Impact of Hypertension on 5-year Clinical Outcomes in Patients with Significant Coronary Artery Spasm; A Propensity Score Matching Study

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Disclosure Information

I have nothing to disclose.

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Background

1. Hypertension (HTN) is known to be a risk factor of significant coronary artery disease (CAD).

2. However, there is limited available data with larger study population regarding long-term clinical outcomes of HTN with coronary artery spasm (CAS) in real world clinical practice, particularly in a series of Korean population.

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ORIGINAL ARTICLE

Impact of hypertension on coronary artery spasm as assessed with intracoronary acetylcholine provocation test

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Hypertension and acetylcholine-induced coronary artery spasm

Results; Although the incidences of significant ACh-induced CAS were similar between hypertensive and normotensive patients (35.8 vs 39.2%, P=0.303), multivariate logistic analysis showed that hypertension was negatively associated with ACh-induced CAS (odds ratio: 0.70, 95% confidence interval: 0.51–0.94, P=0.020). The angiographic characteristics of ACh-induced CAS were similar between these two groups. Subgroup analysis regarding the impact of the status of blood pressure control on CAS showed that hypertensive patients with controlled blood pressure had a significantly higher incidence of CAS than those with uncontrolled blood pressure (45.2 vs 27.9%, P=0.001), and that uncontrolled blood pressure was negatively associated with ACh-induced CAS (odds ratio: 0.56, 95% confidence interval: 0.40–0.79, P=0.001).

Conclusion, despite the expected endothelial dysfunction, hypertension and uncontrolled blood pressure are negatively associated with CAS, suggesting that the mechanisms and risk factors of CAS may be significantly different from those of coronary artery disease.

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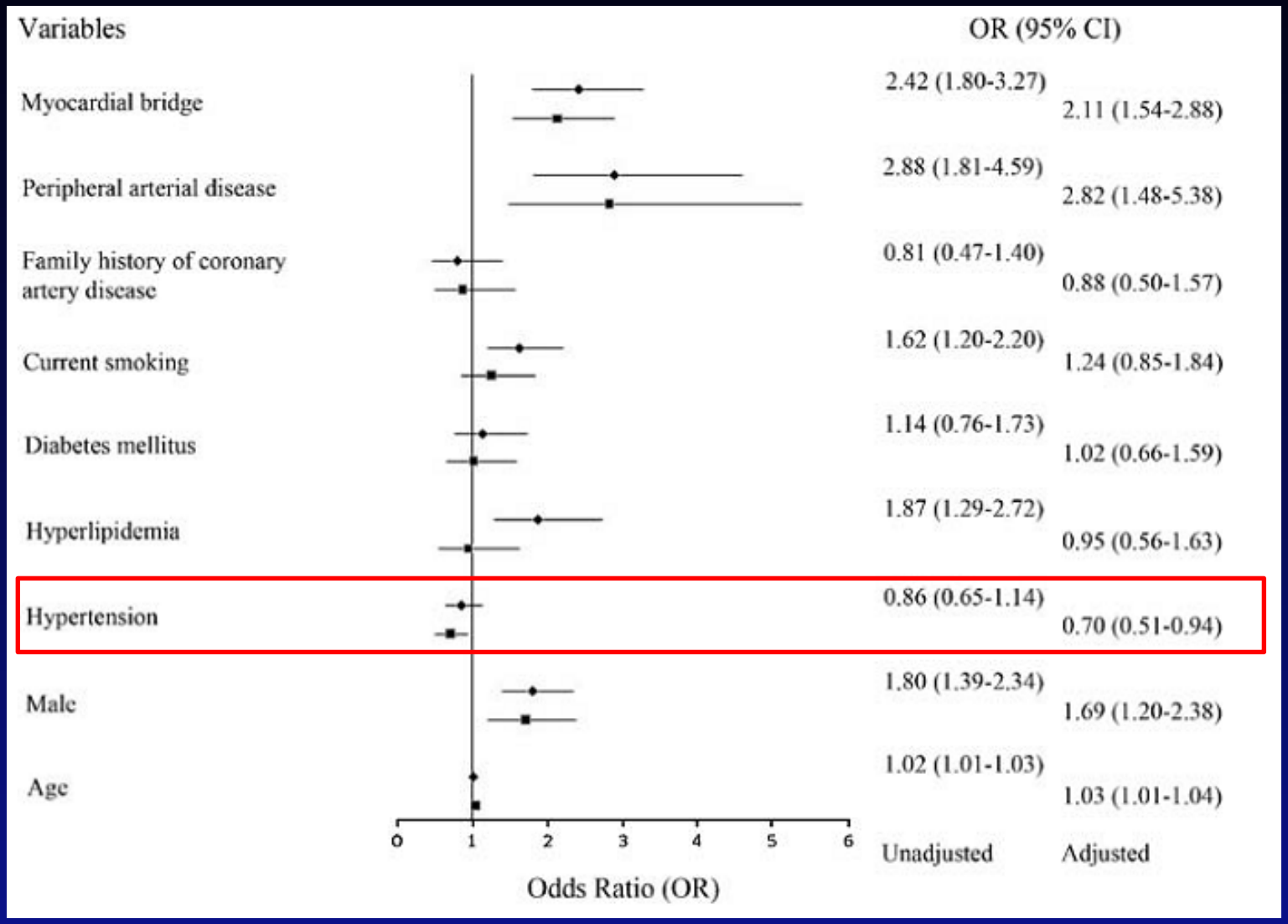
The predictors for acetylcholine-induced significant coronary artery spasm



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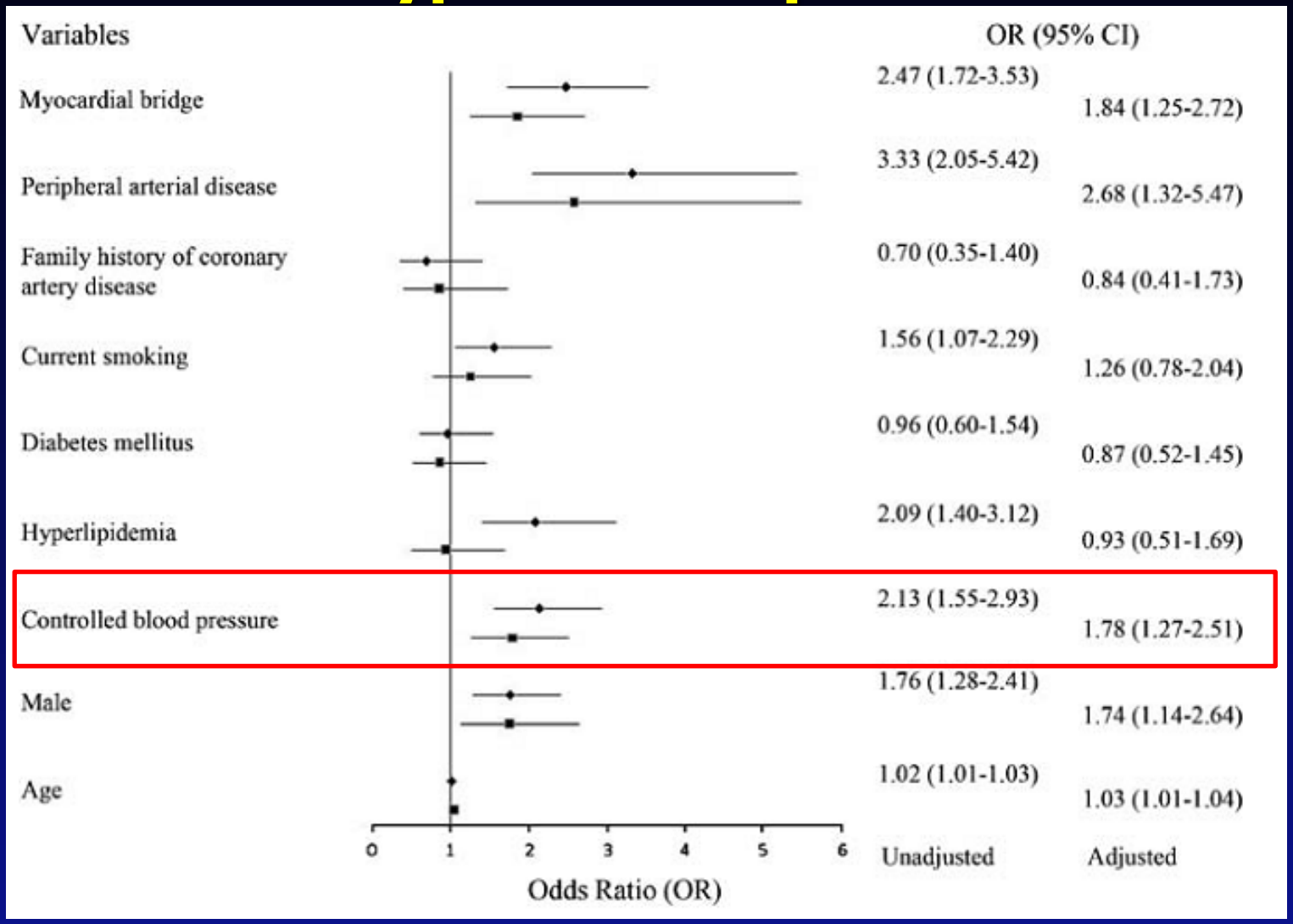
The predictors for acetylcholine-induced significant coronary artery spasm in hypertensive patients



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Methods

1. Study Population

A total of 3,349 consecutive CAS pts without significant coronary artery disease who underwent Ach provocation test were enrolled between November 2004 and May 2014.

2. Study Groups

Hypertension group (HTN; n=1,489)

Normotension group (NTN: n=1,860)

Methods

3. Intracoronary Ach Provocation Test

1) Ach was injected by incremental doses of 20μg (A1), 50 μg (A2) and 100 μg (A3) into the left coronary artery.

2) Significant CAS was defined as transient >70% luminal narrowing with/without ischemic ST-T Change or chest pain.

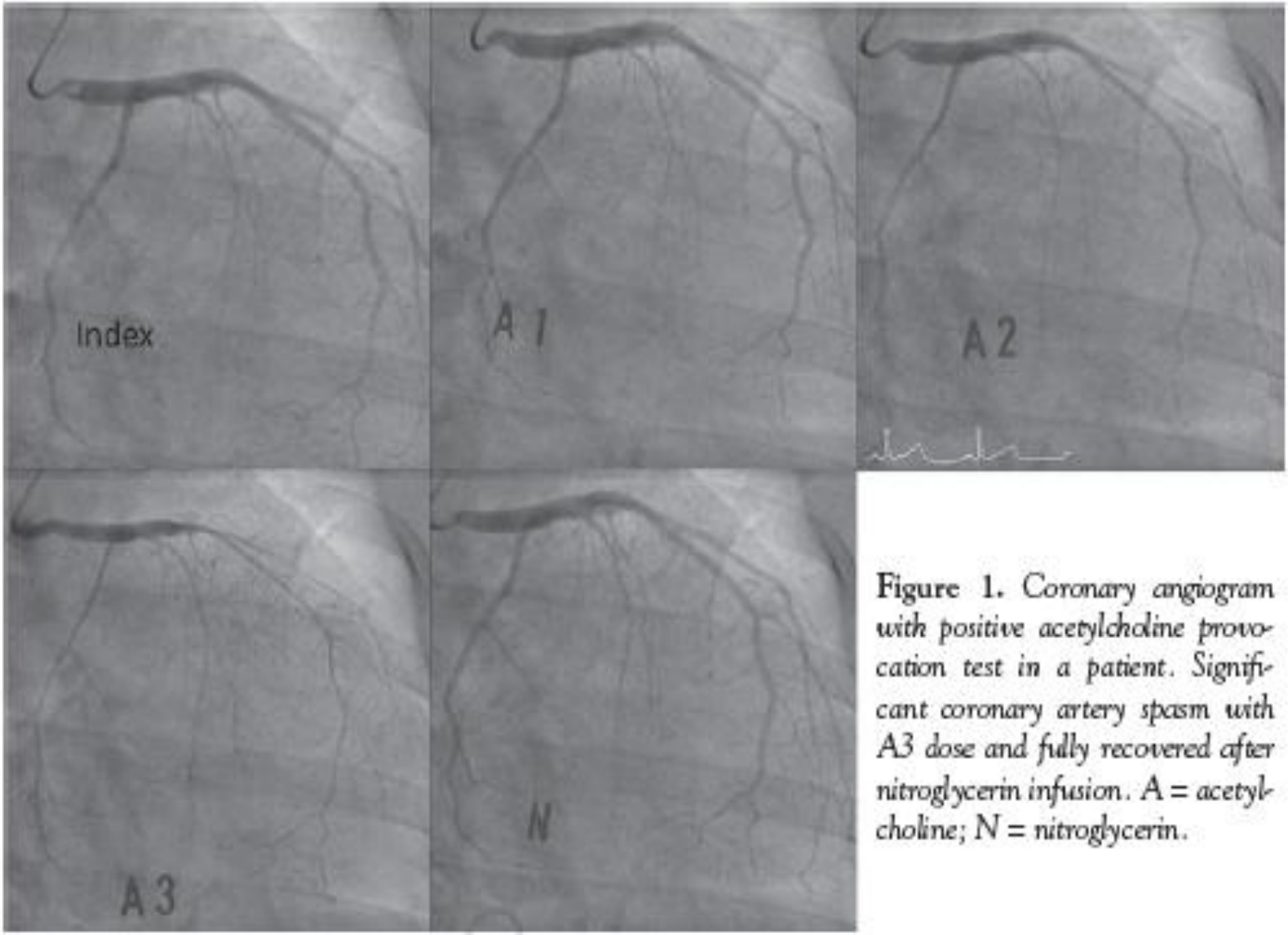


Figure 1. *Coronary angiogram with positive acetylcholine provocation test in a patient. Significant coronary artery spasm with A3 dose and fully recovered after nitroglycerin infusion. A = acetylcholine; N = nitroglycerin.*

Statistics

1. All statistical analyses were performed using SPSS 20.0.

2. Continuous variables were expressed as means ± standard deviation and were compared using Student's t-test.

3. Categorical data were expressed as percentages and were compared using chi-square statistics or Fisher's exact test.

4. A *P*-value of 0.05 was considered statistically significant.

5. Multivariate logistic regression analysis, which included baseline confounding factors, was used for assessing the independent impact factors.

Statistics

6. To account for the selection bias of treatment methods, we calculated ***propensity score*** predicting probability for HTN in each patient.
7. The covariates that were adjusted for Gender (male), Age, blood pressure, left Ventricular ejection fraction%, factors of risk (hypertension, diabetes, dyslipidemia, current smokers, current alcoholics), medication Treatments (diltiazem, nitrate, trimetazidine, nicorandil, molsidomine, calcium channel blockers, beta blokers, diuretics, angiotensin receptor blockers, angiotensin converting enzyme inhibitors, aspirin, clopidogrel, cilostazol, warfarin, statins), angiographic and clinical parameters (Left anterial decending, Left circumflex, CAS narrowing length, EKG change, and chest pain).
8. The C-statistic for the logistic regression model that was used to calculate the propensity score matching for the 2 groups was 0.720.

Results

Baseline Clinical Characteristics

Variable, N (%)	Entire Patients				Propensity Score-Matched Patients			
	Total (N=3349)	HTN (N=1489)	NTN (N=1860)	p Value	Total (N=2286)	HTN (N=1143)	NTN (N=1143)	p Value
Gender (male)	1738 (51.8)	784 (52.6)	954 (51.2)	0.433	1217 (53.2)	606 (53.0)	611 (53.4)	0.834
Age	56.6 ± 11.1	59.8 ± 10.5	54.1 ± 11.6	< 0.001	58.2 ± 10.1	58.2 ± 10.4	58.3 ± 9.76	0.794
Blood pressure; BP								
Systolic BP	134 ± 19	139 ± 20	129 ± 18	< 0.001	135 ± 18	136 ± 19	135 ± 18	0.356
Diastolic BP	77.7 ± 12.5	79.5 ± 12.6	76.2 ± 12.4	< 0.001	78.8 ± 12.5	78.8 ± 12.5	78.7 ± 12.6	0.854
Heart rate	70.2 ± 12.5	70.8 ± 12.7	69.7 ± 12.3	0.015	70.2 ± 12.5	70.4 ± 12.7	70.0 ± 12.2	0.480
Pulse pressure	56.3 ± 15.8	60.3 ± 17.4	53.1 ± 14.6	< 0.001	57.1 ± 15.6	57.4 ± 16.4	56.8 ± 14.9	0.333
Left Ventricular ejection fraction, %	58.9 ± 3.8	58.9 ± 3.6	59.0 ± 3.9	0.744	58.9 ± 4.2	59.0 ± 3.7	58.8 ± 4.6	0.510
Factors of Risk								
Diabetes	565 (16.8)	349 (23.4)	216 (11.6)	< 0.001	381 (16.6)	193 (16.8)	188 (16.4)	0.779
New-onset diabetes	130 (3.8)	74 (4.9)	56 (3.0)	0.004	94 (4.1)	49 (4.2)	45 (3.9)	0.674
Insulin	65 (1.9)	46 (3.0)	19 (1.0)	< 0.001	36 (1.5)	17 (1.4)	19 (1.6)	0.737
Medication	354 (10.5)	229 (15.3)	125 (6.7)	< 0.001	236 (10.3)	121 (10.5)	115 (10.0)	0.680
Dietary	44 (1.3)	19 (1.2)	25 (1.3)	0.864	33 (1.4)	15 (1.3)	18 (1.5)	0.599
Dyslipidemia	1089 (32.5)	593 (39.8)	496 (26.6)	< 0.001	809 (35.3)	402 (35.1)	407 (35.6)	0.827
History smokers	1122 (33.5)	499 (33.5)	623 (33.4)	0.991	760 (33.2)	380 (33.2)	380 (33.2)	ns
Current smokers	795 (23.7)	337 (22.6)	458 (24.6)	0.178	530 (23.1)	263 (23.0)	267 (23.3)	0.843
History alcoholics	1297 (38.7)	567 (38.0)	730 (39.2)	0.490	873 (38.1)	432 (37.7)	441 (38.5)	0.698
Current alcoholics	1189 (35.5)	515 (34.5)	674 (36.2)	0.322	800 (34.9)	392 (34.2)	408 (35.6)	0.483

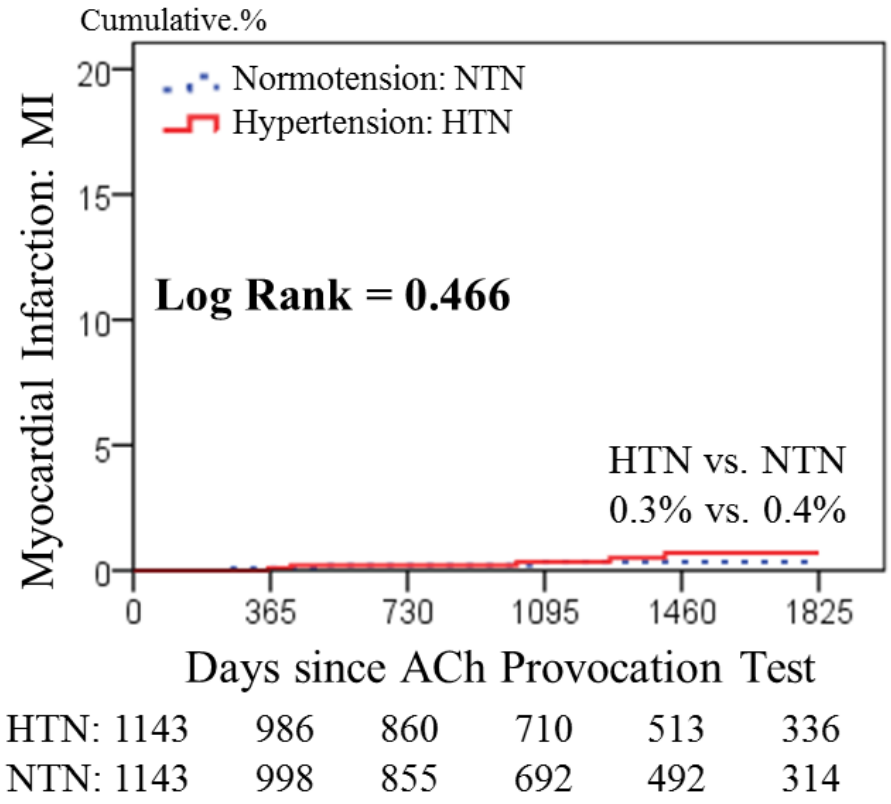
Medication Treatments

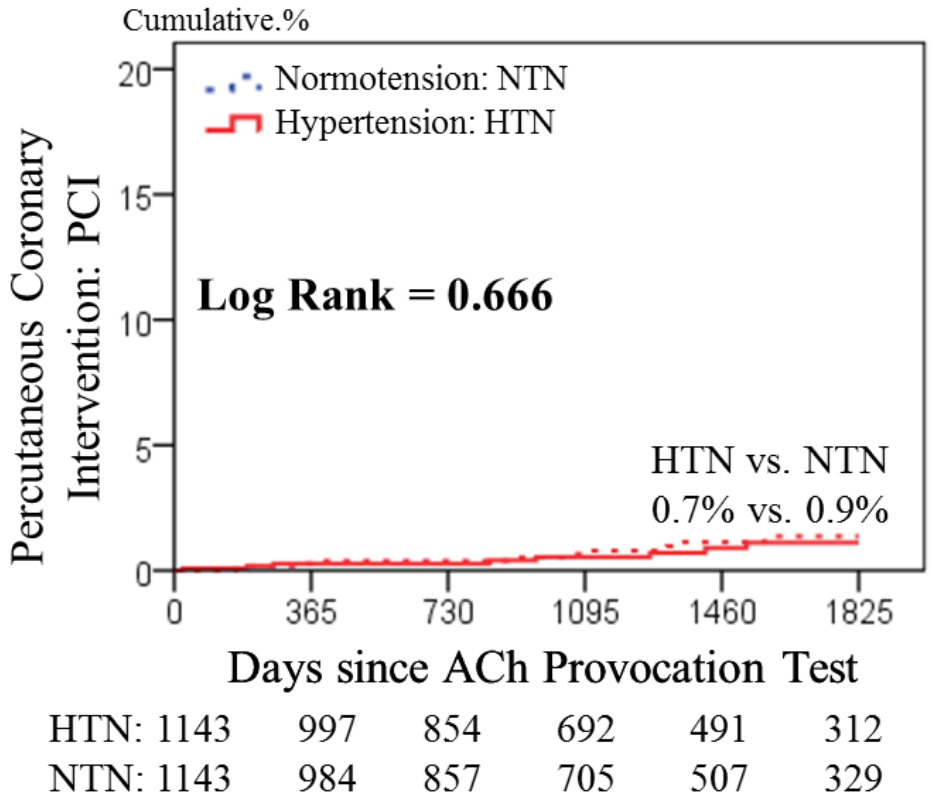
Variable, N (%)	Entire Patients				Propensity Score-Matched Patients			
	Total (N=3349)	HTN (N=1489)	NTN (N=1860)	p Value	Total (N=2286)	HTN (N=1143)	NTN (N=1143)	p Value
Diltiazem	2741 (81.8)	1216 (81.6)	1525 (81.9)	0.809	1877 (82.1)	936 (81.8)	941 (82.3)	0.785
Nitrate	2194 (65.5)	951 (63.8)	1243 (66.8)	0.073	1492 (65.2)	730 (63.8)	762 (66.6)	0.160
Trimetazidine	1784 (53.2)	795 (53.3)	989 (53.1)	0.899	1225 (53.5)	609 (53.2)	616 (53.8)	0.769
Molsidomine	248 (7.4)	108 (7.2)	140 (7.5)	0.764	170 (7.4)	87 (7.6)	83 (7.2)	0.750
Nicorandil	1070 (31.9)	484 (32.5)	586 (31.5)	0.538	739 (32.3)	360 (31.5)	379 (33.2)	0.396
Calcium channel blockers	2833 (84.5)	1280 (85.9)	1553 (83.4)	0.049	1951 (85.3)	984 (86.0)	967 (84.6)	0.315
Beta blokers	307 (9.1)	203 (13.6)	104 (5.5)	< 0.001	231 (10.1)	150 (13.1)	81 (7.0)	< 0.001
Diuretics	301 (8.9)	219 (14.7)	82 (4.4)	< 0.001	214 (9.3)	153 (13.3)	61 (5.3)	< 0.001
Angiotensin receptor blockers	550 (16.4)	454 (30.4)	96 (5.1)	< 0.001	405 (17.7)	323 (28.2)	82 (7.1)	< 0.001
Angiotensin converting enzyme inhibitors	138 (4.1)	96 (6.4)	42 (2.2)	< 0.001	96 (4.1)	65 (5.6)	31 (2.7)	< 0.001
Aspirin	544 (16.2)	323 (21.6)	221 (11.8)	< 0.001	385 (16.8)	196 (17.1)	189 (16.5)	0.696
Clopidogrel	179 (5.3)	100 (6.7)	79 (4.2)	0.002	136 (5.9)	67 (5.8)	69 (6.0)	0.860
Cilostazol	63 (1.8)	40 (2.6)	23 (1.2)	0.002	41 (1.7)	24 (2.0)	17 (1.4)	0.270
Warfarin	39 (1.1)	19 (1.2)	20 (1.0)	0.590	27 (1.1)	11 (0.9)	16 (1.3)	0.333
Statins	1375 (41.0)	716 (48.0)	659 (35.4)	< 0.001	999 (43.7)	504 (44.0)	495 (43.3)	0.704

Angiographic Characteristics

Variable, N (%)	Entire Patients				Propensity Score-Matched Patients			
	Total (N=3349)	HTN (N=1489)	NTN (N=1860)	p Value	Total (N=2286)	HTN (N=1143)	NTN (N=1143)	p Value
Quantitative coronary angiography; QCA								
Minimum narrowing diameter, mm (during Acetylcholine Provocation Test)	0.7 ± 0.3	0.6 ± 0.3	0.7 ± 0.3	0.002	0.6 ± 0.3	0.6 ± 0.3	0.6 ± 0.3	0.832
Minimum narrowing diameter, % (during Acetylcholine Provocation Test)	70.4 ± 12.8	70.8 ± 12.4	70.0 ± 13.2	0.065	70.9 ± 13.0	70.8 ± 12.6	71.0 ± 13.3	0.802
Reference diameter, mm (after nitroglycerin injection)	2.3 ± 0.6	2.3 ± 0.5	2.4 ± 0.7	< 0.001	2.3 ± 0.7	2.3 ± 0.5	2.4 ± 0.8	0.326
Acetylcholine dose								
A1 (20ug)	185 (5.5)	85 (5.7)	100 (5.3)	0.669	129 (5.6)	69 (6.0)	60 (5.2)	0.409
A2 (50ug)	1193 (35.6)	520 (34.9)	673 (36.1)	0.467	840 (36.7)	399 (34.9)	441 (38.5)	0.073
A3 (100ug)	1969 (58.8)	882 (59.3)	1087 (58.4)	0.610	1315 (57.5)	673 (58.9)	642 (56.1)	0.173
Spasm site	7 (0.2)	2 (0.1)	5 (0.2)	0.473	5 (0.2)	2 (0.1)	3 (0.2)	ns
Left anterial decending	3145 (93.9)	1396 (93.7)	1749 (94)	0.738	2145 (93.8)	1070 (93.6)	1075 (94)	0.664
Left circumflex	1279 (38.1)	541 (36.3)	738 (39.6)	0.048	836 (36.5)	422 (36.9)	414 (36.2)	0.728
Spasm location	19 (0.5)	7 (0.4)	12 (0.6)	0.503	14 (0.6)	7 (0.6)	7 (0.6)	ns
Proximal	1614 (48.1)	625 (41.9)	989 (53.1)	< 0.001	1053 (46.0)	490 (42.8)	563 (49.2)	0.002
Mid	3047 (90.9)	1369 (91.9)	1678 (90.2)	0.083	2077 (90.8)	1038 (90.8)	1039 (90.9)	0.942
Distal	2736 (81.6)	1223 (82.1)	1513 (81.3)	0.556	1868 (81.7)	938 (82.0)	930 (81.3)	0.665
Diffuse spasm (narrowing > 20mm)	2882 (86.0)	1277 (85.7)	1605 (86.2)	0.661	1966 (86.0)	979 (85.6)	987 (86.3)	0.630
Multi-vessel spasm	1108 (33.0)	462 (31.0)	646 (34.7)	0.024	720 (31.4)	363 (31.7)	357 (31.2)	0.787
EKG change	211 (6.3)	89 (5.9)	122 (6.5)	0.491	140 (6.1)	68 (5.9)	72 (6.2)	0.727
ST-segment elevation	70 (2.0)	34 (2.2)	36 (1.9)	0.484	45 (1.9)	26 (2.2)	19 (1.6)	0.292
ST-segment depreesion	75 (2.2)	29 (1.9)	46 (2.4)	0.307	51 (2.2)	21 (1.8)	30 (2.6)	0.202
T-inversion	37 (1.1)	12 (0.8)	25 (1.3)	0.139	23 (1.0)	10 (0.8)	13 (1.1)	0.530
Atrial fibrillation	29 (0.8)	14 (0.9)	15 (0.8)	0.678	21 (0.9)	11 (0.9)	10 (0.8)	0.826
Chest pain	2167 (64.7)	950 (63.8)	1217 (65.4)	0.327	1485 (64.9)	744 (65.0)	741 (64.8)	0.895
AV Block	881 (26.3)	389 (26.1)	492 (26.4)	0.831	588 (25.7)	294 (25.7)	294 (25.7)	ns

Cumulative Clinical Outcomes up to 5-year. (MI & De Novo PCI)

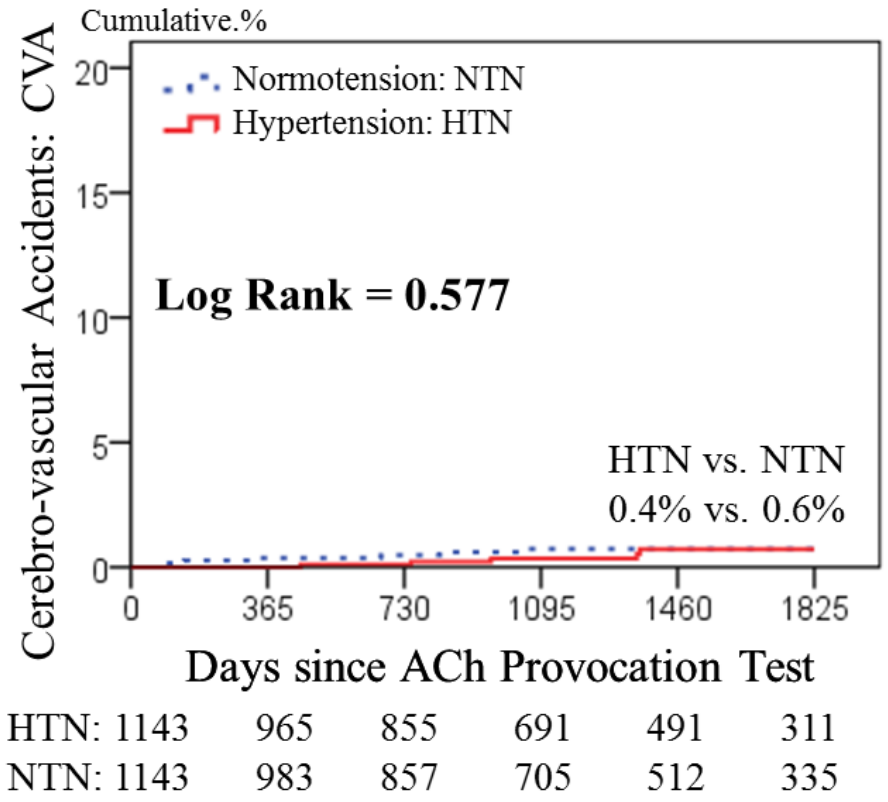


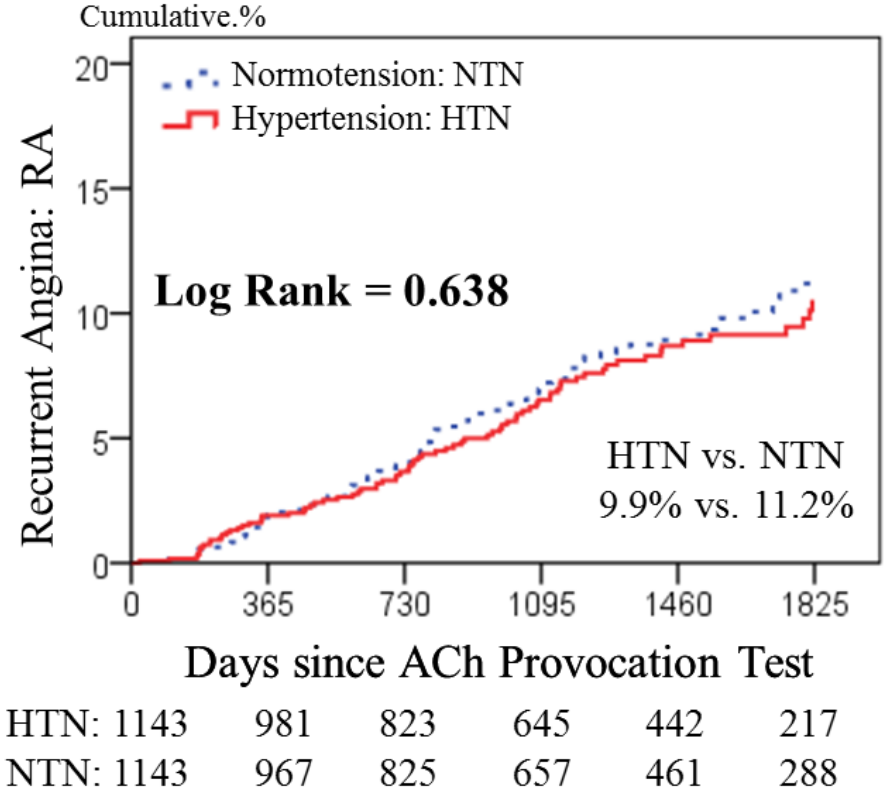


AMI

De Novo PCI

Cumulative Clinical Outcomes up to 5-year. (CVA & Recurrent Angina)

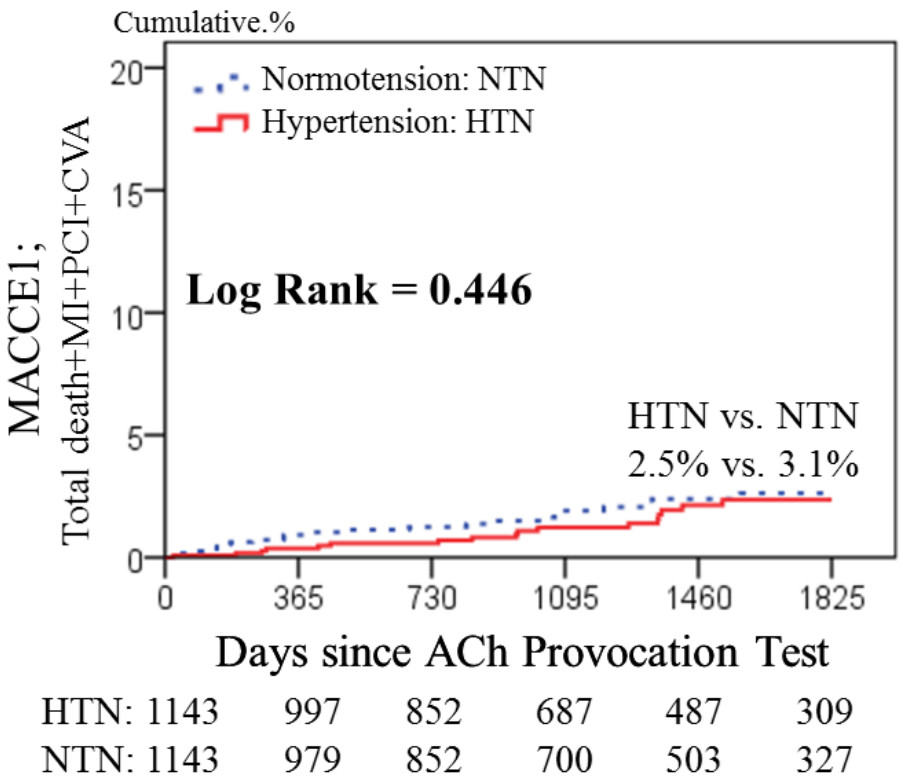


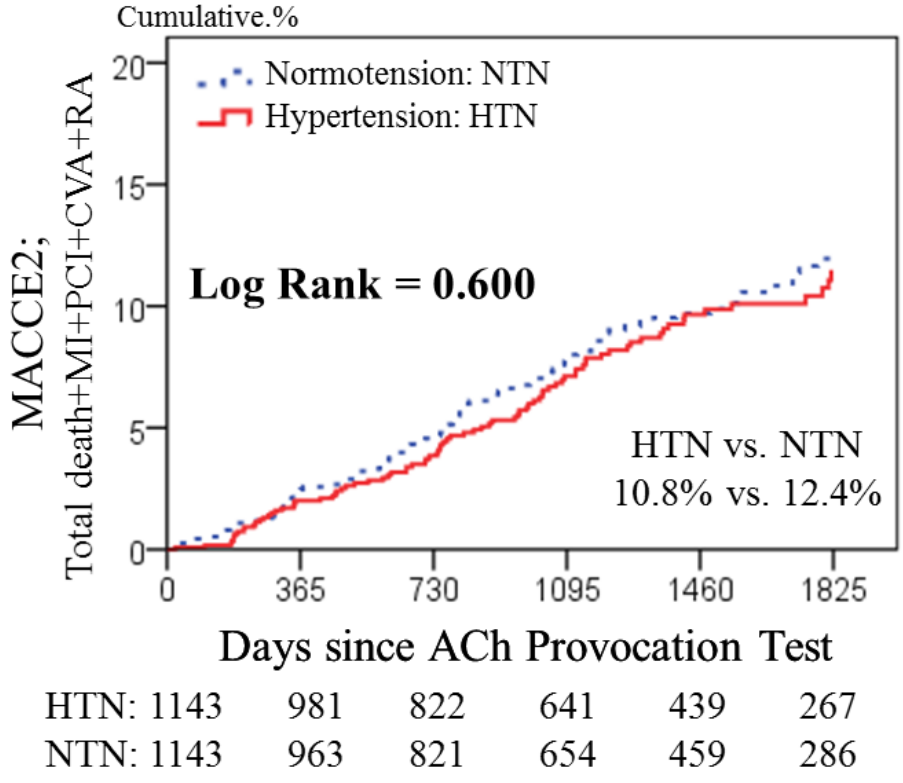


CVA

Recurrent Angina

Cumulative Clinical Outcomes up to 5-year.
(Composite Major Adverse Cerebral Cardiac Events)





MACCE-1

MACCE-2

Summary

1. After PSM analysis, 2 propensity-matched groups (1,143 pairs, n = 2,286, C-statistic=0.720) were generated and, the baseline characteristics of the two groups were balanced.
2. In clinical outcomes up to 5-year, there were similar incidence of individual hard endpoints including mortality, myocardial infarction, revascularization and recurrent angina requiring repeat coronary angiography.
3. Hypertension was not an independent predictor of adverse clinical outcomes in pts with CAS up to 5 years.

Conclusion

Despite the expected endothelial dysfunction, hypertension was not associated with a worsening factor for adverse clinical outcomes in pts with significant CAS documented by intracoronary Ach provocation test up to 5 years, suggesting that the mechanisms and risk factors of CAS may be different from those of atherosclerotic CAD.

Thank you for your attention