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Differential prediction of high-sensitivity cardiac troponin-I, but not N-terminal pro-brain natriuretic peptide, in different pitavastatin doses on cardiovascular events in stable coronary artery disease

Yoshiaki Mitsutake [a,1], Junnichi Ishii [b,c,1], Yoshihiro Fukumoto [a,*,1], Sohei Ito [a,1], Kosuke Kashiwabara [d,1], Kouhei Uemura [d,1], Yutaka Matsuyama [d,1], Yoichi Sugiyama [a,1], Yukio Ozaki [b,1], Satoshi Iimuro [e,1], Hiroshi Iwata [f,1], Ichiro Sakuma [g,1], Yoshihisa Nakagawa [h,1], Kiyoshi Hibi [i,1], Takafumi Hiro [j,1], Seiji Hokimoto [k,1], Katsumi Miyauchi [f,1], Hiroyuki Daida [f,1], Hiroaki Shimokawa [l,1], Yasushi Saito [m,1], Takeshi Kimura [n,1], Masunori Matsuzaki [o,1], Ryozo Nagai [p,1]

[a] Division of Cardiovascular Medicine, Kurume University School of Medicine, Kurume, Japan
[b] Department of Cardiology, Fujita Health University School of Medicine, Toyoake, Japan
[c] Toyota Auto Body Yoshiwara Clinic, Toyota, Japan
[d] Data Science Office, Clinical Research Promotion Center, The University of Tokyo Hospital, Tokyo, Japan
[e] Innovation and Research Support Center, International University of Health and Welfare, Tokyo, Japan
[f] Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan
[g] Caress Sapporo Hokko Memorial Clinic, Sapporo, Japan
[h] Department of Cardiovascular Medicine, Shiga University of Medical Science, Otsu, Japan
[i] Division of Cardiology, Yokohama City University Medical Center, Yokohama, Japan
[j] Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan
[k] Kumamoto Municipal Ueki Hospital, Kumamoto, Japan
[l] International University of Health and Welfare, Narita, Japan
[m] Chiba University, Chiba, Japan
[n] Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan
[o] St. Hill Hospital, Ube, Japan
[p] Jichi Medical University, Shimotsuke, Japan

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ABSTRACT

Background: This study aimed to examine whether high-sensitivity cardiac troponin-I (hsTnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) could predict future major adverse cardiovascular events (MACE) in stable coronary artery disease (CAD) patients with high- or low-dose of pitavastatin.
Methods: This was a case-cohort analysis of the REAL-CAD study, a randomized trial of high- or low-dose (4 or 1 mg/day) pitavastatin therapy in patients with stable CAD. We examined the MACE risk according to the quartile of hsTnI and NT-proBNP at baseline.
Results: A total of 1336 and 1396 patients including 582 MACE cases were randomly examined into the hsTnI and NT-proBNP cohort, respectively. Both higher levels of hsTnI and NT-proBNP at baseline were significantly associated with increased risk of MACE ($p < 0.001$, respectively). When separately analyzed in statin dose, the higher marker levels were significantly associated with higher MACE risk in all cohorts ($p < 0.001$ in all cohorts). After multivariable adjustment, hsTnI levels were significantly associated with MACE risk in low-dose statin

Abbreviations: ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CI, confidence intervals; HR, hazard ratios; hsTnI, high-sensitivity cardiac troponin-I; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular events; MI, myocardial infarction; NT-proBNP, N-terminal pro-brain natriuretic peptide; REAL-CAD, Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease.

* Corresponding author at: Division of Cardiovascular Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 8300011, Japan.
E-mail address: fukumoto_yoshihiro@kurume-u.ac.jp (Y. Fukumoto).

[1] This authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation

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group (HR 2.54, $p = 0.0001$); however, in high-dose pitavastatin therapy, a significant association was diminished in MACE risk among the quartiles of baseline hsTnI levels ($p = 0.154$). Conversely in the NT-proBNP cohort, the association between NT-proBNP levels and MACE risk was constantly observed regardless of pitavastatin dose even after multivariable adjustment (both $p < 0.0001$).

Conclusions: Patients with high hsTnI levels had high risk of MACE in low-dose statin group, but not in high-dose, suggesting that high-dose statin treatment might decrease MACE risk in stable CAD patients with high hsTnI levels.

1. Introduction

Low-density lipoprotein cholesterol (LDL-C) plays a key role in atherosclerosis progression, which is one of the major risk factors in cardiovascular events [1]. LDL-C lowering therapy by statin is effective in both primary and secondary prevention of cardiovascular events, as shown in several clinical trials [2–5]. The Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) study demonstrated that high- (4 mg/day) compared with low- (1 mg/day) dose pitavastatin therapy significantly reduced major adverse cardiovascular events (MACE) by 19% in Japanese patients with stable CAD, who commonly receive low-dose statin therapy [6]. Also, this study showed the safety of high-dose statin therapy [6]. Statin therapy has been well established in patients with CAD, but high-intensity statin therapy is not still widely implemented in daily clinical practice. Having more information to identify those who may benefit from high-intensity statin may be helpful.

High-sensitivity cardiac troponin-I (hsTnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are well-known diagnostic markers of cardiovascular diseases. These biomarkers could be useful for risk stratification of patients with CAD [7–9]. It has been previously reported that statin therapy is consistently effective compared with placebo for MACE reduction regardless of the concentration of hsTnI and BNP [8]. However, there have been no reports investigating a relationship between MACE and cardiac biomarkers in different doses of statins.

Therefore, the aim of this REAL-CAD sub-study was to examine whether hsTnI and NT-proBNP at baseline could predict future MACE in stable CAD patients, who were treated with high- and low-dose of pitavastatin.

2. Methods

2.1. Study population and endpoints

This was a case-cohort analysis of the REAL-CAD study. The REAL-CAD study is a prospective, multicenter, randomized trial to assess the efficacy of high- (4 mg/day) as compared with low-dose (1 mg/day) pitavastatin in Japanese patients with stable CAD. The detail of study design, patient enrolment, definition of the measurements was previously described [6]. Briefly, eligible patients in the REAL-CAD study were 20 to 80 years of age with stable CAD defined as a history of acute coronary syndrome (ACS) or coronary revascularization >3 months ago or a clinical diagnosis of CAD with angiographically documented coronary artery stenosis of at least 75% diameter narrowing according to the American Heart Association Classification [10]. Patients with LDL-C < 100 mg/dL without statin therapy before enrollment, were excluded.

The primary endpoint of this study was MACE as the same as in the main study: a composite of cardiovascular death, non-fatal myocardial infarction (MI), non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization. The secondary endpoint was cardiovascular death, non-fatal MI, non-fatal ischemic stroke, or unstable angina requiring emergency hospitalization [6].

The REAL-CAD study was granted by the Public Health Research Foundation. The company manufacturing the study drug (Kowa Pharmaceutical Co. Ltd.) provided financial support. All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki. The present case-cohort study was also approved by the ethic committee of Kurume University (certification number: 18017).

2.2. Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Continuous variables are presented as the means with standard deviations or the median with range, according to their normal or not normal distribution. Categorical variables are presented as frequency counts. All subjects were categorized into quartiles for each baseline cardiac marker according to the distribution in the random cohort. MACE rates were estimated using the weighted Kaplan-Meier method and differences in MACE risk in subgroups according to quartile of hsTnI or NT-proBNP at baseline were examined with Barlow's log-rank test [11]. The weights were the inverse of patients' sampling probability of this case-cohort design.

To calculate hazard ratios (HR) and 95% confidence intervals (CI) of MACE, the univariable and multivariable Cox proportional hazard regression models with Barlow's methods were used [11]. The interactions between baseline cardiac markers were also examined by the Cox multivariable model.

3. Results

3.1. Baseline characteristic in random cohort according to quartile of baseline biomarkers

There were 11,896 participants with baseline blood sample in the full analysis population of the REAL-CAD study. We conducted a case-cohort analysis based on 582 cases who developed MACE during a median follow-up period of 3.9 years and a random cohort sampling of 1745 participants (three times the number of MACE cases) [12]. Among the 1745 random cohort patients, 1336 patients (high-dose, $n = 660$; low-dose pitavastatin, $n = 676$) after excluding 409 with insufficient blood samples were analyzed in the hsTnI cohort. Similarly, 1396 patients (high-, $n = 685$; low-dose pitavastatin, $n = 711$) were included in the NT-proBNP cohort.

The median hsTnI and NT-proBNP concentration was 8.0 pg/mL and 130.0 pg/mL, the minimum was 1.3 pg/mL and 18 pg/mL, and the maximum was 4413.6 pg/mL and 11,304 pg/mL, respectively. According to the quartile of the hsTnI or NT-proBNP levels, all participants were divided into 4 groups (low, mid-low, mid-high, and high group) in each cohort, respectively (hsTnI, low [≤4.7 pg/mL], $n = 376$, mid-low [4.7<, ≤8.0], $n = 355$, mid-high [8.0<, ≤15.5], $n = 326$, high [15.5<], $n = 279$; NT-proBNP, low [≤49 pg/mL], $n = 393$, mid-low [49<, ≤130], $n = 375$, mid-high [130<, ≤329], $n = 338$, high [329<], $n = 290$). Baseline characteristics in each cohort were shown in Table 1.

3.2. Baseline cardiac biomarkers and MACE

In the hsTnI cohort, the higher hsTnI levels at baseline was significantly associated with increased risk of MACE (log-rank test, $p < 0.001$) (Fig. 1A). Similarly, the NT-proBNP levels at baseline were significantly related to MACE risk (log-rank test, $p < 0.001$) (Fig. 1B).

Table 1
Baseline characteristics according to baseline hsTnI or NT-proBNP quartiles.

	HsTnI (pg/ml)			
	Low quartile (≤4.7)	Mid-low quartile (4.7<, ≤8.0)	Mid-high quartile (8.0<, ≤15.5)	High quartile (15.5<)
	N = 376	N = 355	N = 326	N = 279
Pitavastatin				
4 mg	49.7% (187)	49.6% (176)	49.7% (162)	48.4% (135)
1 mg	50.3% (189)	50.4% (179)	50.3% (164)	51.6% (144)
Age, years	66.4 ± 8.5	68.6 ± 8.6	69.3 ± 8.2	69.5 ± 7.6
Female sex	21.8% (82)	17.7% (63)	16.6% (54)	15.8% (44)
BMI, kg/m2	24.3 ± 3.1	24.9 ± 3.5	24.7 ± 3.1	24.7 ± 3.1
SBP, mmHg	125.7 ± 14.8	127.9 ± 15.2	128.9 ± 17.5	129.0 ± 18.0
DBP, mmHg	72.7 ± 9.8	72.8 ± 10.1	72.7 ± 11.4	72.3 ± 11.7
Heart rate, /min	70.1 ± 10.2	69.4 ± 11.9	68.7 ± 11.4	70.0 ± 12.4
LVEF, %	64.6 ± 9.8	61.0 ± 10.6	59.2 ± 12.7	56.1 ± 14.1
Family history of CAD	16.5% (62)	20.8% (74)	17.5% (57)	16.8% (47)
Prior PCI	84.3% (317)	82.0% (291)	78.8% (257)	81.4% (227)
Prior MI	36.4% (137)	49.0% (174)	54.9% (179)	58.1% (162)
Prior CABG	6.6% (25)	12.7% (45)	19.0% (62)	14.0% (39)
Heart failure	3.7% (14)	3.1% (11)	5.8% (19)	7.9% (22)
DM	37.2% (140)	37.2% (132)	46.0% (150)	45.5% (127)
History of malignant disease	2.9% (11)	4.5% (16)	4.3% (14)	8.6% (24)
Hypertension	71.0% (267)	73.0% (259)	80.7% (263)	78.1% (218)
Atrial fibrillation	2.9% (11)	6.2% (22)	8.0% (26)	6.8% (19)
Prior stroke	6.4% (24)	5.6% (20)	10.7% (35)	9.0% (25)
Prior cranial bleeding	0.3% (1)	1.4% (5)	3.7% (12)	1.1% (3)
PAD	5.6% (21)	6.8% (24)	6.7% (22)	9.3% (26)
Current smoking	14.1% (53)	16.6% (59)	12.0% (39)	17.6% (49)
Statin use at baseline	92.3% (347)	93.2% (331)	88.7% (289)	90.3% (252)
Blood test				
Total cholesterol, mg/dL	167.3 ± 23.9	167.3 ± 24.7	164.0 ± 23.3	164.8 ± 24.7
LDL-C, mg/dL	88.0 ± 18.6	88.8 ± 17.8	86.0 ± 18.3	86.8 ± 18.7
HDL-C, mg/dL	51.1 ± 12.0	51.0 ± 13.0	51.1 ± 13.4	49.4 ± 13.6
Triglycerides, mg/dL	145.5 ± 88.0	142.1 ± 92.4	135.1 ± 62.8	151.5 ± 126.2
HsTnl, pg/ml	3.3 (1.3, 4.7)	6.2 (4.8, 8.0)	10.7 (8.1, 15.5)	32.9 (15.6, 4413.6)
NT-proBNP, pg/ml	49.0 (18, 1393)	107.0 (18, 3444)	189.0 (18, 5075)	236.0 (18, 11,304)
HsCRP, mg/L	0.45 (0.05, 119.0)	0.52 (0.05, 64.5)	0.56 (0.05, 111.0)	0.59 (0.05, 53.1)
Glucose, mg/dL	126.9 ± 46.2	120.4 ± 37.1	127.5 ± 40.1	128.4 ± 46.1
Hb A1c, %	5.9 ± 0.9	5.8 ± 0.9	5.9 ± 0.8	5.9 ± 0.9
eGFR, mL/min/**1.73 m2**	70.8 ± 15.9	66.4 ± 15.0	65.2 ± 42.5	61.3 ± 18.1
CKD				
Stage 1	12.0% (45)	8.5% (30)	4.3% (14)	6.5% (18)
Stage 2	58.8% (221)	55.2% (196)	53.7% (175)	45.5% (127)
Stage 3	27.4% (103)	35.2% (125)	38.0% (124)	44.1% (123)
Stage 4	0	0.3% (1)	2.1% (7)	3.2% (9)
Stage 5	0	0	0	0
Medications				
Aspirin	86.2% (324)	87.3% (310)	85.0% (277)	84.6% (236)
P2Y12-inhibitor	44.9% (169)	37.5% (133)	46.9% (153)	43.4% (121)
DAPT	41.8% (157)	35.8% (127)	44.8% (146)	39.4% (110)
β-blocker	30.9% (116)	36.9% (131)	40.8% (133)	43.4% (121)
ACEI and/or ARB	52.7% (198)	63.7% (226)	66.9% (218)	70.3% (196)

	NT-proBNP (pg/ml)			
	Low Quartile (≤49)	Mid-low quartile (49<, ≤130)	Mid-high quartile (130<, ≤329)	High quartile (329<)
	N = 393	N = 375	N = 338	N = 290
Pitavastatin				
4 mg	49.9% (196)	53.3% (200)	46.4% (157)	45.5% (132)
1 mg	50.1% (197)	46.7% (175)	53.6% (181)	54.5% (158)
Age, years	64.6 ± 8.8	68.2 ± 8.3	71.0 ± 7.2	70.9 ± 6.9
Female sex	12.5% (49)	18.4% (69)	21.3% (72)	22.4% (65)
BMI, kg/m2	25.1 ± 3.2	24.8 ± 3.2	24.4 ± 3.2	24.2 ± 3.3
SBP, mmHg	127.1 ± 14.3	126.6 ± 15.1	128.9 ± 17.0	129.2 ± 19.2
DBP, mmHg	73.8 ± 9.9	72.5 ± 10.2	72.4 ± 11.1	71.4 ± 11.8
Heart rate, /min	70.6 ± 10.7	68.8 ± 12.1	69.1 ± 11.1	69.7 ± 11.7
LVEF, %	64.9 ± 8.9	63.3 ± 11.0	59.8 ± 10.7	52.1 ± 13.9
Family history of CAD	14.5% (57)	20.5% (77)	20.4% (69)	17.2% (50)
Prior PCI	85.5% (336)	82.9% (311)	78.7% (266)	79.0% (229)
Prior MI	36.1% (142)	48.8% (183)	52.7% (178)	60.0% (174)
Prior CABG	4.8% (19)	8.8% (33)	18.3% (62)	23.1% (67)
Heart failure	2.5% (10)	4.0% (15)	3.6% (12)	11.7% (34)

(*continued on next page*)

After adjustment for multivariables (including pitavastatin dose, gender, high age, body mass index, blood pressure, heart rate, history of percutaneous coronary intervention, MI, coronary artery bypass grafting, and heart failure, diabetes mellitus, history of malignant disease, hypertension, atrial fibrillation, peripheral artery disease, smoking, LDL-C, low-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, hemoglobin A1c, and eGFR), the relationships between MACE and those cardiac markers remained significant (Table 2). The high hsTnI quartile compared to the low quartile was at the highest risk for MACE (HR 1.94; 95% CI, 1.35–2.79; $p = 0.0003$). The relationships between hsTnI quartile and each of the individual components of the primary endpoint; cardiovascular death, non-fatal MI, non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization, were displayed in Supplementary Figs. 1–4 and Supplementary Tables 1–4.

After multivariable adjustment, the patients with the high hsTnI quartile compared to the low quartile were at increased risk of cardiovascular death (HR 3.07; 95% CI, 1.69–5.59; $p = 0.0002$), non-fatal MI (HR 2.20; 95% CI, 1.08–4.48; $p = 0.031$) and non-fatal stroke (HR 2.38; 95% CI, 1.15–4.94; $p = 0.020$), but no significant association was observed in emergency hospitalization for unstable angina (HR 1.03; 95% CI, 0.55–1.93; $p = 0.935$).

In the NT-proBNP cohort, the high and the mid-high quartiles compared to the low quartile had higher risk for MACE (high vs. low, HR 3.66; 95% CI, 2.53–5.30; $p < 0.0001$; mid-high vs. low, HR 1.96; 95% CI, 1.35–2.84; $p = 0.0004$) (Table 2). Compared to the low NT-proBNP quartile, the high and mid-high quartiles were at increased risk of cardiovascular death (high vs. low, HR 7.11; 95% CI, 3.74–13.51; $p < 0.0001$; mid-high vs. low, HR 2.68; 95% CI, 1.34–5.36; $p = 0.005$), and non-fatal stroke (high vs. low, HR 6.09; 95% CI, 2.68–13.80; $p < 0.0001$; mid-high vs. low, HR 3.70; 95% CI, 1.64–8.36; $p = 0.002$). Only the high quartile had a significantly higher risk for unstable angina (HR 2.49; 95% CI, 1.30–4.75; $p = 0.006$). There was no significant relationship between NT-proBNP levels and non-fatal MI ($p = 0.121$) (Supplementary Figs. 1–4 and Supplementary Tables 1–4).

3.3. MACE risk stratification in low- and high-dose statin groups

When separately analyzed in the subjects treated with high- or low-dose pitavastatin, the higher levels of biomarkers at baseline were significantly associated with increased MACE risk in all cohorts ($p < 0.001$ in all cohorts) (Fig. 2 **panel A-D)**.

After multivariable adjustment, the high hsTnI quartile compared to the low quartile had a significantly higher risk for MACE in low-dose statin therapy (HR 2.54; 95% CI, 1.57–4.11; $p = 0.0001$) (Table 2). Conversely, in high-dose statin therapy, a significant difference in MACE risk was not found among the quartiles of baseline hsTnI levels ($p = 0.154$) (Table 2). Regarding each of the individual components of the primary endpoint, the high hsTnI quartile had a significantly higher risk of cardiovascular death (HR 3.61; 95% CI, 1.67–7.79; $p = 0.001$), and non-fata MI (HR 3.00; 95% CI, 1.15–7.80; $p = 0.024$) in low-dose statin therapy, but not in non-fatal stroke ($p = 0.099$) or unstable angina ($p =$

Table 1 (*continued*)

	NT-proBNP (pg/ml)			
	Low Quartile (≤49)	Mid-low quartile (49<, ≤130)	Mid-high quartile (130<, ≤329)	High quartile (329<)
	N = 393	N = 375	N = 338	N = 290
DM	39.2% (154)	38.1% (143)	41.4% (140)	47.6% (138)
History of malignant disease	3.1% (12)	4.8% (18)	6.5% (22)	6.2% (18)
Hypertension	70.7% (278)	77.1% (289)	76.6% (259)	78.6% (228)
Atrial fibrillation	2.3% (9)	1.9% (7)	4.7% (16)	17.9% (52)
Prior stroke	4.8% (19)	7.5% (28)	7.7% (26)	12.1% (35)
Prior cranial bleeding	1.0% (4)	1.6% (6)	0.9% (3)	3.1% (9)
PAD	4.8% (19)	5.9% (22)	9.5% (32)	9.7% (28)
Current smoking	17.8% (70)	13.3% (50)	15.1% (51)	12.8% (37)
Statin use at baseline	92.6% (364)	89.9% (337)	89.1% (301)	93.1% (270)
Blood tests				
Total cholesterol, mg/dL	167.9 ± 23.5	166.4 ± 24.3	164.2 ± 24.6	165.2 ± 24.5
LDL-C, mg/dL	87.2 ± 18.2	87.8 ± 18.3	87.0 ± 19.1	87.9 ± 17.6
HDL-C, mg/dL	51.2 ± 12.9	51.4 ± 13.6	50.3 ± 12.5	50.2 ± 12.7
Triglycerides, mg/dL	153.5 ± 94.2	140.9 ± 103.3	135.9 ± 81.1	140.2 ± 89.0
HsTnl, pg/ml	4.7 (1.3, 146.8)	6.3 (1.3, 4413.6)	8.5 (1.3, 627.8)	14.0 (1.3, 1064.0)
NT-proBNP, pg/ml	17.5 (18, 49)	84.0 (50, 130)	207.0 (131, 328)	619.0 (329, 11,304)
HsCRP, mg/L	0.46 (0.05, 32.9)	0.51 (0.05, 53.9)	0.53 (0.05, 119.0)	0.64 (0.05, 111.0)
Glucose, mg/dL	130.5 ± 47.2	121.2 ± 35.7	123.7 ± 37.9	127.2 ± 48.2
Hb A1c, %	6.0 ± 1.0	5.8 ± 0.8	5.9 ± 0.8	5.9 ± 0.9
eGFR, mL/min/1.73 m2	72.6 ± 15.4	69.0 ± 39.6	63.2 ± 14.9	57.9 ± 17.1
CKD				
Stage 1	14.0% (55)	7.5% (28)	5.3% (18)	3.1% (9)
Stage 2	64.9% (255)	56.3% (211)	50.9% (172)	41.4% (120)
Stage 3	19.6% (77)	34.1% (128)	41.7% (141)	49.7% (144)
Stage 4	0	0.5% (2)	0.6% (2)	4.8% (14)
Stage 5	0	0	0	0
Medications				
Aspirin	85.2% (335)	85.1% (319)	88.8% (300)	85.2% (247)
P2Y12-I	44.3% (174)	39.5% (148)	43.5% (147)	45.9% (133)
DAPT	42.0% (165)	37.1% (139)	40.5% (137)	42.4% (123)
β-blocker	20.1% (79)	29.9% (112)	45.0% (152)	62.4% (181)
ACEI and/or ARB	57.3% (225)	60.8% (228)	67.5% (228)	68.3% (198)

All values are presented as % (N), mean ± standard deviation, or median (minimum. maximum).
ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, CABG = coronary artery bypass grafting, CAD = coronary artery disease, CKD = chronic kidney disease, DAPT = dual antiplatelet therapy, DBP = diastolic blood pressure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, Hb = hemoglobin, HDL-C = high-density lipoprotein cholesterol, hsCRP = high-sensitivity C-reactive protein, hsTnI = high-sensitivity cardiac troponin I, LDL-C = low-density lipoprotein cholesterol, LVEF = left ventricular ejection fraction, MI = myocardial infarction, NT-proBNP = N-terminal pro-brain natriuretic peptide, PAD = peripheral artery disease, PCI = percutaneous coronary intervention, SBP = systolic blood pressure.

0.238). In high-dose pitavastatin treatment cohort, the quartiles of hsTnI levels had significant association with cardiovascular death ($p = 0.043$), but not with non-fatal MI ($p = 0.701$), non-fatal stroke ($p = 0.101$), or unstable angina ($p = 0.455$) (Supplementary Figs. 5, 7, 9, 11 and Supplementary Tables 5–12).

In the NT-proBNP cohort, the higher NT-proBNP levels at baseline were constantly associated with increased MACE risk regardless of pitavastatin doses even after multivariable adjustment ($p < 0.0001$ and $p < 0.0001$) (Table 2).

The high NT-proBNP quartile was at significantly higher risk of cardiovascular death and non-fatal stroke in both doses of pitavastatin treatment (cardiovascular death, HR 7.90; 95% CI, 3.12–20.02; $p < 0.0001$ in low-dose; HR 6.08; 95% CI, 2.45–15.06; $p < 0.0001$ in high-dose; non-fatal stroke, HR 5.21; 95% CI, 1.75–15.50; $p = 0.003$ in low-dose; HR 7.04; 95% CI, 2.03–24.40; $p = 0.002$ in high-dose) (Supplementary Tables 5, 6, 9, 10). No significant relationship between NT-proBNP levels and non-fatal MI was observed in both high- and low-dose treatment ($p = 0.323$ and $p = 0.299$, respectively) (Supplementary Tables 7, 8). Regarding unstable angina, high NT-proBNP quartile had a higher risk in high-dose treatment (HR 5.13; 95% CI, 2.01–13.11, $p = 0.0006$); however, there was no significant relationship between NT-proBNP levels and unstable angina in low-dose treatment ($p = 0.574$) (Supplementary Tables 11, 12).

4. Discussion

The major findings of this study were as follows: First, both hsTnI and NT-proBNP at baseline predicted future MACE in stable CAD patients who commonly received low-dose pitavastatin therapy. Second, when separately analyzed the relationship between MACE and biomarkers in patients treated with high- and low-dose pitavastatin, the higher hsTnI levels were significantly associated with increased risk of MACE in both treatment groups. After adjustment for multivaliables, a significant association in MACE risk was remained in low-dose pitavastatin therapy, but not in high-dose. Third, the higher NT-proBNP levels at baseline were constantly associated with increased MACE risk in both groups, even after multivariable adjustment.

4.1. Troponin I and MACE

Cardiac troponin is a specific biomarker representing myocardial injury and widely used for diagnosis of ACS. HsTnI is one of two discrete myocardial specific forms of cardiac troponin. Although all participants in the REAL-CAD study represented stable CAD, hsTnI levels were elevated in some patients. Previous studies have proposed that stable CAD patients might continuously release troponin by increased rates of myocardial cell turnover or changes in cell wall permeability [13,14]. Although the precise mechanisms are not fully elucidated, increased hsTnI levels would represent a certain myocardial damage. Previous clinical studies have reported that elevated cardiac troponin release was observed in patients with atrial fibrillation, heart failure, and coronary microvascular dysfunction [15–17].

In the present study, higher hsTnI levels at baseline were significantly related to higher risk for future MACE, as previously reported [7,8]. This is probably because the high hsTnI quartile group, compared with the low hsTnI, had more severe comorbidities, such as more history of MI, coronary artery bypass grafting and malignant disease, and higher stage of chronic kidney disease. In this high-risk population, low-dose statin therapy may not be enough to prevent MACE. We also evaluated the relationship between MACE and biomarkers according to the dose of pitavastatin. Interestingly, there was a significant hsTnI-dependent risk in MACE in low-dose of pitavastatin, but not in high-dose, suggesting that high-dose of pitavastatin can lower the future MACE risk. As Fig. 2 shows, the MACE rate in high hsTnI quartile was

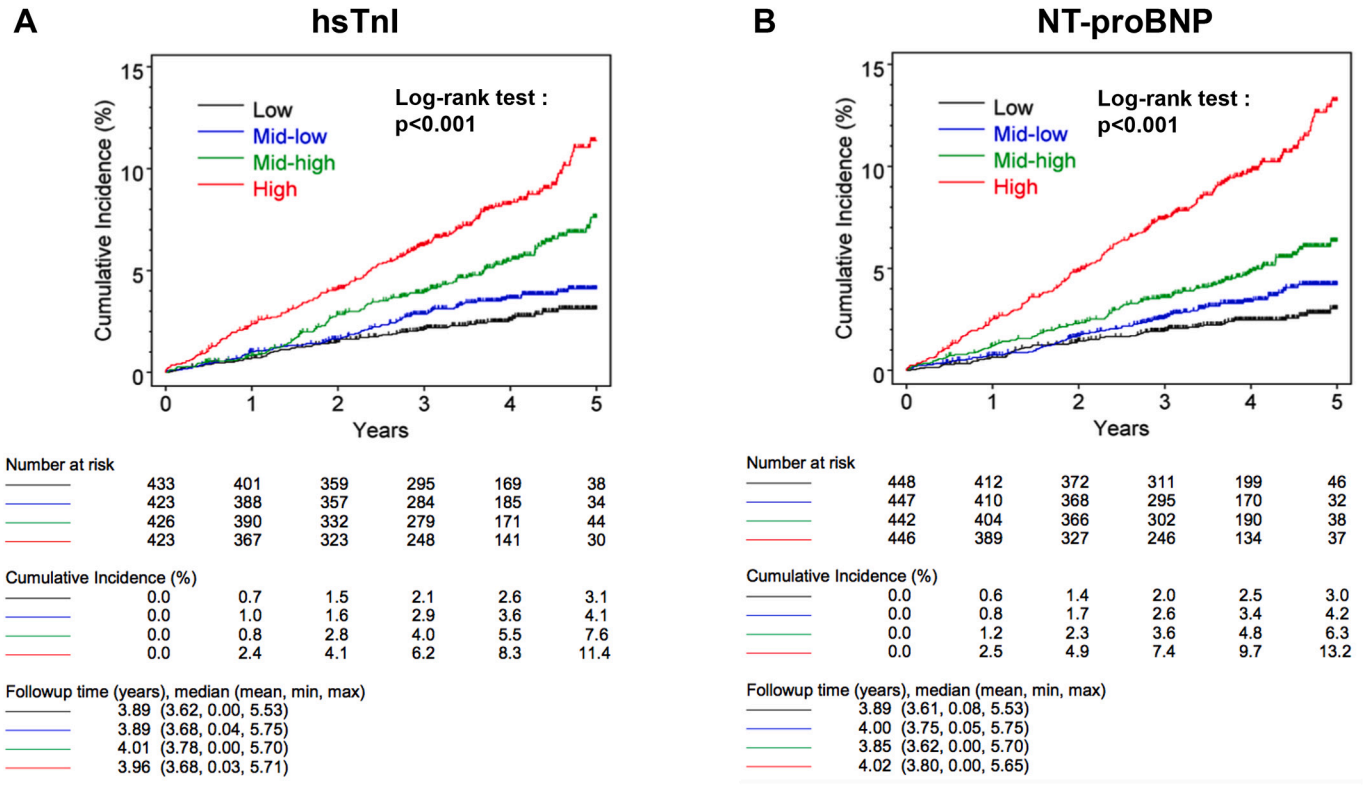

Fig. 1. Primary endpoint in whole subjects.
Cumulative incidence of major adverse cardiovascular events according to baseline high-sensitivity cardiac troponin-I (hsTnI, panel A) and N-terminal pro-brain natriuretic peptide quartile (NT-proBNP, panel B).
hsTnI: high-sensitivity cardiac troponin-I, NT-proBNP: N-terminal pro-brain natriuretic peptide.

Table 2
Hazard ratio of major adverse cardiovascular events.

Overall

	Univariable		Multivariable	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	P value
HsTnl (vs. Low quartile)		0.014		0.0002
Mid-low quartile	0.97 (0.65, 1.45)	0.870	1.04 (0.72, 1.51)	0.837
Mid-high quartile	1.27 (0.84, 1.90)	0.256	1.32 (0.91, 1.92)	0.148
High quartile	1.57 (1.05, 2.36)	0.029	1.94 (1.35, 2.79)	0.0003
NT-proBNP (vs. Low quartile)		<0.0001		<0.0001
Mid-low quartile	1.38 (0.91, 2.07)	0.119	1.45 (0.99, 2.12)	0.058
Mid-high quartile	1.66 (1.08, 2.56)	0.021	1.96 (1.35, 2.84)	0.0004
High quartile	3.28 (2.07, 5.19)	<0.0001	3.66 (2.53, 5.30)	<0.0001
Pitavastatin 4 mg (vs. 1 mg)	0.79 (0.61, 1.03)	0.084		
Male (vs. female)	1.67 (1.14, 2.44)	0.008		
High age (vs. <65 years)	1.18 (0.86, 1.62)	0.317		
BMI, kg/m2	1.02 (0.98, 1.06)	0.369		
Blood pressure (by 10 mmHg)	0.97 (0.90, 1.05)	0.470		
Heart rate, /min	1.01 (1.00, 1.02)	0.151		
Prior PCI	0.99 (0.66, 1.47)	0.954		
Prior MI	0.95 (0.72, 1.25)	0.715		
Prior CABG	0.90 (0.57, 1.40)	0.626		
Heart failure	1.55 (0.94, 2.54)	0.083		
DM	0.98 (0.71, 1.35)	0.897		
History of malignant disease	1.09 (0.64, 1.87)	0.743		
Hypertension	1.49 (1.06, 2.09)	0.020		
Atrial fibrillation	1.01 (0.63, 1.62)	0.972		
PAD	1.44 (0.93, 2.23)	0.103		
Current smoking	0.76 (0.51, 1.13)	0.176		
LDL-C (by 10 mg/dl)	1.03 (0.95, 1.11)	0.510		
HDL-C (by 10 mg/dl)	0.92 (0.81, 1.04)	0.194		
Triglycerides (by 10 mg/dl)	1.00 (0.99, 1.01)	0.745		
HsCRP, mg/L, median	1.00 (0.99, 1.02)	0.633		
Hb A1c, %	1.08 (0.92, 1.27)	0.335		
eGFR, (by 5 mL/min/1.73 m2)	0.99 (0.96, 1.02)	0.540		
Interaction: hsTnI x NT-proBNP		0.710		0.404
C-Index	0.70 (0.66, 0.73)		0.68 (0.65, 0.72)	

Low-dose pitavastatin

	Univariable		Multivariable	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
HsTnl (vs. Low quartile)		0.008		0.0002
Mid-low quartile	1.20 (0.68, 2.10)	0.535	1.16 (0.70, 1.91)	0.557
Mid-high quartile	1.30 (0.73, 2.31)	0.377	1.40 (0.84, 2.32)	0.197
High quartile	2.24 (1.26, 3.98)	0.006	2.54 (1.57, 4.11)	0.0001
NT-proBNP (vs. Low quartile)		0.0005		<0.0001
Mid-low quartile	1.70 (0.96, 3.01)	0.071	1.82 (1.08, 3.06)	0.024
Mid-high quartile	1.56 (0.86, 2.85)	0.147	1.71 (1.02, 2.86)	0.040
High quartile	2.80 (1.46, 5.36)	0.002	3.01 (1.81, 5.04)	<0.0001
Male (vs. female)	1.60 (0.96, 2.68)	0.072		
High age (vs. <65 years)	1.10 (0.70, 1.72)	0.692		
BMI, kg/m2	1.03 (0.97, 1.09)	0.357		
Blood pressure (by 10 mmHg)	0.99 (0.88, 1.12)	0.914		
Heart rate, /min	1.00 (0.99, 1.02)	0.775		
Prior PCI	1.11 (0.60, 2.05)	0.743		
Prior MI	0.85 (0.57, 1.27)	0.420		
Prior CABG	0.98 (0.49, 1.97)	0.960		
Heart failure	2.91 (1.49, 5.67)	0.002		
DM	1.03 (0.66, 1.62)	0.892		
History of malignant disease	1.28 (0.62, 2.65)	0.510		
Hypertension	2.01 (1.21, 3.36)	0.007		
Atrial fibrillation	0.79 (0.40, 1.54)	0.486		
PAD	1.39 (0.74, 2.59)	0.306		
Current smoking	0.76 (0.44, 1.33)	0.341		
LDL-C (by 10 mg/dl)	1.07 (0.96, 1.19)	0.200		
HDL-C (by 10 mg/dl)	0.86 (0.72, 1.04)	0.114		
Triglycerides (by 10 mg/dl)	1.02 (1.00, 1.04)	0.033		
HsCRP, mg/L	1.03 (0.99, 1.06)	0.123		
Hb A1c, %	1.13 (0.89, 1.43)	0.317		
eGFR (by 5 mL/min/1.73 m2)	0.99 (0.96, 1.03)	0.640		
Interaction: hsTnI x NT-proBNP		0.503		0.233

(*continued on next page*)

Table 2 (*continued*)

Low-dose pitavastatin				
	Univariable		Multivariable	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
C-Index	0.70 (0.63, 0.76)		0.67 (0.62, 0.72)	

	High-dose pitavastatin			
	Univariable		Multivariable	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
hsTnI (vs. Low quartile)		0.382		0.154
Mid-low quartile	0.73 (0.39, 1.36)	0.322	0.92 (0.52, 1.62)	0.769
Mid-high quartile	1.26 (0.68, 2.32)	0.462	1.21 (0.69, 2.12)	0.502
High quartile	1.13 (0.59, 2.19)	0.713	1.40 (0.80, 2.45)	0.236
NT-proBNP (vs. Low quartile)		<0.0001		<0.0001
Mid-low quartile	1.11 (0.59, 2.08)	0.739	1.10 (0.62, 1.93)	0.754
-high quartile	1.92 (1.02, 3.63)	0.044	2.26 (1.31, 3.89)	0.003
High quartile	4.09 (2.03, 8.24)	<0.0001	4.47 (2.61, 7.66)	<0.0001
Male (vs. female)	1.76 (0.96, 3.23)	0.070		
High age (vs. <65 years)	1.30 (0.79, 2.15)	0.306		
BMI, kg/m2	1.01 (0.94, 1.08)	0.808		
Blood pressure (by 10 mmHg)	0.90 (0.79, 1.02)	0.094		
Heart rate, /min	1.01 (0.99, 1.03)	0.198		
Prior PCI	0.92 (0.51, 1.67)	0.792		
Prior MI	1.08 (0.70, 1.65)	0.730		
Prior CABG	0.94 (0.50, 1.75)	0.842		
Heart failure	0.90 (0.35, 2.31)	0.820		
DM	1.00 (0.60, 1.68)	0.999		
History of malignant disease	0.82 (0.35, 1.91)	0.645		
Hypertension	1.01 (0.63, 1.64)	0.963		
Atrial fibrillation	1.21 (0.56, 2.60)	0.632		
PAD	1.80 (0.86, 3.77)	0.120		
Current smoking	0.82 (0.44, 1.53)	0.527		
LDL-C (by 10 mg/dl)	0.95 (0.84, 1.08)	0.461		
HDL-C (by 10 mg/dl)	0.95 (0.78, 1.16)	0.630		
Triglycerides (by 10 mg/dl)	0.99 (0.97, 1.01)	0.258		
HsCRP, mg/L	0.99 (0.97, 1.01)	0.358		
Hb A1c, %	0.99 (0.75, 1.30)	0.936		
eGFR (by 5 mL/min/1.73 m2)	0.98 (0.91, 1.05)	0.564		
Interaction: hsTnI x NT-proBNP		0.917		0.704
C-Index	0.71 (0.66, 0.76)		0.70 (0.65, 0.75)	

BMI = body mass index, BP = blood pressure, CABG = coronary artery bypass grafting, CI = confidence intervals, DM = diabetes mellitus, eGFR = estimated glemerular filtration rate, Hb = hemoglobin, HDL-C = high-density lipoprotein cholesterol, hsCRP = high-sensitivity C-reactive protein hsTnI = high-sensitivity cardiac troponin I, LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction, NT-proBNP = N-terminal pro-brain natriuretic peptide, PAD = peripheral artery disease, PCI = percutaneous coronary intervention,

numerically higher in low-dose pitavastatin than in high-dose (MACE rate in high hsTnI quartile: 13.7% in low-dose, 9.0% in high-dose treatment), while the MACE rate in other hsTnI quartiles was similar between high- and low-dose treatment. Considering our supplemental data, risk reduction by high-dose statin therapy in cardiovascular death and non-fatal MI would contribute to the overall risk reduction of MACE in high hsTnI quartile. Although we were not able to show the precise mechanism, high-dose pitavastatin therapy might be effective to reduce MACE risk in patients with high levels of hsTnI, and aggressive LDL-C lowering should be performed in patients with high hsTnI, expecting protective cardiovascular effects such as regression and/or stabilization of atherosclerotic plaques, anti-inflammatory effects, and improvement of vascular endothelial function [18–23]. Indeed, several clinical studies demonstrated that high-dose statin therapy reduce cardiovascular event risk [6,24,25]. For primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD), the American College of Cardiology/American Heart Association and the European Society of Cardiology guidelines recommend high-intensity statin therapy for high-risk patients such as history of ASCVD, LDL-C level ≥ 190 mg/dL, comorbid DM, and so on [26–29]. In addition, measurement of hsTnI may be helpful to identify the highest risk group of patients requiring high-intensity statin treatment.

4.2. NT-proBNP and MACE

NT-proBNP is also a predictor of future MACE in stable CAD patients. The higher NT-proBNP concentration was constantly associated with the increased MACE risk regardless of pitavastatin dose, as shown in the present study. The MACE rates in the NT-proBNP quartiles were equivalent between high- and low-dose treatment group as demonstrated in Fig. 2. Although the precise mechanisms for this phenomenon are still unclear, this result suggested that statin therapy might not be effective in cardiac overload in these enrolled subjects. Actually, the CORONA trial, investigating the benefit of rosuvastatin compared to placebo in patients with heart failure, did not show significant reduction in the composite of cardiac death, non-fatal MI, or nonfatal stroke [30]. Similarly, the GISSI-HF trial failed to show benefit of rosuvastatin treatment for heart failure patients regarding all-cause death or hospitalization for cardiovascular causes [31], supporting the present study results of NT-proBNP. Therefore, the high-dose statin should be used in high hsTnI levels regardless of NT-proBNP levels.

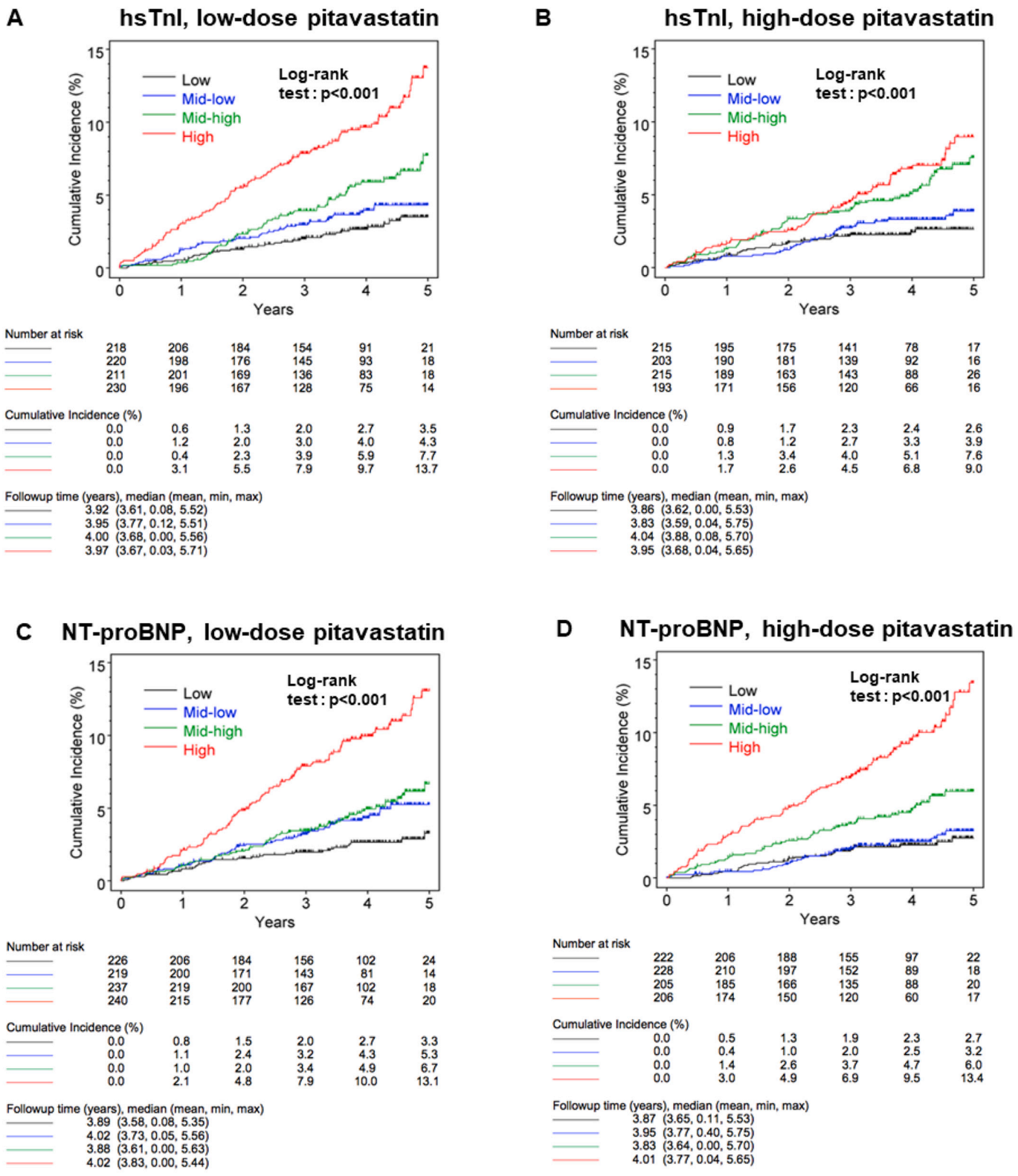

Fig. 2. Primary endpoint according to high-sensitivity cardiac troponin I and N-terminal pro-brain natriuretic peptide in low-dose or high-dose pitavastatin treatment.

Cumulative incidence of major adverse cardiovascular events stratified by treatment groups of low-dose (panel A) and high-dose (panel B) of pitavastatin according to baseline high-sensitivity cardiac troponin-I (hsTnI) quartile, and by low-dose (panel C) and high-dose (panel D) of pitavastatin according to baseline N-terminal pro-brain natriuretic peptide (NT-proBNP) quartile.

hsTnI: high-sensitivity cardiac troponin-I, NT-proBNP: N-terminal pro-brain natriuretic peptide.

4.3. Limitations

Some limitations in this study should be noted. First, the present study population was only the Japanese patients with stable CAD. In addition, all participants were treated with pitavastatin, which might limit the generalizability of the present findings to other populations or to patients on other statin medications. Due to the enrollment criteria in the original study, the very elderly patients (ages >80), ACS patients, or patients treated with other statins were not included in this case-cohort analysis. Therefore, the results may not be generally applicable to other populations. Second, the sample size was relatively small because of post-hoc analysis, which could lead to a loss in power. Third, our results are based on the biomarkers at baseline. Thus, changes in biomarkers during the follow-up period were unclear. Fourth, due to the observational study in nature, it is impossible to determine if hsTnI, NT-proBNP, or MACE are causally related. The results might be influenced by confounding variables that the multivariable analysis did not take into consideration. Fifth, there were more use of β-blocker and angiotensin converting enzyme inhibitor/angiotensin receptor blocker in higher hsTnI or NT-proBNP levels, probably because these patients had more comorbidities, including hypertension or heart failure. We were not able to adjust these comorbidities among hsTnI or NT-proBNP quartiles, because these more severe cardiac conditions should be related to the higher hsTnI or NT-proBNP levels. Finally, since this is a post-hoc analysis study in a specific population, further investigations with larger number of cases including other populations are warranted.

5. Conclusions

Both hsTnI and NT-proBNP were useful biomarkers for risk stratification of stable CAD patients who commonly received low-dose pitavastatin therapy. Patients with higher hsTnI levels in low-dose statin group had higher risk of MACE, whereas no significant difference in MACE risk was observed according to hsTnI levels in high-dose pitavastatin group. Higher NT-proBNP levels were constantly associated with higher MACE risk regardless of pitavastatin dose. These results suggested that high-dose statin therapy might decrease MACE risk in stable CAD patients with high hsTnI levels.

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