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Short communication

Study design of the influence of SErotonin inhibition on patients with RENAl impairment or diabetes undergoing drug-eluting stent implantation (SERENADE) study: A multicenter, open-label, prospective, randomized study

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ABSTRACT

Background: The rates of stent failure after percutaneous coronary intervention have decreased since the introduction of the drug-eluting stent (DES). However, chronic kidney disease (CKD) and diabetes mellitus (DM) remain strong clinical predictors of poor prognosis despite DES implantation. Sarpogrelate, a selective serotonin (5-hydroxytryptamine (HT)2a [5-HT2A]) receptor antagonist, has antiproliferative effects, reducing neointimal hyperplasia and smooth muscle cell proliferation, as well as potent antiplatelet action, inhibiting 5-HT-induced platelet aggregation. However, efficacy and safety data for sarpogrelate in patients with CKD or DM are limited. We aim to determine whether sarpogrelate has beneficial effects in patients with CDK or DM treated with DES implantation.

Methods/design: The SERENADE trial is a multicenter, open-label, prospective, randomized study that will test the superiority of triple anti-platelet therapy (TAT; aspirin, clopidogrel, and sarpogrelate) to conventional dual antiplatelet therapy (DAT; aspirin and clopidogrel) in preventing late lumen loss 9 months after the index procedure in patients with CKD or DM. A total of 220 patients diagnosed with coronary artery disease with DM or CKD will be randomized to the TAT or DAT groups (1:1 ratio) after DES implantation. The primary endpoint is late lumen loss at 9 months assessed by quantitative coronary angiography. Secondary efficacy endpoints are composites of major adverse cardiovascular events including cardiac death, nonfatal myocardial infarction, and target lesion revascularization. Secondary safety endpoints are major bleeding events and hepatic or renal impairment.

Discussion: The SERENADE trial will provide insight on the efficacy of adjunctive therapy with sarpogrelate after DES implantation for patients with high-risk profiles such as CKD or DM.

Trial registration: National Institutes of Health Clinical Trials Registry (ClinicalTrials.gov NCT02294643).

1. Background

It is well established that the incidence of major adverse cardiac events (MACE) after primary coronary intervention (PCI) is high in patients with diabetes mellitus (DM) or chronic

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kidney disease (CKD) [1]. However, an optimal method to prevent stent failure in these patients has not been established.

Serotonin is mainly stored in the platelets and released when platelets adhere to injured vascular endothelium. This adherence induces platelet aggregation, neointimal hyperplasia, and smooth muscle cell proliferation. The proliferation of endothelial cells and vascular smooth muscle cells in response to vascular injury is a major cause of restenosis after stent implantation [2]. Some experimental studies have suggested that sarpogrelate, a selective serotonin (5-hydroxytryptamine (HT)2a [5-HT2A]) receptor antagonist and could effectively prevent restenosis and thrombosis after stent implantation because of its antiproliferative and antiplatelet effects [3–5]. In patients with bare metal stents, the administration of sarpogrelate with aspirin and ticlopidine reduced the restenosis rate [6,7]. The effect of sarpogrelate on restenosis after drug-eluting stent (DES) implantation, however, has not been evaluated in patients at high risk of restenosis. The SERENADE trial will evaluate the safety and efficacy of sarpogrelate in patients with CKD or DM after DES implantation.

2. Methods/design

2.1. Study design

The SERENADE trial is a multicenter, open-label, prospective, randomized study that will test the superiority of triple anti-platelet therapy (TAT) consisting of aspirin, clopidogrel, and sarpogrelate to conventional dual antiplatelet therapy (DAT) in terms of reducing late lumen loss 9 months after the index procedure in patients with CKD or DM. The protocol of the trial has been registered at http://www.clinicaltrials.gov (NCT02294643) and a brief flowchart of the whole study is summarized in Fig. 1.

A total of 220 patients with coronary artery disease (CAD) will be enrolled at three centers in Korea. All patients will receive one of three second-generation DESs: zotarolimus-eluting stent, everolimus-eluting stent, or biolimus-eluting stent. The type of stent will be chosen by the physician. PCI will be performed according to the standard technique and the use of predilatation, glycoprotein IIb/IIIa inhibitors, or heparin will be left to the operator's discretion. Intravascular ultrasound analyses are not mandatory, but can be performed for clinical indications at the investigator's discretion. Immediately after the PCI, the patients will be randomized either to the TAT group (aspirin 100 mg, clopidogrel 75 mg, and sarpogrelate [Anplag®; Yuhan Corporation, Seoul, South Korea] 100 mg twice daily) or the DAT group (aspirin 100 mg, clopidogrel 75 mg). An investigator with no clinical involvement in the trial will randomize the patients to either the DAT or TAT group (1:1 allocation ratio) using a 6 block-randomization scheme via a web-based computerized program (T&W Software, Seoul, Korea). The randomization will be balanced and stratified by a vessel diameter of 3 mm and the presence of CKD or DM. After the research nurse has obtained the patient's consent, each patient will be identified by a linkable patient identification code, and registered along with information relevant to his or her eligibility. Patients and investigators will be aware of the treatment allocation. The researchers in the quantitative coronary angiography (QCA) core lab and clinical event committee will be blinded to the treatment assignments. After discharge, participants will be monitored clinically at 1, 9, and 12 or 36 months to document clinical events and ensure medical compliance. Investigators will follow up with patients either by office visits or by telephone calls as necessary. Patients will be treated according to current guidelines, including the use of β-blockers and lipid-lowering therapy, as tolerated. A sarpogrelate dose of 200 mg daily will be maintained for 1 year. All patients will be recommended to undergo follow-up angiography at 9 months.

This trial is investigator-initiated with grant support from Yuhan Corporation (Seoul, South Korea). Other than financial sponsorship, the company has no role in the study protocol development, implementation, or data collection and analysis. The authors alone are responsible for the trial design and execution, related statistical analyses, and all aspects of manuscript preparation, including drafting, editing, and decisions on

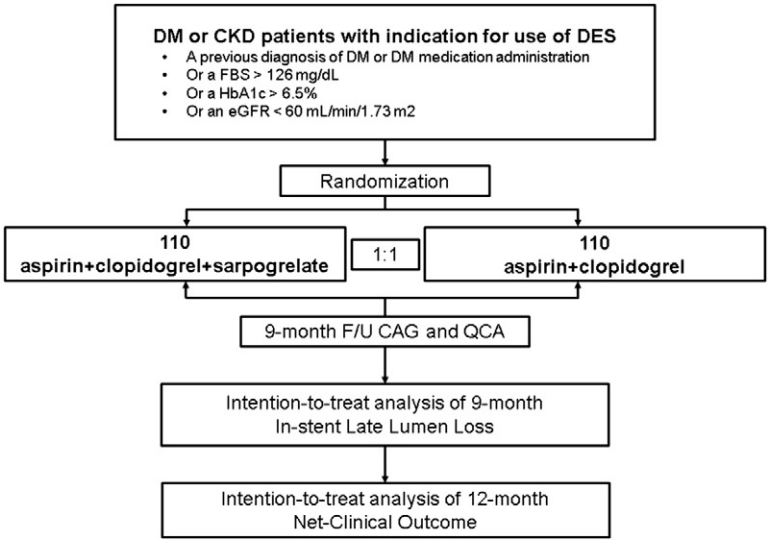

Fig. 1. The SERENADE trial algorithm. CAG, coronary angiography; DES, drug-eluting stent; F/U, follow-up; and QCA, quantitative coronary angiography.