DATA S1. SUPPLEMENTARY METHODS

Diagnosis of coronary artery spasm

Intracoronary ACh provocation tests were performed according to the Japanese Circulation Society guidelines for the diagnosis and treatment of patients with CSA. In brief, after insertion of a temporary pacing electrode in the right ventricle via basilic, cephalic, or internal jugular vein, ACh was injected in incremental doses of 50, and 100 μg into the left coronary artery (LCA), and 20 and 50 μg into the right coronary artery (RCA) over a period of 20 s. After the ACh provocation test, 1 mg of isosorbide dinitrate was administered into the RCA and LCA. Coronary angiography was performed before and 1 min after each ACh injection, after isosorbide dinitrate injection, and when chest pain or ischemic ECG changes were observed. All vasodilators, such as calcium channel blocker, long-acting nitrate, and nicorandil were discontinued at least 48 h before the examination in the setting of non-emergency ACh provocation.

Positive coronary artery spasm was defined as transient luminal narrowing (99 % focal spasm or 90 % severe diffuse vasoconstriction associated with usual chest pain/symptom or ischemic ECG findings induced by the ACh provocation test or due to spontaneous coronary artery spasm. Ischemic ECG changes include transient ST elevation ≥0.1 mV, ST depression ≥0.1 mV, or new appearance of negative U waves, recorded in at least two contiguous leads on the 12-lead ECG. Focal spasm was defined as ACh-induced or spontaneous coronary artery spasm <20 mm in length in the major epicardial arteries assessed by angiography, while diffuse spasm was ≥20 mm.

Quantitative coronary angiography analysis

Quantitative coronary angiography (QCA) analysis was performed using standard commercial software (CAAS QCA, Pie Medical Imaging BV, Maastricht, the Netherlands). The QCA software provided automatic contour detection and automated identification of the sites of maximal luminal obstruction and the start and end of the stenosis. The following QCA parameters were obtained in the target lesion: minimum luminal diameter (MLD), reference diameter at the MLD site, proximal and distal reference diameter, percentage diameter stenosis, and lesion length.

OCT Image Acquisition and Analysis
After the ACh provocation test, we performed an OCT imaging using either an OPTIS (Abbott, Santa Clara, CA, USA) or a LUNAWAVE (Terumo Corporation, Tokyo, Japan) system. After the injection of nitrates and confirming the relief of the vasospasm and vasodilation, the OCT imaging catheter (Dragonfly OPTIS / OpSter, Abbott; or FastView, Terumo Corporation) was advanced distally in the target vessel. OCT images were acquired during continuous injection of contrast medium at a pullback rate of 36 mm/s (180 frames/s) or 40 mm/s (160 frames/s) in the OPTIS and LUNAWAVE systems, respectively.

Quantitative analysis was performed using a validated OCT analysis software (echoPlaque, Indec Systems, Santa Clara, CA, USA). A significant organic lesion was defined as a stenotic lesion due to plaque accumulation where a 50% or greater plaque burden exists. External elastic membrane (EEM) and lumen area were manually traced at the leading edge of boundaries at 1-mm intervals from proximal to distal 5-mm reference segments throughout the organic lesion segment with automated interpolated measurements of the remaining frames. Plaque (intima + media) areas were defined as EEM area minus lumen area. When the EEM was not visible >90 degrees or greater at a certain frame, manual tracing of the EEM was not performed at the frame, but the automated interpolation based on the EEM boundaries in the neighboring frames was applied. Maximum plaque burden and minimum lumen area within the organic lesions were evaluated.

Qualitative OCT analyses were analyzed at significant coronary artery lesions, including stenotic lesion and reference segments by two experienced investigators blinded to clinical and angiographic information. A layered plaque was defined as a region having one or more layers with different optical densities from underlying components and a clear border. The other qualitative OCT analyses were based on previously established criteria. Lipid was defined as a signal-poor region with a poorly defined or diffuse border. Calcification was defined as a signal-poor or heterogeneous region with a sharply delineated border. The calcification arc and the lipid arc degrees were measured. Macrocalkification was defined as maximal calcium arc >90 degrees. Lipid-rich plaques were defined as having lipid arcs >90 degrees, and thin-cap fibroatheroma (TCFA) were defined as lipid-rich plaques with a fibrous cap thickness <65 μm. Plaque cavity was defined as an intimal discontinuity with an empty space within a plaque. Macrophage images were defined as signal-rich, distinct or confluent punctuate regions with shadowing. A fresh thrombus
was defined as a mass attached to the luminal surface or floating within the lumen. Microchannels were defined as no-signal tubuloluminal structures without a connection to the vessel lumen recognized on 3 consecutive cross-sectional OCT images.