



A randomized clinical trial comparing long-term clopidogrel vs aspirin monotherapy beyond dual antiplatelet therapy after drug-eluting coronary stent implantation: Design and rationale of the Harmonizing Optimal Strategy for Treatment of coronary artery stenosis-Extended Antiplatelet Monotherapy (HOST-EXAM) trial

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Background Percutaneous coronary intervention (PCI) has been developed by drug-eluting stent (DES), but stent implantation has brought the issue of stent thrombosis and optimal antiplatelet therapy. Guidelines recommend at least 6- to 12 months of dual antiplatelet therapy (DAPT) with aspirin and a P2Y₁₂ receptor inhibitor such as clopidogrel. Beyond DAPT after PCI with DES, however, there has been still a debate for antiplatelet regimen. Therefore, we report on the upcoming HOST-EXAM trial (NCT02044250), which will evaluate the efficacy and safety of aspirin and clopidogrel monotherapies beyond DAPT after DES implantation.

Trial design The HOST-EXAM is a prospective, randomized, open-label, multicenter, comparative effectiveness trial, to compare between clopidogrel (75 mg once daily) and aspirin (100 mg once daily) as long-term antiplatelet agents. A total of 5,530 patients with no clinical events during combined antiplatelet therapy for 12 ± 6 months after index PCI will be screened, enrolled, and randomized to either group (1:1 ratio) receiving antiplatelet monotherapy for 2 years. The primary endpoint will be the *rate of clinical events* defined as a composite of all-cause death, nonfatal myocardial infarction, stroke, readmission due to acute coronary syndrome, or major bleeding at 24 months after randomization.

Conclusions The HOST-EXAM will be the first large-scale randomized controlled study to directly compare the efficacy and safety of long-term antiplatelet monotherapy beyond DAPT after DES implantation. This study will provide clinical evidence to establish optimal regimen for long-term antiplatelet therapy after DES implantation. (Am Heart J 2017;185:17-25.)

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Background

Coronary artery disease (CAD) is the leading cause of mortality and morbidity worldwide, and numerous studies have investigated its proper management and prevention.¹ The advent of percutaneous coronary intervention (PCI) with drug-eluting stents (DESs) after antiplatelet therapy was an important advance in CAD management.²⁻⁷ Previous studies proposed different antiplatelet regimens to protect against thrombotic/ischemic events and minimize bleeding complications after stent implantation.⁸⁻¹⁷ However, the optimal regimen after PCI with DES is still a subject of debate. Several randomized trials including the RESET, OPTIMIZE, and PRODIGY have compared dual antiplatelet therapy (DAPT) for durations of 3-6 or 12-24 months and consistently showed no benefit with respect to thrombotic/ischemic events and a higher risk of bleeding complications for longer therapy.¹⁸⁻²⁰ The recent DAPT, PEGASUS-TIMI 54, and OPTIDUAL trials reported a better efficacy of extended duration of DAPT over 12 months in common, whereas the ARCTIC-Interruption trial suggested no apparent benefit but instead harm with extended duration of DAPT.^{16,17,21,22}

Current guidelines recommend at least 6- to 12 months of DAPT with aspirin and a P2Y₁₂ receptor inhibitor, such as clopidogrel, after DES implantation, according to clinical event leading to PCI.^{23,24} Therefore, in real-world practice, clinicians usually switch from DAPT to a single agent beyond 1 year after PCI with DES. The currently preferred choice for antiplatelet monotherapy tends to be aspirin, because low-dose aspirin has known efficacy for occlusive vascular disease and the issue of clopidogrel resistance is considered as an obstacle for effective post-PCI management.^{25,26} However, routine screening for clopidogrel responsiveness has not been shown to improve clinical outcomes, and guidelines do not recommend a platelet function test for all patients undergoing PCI with DES, implying clopidogrel monotherapy may also be beneficial for patients with DES implantation.^{23,27,28} It remains uncertain whether aspirin monotherapy is superior to clopidogrel monotherapy in the stable phase after PCI with DES for reducing the risk of thrombotic/ischemic events and bleeding complications, although the CAPRIE trial demonstrated the superiority of clopidogrel to aspirin in patients with vascular disease including myocardial infarction (MI).²⁹ To our knowledge, there have been no large-scale randomized controlled trials comparing antiplatelet monotherapies for patients in the chronic phase after PCI with DES. For now, there is only one single-center observational study directly comparing aspirin and clopidogrel monotherapies in the chronic phase beyond DAPT after PCI with DES.³⁰

To present a new direction of long-term medical therapy after DES implantation, we designed this study entitled "harmonizing optimal strategy for treatment of

coronary artery stenosis-extended antiplatelet monotherapy (HOST-EXAM)." This randomized trial will compare the incidence of major adverse cardiovascular events (MACEs) and bleeding complications during clopidogrel or aspirin monotherapy for 2 years. We hypothesize that long-term maintenance with clopidogrel will have better outcomes than those of aspirin in patients with PCI with DES.

Study design and methods

Study objectives

The primary purpose of this study is to compare the efficacy and safety of antiplatelet monotherapy with aspirin or clopidogrel for 2 years in patients who have not experienced MACE including all-cause death, acute coronary syndrome (ACS) including nonfatal MI, or urgent revascularization or bleeding under combined antiplatelet therapy for 12 ± 6 months after PCI with DES. The trial tests the hypothesis that clopidogrel is superior to aspirin in preventing clinical events and device-oriented outcomes. *Clinical events* are defined as a composite of all-cause death, nonfatal MI, stroke, readmission due to ACS, or Bleeding Academic Research Consortium (BARC) class ≥3.³¹ Device-oriented outcomes include target lesion/vessel revascularization (TLR/TVR) and Academic Research Consortium-defined stent thrombosis.

Study population

Patients 20 years or older who maintained combined antiplatelet therapy after PCI with DES without clinical events during this period according to clinical event leading to PCI will be eligible for this study. Eligible patients will be screened and enrolled in this study after silent combined antiplatelet therapy period. The PCI was performed using the standard technique and DES was placed in a native coronary artery following recommendations of the guidelines.^{24,28,32} We do not impose restrictions regarding the location, length, or numbers of lesions/vessels to validate the study in as many patients as possible. At the time of study enrollment, antiplatelet therapy should be aspirin combined with any other antiplatelet agents for 12 ± 6 months after PCI.²⁸ Patients with known hypersensitivity or contraindications for aspirin or clopidogrel, or those who cannot cease their current antiplatelet agent(s) for medical, financial, or personal reasons will be excluded. Additional exclusion criteria are as follows: (1) active bleeding at enrollment; (2) history of major bleeding (BARC class ≥3) resulting in the cessation of antiplatelet agents within 3 months; (3) bleeding diathesis; (4) known coagulopathy (including heparin-induced thrombocytopenia) or refusal of blood transfusion; (5) presence of noncardiac comorbid conditions with life expectancy ≤2 years from randomization; (6) women with childbearing potential or breastfeeding;

(7) conditions that may result in protocol noncompliance; and (8) coadministration of contraindicated medications that included other P2Y₁₂ inhibitors (prasugrel or ticagrelor), anticoagulants (warfarin, new oral anticoagulants, or heparin), cytochrome P450 2C19 inhibitors (fluoxetine, moclobemid, and voriconazole), probenecid, high-dose methotrexate (≥ 15 mg/wk), and lithium.³³⁻³⁵

Study design

The HOST-EXAM is designed as a prospective, randomized, open-labeled, multicenter, comparative effectiveness trial. The study algorithm is shown in Figure. This trial is investigator-initiated with grant support from the 4 Korean pharmaceutical firms: Chong Kun Dang Pharmaceutical Corp; Samjin Pharmaceutical Co, Ltd; HANMI PHARMA Co, Ltd; and Daewoong Pharmaceutical Co, Ltd. Other than financial support, the companies will not be involved in protocol development or the study process, including site selection, implementation, management, data collection, or data analysis. We are responsible for the design and implementation of the trial, related statistical analyses, and all aspects of manuscript preparation including drafting, editing, and approving final content. This study is based on principles outlined in the Declaration of Helsinki. All patients will be required to provide written informed consent at the time of enrollment. The study will be conducted by the independent Seoul National University Hospital Clinical Trial Center, which includes 2 managing clinical research associates who are independent from the study and have no conflicts of interest. The Medical Research Collaborating Center will help the Clinical Trial Center conduct the study.

Randomization and interventions with study drugs

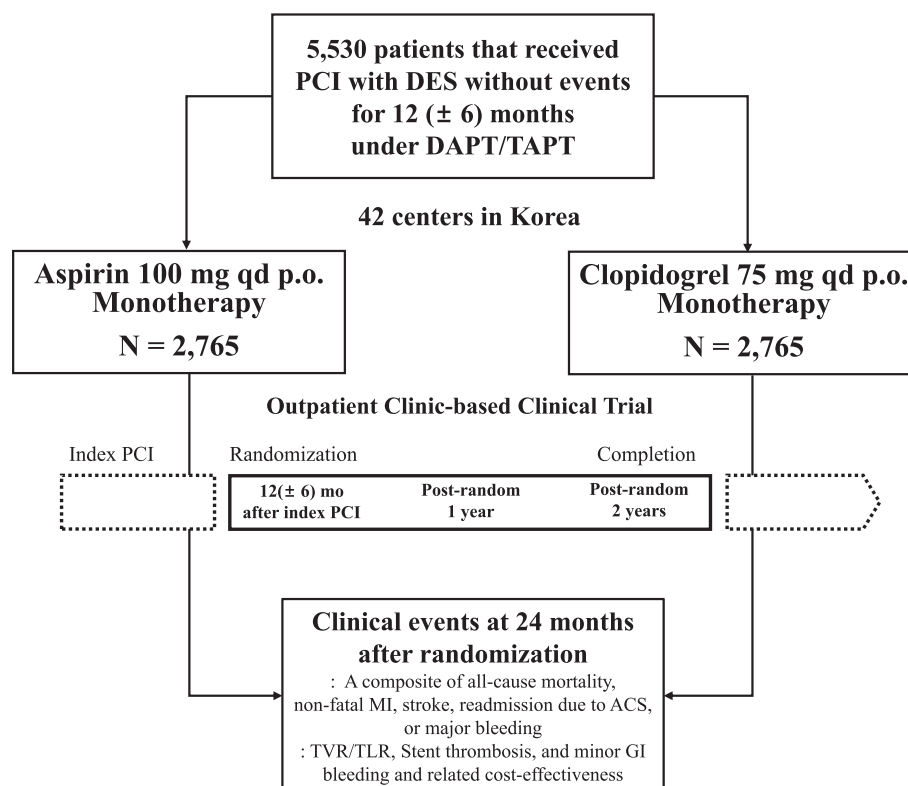
Once all eligible criteria are satisfied and written informed consent is obtained by the investigators, patients will be randomized to aspirin or clopidogrel monotherapy in a 1:1 ratio. The randomization will be balanced, stratified by the center, and independently conducted online via Interactive Web Response Service, a Web-based application by the Seoul National University Hospital Medical Research Collaborating Center. A total of 5,530 patients will be enrolled from 42 high-volume PCI centers in Korea. The study participants will be randomized to the experimental (clopidogrel 75 mg) or control (aspirin 100 mg) group. The medication is maintained for up to 24 months after randomization. A clinical follow-up is planned at 12 and 24 months, and additional visits are at the discretion of attending physicians. The investigators will be urged to follow up the patients by office visits or telephone contacts as necessary. When a patient does not appear at the scheduled time, an investigator or research coordinator checks his/her status via telephone visits to minimize the risk of underreporting clinical events. On each visit,

patient adherence to the study drug will be assessed, and discontinuation of the allocated drug will always be discussed and checked based on the physician's recommendation. Drug adherence will be evaluated by the indirect method, which includes patient self-reporting, pill counts, and pharmacy refills. These parameters have been established as good tools for assessing drug adherence.³⁶ It is allowed to interrupt antiplatelet therapy within consecutive 14 days, regardless of type of allocated drug or the reason leading to temporary cessation (invasive procedures, medical condition requiring a fast, deficiency of pills, or etc). During the study, some medications should not be administered simultaneously as mentioned above. For example, when the enrolled patients get to initiate anticoagulation treatment during the study, their attending physicians will stop the study progression, assess ischemic and bleeding risk, prescribe oral anticoagulant (warfarin with lower INR or new oral anticoagulants) and 1 antiplatelet (clopidogrel or low-dose aspirin), and consider adding proton pump inhibitors.²⁸ Although, each will be followed up till the study completes.

Outcome measurement

The primary endpoint of this study is the *rate of clinical events* defined as a composite of MACE and major bleeding complications. The MACE includes *all-cause death, nonfatal MI, stroke, or readmission due to ACS*. *Major bleeding* is defined as bleeding (BARC class ≥ 3) at 24 months. Detailed definition of each clinical events was determined by the third universal definition of MI, the American College of Cardiology Foundation and the American Heart Association, or objective evidence, which were described in Supplementary Table III.³⁷⁻³⁹

Secondary endpoints are the rate of device-oriented outcomes including TLR/TVR and stent thrombosis at 24 months, and minor gastrointestinal (GI) complications with the related cost-effectiveness. *Target lesion revascularization* is defined as any repeat revascularization procedure at the original lesion of the index procedure any time during the follow-up period.⁴⁰ *Target vessel revascularization* is defined as any repeat revascularization procedure involving at least one of the target vessels that were treated in the index procedure.⁴⁰ *Stent thrombosis* is defined according to the Academic Research Consortium.^{41,42} Minor *GI complications* are assessed on the basis of newly added GI medications, or symptom-driven GI endoscopy. At each visit, any additional GI medications, including H₂-blockers and proton pump inhibitors, will be documented for each patient. If a patient undergoes endoscopy, the type of endoscopy, test results, and further interventions will be recorded. Additional medical costs related to these minor GI complications (South Korean won/year) will be calculated to assess the cost-effectiveness of each drug based on average Korean expenses. Definitions of clinical

Figure

The HOST-EXAM randomized control trial algorithm. DAPT indicates dual antiplatelet therapy; TAPT, triple antiplatelet therapy; PCI, percutaneous coronary intervention; DES, drug-eluting stent; MI, myocardial infarction; ACS, acute coronary syndrome; TVR, target vessel revascularization; TLR, target lesion revascularization; GI, gastrointestinal.

outcomes will be based on objective aspect, and all endpoints will be assessed primarily by the investigator and adjudicated secondarily by the independent, blinded, and centralized clinical event committee to minimize potential bias by open-labeled method.⁴³

Statistical analysis

Continuous variables will be expressed as mean $\pm$ SD, whereas categorical variables will be presented as absolute values and their proportions. Differences between continuous variables will be compared by Student's *t*-test for independent data or Wilcoxon rank sum test for dependent data; differences between categorical variables will be compared by Pearson's χ^2 test or Fisher's exact test as appropriate. All primary and secondary endpoints will be analyzed both on intention-to-treat and per-protocol sets. For the intention-to-treat set, all patients who sign the written informed consent and randomized in this study will be included in the analysis regardless of their adherence to the entry criteria, the treatment they actually received,

deviation from the prescribed protocol, or withdrawal from the study. Despite discontinuation of the allocated study drug in patients with protocol violation, they will be followed up till the study completes and analyzed for the primary endpoint. Primary endpoints will be analyzed on the intention-to-treat set.⁴⁴ The per-protocol set will be supportive to minimize unanticipated problems that could dilute treatment differences of interest.⁴⁵ The safety evaluation is analyzed on both the intention-to-treat and per-protocol sets. All primary and secondary endpoints will be analyzed on a per-patient basis. Kaplan-Meier survival curves are used to estimate the risk of clinical events according to the type of antiplatelet agent, and differences between the 2 groups will be compared by the log-rank test. To prevent underpowered result, we are considering the interim analysis to calculate the ultimate likelihood of success and determine futility.

Few studies have been performed with a similar design as the current trial. Therefore, we estimated the number of participants needed for statistical significance based on the event rates of previous trials.^{4,29,46,47} Mulukutla et al⁴⁶

reported that the composite rate of all-cause death, nonfatal MI, and stent thrombosis was 9.6% in DES patients on single antiplatelet therapy (primarily aspirin) for 2 years after DAPT for 1 year. In a Korean population, Lee et al⁴ and Park et al⁴⁷ reported that the rates of patient-oriented composite events consisting of all-cause death, nonfatal MI, and any revascularization at 1- and 3-year follow-up were 7.5% and 13.3%, respectively. The CAPRIE trial demonstrated a relative risk reduction in clinical events, a cluster of vascular deaths, ischemic stroke, and MI in favor of clopidogrel. The relative risk reduction rate of clopidogrel was 22.7% in patients with ischemic stroke, peripheral vascular disease, and prior MI and 7.4% in patients with a prior MI.²⁹ Severe bleeding was reported in 0.8% of participants in the clopidogrel group and 1.14% of participants in the aspirin group with a relative risk reduction of 30%. In our study, primary outcomes include stroke, readmission due to ACS, and major bleeding complications. In the CAPRIE trial, clopidogrel reduced the risk of clinical events and bleeding by 20%– to 30%.²⁹ Therefore, we predicted clinical event rates of clopidogrel and aspirin monotherapy to be 9.6% and 12%, respectively, at 24 months after single antiplatelet therapy. Using a log-rank design, with a sampling ratio of clopidogrel to aspirin of 1:1 and an estimated withdrawal rate of 5% in each group for 24 months, 5,530 patients are needed to ensure a power of at least 80% with a 2-sided α of 5%. The expected number of events in each test drug group is 567.

Trial organization and ethical considerations

Executive committee. The executive committee, which consists of the study chairperson and principal investigators of the primary investigating centers, oversees the administrative progress of the study and approves the study design, protocol, and amendment to the data safety and monitoring board (DSMB) and the participating centers. The executive committee is in charge of reviewing the results, determining the adjudication of the publication, and selecting secondary projects. The executive committee also has the final decision to modify or stop the study prematurely based on DSMB recommendations. All the members were described in Appendix 1.

Data safety and monitoring board. An independent DSMB, which consists of cardiologists and biostatisticians, reviews safety data from the study and constructs recommendations for adverse events/serious adverse events, protocol deviations, and follow-up case reports (Appendix 2). Regular DSMB meetings are held before the start of the study to establish the study policies; review the raw data; discuss the issue of patient safety, compliance, and treatment efficacy; and advise the executive committee to modify or stop the study if there are any important issues such as significant harm or benefit to the experimental group. According to the

DSMB report, the executive committee decides whether the study should be continued or stopped. Because there are no formal guidelines to guide the DSMB with regard to the level of significance needed to prematurely stop the trial for either efficacy or safety, a type I error, α will not be changed. The DSMB helps conduct the trial appropriately by reviewing the cumulative investigational data for accuracy and completeness and by ensuring protocol compliance. The independent clinical research associates will regularly check compliance with good clinical practice and protocol, dropouts, systematic deficiency, and quality of data. The risk-based source data verification will be applied to eliminate risk and improve the data quality by cross-referencing data recorded in a case report form to the original source information. The DSMB develops a consensus understanding of all trial endpoints and definitions used in the event adjudication process. All DSMB reports remain strictly confidential but are available to regulatory authorities on request.

Clinical event adjudication committee. The centralized clinical event adjudication committee (CEAC), which consists of independent cardiologists, also helps execute the trial properly and reduces potential bias.⁴³ The CEAC is responsible for all aspects of reviewing the results, determining the adjudication of the publication, and selecting secondary projects. In particular, the CEAC develops specific criteria for categorizing clinical events and endpoints based on the protocol. At the study onset, the CEAC will establish clear rules outlining the minimum amount of data required and the algorithm followed to classify the clinical events. To maximize the procedural justice of our study and guarantee CEAC independence, all CEAC members are masked to the assigned study arm when performing their assessment of clinical events.

Data coordination and site management. Data collection, coordination, and site monitoring will be performed by a research coordinator of the Clinical Trials Center at Seoul National University Hospital, the main investigating center.

Ethical approval. This study was approved by the institutional review boards of Seoul National University Hospital (1208-028-421) and 42 participating centers. The study protocol has been registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (study identifier no. NCT02044250; <https://clinicaltrials.gov/ct2/show/NCT02044250?term=NCT02044250&rank=1>).

The authors are solely responsible for the study design and conduct, all study analyses, and the drafting and editing of the manuscript and its final contents.

Discussion

The necessity of trials providing strong evidence for the best antiplatelet monotherapy beyond DAPT after DES implantation

During the last decade, PCI with DES has been established as the most effective strategy for CAD

management by improving angina symptoms and reducing additional cardiovascular events.^{32,48} However, because a stent is a foreign body, stent thrombosis after PCI is an inevitable problem.⁴⁹ To prevent this complication and reduce cardiovascular mortality, many trials have emphasized adjunctive antiplatelet therapy after PCI.^{8-12,16,17} Although numerous studies have been evaluated the optimal antiplatelet regimen, it is still a subject of debate: in particular, the efficacy and safety according to DAPT duration.^{5,16,17,22,50} Recently, large randomized controlled trials have demonstrated that the extended DAPT had a significant reduction in thrombotic/ischemic events and an increase in bleeding complications as a trade-off. The DAPT trial showed that long-term use, beyond 1 year, of clopidogrel or prasugrel combined with aspirin conferred a significantly lower risk in stent thrombosis and a composite of death, MI, or stroke, but a higher risk of bleeding in patients with DES implantation.¹⁶ The PEGASUS-TIMI 54 trial also showed that sustained treatment with ticagrelor significantly reduced the risk of cardiovascular death, MI, or stroke, but increased the TIMI major bleeding in patients with MI ≥ 1 year previously.¹⁷ In terms of antiplatelet monotherapy after DAPT in patients with PCI, a meta-analysis described that aspirin as secondary prevention yielded a greater reduction in coronary events (4.3% vs 5.3% per year, $P \leq .001$), compared with control rather than other antiplatelet agent.⁵¹ Hence, current guidelines recommend DAPT with aspirin and a P2Y₁₂ receptor inhibitor for at least 6- to 12 months after DES implantation, and subsequent lifelong antiplatelet monotherapy, usually aspirin.^{23,24} Most physicians switch from DAPT to aspirin monotherapy around a year. However, this preference is not based on solid clinical evidence. No trials have directly compared the efficacy and safety of 2 possible monotherapy antiplatelet strategies using aspirin or clopidogrel. Therefore, strong evidence to support either monotherapy is lacking. The HOST-EXAM trial will establish which strategy is better for the chronic phase beyond DAPT after PCI with DES, and will provide clinical evidence for future guidelines on long-term antiplatelet maintenance in post-PCI patients. Although it has an inevitable limitation originated from an open-label study, our study is the first large-scale prospective randomized controlled trial.

The best therapeutic agent for long-term antiplatelet monotherapy

Aspirin, a thromboxane synthesis inhibitor, effectively reduces cardiovascular death in patients with atherosclerotic vascular disease.⁵² Clopidogrel, one of the most frequently used P2Y₁₂ receptor inhibitors, selectively and irreversibly inhibits adenosine diphosphate-dependent activation of the glycoprotein IIb/IIIa complex on the platelet surface.^{27,53} The combination of aspirin and clopidogrel, with their different mechanisms of action,

provides additive antithrombotic effects and is currently the best treatment option for post-PCI management. Although physicians have investigated many aspects of DAPT, clinical evidence for monotherapy in the chronic and stable phases after DES implantation is still lacking. The 2 options for monotherapy are aspirin and clopidogrel, which have different efficacy, safety, pharmacokinetics, and pharmacodynamics. However, they have never been compared directly in terms of long-term cardiovascular outcomes for PCI patients with DES.

The CAPRIE trial previously reported that long-term clopidogrel administration to patients with atherosclerotic vascular disease was more effective than aspirin for reducing the risk of MI, ischemic stroke, or vascular death (relative risk reduction 8.7%, 95% CI 0.3-16.5, $P = .043$).²⁹ However, the subgroup analysis of the CAPRIE trial determined that clopidogrel was not significantly better than aspirin for reducing risk in patients with MI (relative risk reduction -3.7%, 95% CI -22.1 to 12.0, $P = .66$).²⁹ This trial is the first study directly comparing the efficacy and safety of both drugs. However, the results cannot be regarded as direct evidence to guide antiplatelet monotherapy for patients with post-PCI because the study population was not treated with PCI with a contemporary DES. Therefore, a randomized controlled trial is required to assess the efficacy and safety of long-term antiplatelet monotherapy and establish a new perspective on adjunctive medical therapy in the chronic phase after PCI with DES. In this respect, the HOST-EXAM will provide meaningful evidence for an optimal antiplatelet maintenance strategy beyond DAPT for patients with DES implantation. Hereafter, based on the current study result, 3-arm randomized controlled studies are expected to confirm the effect of each antiplatelet agent: aspirin vs clopidogrel vs aspirin and clopidogrel.

Which drug increases bleeding risk?

There have been some controversies regarding bleeding risk in patients on antiplatelet therapy. In the CAPRIE trial, the rates of severe upper GI and intracranial bleeding were reported to be 1.14% in the aspirin group and 0.8% in the clopidogrel group, with weak statistical significance ($P = .05$ for upper GI bleeding, $P = .23$ for intracranial bleeding).²⁹ In a population-based case-control study in Denmark, adjusted odds ratios of upper GI bleeding were 1.8 for low-dose aspirin (95% CI 1.5-2.1) and 1.1 for clopidogrel (95% CI 1.3-2.8).⁵⁴ However, Sørensen et al⁵⁴ more recently reported that the risk of bleeding events is higher in patients treated with clopidogrel alone than in those treated with aspirin alone. These inconsistent results are probably due to different doses of the test drugs, diverse definitions of bleeding events, and variations in the at-risk study populations. Our study design, the HOST-EXAM, will investigate bleeding events in 2 controlled and randomized groups receiving different antiplatelet monotherapies.

The study will gain insight into optimal antiplatelet maintenance regimens to minimize potential hazards of bleeding events in patients undergoing PCI with DES.

Conclusion

After initiation of the HOST-EXAM trial, patient enrollment will be complete within 2 years. To our knowledge, this is the first large-scale randomized controlled study to evaluate the best long-term antiplatelet monotherapy beyond DAPT after PCI with DES. The study will provide clinical evidence that can be used to establish guidelines for long-term antiplatelet therapy in post-PCI patients.

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Appendix. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ahj.2016.12.001>.

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