Received: 1 September 2016 | Revised: 23 June 2017 | Accepted: 6 August 2017

DOI: 10.1111/1755-5922.12291

ORIGINAL RESEARCH ARTICLE

WILEY Cardiovascular Therapeutics

Predictors of candesartan's effect on vascular reactivity in patients with coronary artery disease

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Funding information
This research was supported by the grant of the Korea Health Technology R&D Project, funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI14C1277).

Summary

Introduction and Aims: Endothelial dysfunction and arterial stiffness have a prognostic value on adverse long-term outcomes in coronary artery disease (CAD) patients. We evaluated the efficacy on vascular reactivity of candesartan and analyzed predictors to control the candesartan's effect on vascular reactivity in CAD patients.

Method: Patients were prospectively enrolled and prescribed candesartan for 6 months. The effect on vascular reactivity was evaluated by the change in flow-mediated dilation (FMD) and pulse wave velocity (PWV).

Results: A total of 124 patients completed the study. The better responder in FMD change (≥1.3%) showed significantly lower baseline FMD than the poor responder ($P < .001$). In receiver operating characteristic analysis, baseline FMD 7.5% showed optimal predictive value (sensitivity 79%, specificity 79%) for predicting better responder. The baseline endothelial dysfunction (FMD <7.5%) was the only significant predictor of the better responder to candesartan. The better responder in PWV change (≤−100 cm/s) showed greater blood pressure lowering and significantly higher baseline PWV than the poor responder (both $P < .05$). The poor responder in both FMD and PWV showed a higher prevalence of previous myocardial infarction (38.7% vs 17.2%, $P = .013$).

Conclusion: The candesartan's effect on vascular reactivity is more pronounced in patients with more severe endothelial dysfunction and arterial stiffness. Poor responders on both FMD and PWV showed higher prevalence of previous myocardial infarction.

KEYWORDS

Angiotensin II type 1 receptor blockers, Arterial stiffness, Endothelial dysfunction, Flow-mediated dilation, Pulse wave velocity

1 | INTRODUCTION

Endothelial function is impaired in several pathological conditions, such as hypertension, diabetes, and coronary artery disease (CAD).[1] Endothelial dysfunction (ED), both measured in the coronary and peripheral vasculature, has prognostic impact on adverse long-term outcomes in patients with CAD.[2-4] Endothelial function can be non-invasively assessed by brachial artery flow-mediated dilation (FMD) using high-resolution ultrasonography. Not only a single FMD measurement, but the improvement of FMD is also correlated with lesser

Lee and Chae are co-first authors.

frequent cardiovascular adverse events.[5] Therefore, peripheral ED as measured by FMD could be one of therapeutic targets for CAD patients. Also, increased arterial stiffness is associated with major cardiovascular risk factors and a strong predictor of prognosis in hypertensive patients.[6,7] It can be assessed by a simple, noninvasive method of measuring brachial-ankle pulse wave velocity (baPWV), and the decrease in PWV has been suggested improved arterial compliance.[8,9] According to previous studies, both FMD and baPWV were significant predictors of coronary events in patients with chronic CAD, and the addition of these vascular parameters had an incremental effect on the ability of traditional risk factors to predict future adverse outcomes.[10]

Angiotensin II receptor blocker (ARB) is reported to have a blood pressure (BP)-independent protective effect on the endothelial function and arterial compliance.[11-13] ARB stimulates production of bradykinin and promotes NO production, thus enhancing endothelial function.[14,15] A recent meta-analysis revealed the effect of a variety of ARBs on improving ED using FMD, which was superior to calcium channel blockers (CCB), beta-blockers and diuretics.[16] Several trials that analyzed the effect of candesartan showed a consistent increase in FMD ranging from 1.32% to 1.88%.[11-13] Not as much as FMD, but several previous studies reported that reduction in PWV was observed after short-term ARB treatment.[17,18]

This study was aimed to identify the effect of candesartan on vascular reactivity and evaluate the predictors to control the candesartan's effect on vascular reactivity in patients with stable CAD.

2 | METHODS

2.1 | Study design

The study population was the pooled cohort from "Comparing the effect of cAndemore and ataca Nd on flow mediated dilatiOn in Patients with cardiovascUlar diseaSe" (CANOPUS) randomized controlled trial (RCT), which was a 24-week, prospective, multicenter, open-label, parallel-group, phase IV trial conducted at Seoul National University Hospital and Boramae Medical Center in South Korea. The detailed information about CANOPUS RCT is presented in the supplementary materials. It was performed in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice and the ethical principles of the Declaration of Helsinki.[19]

2.2 | Study participants

Individuals aged 20 years or older with CAD were eligible in the study. CAD was defined as (1) the presence of luminal narrowing ≥50% of the vessel diameter in at least one major coronary artery on coronary computed tomography or angiography; (2) a history of coronary revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG).

Patients were excluded if they had any of the following: (1) symptomatic orthostatic hypotension; (2) mean systolic BP <110 mm Hg or diastolic BP <70 mm Hg; (3) mean systolic BP ≥180 mm Hg or diastolic BP ≥110 mm Hg; (4) known hypersensitivity to angiotensin-converting enzyme (ACE) inhibitors, ARBs, renin inhibitors; (5) a history of acute coronary syndrome or coronary revascularization <12 weeks previously; (6) congestive heart failure with NYHA class III or IV; (7) perioperative unstable valvular heart disease; (8) type I diabetes mellitus (DM) or uncontrolled type II DM (HbA1C >8%); (9) hepatic disease with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 times the upper limit of normal (>40 IU/L); (10) chronic kidney disease with a serum creatinine >1.5 times the upper limit of normal; (11) renal artery stenosis; and (12) a history of autoimmune disease or chronic inflammatory disease. Patients who used ACE inhibitors, ARBs, renin inhibitors, antioxidant (vitamin C, E), or vasodilators (long-acting nitrate, CCB, alpha-blocker) within 4 weeks before starting to administer the study drug were also excluded. Patients using lipid-lowering agent, hormone replacement therapy or thiazolidinediones could be enrolled unless they did not change the dose or ingredient since 12 weeks before participating in the study.

2.3 | Study design and treatment

The detailed study protocol was presented in the supplementary materials and Figure S1A. Patients who had previously taken ACE inhibitor, ARB, renin inhibitor, antioxidative vitamin, and vasodilators underwent a 4-week washout period before participating in the trial. After the screening period, eligible patients performed a baseline FMD and PWV test, and started to administer candesartan 8 mg/d for 4 weeks. After 4 weeks, if systolic BP was ≥110 mm Hg and diastolic BP was ≥70 mm Hg, candesartan dose was increased to 16 mg/d for the remaining 20 weeks. The use of other ACE inhibitor, ARB, renin inhibitor, antioxidative vitamins, long-acting nitrates, CCB, alpha-blockers, adrenergic, and dopaminergic agents was not permitted during the study. The use of nonsteroidal anti-inflammatory drugs (NSAID) was prohibited except for the temporary use and acetylsalicylic acid <200 mg/d for the antiplatelet function. After 24 weeks since candesartan administration, study participants evaluated the efficacy outcomes.

2.4 | Evaluation of study endpoints

The primary endpoint was the change in FMD and PWV from baseline to week 24. The endothelial function was measured by flow-mediated, endothelium-dependent vasodilation (FMD) of the upper arm. After an 8-hour fast, patients were stabilized more than 10 minutes in the supine position, and their right upper arm was placed in a BP cuff. The FMD was measured by a high-resolution ultrasonography unit (Sequoia 512, Acuson, CA, USA) with 10 Hz linear array transducer. The baseline diameter of the brachial artery was measured, and the BP cuff was inflated on the proximal portion of the upper arm to 220 mm Hg for 5 minutes. After release the cuff, reactive hyperemia occurs, and the hyperemic diameter of the brachial artery was measured 60-90 seconds after release. The FMD was calculated by following formula; {FMD (%) = (hyperemic diameter − baseline diameter)/baseline diameter × 100}. The measurement was performed after 12-hour discontinuation of smoking and caffeine. The use of NSAID was not permitted 10 days before measurement.[20]

TABLE 1 Baseline characteristics of participants divided by the change of the FMD

	Poor responder (Change of FMD <1.3) (n = 62)	Better responder (Change of FMD ≥1.3) (n = 62)	*P*-value
Baseline characteristics			
Age (y)	65.5 ± 9.6	64.5 ± 8.6	.561
Men	49 (79.0)	47 (75.8)	.668
Body mass index (kg/m^2)	25.4 ± 2.9	25.1 ± 2.6	.630
Hypertension	45 (72.5)	42 (67.7)	.692
Diabetes	16 (25.8)	12 (19.4)	.390
Dyslipidemia	59 (95.2)	59 (95.2)	1.000
Current smoker	11 (17.7)	10 (16.1)	.811
Previous MI	18 (29.0)	10 (16.1)	.086
Previous CVA	1 (1.6)	3 (4.8)	.309
Previous PCI	61 (98.4)	58 (93.5)	.171
Multivessel disease	44 (71.0)	40 (64.5)	.442
Heart rate (/min)	66.1 ± 8.9	65.2 ± 8.7	.598
Medication			
Aspirin	60 (96.8)	58 (93.5)	.403
Statin	62 (100)	61 (98.4)	.315
Beta-blocker	55 (88.7)	53 (85.5)	.592
Laboratory findings			
Hemoglobin (g/dL)	14.2 ± 1.6	14.0 ± 1.2	.342
Potassium (mmol/L)	4.4 ± 0.3	4.4 ± 0.4	.865
Creatinine (mg/L)	1.0 ± 0.3	1.0 ± 0.2	.080
Total cholesterol (mg/dL)	144.4 ± 22.2	143.0 ± 24.8	.743
LDL-Cholesterol (mg/dL)	76.4 ± 18.9	73.8 ± 19.9	.464
HDL-Cholesterol (mg/dL)	48.2 ± 10.6	51.4 ± 10.6	.088
Triglyceride (mg/dL)	128.8 ± 64.4	123.9 ± 57.5	.659
Fasting glucose (mg/dL)	107.9 ± 27.4	104.9 ± 14.3	.453
CRP (mg/dL)	0.12 ± 0.19	0.09 ± 0.15	.402
Blood pressure			
Baseline SBP (mm Hg)	141 ± 15	136 ± 16	.090
SBP after 24 wk (mm Hg)	129 ± 20	128 ± 19	.829
Change of SBP (mm Hg)	−12 ± 17	−8 ± 17	.184
Baseline DBP (mm Hg)	82 ± 8	81 ± 8	.559
DBP after 24 wk (mm Hg)	73 ± 10	73 ± 8	.865
Change of DBP (mm Hg)	−9 ± 10	−8 ± 8	.719
FMD and PWV			
Baseline FMD (%)	11.5 ± 4.9	6.0 ± 3.9	<.001
FMD after 24 wk (%)	8.0 ± 4.3	11.1 ± 4.5	<.001
Change of FMD (%)	−3.5 ± 4.2	5.1 ± 3.6	<.001
Baseline baPWV, rt. (cm/s)	1649 ± 316	1631 ± 305	.741
baPWV, rt after 24 wk (cm/s)	1556 ± 285	1548 ± 310	.876
Change of PWV (cm/s)	−93 ± 195	−83 ± 189	.770

(Continues)

The arterial stiffness was assessed noninvasively by PWV. PWV was measured based on conventional methods with the use of auto-wave form analysis (VP-2000; Colin Medical Technology Co., Komaki, Japan) in a fasting state following stabilization of the heart rate. The PWV between the right brachial arteries and the ankle (baPWV) was measured by placing both arm and the ankle in a cuff, to which an

TABLE 1 (Continued)

	Poor responder (Change of FMD <1.3) (n = 62)	Better responder (Change of FMD ≥1.3) (n = 62)	*P*-value
Candesartan formulation			
Candemore	30 (48.4)	31 (50.0)	.857
Maintenance dose after 4 wk (16 mg)	40 (64.5)	39 (62.9)	.852
Drug compliance	88.9 ± 7.2	89.0 ± 8.5	.955

baPWV, brachial-ankle pulse wave velocity; CABG, coronary artery bypass graft surgery; CRP, C-reactive protein; CVA, cerebrovascular accident; DBP, diastolic blood pressure; FMD, flow-mediated dilation; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
Values are n (%) or mean ± SD.

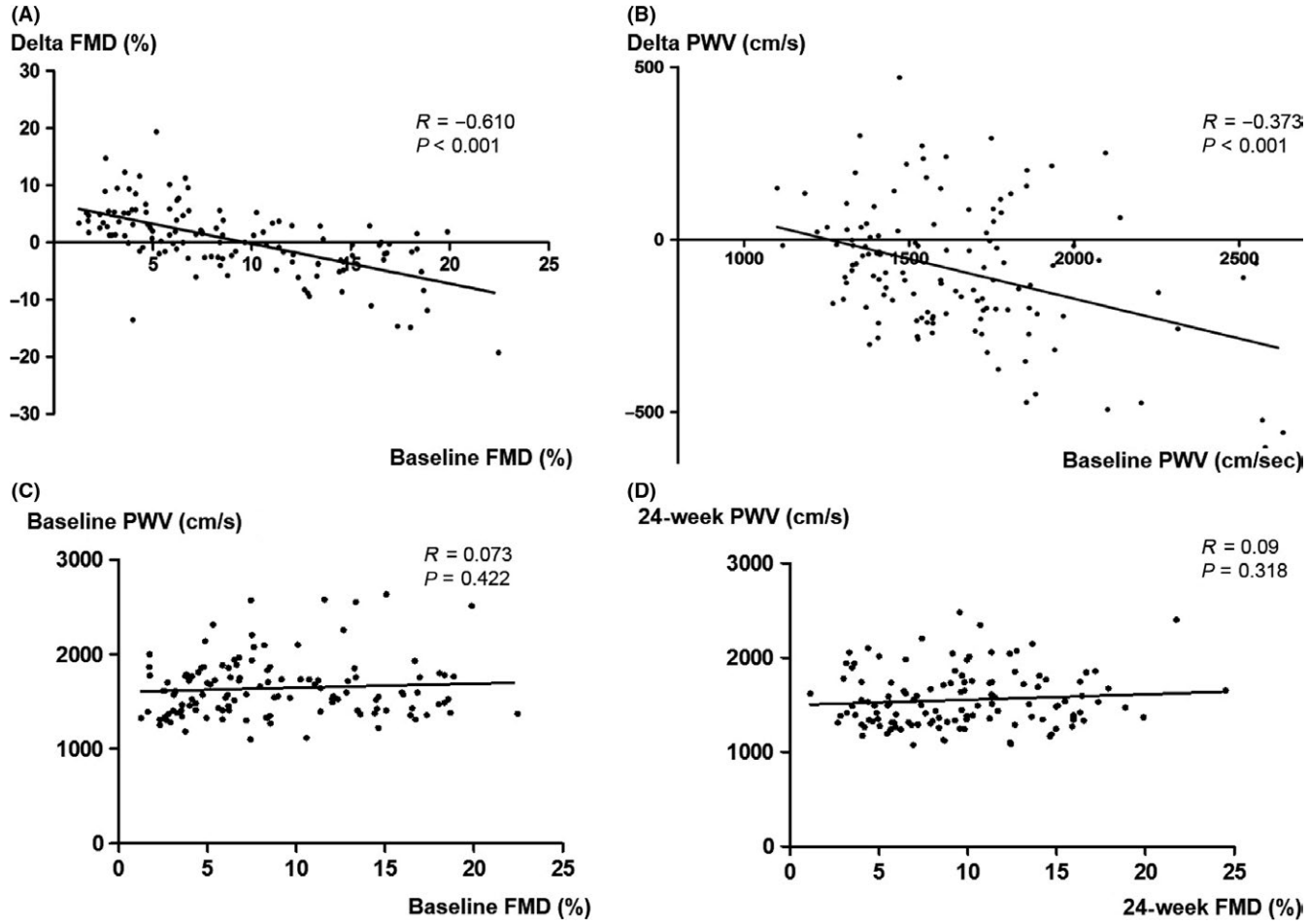


FIGURE 1 Relation between FMD and PWV. (A) Scatterplot showing the significant inverse relation between baseline FMD and change of FMD ($r = -.610$, $P < .001$). (B) Scatterplot of baseline PWV and change of PWV. There was a modest inverse correlation ($r = -.373$, $P < .001$). (C) Relation between baseline FMD and PWV. Scatterplot showing that there was no statistically significant relation between baseline FMD and PWV ($r = .073$, $P = .422$). (D) Relation between 24-week FMD and PWV. Scatterplot showing that there was no statistically significant relation between 24-week FMD and PWV ($r = .09$, $P = .318$). FMD, flow-mediated dilation; PWV, pulse wave velocity

oscillometric sensor was implanted. PWV was calculated based on the time delay between synchronous waveforms of the right brachial artery and the right tibial artery. The length from the right brachial cuff to the right ankle cuff was measured from the body length and divided by the time interval between the waveforms of the brachial and tibial artery to obtain baPWV.[18]

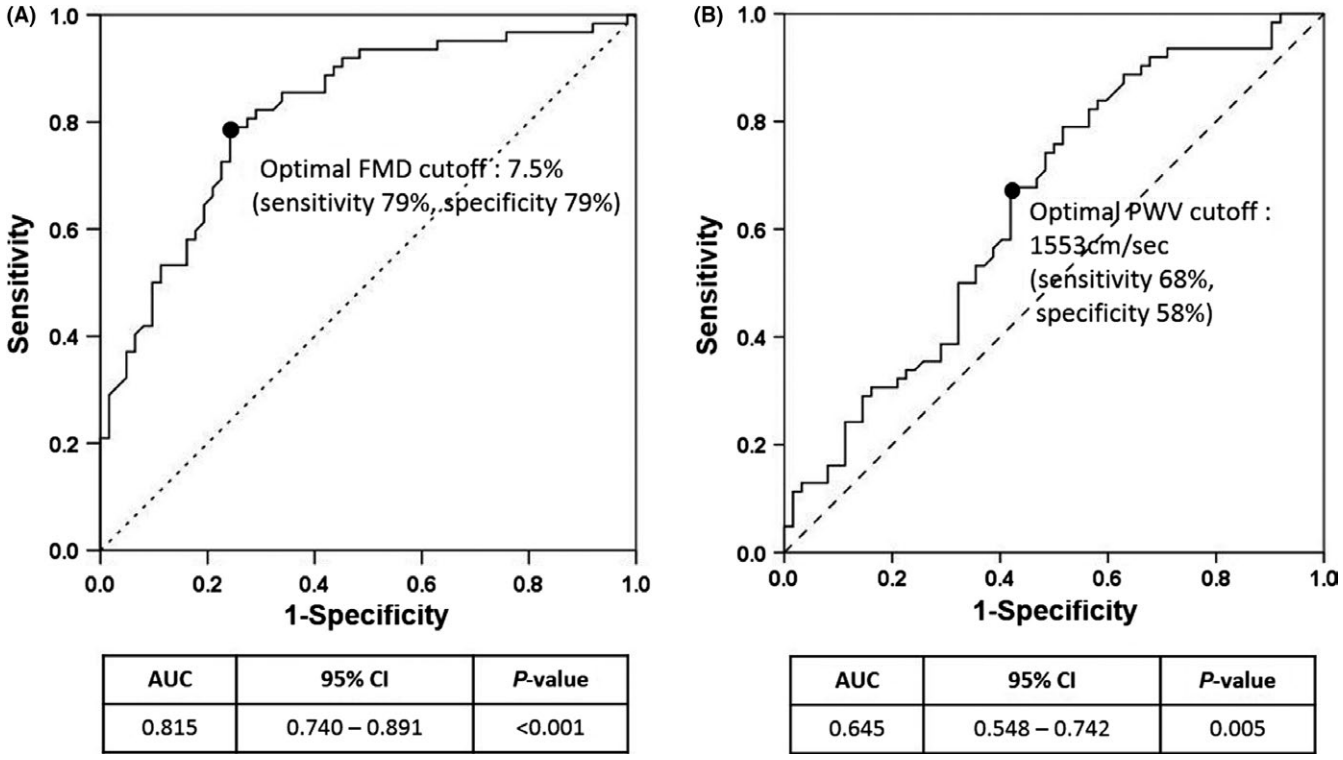
2.5 | Statistical analysis

The analysis was performed by the full analysis set principle, including all the patients who received ≥1 dose of study drug, had a valid FMD and PWV measurement at baseline and at week 24. All descriptive data are expressed as either the mean ± standard deviation or percentages. The

TABLE 2 Multivariable logistic regression for the better responder of ED improvement

	Odds ratio	95% Confidence interval	*P*-value
Baseline FMD (%)	1.306	1.180-1.444	<.001
Serum creatinine (mg/dL)	3.654	0.642-20.921	.144
Serum HDL-Cholesterol (mg/dL)	0.989	0.950-1.029	.580
Baseline SBP (mm Hg)	1.009	0.982-1.037	.511
Previous myocardial infarction	1.913	0.667-5.488	.228

ED, endothelial dysfunction; FMD, flow-mediated dilation; HDL, high-density lipoprotein; SBP, systolic blood pressure.



AUC	95% CI	*P*-value
0.815	0.740 – 0.891	<0.001

AUC	95% CI	*P*-value
0.645	0.548 – 0.742	0.005

FIGURE 2 ROC curve of the baseline FMD and PWV for predicting better responder. (A) ROC curve of the baseline FMD for predicting better responder of FMD. AUC was 0.815 (95% CI 0.740-0.891, $P < .001$), and baseline FMD 7.5% showed optimal predictive value (sensitivity 79%, specificity 79%). (B) ROC curve of the baseline PWV for predicting better responder of PWV. AUC was 0.645 (95% CI 0.548-0.742, $P = .005$), and baseline PWV 1553 cm/s was optimal predictive value (sensitivity 68%, specificity 58%). AUC, area under the curve; FMD, flow-mediated dilation; PWV, pulse wave velocity; ROC, receiver operating characteristic

continuous variables were compared using unpaired *t* test, and the discrete variables were compared using chi-squared test. The study endpoints including the FMD, PWV, and BP from baseline to week 24 were compared using unpaired *t* test. The multivariable logistic regression analysis was performed to search the predictive variables for the better responder of FMD, which was defined as the participants with upper half of the FMD change, as well as for PWV. The variables showing significant univariate association ($P < .1$) between patients with lower half and upper half of FMD change were selected for the multivariable logistic regression. We used receiver operating characteristic (ROC) curve to find the best threshold of the baseline FMD or PWV to predict the better responder. Data are expressed as mean ± standard deviation. SPSS version 19.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses, and $P < .05$ was considered statistically significant.

3 | RESULTS

3.1 | Study population

A total of 160 patients consented to participate in this study and were screened (Figure S1B). Of these, 124 were included in the analysis, and the baseline characteristics of all 124 patients are shown in Table S1. The results of comparison between generic and original formula of candesartan were comparable and were presented in Table S2 and Figure S2. We analyzed the effect of candesartan in the pooled cohort. After 24 weeks of maintenance treatment, the systolic and diastolic BP decreased significantly (from 139 ± 16 to 128 ± 20 mm Hg, from 82 ± 8 to 73 ± 9 mm Hg, respectively, both $P < .001$) in the study patients. FMD showed

TABLE 3 Baseline characteristics of participants divided by the change of the PWV

	Poor responder (Change of PWV >−100 cm/s) (n = 62)	Better responder (Change of PWV ≤−100 cm/s) (n = 62)	*P*-value
Baseline characteristics			
Age (y)	64.9 ± 9.9	65.1 ± 8.1	.929
Men	50 (80.6)	46 (74.2)	.390
Body mass index (kg/m^2)	25.5 ± 2.8	25.0 ± 2.6	.382
Hypertension	45 (72.6)	43 (69.4)	.692
Diabetes	16 (25.8)	12 (19.4)	.390
Dyslipidemia	61 (98.4)	57 (91.9)	.094
Current smoker	9 (14.5)	12 (19.4)	.473
Previous MI	16 (25.8)	12 (19.4)	.390
Previous CVA	2 (3.2)	2 (3.2)	1.000
Previous PCI	60 (96.8)	59 (95.2)	.648
Multivessel disease	43 (69.4)	41 (66.1)	.701
Heart rate (/min)	65.7 ± 8.5	65.6 ± 9.1	.984
Medication			
Aspirin	60 (96.8)	58 (93.5)	.403
Statin	62 (100)	61 (98.4)	.315
Beta-blocker	51 (82.3)	57 (91.9)	.108
Laboratory findings			
Hemoglobin (g/dL)	14.2 ± 1.4	13.9 ± 1.4	.348
Potassium (mmol/L)	4.4 ± 0.3	4.4 ± 0.4	.066
Creatinine (mg/L)	1.0 ± 0.2	1.0 ± 0.3	.743
Total cholesterol (mg/dL)	142.1 ± 18.7	145.3 ± 27.4	.437
LDL-Cholesterol (mg/dL)	75.4 ± 16.3	74.8 ± 22.2	.872
HDL-Cholesterol (mg/dL)	49.3 ± 10.9	50.3 ± 10.5	.598
Triglyceride (mg/dL)	116.2 ± 52.4	136.5 ± 67.1	.064
Fasting glucose (mg/dL)	108.5 ± 27.5	104.3 ± 16.9	.281
CRP (mg/dL)	0.10 ± 0.18	0.10 ± 0.15	.713
Blood pressure			
Baseline SBP (mm Hg)	137 ± 15	140 ± 16	.232
SBP after 24 wk (mm Hg)	130 ± 19	127 ± 20	.352
Change of SBP (mm Hg)	−7 ± 15	−13 ± 19	.027
Baseline DBP (mm Hg)	81 ± 7	82 ± 8	.291
DBP after 24 wk (mm Hg)	74 ± 10	72 ± 8	.216
Change of DBP (mm Hg)	−7 ± 9	−10 ± 8	.024
FMD and PWV			
Baseline FMD (%)	8.9 ± 5.5	8.7 ± 4.9	.836
FMD after 24 wk (%)	10.0 ± 4.7	9.1 ± 4.6	.311
Change of FMD (%)	1.1 ± 6.8	0.5 ± 4.7	.533
Baseline baPWV, rt. (cm/s)	1563 ± 278	1717 ± 322	.005
baPWV, rt after 24 wk (cm/s)	1624 ± 307	1479 ± 269	.006
Change of PWV (cm/s)	61 ± 120	−237 ± 118	<.001

(Continues)

TABLE 3 (Continued)

	Poor responder (Change of PWV >−100 cm/s) (n = 62)	Better responder (Change of PWV ≤−100 cm/s) (n = 62)	*P*-value
Candesartan formulation			
Candemore	30 (48.4)	31 (50.0)	.857
Maintenance dose after 4 wk (16 mg)	37 (59.7)	42 (67.7)	.350
Drug compliance	89.5 ± 6.2	88.4 ± 9.2	.408

baPWV, brachial-ankle pulse wave velocity; CABG, coronary artery bypass graft surgery; CRP, C-reactive protein; CVA, cerebrovascular accident; DBP, diastolic blood pressure; FMD, flow-mediated dilation; PCI, percutaneous coronary intervention; SBP, systolic blood pressure.
Values are n (%) or mean ± SD.

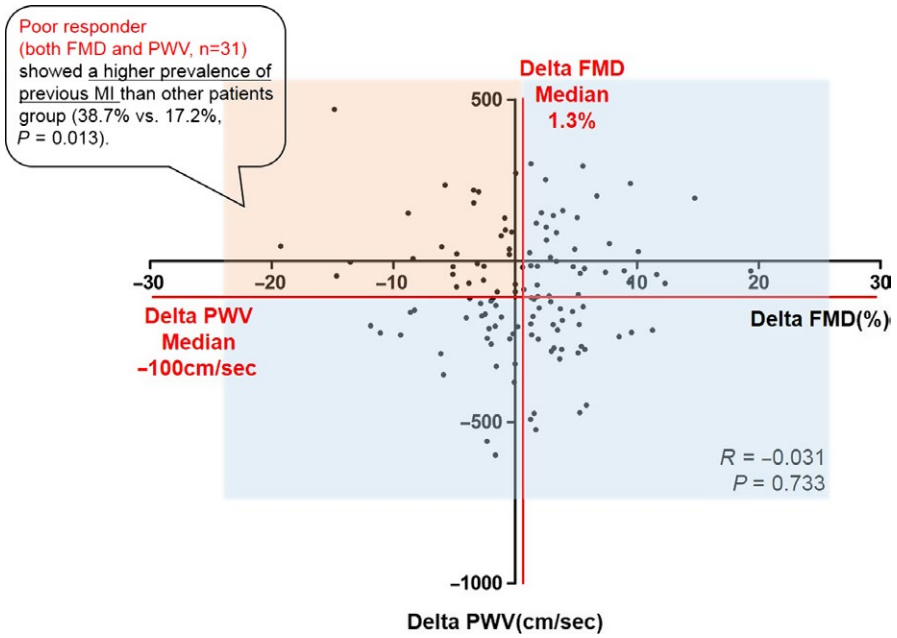


FIGURE 3 Scatterplot showing the correlation between change in FMD and PWV (*P* = .733). Poor responder to candesartan in both FMD and PWV defined as change in FMD less than 1.3% and change in PWV more than −100 cm/s. Poor responder (both FMD and PWV, n = 31) showed a higher prevalence of previous MI than other patients group (38.7% vs 17.2%, *P* = .013). FMD, flow-mediated dilation; MI, myocardial infarction; PWV, pulse wave velocity

a trend toward increased with 24-week candesartan treatment (from 8.8 ± 5.2 to 9.6 ± 4.7%FMD, *P* = .134). The mean change in FMD from baseline to 24-week candesartan treatment was not statistically significant. PWV of brachial artery to ankle decreased after 24-week candesartan treatment (from 1640 ± 309 to 1552 ± 297 cm/s, *P* < .001).

3.2 | Predictors for improvement of endothelial function by candesartan

A subgroup analysis for identifying better responder of candesartan on ED improvement was performed. The better responder was defined as the upper half of the change of FMD (FMD change ≥1.3%, Figure S3A). The comparison of the baseline characteristics of better and poor responders (Table 1) revealed that only baseline FMD was significantly lower in better responder group, while other parameters did not show a difference. There was a significant positive inverse correlation between baseline FMD and change of FMD (*P* < .001) (Figure 1A). In multivariable logistic regression analysis for searching the predictive factors for better responders, baseline FMD was the only significant predictor (odd ratio (OR) to be better responders 1.31 for 1% decrease in baseline FMD, 95% confidence interval (CI) 1.180-1.444, *P* < .001) (Table 2).

Receiver operating characteristic analysis was performed, and we investigated the optimal threshold of baseline FMD for predicting the better responder. Area under the curve (AUC) was 0.815 (95% CI 0.740-0.891, *P* < .001), and baseline FMD 7.5% showed optimal predictive value (sensitivity 79%, specificity 79%) (Figure 2A). Patients with baseline FMD <7.5 (n = 64) showed statistically significant improvement in ED (baseline vs post-treatment, 4.6 ± 1.7 vs 8.7 ± 4.4%FMD, *P* < .001). In univariable analysis, patients with low baseline FMD (<7.5%) were 11.8 times more likely to be better responders to candesartan treatment in terms of ED improvement. In multivariate logistic regression, low baseline FMD (<7.5%) remained significantly associated with ED improvement by candesartan (OR to be better responders 12.5, 95% CI 5.25-30.05, *P* < .001) after adjustment for other clinical parameters such as the presence of DM, history of myocardial infarction, multivessel disease, systolic BP, serum creatinine, and high-density lipoprotein cholesterol (HDL-C) levels.

3.3 | Predictor for improvement of arterial compliance by candesartan

The better responder of candesartan on arterial compliance was defined as the lower half of the change of PWV (PWV change ≤−100 cm/s, Figure S3B). The comparison of the baseline characteristics of better and poor responders on PWV (Table 3) showed that the decreases in systolic and diastolic BP after treatment were significantly greater in better responder group (change in systolic BP, −7 ± 15 vs −13 ± 19 mm Hg, P = .027; diastolic BP, −7 ± 9 vs −10 ± 8 mm Hg, P = .024). Also, same as in FMD, baseline PWV was significantly higher in better responder group (1717 ± 322 vs 1563 ± 278 cm/s, P = .005). There was a significant but modest inverse correlation between baseline PWV and change of PWV (r = −.373, P < .001) (Figure 1B). ROC analysis was performed to find the optimal threshold of baseline PWV for predicting the better responder. AUC was 0.645 (95% CI 0.548-0.742, P = .005), and baseline PWV 1553 cm/s was the optimal predictive value (sensitivity 68%, specificity 58%) (Figure 2B).

3.4 | Absence of association between FMD and PWV

There was no significant correlation between FMD and PWV before treatment (r = .073, P = .422), also after treatment (r = .09, P = .318) (Figure 1C,D).

3.5 | Combined analysis of FMD and PWV on candesartan's effect on vascular reactivity

We evaluated the characteristics of the patients whose FMD and PWV responses after treatment were both poor (change of FMD <1.3% and change of PWV >−100 cm/s, Figure 3). The poor responder group (n = 31) showed no significant difference in baseline characteristics than other patients (n = 93), but a higher prevalence of previous myocardial infarction (38.7% vs 17.2%, P = .013). In univariable analysis, patients with previous MI were 3.04 times more likely to be poor responders to candesartan treatment in terms of both ED and arterial stiffness improvement. In multivariate logistic regression, history of MI remained significantly associated with poor responses in FMD and PWV by candesartan (OR to be poor responders 3.3, 95% CI 1.310-8.277, P = .011) after adjustment for other clinical parameters such as the presence of DM, hypertension, and dyslipidemia.

4 | DISCUSSION

In the present study of CAD patients, the candesartan improved the endothelial dysfunction (ED) and arterial stiffness. Furthermore, baseline ED (FMD <7.5%) was an important predictor of better response to candesartan's effect on ED improvement. On the improvement of arterial stiffness, decreases BP after candesartan treatment and baseline arterial stiffness (PWV >1553 cm/s) were important factors for predicting better response. Combined analysis of FMD and PWV as parameters for assessing vascular reactivity showed that the poor responder group in both FMD and PWV had a higher prevalence of previous MI than other patients.

The effect of candesartan on endothelial function has been reported from several small-sized studies in patients with hypertension and/or CAD. In the previous studies, the study population had more clinical risk factors, a definite ED (baseline FMD <9%) or were prohibited from the use of other medications.[11,13] The present study is the first large-scale study to identify efficacy of candesartan to improve ED and predictors on this effect. In addition, this study included normotensive as well as hypertensive patients with CAD and did not restrict the use of beta-blocker or statin. Therefore the results would be more easily applicable to the daily clinical practice. Several mechanisms of ARB in ED improvement have been suggested. ARB exerts an antioxidative action by inhibition of angiotensin II-stimulated NADPH activity, leading to reduction in superoxide production and nitric oxide degradation.[21] Furthermore, AT1 blocker reduces oxidative stress through induction of extracellular superoxide dismutase activity.[15] AT1 blocker also stimulates the AT2 receptor and then activates bradykinin/B2 receptor-mediated NO production.[14]

In the total population (n = 124) treated with candesartan for 6 months, post-treatment FMD was just mildly improved compared to baseline FMD (baseline vs post-treatment FMD, 8.8 ± 5.2 vs 9.6 ± 4.7%FMD, P = .134). The mean of FMD change in total study patients was 0.62 ± 5.94% for 6 months, and it was smaller than previous studies that restricted the study population to patients with moderate HTN or patients with impaired baseline FMD (less than 9%).[11-13] Therefore, we did a subgroup analysis to identify which patients could be a better responder to candesartan in terms of ED improvement. Patients with poor baseline endothelial function could achieve more benefit on ED improvement by candesartan. These results suggest that the beneficial effect of ARB on endothelial function would be more apparent when the patients' profiles are worse in terms of ED or clinical risk factors. According to the comparison of baseline characteristics by change in FMD (Table 1), baseline FMD was the only parameter that showed a statistically significant difference between better versus poor responders to candesartan. Also the baseline FMD showed significant correlation with the change of FMD (Figure 1A). We divided study population by FMD changes using binary, tertile, and quartile values and thoroughly explored all variables that could predict the FMD changes. No matter how we divided the groups, baseline FMD was the only factor that showed a significant difference between better and poor responders to candesartan. The traditional clinical risk profiles were not significantly different between better versus poor responders to candesartan, such as the prevalence of diabetes, previous MI and multivessel disease, systolic BP, serum creatinine, and HDL-C levels. After adjusting these parameters in multivariable analysis, the baseline ED presented as low FMD was an independent and strong predictor of the better responder to candesartan in terms of ED improvement. In other words, the poorer the baseline endothelial function is the better effect of candesartan we could achieve.

Not only ED, but arterial stiffness has been regarded as an independent predictor for future cardiovascular events.[10,22] The effect of

ARB on arterial stiffness has been reported, and recently Peng et al.[23] suggested that ARB treatment significantly reduced carotid-femoral PWV (cfPWV) and baPWV in hypertensive patients by a meta-analysis. However, they reported that particularly telmisartan and valsartan significantly reduced PWV. A few studies of candesartan treatment were included in the meta-analysis, and they were relatively small-sized studies.[24,25] In the total population (n = 124), post-treatment PWV was significantly reduced compared to baseline PWV (baseline vs post-treatment PWV, 1640 ± 309 vs 1552 ± 297 cm/s, $P < .001$). In our study, BP lowering after candesartan treatment was associated with improvement in arterial stiffness. The relation between effect of ARB on arterial stiffness and BP lowering was controversial. Compared to diuretics, only ARB induced a significant decrease in PWV although both treatments showed similar decrease in BP.[26] AT1 blocker decreased mean BP and directly influenced on the arterial wall. Also it reversed cardiac/vascular hypertrophy, improved NO release, and reduced vasoconstriction independent of BP.[14,21,27] According to the comparison of baseline characteristics by change in PWV (Table 3), baseline PWV showed a significant difference between better and poor responders to candesartan. Both in FMD and PWV, patients with worse endothelial function and arterial compliance could get more benefit from candesartan treatment.

In this study, there was no correlation between FMD and PWV. This is similar to the previous study which reported only relatively weak correlations between FMD and PWV in healthy population.[10,28] However, ARB is known to prevent both the increase in PWV and the decrease in FMD. The patient who showed poor FMD and PWV response even after candesartan treatment had a higher prevalence of previous MI than other population. The baseline FMD and PWV were known as the predictors of future cardiovascular events and could be useful tool for risk assessment of patients with acute coronary syndrome, chronic CAD, or stable angina.[10,29] Furthermore, after ST-elevation MI, aortic stiffness was associated with myocardial wall stress, left ventricular remodeling, and N-terminal pro-B-type natriuretic peptide. Therefore arterial stiffness and ED could be the targets of intervention. Previous MI patients are needed more aggressive risk reduction and medical treatment for ED and arterial stiffness improvement.

In this study, study patients administered two types of candesartan either generic or branded candesartan. Between two groups, there was no significant difference in the baseline characteristics, primary, and secondary endpoints. We concluded that the effects of generic and branded candesartan were comparable. The detailed results of the comparisons between two types of candesartan were presented in the supplementary materials.

4.1 | Study limitations

This study had several limitations. We analyzed the effect of candesartan on ED improvement using FMD measurement. However, it still remained uncertain whether the FMD improvement in serial follow-up could be a therapeutic target. One retrospective study suggested that improved FMD was related to a lower risk of future cardiovascular events.[5] Although the measurement of FMD is inevitably associated with several limitations such as the lack of normal cutoff values and interobserver variability, it may be used as a surrogate marker for cardiovascular outcomes.

We analyzed the factors that were associated with better response on vascular reactivity after candesartan treatment, and the poor baseline endothelial function was associated with good response on ED improvement. The regression to the mean should be considered when interpret this data. Although we considered this point, mean FMD value at week 24 of better responders was still significantly higher than poor responders (Table 1).

According to a meta-analysis of the ARB effect on ED improvement, the effect of ARB would not be well maintained more than 6 months.[12] There were few studies that had follow-up data after 6 months, and further investigation is needed to evaluate the long-term effect on ED.

5 | CONCLUSIONS

Our study demonstrated that the candesartan treatment was more beneficial in patients with more severe baseline endothelial dysfunction and arterial stiffness. Furthermore, poor responder group on both FMD and PWV as a surrogate marker for vascular reactivity showed higher prevalence of previous MI.

ACKNOWLEDGMENTS

The contribution of the CANOPUS study investigators and Chong Kung Dang Pharmaceutical is gratefully acknowledged.

CONFLICT OF INTEREST

The all authors declare that they have no conflict of interest.

ETHICS

Protocol was approved by the Institutional Review Board at each study site before the study was initiated (Date of approval by Seoul National University Hospital Institutional Review Board: August, 29th, 2011). Written informed consent was obtained from each patient before the screening procedure.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Lee S-R, Chae I-H, Kim H-L, Kang D-Y, Kim S-H, Kim H-S. Predictors of candesartan's effect on vascular reactivity in patients with coronary artery disease. *Cardiovasc Ther*. 2017;35:e12291. https://doi.org/10.1111/1755-5922.12291