The development of CIN resulted in an increase of in-hospital mortality (OR 25.47, 95% CI 12.54–51.71; $p < 0.001$). This was maintained in both STEMI (OR 31.28, CI 95% 11.02–88.78, $p < 0.001$) and NST-ACS (OR 19.13, 95% CI 7.04–51.99, $p = 0.001$). Similar results were obtained for in-hospital bleeding and in-hospital mortality risk (OR 7.61, 95% CI 3.65–15.88, $p < 0.001$ in all patients; OR 9.05, 95% CI 3.33–24.55, $p < 0.001$ in STEMI; OR 4.25, 95% CI 1.64–16.77, $p = 0.005$ in NST-ACS). After adjusting for the GRACE risk score [6], both variables (CIN and bleeding) were independent predictors of in-hospital death and its power was increased when both were combined.

We made several clinically important observations in this study. First, CIN and in-hospital bleeding are common complications during admission for ACS (± 1 of 15 patients). However, few patients require renal replacement therapy (<1%) or transfusion of blood products (3%). Second, pre-cath bleeding was an independent predictor for the occurrence of CIN, and in a bilateral way, the development of CIN resulted an independent predictor for post-cath bleeding. Third, CIN and post-cath bleeding (but not pre-cath bleeding) increase the in-hospital death risk independently of the GRACE risk score, and the combination of both enhances this risk, especially in STEMI patients.

In summary, we have proved that CIN and in-hospital bleeding are bidirectionally interrelated, and with independent additive value for in-hospital death (Fig. 1). With our results we emphasize the importance of identifying patients at high risk of CIN and/or bleeding in the context of an ACS. We hypothesize that the implantation of appropriate strategies for the reduction of CIN would lead to a decrease in the bleeding risk of NST-ACS patients, and vice versa, as well as a reduction in in-hospital mortality across all the spectrum of ACS patients.

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Risk stratification using a combination of left ventricular fibrosis and number of morphological types of ventricular premature beats in cardiomyopathy subjects without obstructed coronary arteries

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Hypertrophic cardiomyopathy (HCM) subjects with late enhancement of the left ventricular (LV) myocardium measured by cardiac magnetic resonance (CMR) are likely to have myocardial fibrosis and a poor prognosis [1–3].

Recently, enhanced multislice computed tomography (CT) has also been shown to detect myocardial fibrosis and edema in the LV myocardium as a contrast defect in the early phase and abnormal enhancement in the late phase (Fig. 1) [4].

Various morphologies of ventricular premature beats (VPBs) are observed in cardiomyopathy subjects without obstructed coronary arteries, but their significance is unknown.

In this study we performed risk stratification of cardiomyopathy subjects with LV fibrosis but without obstructed coronary arteries on multislice CT, using the numbers of morphological types of VPBs detected by 12-lead Holter electrocardiogram (ECG).

This was a retrospective analysis of 64 consecutive subjects (46 males, mean age 61 ± 14 years) who satisfied the definitions of cardiomyopathies published in Circulation 2006 [5] and did not have any obstructed coronary arteries on CT. Final clinical diagnosis was represented in Table 1. The percentage of HCM was 75%. Patients' characteristics were represented in Table 2. They underwent cardiac multislice CT and 12-lead Holter ECG within 12 months of each other from July 2007 to April 2012. Exclusion criteria was as follows; coronary artery stenosis (>50%) on CT and previous myocardial infarction. Subjects were followed for a median of 50 months for occurrence of major adverse cardiovascular events (MACE). MACE included cardiovascular death critical ventricular arrhythmia and hospitalization due to heart failure. Critical ventricular arrhythmias included subjects with appropriate implantable cardioverter defibrillator therapy such as appropriate discharge of implantable

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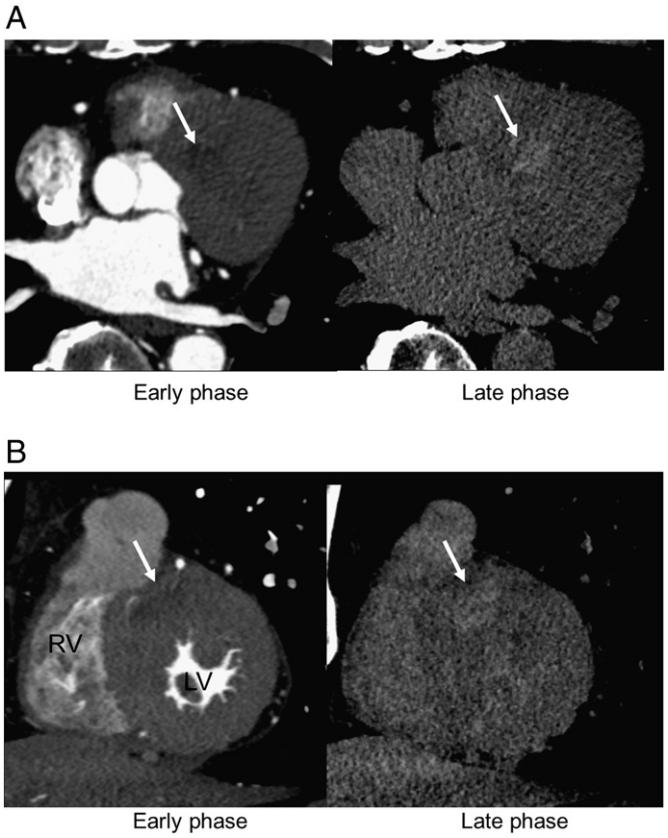

Fig. 1. Typical multislice computed tomographic images of myocardial fibrosis (arrows) in a subject with Maron type 2 hypertrophic cardiomyopathy.A: Axial source images.B: Multiplanar reconstruction images of left ventricular (LV) short axis. As there was a contrast defect in LV myocardium in the early phase (arrows), a late phase acquisition was added and abnormal late enhancement was observed at the corresponding site, we diagnosed this as myocardial fibrosis. RV indicates right ventricle.

cardioverter defibrillator and anti-tachycardia pacing for ventricular tachycardia and performance of radiofrequency catheter ablation of ventricular arrhythmia.

On 12-lead Holter ECG protocol, the numbers of morphological types of VPBs were counted automatically, but were checked manually by experienced technologists. An experienced cardiologist, blinded to the CT findings, then confirmed these results.

On multislice CT protocol, retrospective ECG gated CT scans were performed on all subjects to evaluate coronary arteries, myocardium and cardiac function [6–10]. If there was a contrast defect in LV myocardium in the early phase, a late phase acquisition was added. If abnormal late enhancement was observed at the corresponding site, we diagnosed this as myocardial fibrosis [4]. If the contrast defect continued in the late phase with <0 Hounsfield Unit CT attenuation values, we diagnosed this site as myocardial fatty change.

The total number of morphological types of VPBs was 10.1 ± 21.6. LV fibrosis and fat were detected on CT in 41 (64.1%) and 20 (31.3%) subjects, respectively. MACE occurred in a total of 9 subjects (14.1%) (7 males, mean age 50 ± 21 years) (cardiovascular death 1, critical ventricular arrhythmia 5, and hospitalization due to heart failure 3).

Table 1
Final clinical diagnosis (N = 64).
Percentage of hypertrophic cardiomyopathy was 75%.

Hypertrophic cardiomyopathy	48 (75.0%)
Dilated cardiomyopathy	5 (7.8%)
Arrhythmogenic right ventricular cardiomyopathy	1 (1.6%)
Inflammatory cardiomyopathy	4 (6.3%)
Cardiac amyloidosis	1 (1.6%)
Left ventricular noncompaction	1 (1.6%)
Stress cardiomyopathy	1 (1.6%)
Unidentified cardiomyopathy	3 (4.7%)

Table 2
Patients' characteristics.

Age (years)	61 ± 14
Male	46 (71.9%)
Hypertension	30 (46.9%)
Diabetes mellitus	9 (14.1%)
Hyperlipidemia	20 (31.3%)
Smoking	21 (32.8%)
Administration of angiotensin receptor blocker	27 (42.2%)
Administration of angiotensin converting enzyme inhibitor	3 (4.7%)
Administration of β blocker	45 (70.3%)
Administration of statin	17 (26.6%)
Follow-up period (months)	39.5 ± 24.2 (median 50)

A significant difference between the cardiomyopathy subjects with and without myocardial fibrosis on CT was seen at each time point for occurrence of MACE when the complete follow up-period was compared by Kaplan–Meier analysis and log rank testing (P = 0.009) (Fig. 2). According to the receiver operating characteristic (ROC) curve, the best cutoff value for the numbers of morphological types of VPBs to distinguish between subjects with and without MACE was 12 with sensitivity of 66.7%, specificity of 92.7% and area under the curve of 0.783 (Fig. 3). By Kaplan–Meier analysis, there was a significant difference in the occurrence of MACE between subjects with morphological types of VPBs ≥ 12 and < 12 (P < 0.001) during the follow-up period (Fig. 4).

We then divided the subjects into 3 groups as follows; Group 1: presence of LV fibrosis and numbers of morphological types of VPBs ≥ 12, Group 2: presence of LV fibrosis with numbers of morphological types of VPBs < 12 and Group 3: absence of LV fibrosis. Kaplan–Meier analysis revealed significant differences in the occurrence of MACE between Group 1 and Group 3 (P < 0.001) and Group 1 and Group 2 (P < 0.001) (Fig. 5).

We have previously reported that LV fibrosis can act as both the origin of and the substrate for critical ventricular arrhythmia in subjects with confirmed absence of obstructed coronary artery disease [4]. Myocardial scarring is known to act both as the origin of, and a specific substrate for, ventricular arrhythmia, and the border zone

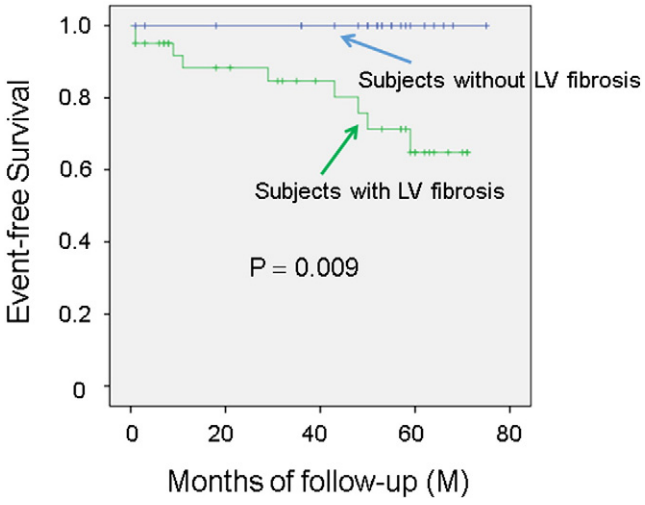

Fig. 2. Kaplan–Meier survival curve of the cardiomyopathy subjects without obstructed coronary arteries for major adverse cardiovascular events (MACE) using presence of left ventricular (LV) fibrosis on computed tomography.A significant difference between the subjects with and without LV fibrosis was seen at each time point for occurrence of MACE when the complete follow-up period was compared by Kaplan–Meier analysis and log rank testing (P = 0.009).