

# Predictors of Major Adverse Clinical Events up to 5 Years in Patients with Chest Pain but without Significant Coronary Artery Disease in Korean Population

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# Disclosure

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- Nothing to disclose
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# Background

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- Obstructive coronary artery disease (CAD) is a well-known risk factor for long-term adverse cardiovascular events.  
*Gibbons et.al. Circulation. 2003;107:149-58*
- However, if no significant coronary lesion is seen on CAG despite of chest pain, the scope of determining the prognosis and its risk factors are limited.

# Study Purpose

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- We aimed to evaluate the predictors for long-term major adverse cardiac events (MACE) up to 5 years in patients presented with chest pain but without significant CAD.

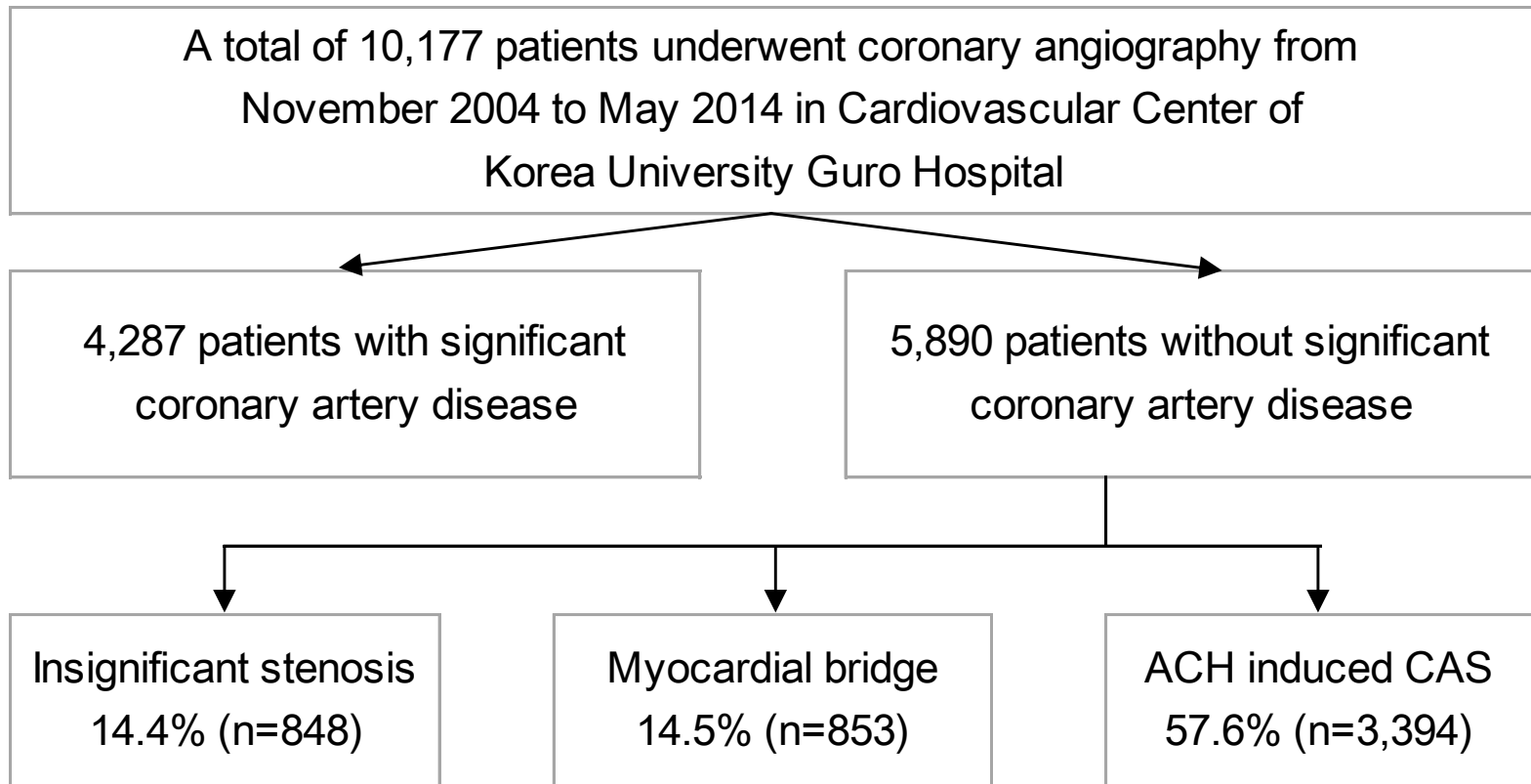
# Methods

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- Study Population

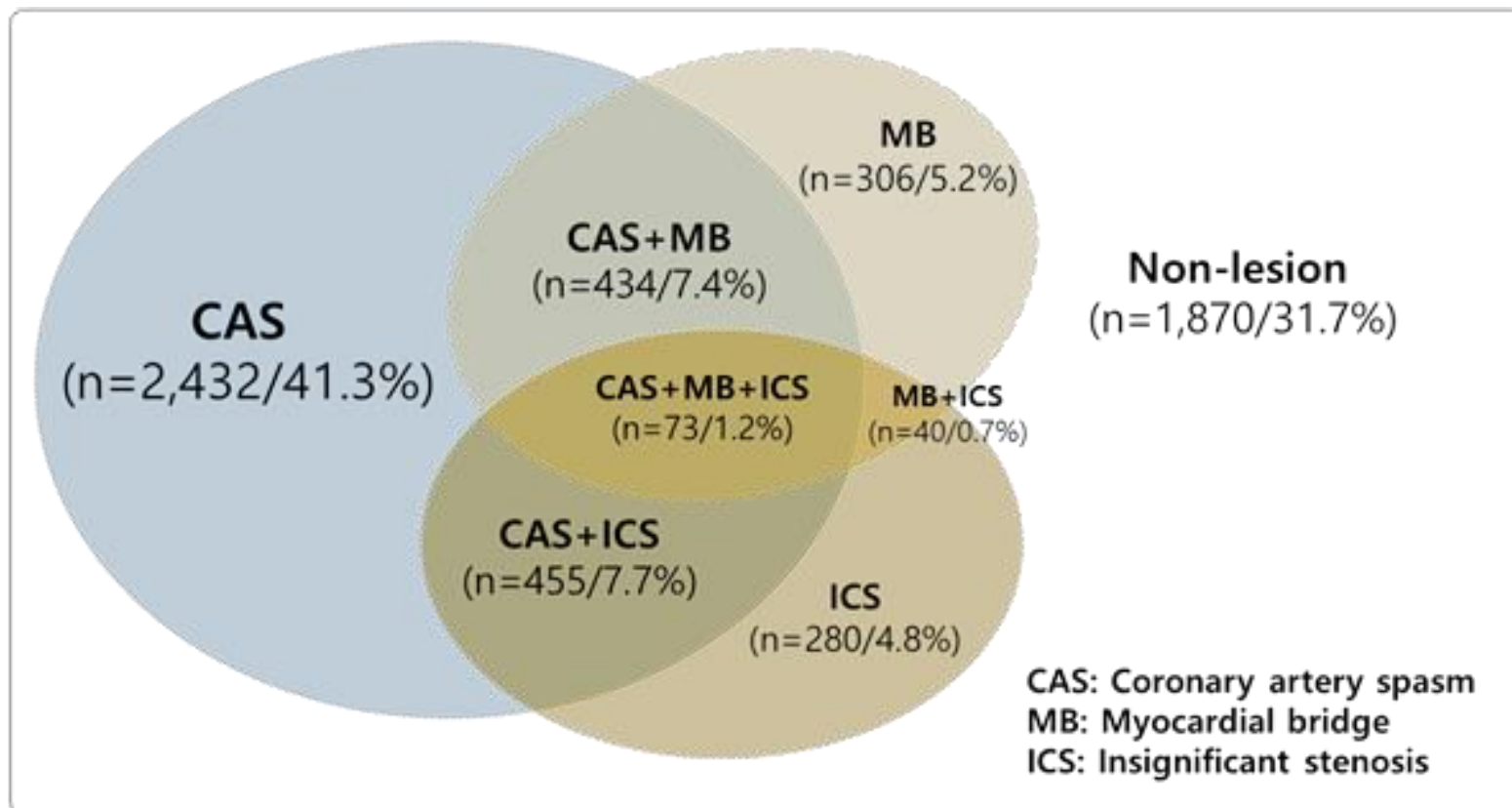
- A total of 10,177 subjects with typical or atypical chest pain who underwent CAG at the Cardiovascular Center of KUGH, Seoul, South Korea between November 2004 and May 2014 were enrolled for this study.
- Among these, 5,890 subjects with typical or atypical chest pain and without significant coronary artery stenosis (defined as having a diameter stenosis of less than 70%, as seen on the quantitative coronary angiography) underwent an intracoronary acetylcholine (ACH) provocation test.

# Flow Chart(1)



ACH: acetylcholine, CAS: Coronary artery spasm, MB: myocardial bridge, ICS: insignificant coronary stenosis.

# Flow Chart (2)



ACH: acetylcholine, CAS: Coronary artery spasm, MB: myocardial bridge, ICS: insignificant coronary stenosis.

# Methods

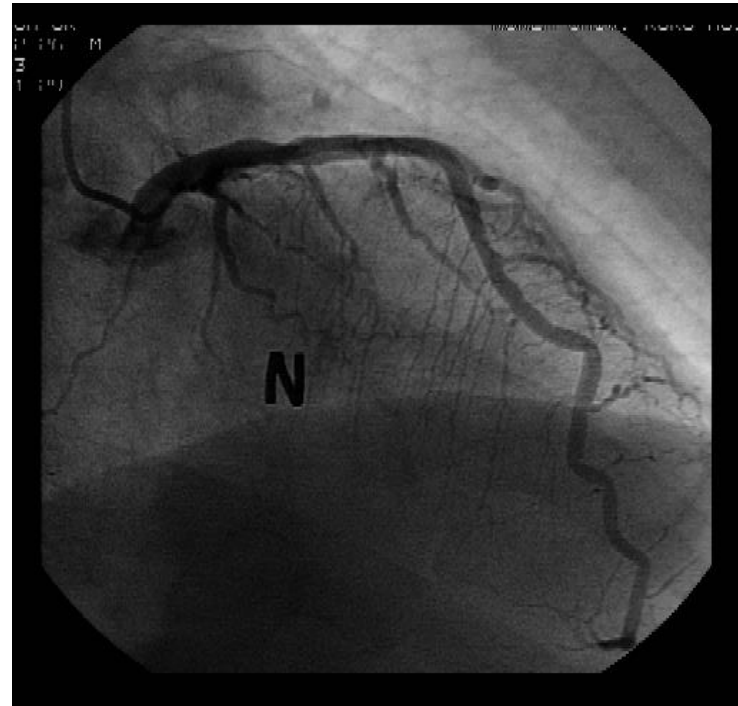
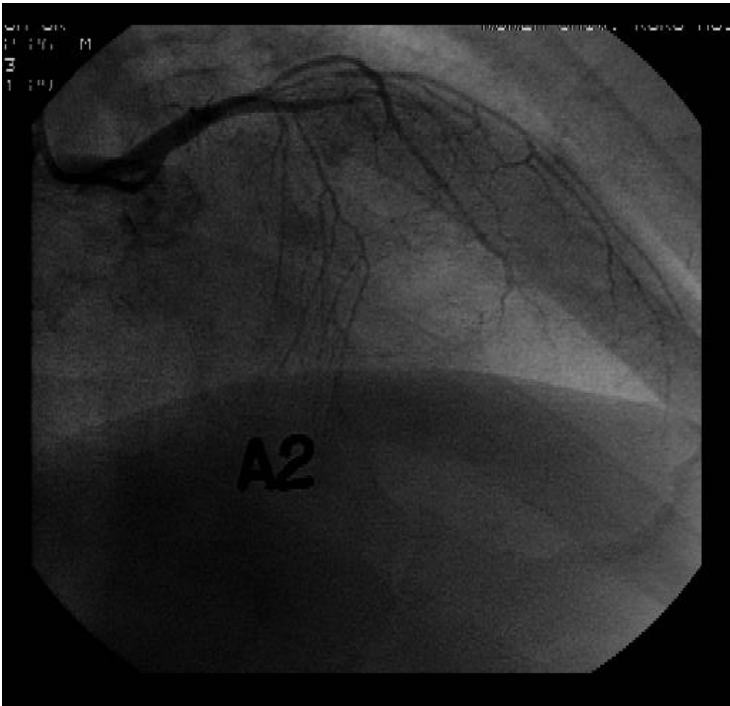
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- Intracoronary Ach Provocation Test
  - ✓ Ach was injected by incremental doses of 20 $\mu$ g (A1), 50  $\mu$ g (A2) and 100  $\mu$ g (A3) into the left coronary artery.
  - ✓ Significant CAS was defined as transient >70% luminal narrowing with/without ischemic ST-T Change or chest pain.



# Methods

## Coronary Angiogram with Positive Acetylcholine (ACH) Provocation Test in a Patient



A; Acetylcholine, N; Nitroglycerin

\*\* Total occlusion at mid LAD with A2 injection

# Methods (3)

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- Study endpoints
  - ✓ **Primary endpoint** was the incidence of MACE as defined as the composite of total death, MI, and revascularization, including PCI and CABG.
  - ✓ **Secondary endpoint** was the incidence of recurrent angina requiring repeat CAG.

# Statistics

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1. For continuous variables, differences between the two groups were evaluated using the unpaired t-test or Mann-Whitney rank test. Data were expressed as mean  $\pm$  standard deviations.
2. For discrete variables, differences were expressed as counts and percentages and analyzed with the  $\chi^2$  or Fisher's exact test between two groups.
3. To adjust for any potential confounders, multiple logistic regression model analysis was performed.
4. Various clinical outcomes were estimated with the Kaplan-Meier method, and differences between the groups were compared with the log-rank test.
5. For all analyses, a two-sided  $p < 0.05$  was considered statistically significant. All data were processed with SPSS 20.0 (IBM Corp., Armonk, NY, USA).

# Results (1)

Table. Baseline Clinical, Angiographic Characteristics

Variables	Total (n=5,890)	Variables	Total (n=5,890)	Variables	Total (n=5,890)
Sex, male	2703 (45.9)	<b>Medication history</b>		CAS site	
Age, years	55.3 ± 12.4	Calcium channel blockers	2570 (43.6)	Left main	8 (0.2)
Blood pressure, mmHg		Diltiazem	315 (5.3)	Left anterior descending	3181 (93.7)
Systolic	135 ± 21	Nitrate	279 (4.7)	Left circumflex	1300 (38.3)
Diastolic	78 ± 12	Trimetazidine	176 (2.9)	CAS location	
Heart rates, bpm	71 ± 13	Nicorandil	143 (2.4)	Mid to distal	1296 (38.1)
Body mass index	24 ± 3	β-blockers	270 (4.5)	Proximal; to distal	1409 (41.5)
<b>Risk factors</b>		Diuretics	292 (4.9)	Proximal only	246 (7.2)
Hypertension	2694 (45.7)	ARB	442 (7.5)	Mid only	380 (11.1)
Diabetes mellitus	928 (15.7)	ACEI	82 (1.3)	Distal only	63 (1.8)
New-onset diabetes	210 (3.5)	Statins	488 (8.2)	Diffuse CAS (>20 mm)	2913 (85.8)
Insulin	100 (1.6)	Coronary angiography		Multi-vessel CAS	1129 (33.2)
Medication	594 (10.0)	Insignificant stenosis		EKG Change	255 (4.3)
Dietary	71 (1.2)	Minimal (< 30%)	2834 (48.1)	ST-segment elevation	80 (1.3)
Dyslipidemia	1757 (29.8)	Mild (30-50%)	481 (8.1)		
History smokers	1699 (28.8)	Moderate (50-70%)	367 (6.2)		
Current smokers	1213 (20.5)	Myocardial bridge (>30%)	853 (14.4)		
History alcoholics	2050 (34.8)	CAS (after ACH provocation test)			
Current alcoholics	1881 (31.9)	Significant CAS (>70%)	3394 (57.6)		

Data are presented as N (%) or mean ± standard deviation. ARB: angiotensin receptor blockers, ACEI: angiotensin converting enzyme inhibitors, CAS: Coronary artery spasm, ACH: acetylcholine, EKG: electrocardiogram, MACE: major adverse cardiac events.

# Results (2)

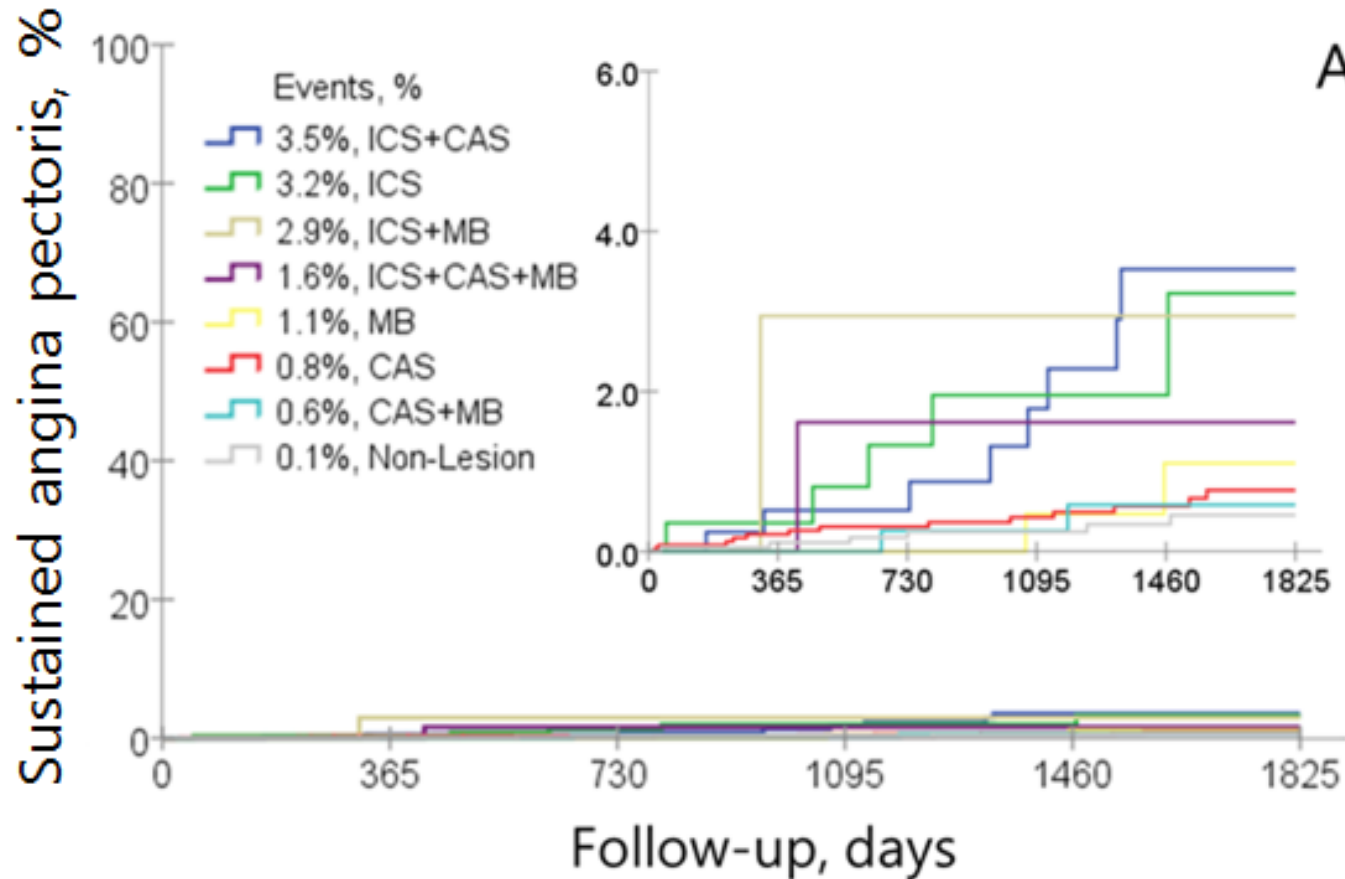
Table. Various Clinical Outcomes at 5-year

Incidence, %	Total (n=5,890)
<b>Clinical outcomes at 5-year</b>	
Sustained angina pectoris	309 (8.1)
MACE	38 (0.9)
Total death	16 (0.4)
Cardiac death	6 (0.1)
Myocardial infarction: MI	12 (0.3)
MI due to CAS	8 (0.2)
Coronary revascularization	15 (0.4)

Data are presented as N (%). MACE: major adverse cardiac events, CAS: coronary artery spasm.

# Results (3)

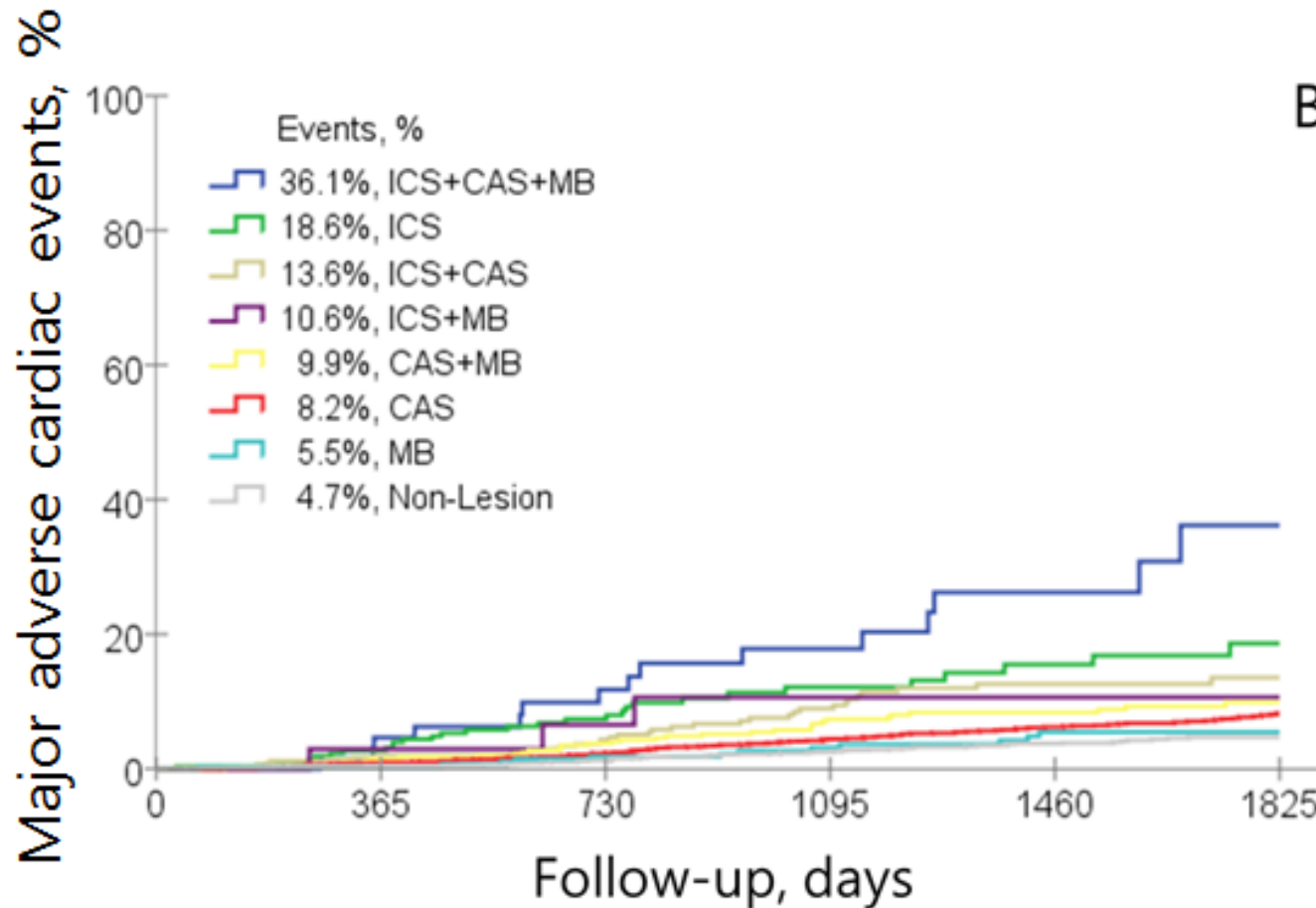
Cumulative 5-Year Clinical Outcomes in Patients without Significant Coronary Artery Disease



CAS: Coronary artery spasm, MB: myocardial bridge, ICS: insignificant coronary stenosis.

# Results (4)

Cumulative 5-Year Clinical Outcomes in Patients without Significant Coronary Artery Disease



CAS: Coronary artery spasm, MB: myocardial bridge, ICS: insignificant coronary stenosis.

# Results (5)

Table. Predictors of major adverse cardiac events (MACE) after multivariable Cox-proportional hazard model analysis

Variables, N (%)	Total	MACE up to 5 years		
		Incidence, %	Hazard Ratio (95% CI)	P-value
<b>Sex</b>	5890	38 (0.8%)		0.297
Male	2703	21 (1.1%)	1.527 (0.688 - 3.385)	
Female	3187	17 (0.8%)	0.655 (0.295 - 1.452)	
<b>Age, years</b>	5890	55.3 ± 12.4	<b>1.294 (1.099 - 1.524)</b>	<b>0.002</b>
<b>Hypertension</b>	2694	24 (1.3%)	1.275 (0.632 - 2.572)	0.497
<b>Diabetes mellitus</b>	928	11 (1.8%)	1.338 (0.645 - 2.773)	0.433
<b>Dyslipidemia</b>	1757	16 (1.3%)	1.428 (0.735 - 2.776)	0.292
<b>Cerebrovascular accidents</b>	122	3 (3.1%)	2.062 (0.610 - 6.969)	0.244
<b>Peripheral artery disease</b>	156	1 (0.7%)	0.382 (0.049 - 2.967)	0.358
<b>Chronic kidney insufficiency</b>	40	0 (0.0%)	-	0.975
<b>Current smokers</b>	1213	12 (1.4%)	2.239 (0.959 - 5.228)	0.062
<b>Alcohol drinkers</b>	1881	9 (0.7%)	0.549 (0.236 - 1.277)	0.164
<b>Myocardial bridge</b>	853	6 (1.0%)	1.076 (0.447 - 2.592)	0.869
<b>Coronary artery spasm</b>	3394	24 (1.0%)	1.040 (0.529 - 2.041)	0.909
<b>Insignificant stenosis</b>				<b>0.006</b>
30 - 50%	481	7 (2.7%)	<b>2.629 (1.098 - 6.291)</b>	<b>0.030</b>
50 - 70%	367	8 (3.7%)	<b>3.482 (1.501 - 8.074)</b>	<b>0.004</b>

MACE was defined as the composite of total death, MI, and coronary revascularization. MACE: major adverse clinical events, CI: confidence interval



# Results (6)

Table. Predictors of sustained angina pectoris after multivariable Cox-proportional hazard model analysis

Variables, N (%)	Total	Sustained Angina Pectoris up to 5 years		
		Incidence, %	Hazard Ratio (95%CI)	P-value
<b>Sex</b>	5890	309 (8.1)		0.243
Male	2703	153 (8.7%)	1.173 (0.896 - 1.535)	
Female	3187	156 (7.6%)	0.852 (0.651 - 1.115)	
<b>Age, years</b>	5890	55.3 ± 12.4	<b>1.059 (1.005 - 1.115)</b>	<b>0.031</b>
<b>Hypertension</b>	2694	157 (8.8%)	0.933 (0.731 - 1.191)	0.582
<b>Diabetes mellitus</b>	928	58 (9.8%)	1.038 (0.773 - 1.394)	0.803
<b>Dyslipidemia</b>	1757	117 (10.1%)	1.270 (0.994 - 1.622)	0.055
<b>Cerebrovascular accidents</b>	122	12 (12.7%)	1.417 (0.784 - 2.561)	0.247
<b>Peripheral artery disease</b>	156	22 (15.8%)	1.415 (0.880 - 2.276)	0.151
<b>Chronic kidney insufficiency</b>	40	2 (6.3%)	0.602 (0.147 - 2.454)	0.479
<b>Current smokers</b>	1213	73 (8.6%)	1.159 (0.849 - 1.582)	0.351
<b>Alcohol drinkers</b>	1881	81 (6.9%)	<b>0.740 (0.556 - 0.985)</b>	<b>0.039</b>
<b>Myocardial bridge</b>	853	63 (10.0%)	<b>1.390 (1.050 - 1.840)</b>	<b>0.021</b>
<b>Coronary artery spasm</b>	3394	208 (9.6%)	<b>1.398 (1.097 - 1.782)</b>	<b>0.007</b>
<b>Insignificant stenosis</b>				<b>&lt; 0.001</b>
30 - 50%	481	32 (13.3%)	<b>1.736 (1.188 - 2.534)</b>	<b>0.004</b>
50 - 70%	367	49 (22.0%)	<b>3.502 (2.530 - 4.847)</b>	<b>&lt; 0.001</b>

MACE was defined as the composite of total death, MI, and coronary revascularization. MACE: major adverse clinical events, CI: confidence interval

# Summary (1)

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- 1) Among the patients with chest pain, but without significant CAD, **68.3%** had CAS, MB, and/or ICS.
- 2) Of these patients, those with **MACE**, composite of all-cause deaths, MI, or revascularization were rare (**0.9%**), but **sustained AP** were frequent (**8.1%**) within the 5-year follow-up.

# Summary (2)

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- 3) On multivariable Cox-proportional hazard model analysis, the main **predictors of MACE** were aging and ICS; additionally, aging and ICS, along with MB and CAS were the main **predictors of sustained AP** at the 5-year follow-up.
- 4) In particular, both **aging and ICS** were seen as the strongest risk factors for MACE and sustained AP.

# Limitations

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- It is a non-randomized trial analysis conducted at a single center.
- The results were analyzed retrospectively and multivariable Cox-proportional regression analysis was performed to minimize the confounding factors; this might have influenced the results.
- We could not adjust all the limiting factors that were not shown through medical records or collected through telephone contact.
- Finally, we could not gather any detailed follow-up data on anti-angina medication during the follow-up. However, all patients received anti-angina medication until they were free of angina symptoms and in clinical remission, although the medication type and duration were based on the discretion of the individual physicians.

# Conclusion

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- In patients without significant CAD, aging and ICS (<70%) are strong predictors for future long-term MACE.
- Aging, CAS, and MB are also strongly associated with future AP.
- Further well-designed and longer-term follow-up studies are needed to obtain more accurate answers to all these questions.

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