%, and (3) no dissection involving media and greater than 3 mm. Further treatment will be required if any of these three criteria are not met. IVUS will not be performed in the angiography-guided group.

Protocol-mandated therapy will include an open-label phase for the first 1 month and a blinded phase from 1 month to 12 months after the index PCI. The open-label phase will include a 1-month course of open-label ticagrelor at a dose of 90 mg twice daily and aspirin at a dose of 100 mg once daily for enrolled participants after the index PCI. Patients who are pretreated with clopidogrel before PCI will be switched to receive ticagrelor with a loading dose of 180mg after the index PCI. All other periprocedural medications will be left to the discretion of the treating physician and not be dictated by the study protocol. The blinded phase will include ticagrelor alone at a dose of 90 mg twice daily plus blinded placebo once daily for the study group or ticagrelor at a dose of 90 mg twice daily plus blinded aspirin at a dose of 100 mg once

daily for the control group from 1 month to 12 months after the index PCI for participants who are eligible for the second randomization. For patients who do not tolerate ticagrelor, a dosage of 60 mg twice daily or clopidogrel at a dose of 75 mg once daily will be prescribed.

Randomization and follow-up

Randomization will be performed within the EDC system. The EDC will allocate subjects to the treatment group and provide the research personnel of each study site with the appropriate bottle number. Subjects who meet any one of the inclusion criterion and none of the exclusion criterion will be randomly (*first randomization*) enrolled into the IVUS-ACS (IVUS- vs angiography-guided DES implantation). All patients will receive open-label ticagrelor plus aspirin for 1 month after the index PCI.

Then, 30 days after the index PCI, patients enrolled into the IVUS-ACS will return for an in-person visit. The patients eligible for the second randomization will be randomized in a 1:1 fashion (*second randomization*) to the SAPT and DAPT groups, stratified by IVUS or angiography guidance. Subjects meeting any of the exclusion criteria for the second randomization will be excluded and will be followed up until the completion of the study. The exclusion criteria for the second randomization are listed in Table 2. These patients will be analyzed in the IVUS-ACS for the calculation of TVF, and antiplatelet therapy will be administered at the discretion of the treating physician in accordance with the local standard of care. The vital status of these subjects will be determined at the 12-month time point.

Adherence to study-provided medications will be assessed by manual pill counting at 1-, 4-, and 12-month in-person visits. Details about the date, duration, and reason for study medication cessation should be entered in the appropriate section of the EDC. Although these patients will no longer receive study-related medication, they will be followed until the end of the study. Time points of in-person visits and phone calls throughout the trial are shown in Figure 2.

Blinding and unblinding

The study is a double-blind design with aspirin and a matching placebo. The subjects, study site research personnel, academic research center staff, and referring physicians involved in the treatment and/or clinical evaluation of the subjects will not be aware of the treatments received. An independent data safety monitoring board (DSMB) will be used to monitor the data on a periodic basis. An independent statistician, not otherwise involved in the study, will prepare and provide the required reports to the DSMB as per the DSMB charter.

Study endpoints

Primary endpoints

The primary endpoint of the IVUS-ACS is the time to first occurrence of TVF at 12 months after the index PCI, including cardiac death, target vessel myocardial infarction (TVMI), or clinically driven target vessel revascularization (CD-TVR).

The primary superiority endpoint of the ULTIMATE-DAPT is the time to first occurrence of clinically relevant bleeding, defined as Bleeding Academic Research Consortium (BARC)[16] Types 2, 3, or 5 bleeding occurring 1 to 12 months after the index PCI.

The primary noninferiority endpoint of the ULTIMATE-DAPT is the time to first occurrence of composite MACCE defined as cardiac death, myocardial infarction, ischemic stroke, CD-TVR, or definite stent thrombosis (ST) occurring 1 to 12 months after the index PCI.

Cardiac death is defined as any death without a clear noncardiac cause. Protocol-defined MI will include periprocedural MI (within 48 hours of the index procedure) and spontaneous MI (48 hours after the index procedure). Specific definitions of MI are shown in Appendix Table 1. CD-TVR is defined as angina or ischemia associated with the target vessel requiring repeat PCI or CABG. ST is classified according to the Academic Research Consortium (ARC) criteria.[17] Ischemic stroke is defined as an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.[18]

Second endpoints

The secondary endpoint of the study is the time to first occurrence of net adverse cardiovascular and cerebrovascular events (ie, MACCE or any bleeding). The secondary bleeding endpoints include the time to first occurrence of (1) BARC types 3 or 5 bleeding, (2) major or minor bleeding according to the TIMI score,[19] (3) severe or life-threatening, moderate, or minor bleeding according to definitions of the Global Strategies for Opening Occluded Coronary Arteries (GUSTO),[20] and (4) major bleeding according to definitions of the International Society of Thrombosis or Hemostasis (ISTH).[21] Individual components of the primary endpoints and the primary and secondary endpoints of the current study are shown in Table 3. The definitions of the primary and secondary endpoints are shown in Appendix Table 1 to 10.

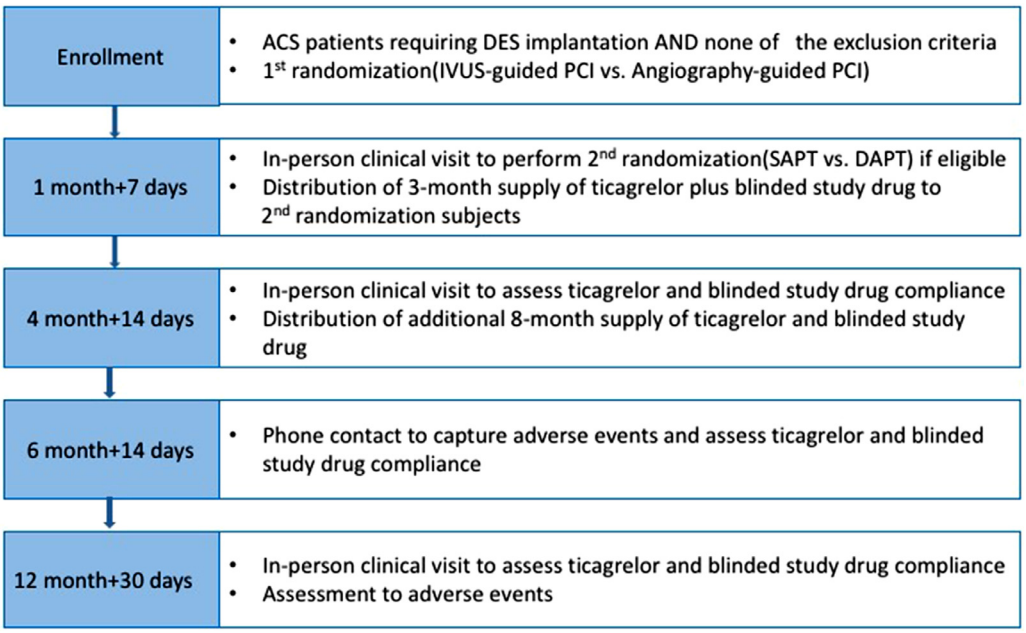
Sample size and statistical methods

Sample size

The current study is a two-stage randomization design, and analyses of primary TVF, clinically relevant bleeding, and MACCE will based on a sequential testing framework. As a result, there is no need to adjust the test level ($\alpha = 0.05$).

TVF endpoint: The rate of TVF is estimated to be 7.2% in the IVUS-guided group and 10.0% in the angiography-guided group 12 months after the index PCI.[11,12,22] As-

Figure 2



Time points of in-person visits and phone calls. ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; IVUS, intravascular ultrasound; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

Table 3. Study endpoints

Primary endpoints

- The primary endpoint of the IVUS-ACS is the time to first occurrence of target vessel failure (TVF), including cardiac death, target vessel myocardial infarction (TVMI), or clinically-driven target vessel revascularization (CD-TVR).
- The primary superiority endpoint of the ULTIMATE-DAPT is the time to first occurrence of clinically relevant bleeding, defined as Bleeding Academic Research Consortium (BARC) Types 2, 3 or 5 bleeding occurring from 1 month to 12 months.
- The primary non-inferiority endpoint of the ULTIMATE-DAPT trial is the time to first occurrence of composite major adverse cardiovascular and cerebrovascular events (MACCE), defined as cardiac death, myocardial infarction, ischemic stroke, CD-TVR or definite stent thrombosis occurring between 1 month to 12 months.

Secondary endpoints

- Net adverse cardiovascular and cerebrovascular events (NACCE), including MACCE or any bleeding
- BARC types 3 or 5 bleeding
- Major or minor bleeding according to definitions from Thrombolysis in Myocardial Infarction (TIMI)
- Moderate or severe or life-threatening bleeding according to definitions from Global Strategies for Opening Occluded Coronary Arteries (GUSTO)
- Major bleeding according to definitions from International Society of Thrombosis or Hemostasis (ISTH)
- Cardiac death, myocardial infarction, ischemic stroke or clinically-driven revascularization
- Cardiac death, non-fatal myocardial infarction or ischemic stroke
- Definite or probable stent thrombosis
- Cardiovascular death
- Individual components of the primary endpoints

suming a 5% loss to follow-up, the current study will require 3,486 patients to achieve a significant difference in the primary endpoint with 80% power and a Type I error of 0.05.

Clinically relevant bleeding endpoint: The rate of clinically relevant bleeding is estimated to be 3.0% in the DAPT group and 1.5% in the SAPT group between 1 month and 12 months after the index PCI,[5,7,8] resulting in the requirement of 3,316 patients to achieve significant difference with 5% patients lost to follow-up and non-compliance/crossover ($\alpha = 0.05$, 80% power, 2-sided). The rate of major bleeding (≥BARC 3b) or

MACCE within 30 days after stenting is anticipated to be in 1.0% or 1.5% of patients, respectively.[23] As a result, a total of 86 patients at 30 days will be excluded from the second randomization, with the remaining 3,400 patients (30-day event-free) who will be randomized at the second randomization. Therefore, this number (n = 3400) will meet the requirement of the sample size (n = 3316) for the second randomization.

MACCE endpoint: Assuming an event rate of 6.2% in the DAPT group between 1 month and 12 months after the index PCI,[5,7,8] a sample size of 2,922 (1,461 in each group) will yield 80% power to exclude an absolute noninferiority margin of 2.5%. If the upper limit of the 95% CI for the point estimate of the absolute risk difference between groups is ≤2.5%, then the criteria for noninferiority will be met. If 5% of the patients are expected to be lost to follow-up, 3068 patients will be required. Therefore, in total, 3,486 patients will meet the requirements of all three primary endpoints.

Statistical methods

Statistical analyses will be performed for both the intention to treat (ITT) and per-protocol (PP) cohorts. The ITT population will consist of all subjects who have been randomized (ie, when the subject number and allocated treatment are recorded in the EDC). The subjects will be analyzed in the treatment group assigned by the EDC. The PP population will consist of all randomized subjects without any major deviations from the protocol.

The study will include two randomizations, therefore, there will be two ITT populations and two PP populations. Analyses in the ITT population will be censored by last contact date, at the time of death or 12-month visit, whichever comes first. Analyses in the PP population will be censored by date of study-related medication discontinuation > 7 days, at the time of death or 12-month visit, whichever comes first.

Analysis of the primary superiority TVF endpoint

The analysis for the TVF endpoint will be performed for the first randomized ITT population. A test of superiority at the 2-sided 0.05 level with log-rank test will be performed. A point estimate and 2-sided 95% CI for the relative risk as measured by the hazard ratio (HR) will be calculated based on the Cox proportional hazards model. The treatment (SAPT, DAPT) received by the subjects in the second randomization will be considered as a covariate in the model. The linear relationship between log(time) and log (log[survival]) will be explored to investigate whether the assumption of the Cox proportional risk is valid. Event rates will be estimated between 0 and 12 months, and Kaplan-Meier curves for the time to first TVF event will be plotted by experimental groups. Sensitivity analysis based on the 1st randomized PP population will be performed to support the primary endpoint.

Analysis of the primary superiority clinically relevant bleeding endpoint

The analysis for the primary clinically relevant bleeding endpoint will be based on the ITT principle of the second randomized population. A test of superiority at the 2-sided 0.05 level with log-rank test will be performed. A point estimate and 2-sided 95% CI for the relative risk as measured by the HR will be calculated based on the Cox proportional hazards model. The treatment (IVUS- and angiography- guided) received by the subjects in the first randomization will be considered as a covariate in the model. Event rates will be estimated between 1 month and 12 months, and Kaplan-Meier curves for the time to first bleeding event will be plotted by experimental groups. A sensitivity analysis based on the second randomized PP population will be performed to support the primary endpoint.

Analysis of the primary non-inferiority MACCE endpoint

This analysis will be based on the ITT principle of the second randomized population. Event rates will be estimated between 1 month and 12 months, and Kaplan-Meier curves for the time to first MACCE will be plotted by experimental groups. A test of noninferiority at the one-sided 0.025 level will be performed. As a sensitivity test, the primary non-inferiority hypothesis will also be tested in the second randomized PP population.

Subgroup analyses

One-year event rates for the primary efficacy and safety endpoints will be calculated in the following clinically relevant subgroups: age ≥65 years vs <65 years, sex (male, female), race (Chinese, non-Chinese), diabetes mellitus, chronic kidney disease (eGFR < 60 mL/min/1.73m2), biomarker-positive ACS at presentation, implanted stent length (<60 mm, ≥60 mm), body mass index (<median, ≥median), history of prior MI, and presence or absence of multivessel disease. HR and its corresponding 95% CI will be calculated for each subgroup using a Cox proportional hazards model. The results of the subgroup analyses are presented by forest plots. Interaction testing will be performed using subgroup treatment allocation as an additional term in the Cox model.

Study organization and safety monitoring

The IVUS-ACS and ULTIMATE-DAPT trial is designed and sponsored by the principal investigator and the executive committee. The steering and executive committees are responsible for the medical, scientific, and operational processes of the study. The executive committee is also responsible for the integrity of data analyses and reporting results.

The current study will be conducted under the auspices of an independent DSMB, whose activities will be described in a DSMB charter. DSMB members will not

have primary affiliation with the study sponsor, the EDC supplier, or the principal investigator of the trial. Members of the DSMB will be selected prior to study enrollment. The DSMB will review data and determine reporting and stopping rules as specified in the DSMB charter. The DSMB members will review safety data while maintaining the scientific integrity of the trial. The data will consist of adjudicated and non-adjudicated MACCE, bleeding, and other serious adverse events to identify potential safety issues. Based on the safety data, the DSMB may recommend modifications to the protocol, suspension or termination of the trial, and advise the executive committee. All final modifications to the trial will be determined by the executive committee.

Discussion

The IVUS-ACS and ULTIMATE-DAPT is a 2-stage randomization trial, which includes the IVUS-ACS and the ULTIMATE-DAPT. The hypothesis of the IVUS-ACS is that IVUS-guided DES implantation is superior to angiography-guided implantation with respect to TVF at 0 to 12 months after the index PCI in patients with ACS. The hypotheses of the ULTIMATE-DAPT are that ticagrelor alone is superior to ticagrelor plus aspirin in reducing clinically relevant bleeding (BARC $\geq$2) between 1 and 12 months and that ticagrelor alone is noninferior to ticagrelor plus aspirin with respect to MACCE between 1 and 12 months in ACS patients undergoing DES implantation guided by either IVUS or angiography who have completed a 1-month course of DAPT with ticagrelor plus aspirin. TVF will be analyzed for the first randomized population. Clinically relevant bleeding and MACCE will be analyzed for the second randomized population. The analyses of primary TVF, clinically relevant bleeding, and MACCE will be based on a sequential testing framework.

The current study differs from several published studies showing the efficacy and safety of short-duration of DAPT versus the standard duration of DAPT recommended by the current guidelines.[5-8] First, only patients with ACS are eligible for the current study. The diagnoses of ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) are based on the fourth universal definition of myocardial infarction.[24] Notably, the definition of unstable angina is predefined as rest chest pain for 5 to 30 minutes or deteriorative exertional angina with either (1) electrocardiogram showing transient ST segment depression or elevation or (2) angiography showing a visually estimated diameter stenosis $\geq$90% or a ruptured plaque or thrombotic lesion. This rigorous definition of unstable angina is used to prevent the enrollment of patients with non-ACS anginal chest pain to this study. Second, the combination of an optimal PCI procedure guided by IVUS and extensive use of potent $P2Y_{12}$ inhibitor offers the potential to further shorten the duration of DAPT. Accordingly, in the current study, one of the major objectives is to test whether ticagrelor monotherapy versus ticagrelor plus aspirin is associated with a reduced risk of bleeding without increasing the risk of ischemic events in ACS patients undergoing PCI with IVUS- or angiography-guided DES implantation after a 1-month course of DAPT.

Optimal DAPT duration depends on the balance between bleeding risk and ischemic event risk for each patient. Current evidence supports the short duration of DAPT (3 or 6 months) in the clinical subset of high bleeding and low ischemic risks.[25,26] Patients with ACS have a high-risk profile of ischemic events; therefore, the current guidelines recommend at least 12 months of DAPT, without contraindications after DES implantation, to reduce the risk of recurrent ischemic events.[1,2] However, in the context of new-generation DES implantation and the use of potent $P2Y_{12}$ inhibitors after PCI, therapeutic strategies are shifting to a shorter duration of DAPT or even antiplatelet monotherapy for all-comers and patients with a high risk of thrombotic events. In the GLOBAL LEADERS trial, a strategy of ticagrelor alone after a 1-month course of DAPT compared with a standard duration of DAPT in 15,968 patients with ACS or stable CAD resulted in a trend toward lower 2-year rates of death or Q-wave MI (3.8 % vs 4.4%, $P = .07$) with similar rates of major bleeding, suggesting that aspirin may be safely withdrawn after 1 month.[5] A post-hoc analysis from that study demonstrated that aspirin was associated with an increased risk of bleeding without additional benefits of ticagrelor on ischemic events 1 to 12 months after the index PCI in ACS patients undergoing DES implantation.[23] The latest TWILIGHT study has also shown that ticagrelor monotherapy reduces the risk of clinically relevant bleeding without increasing the risk of ischemic events compared with 12-month DAPT in patients with high risk of bleeding and ischemic events after a 3-month course of DAPT,[6] and similar findings have been reported in the subset of ACS.[9] Based on the above findings, the hypothesis of further shortening the duration of DAPT in ACS patients undergoing DES implantation may be reasonable and feasible.

Intracoronary imaging may offer the potential benefits of further shortening the duration of DAPT in patients undergoing DES implantation. IVUS-guided DES implantation is associated with a lower 12-month rate of TVF than angiography-stenting stenting,[10-12] in particular, patients who met the IVUS criteria received further clinical benefits. In the ULTIMATE study, the IVUS-defined criteria for the optimal stent deployment included the following: (1) MLA in the stented segment is >5.0 mm^2 or 90% of the MLA at the distal reference segments; (2) plaque burden 5 mm proximal or distal to the stent edge is $<$55%; and (3) absence of $\geq$ Type B edge dissection. IVUS-defined optimal PCI was determined only if these 3 criteria were simultaneously achieved. Otherwise, the PCI procedure was defined as suboptimal if any of those

3 criteria were not met.[11] This is the basis of the central hypothesis of the current study. The STOPDAPT-2 study has shown that clopidogrel monotherapy reduces the risk of bleeding without increasing the risk of ischemic events compared with 11-month DAPT in patients undergoing DES implantation after a 1-month course of DAPT.[8] Notably, almost all patients enrolled in that study underwent PCI guided by intracoronary imaging. Therefore, the optimal PCI procedure under IVUS guidance could play a critical role in further shortening the duration of DAPT by improving stent expansion or endothelial coverage.[27] Nevertheless, the STOPDAPT-2 study did not predefine the IVUS criteria of the optimal PCI procedure. In addition, most patients present a relatively low risk of thrombotic and bleeding events; therefore, the findings could not be generalized to the all-comers population. Our study will predefine the IVUS criteria for optimal PCI to guide operator through onsite measurements during PCI procedures to enable more patients to achieve optimized PCI, which is a prerequisite to further shorten the duration of DAPT in ACS patients undergoing IVUS-guided DES implantation.

To date, it is not known whether PCI with IVUS-guided DES implantation improves the clinical outcomes in the ACS patient population compared with angiography-guided implantation. Previous studies have demonstrated that PCI with DES implantation guided by IVUS is associated with a lower risk of MACE compared with angiography-guided DES implantation.[10-12] Choi et al.[10] reported that IVUS-guided PCI reduces the incidence of MACE in patients with complex lesions such as chronic total occlusion, left main lesion, complex bifurcation lesions, long lesions, and heavily calcified lesions compared with angiography-guided PCI in a real-world registry. Nevertheless, in that study, approximately two-thirds of the patients presented with stable angina. The ULTIMATE study is a large-scale prospective RCT; it showed that IVUS-guided PCI is superior to angiography-guided PCI in reducing TVF in all-comer patients, among whom >70% of the patients presented with ACS.[11] However, in the ULTIMATE study, patients with acute myocardial infarction less than 24 hours from the onset of chest pain to admission were excluded. Furthermore, the definition of unstable angina was not as rigorous as in the current study. Accordingly, the first objective of the current study is to test whether PCI with IVUS-guided DES implantation is superior to angiography-guided in reducing TVF in ACS patients, which is the primary endpoint of the IVUS-ACS trial.

Conclusion

The IVUS-ACS and ULTIMATE-DAPT is designed to test the comparative efficacy and safety of two different antiplatelet strategies in ACS patients undergoing either IVUS-guided or angiography-guided PCI with DES implantation. This study will provide novel insights into the optimal DAPT duration for ACS patients undergoing PCI and provide evidence on the clinical benefits of IVUS-guided PCI in ACS patients.

Current Status

The first patient was enrolled in the IVUS-ACS and ULTIMATE-DAPT trial on 08/20/2019 and enrollment is expected to continue until 12/31/2022. At present, 16 sites have been activated with a total enrollment of 620 patients. The last patient visit is expected to occur in 12/31/2023.

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Contributors

S-LC and J-JZ made substantial contributions to the initial conception and design of the whole study, and to the revision of the manuscript. Z-G and X-FG wrote the first draft. J-K contributed to data management and statistical expertise. X-QK, G-FZ, F-Y, N-LT, S-L, Z-ZL, Y-BS, Y-QH, S-YW, Q-Y, Y-X, Z-ZW, P-XX, F-L, H-SZ, S-Y, Y-W, L-T, Y-LH provided comments and suggestions in critical revision of the article. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Disclosures

None declared.

Ethics approval

The study has been approved by the Institutional Review Board of Nanjing First Hospital (KY20190530-05). Results of the study will be published in a peer-reviewed journal and disseminated at international conferences.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.02.014.

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