Impact of Dyslipidemia on 3-year Clinical Outcomes in Patients with Significant Coronary Artery Spasm

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Background

1. Dyslipidemia is a risk factor of significant coronary artery disease (CAD).

A. Haffner SM et al.. Am J Cardiol. 1999;83(9):17-21.
B. Hopkins PN, et al. Circulation. 2003;108(5):519-523.

2. Coronary artery spasm (CAS) is also known to be a major cause of myocardial ischemia.

A. Yasue H, et al. Circulation research 1983;52(2 Pt 2):I147.
B. Maseri A. JACC 1987;9(2):249-262.

3. However, whether dyslipidemia adds any long-term clinical risk in CAS patients (pts) is largely unknown.

Purpose

We evaluated the impact of dyslipidemia on 3-year clinical outcomes in pts with significant CAS.

Methods

1. Study Population

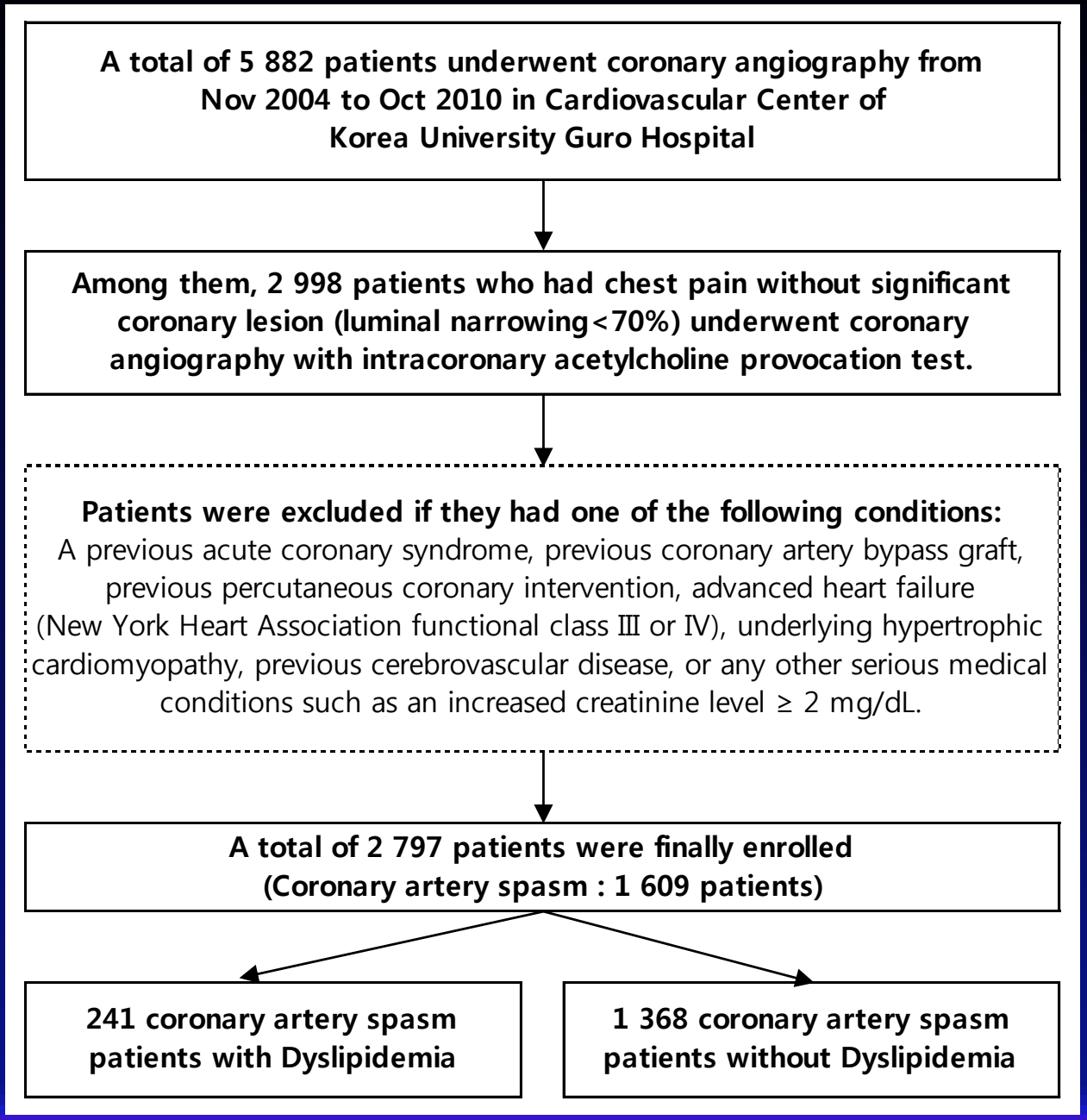
A total of 2,797 consecutive pts without significant CAD who underwent acetylcholine (Ach) provocation test were enrolled between Nov 2004 and Oct 2010.

2. Study Groups

Dyslipidemia group (n=241)

Normal group (n=1368)

Flow Chart


A total of 5 882 patients underwent coronary angiography from Nov 2004 to Oct 2010 in Cardiovascular Center of Korea University Guro Hospital
Among them, 2 998 patients who had chest pain without significant coronary lesion (luminal narrowing<70%) underwent coronary angiography with intracoronary acetylcholine provocation test.
Patients were excluded if they had one of the following conditions:
A previous acute coronary syndrome, previous coronary artery bypass graft, previous percutaneous coronary intervention, advanced heart failure (New York Heart Association functional class Ⅲ or Ⅳ), underlying hypertrophic cardiomyopathy, previous cerebrovascular disease, or any other serious medical conditions such as an increased creatinine level ≥ 2 mg/dL.
A total of 2 797 patients were finally enrolled (Coronary artery spasm : 1 609 patients)
241 coronary artery spasm patients with Dyslipidemia
1 368 coronary artery spasm patients without Dyslipidemia

Methods

3. Definition of Dyslipidemia

The definition of Dyslipidemia was based on the Third Report of the National Cholesterol Education Program(NCEP) guideline.

NCEP guide of the dyslipidemia – Any 2 of the Following:

Risk Factor	Defining Level
Total cholesterol	>240mg/dL
Triglyceride	>200mg/dL
LDL cholesterol	>130mg/dL
HDL cholesterol	<40mg/dL

Methods

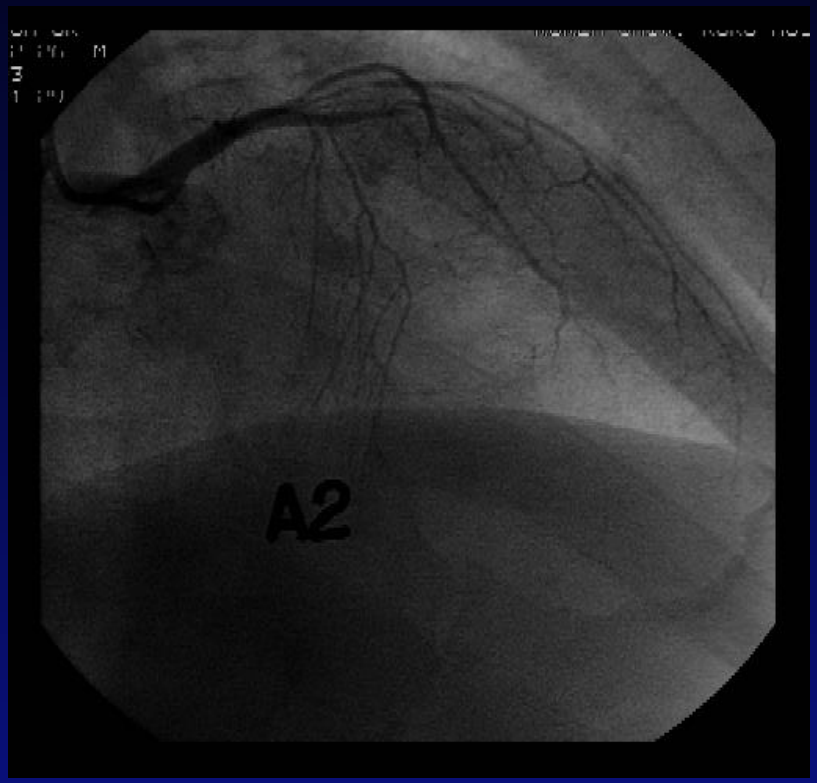
4. Intracoronary Ach Provocation Test

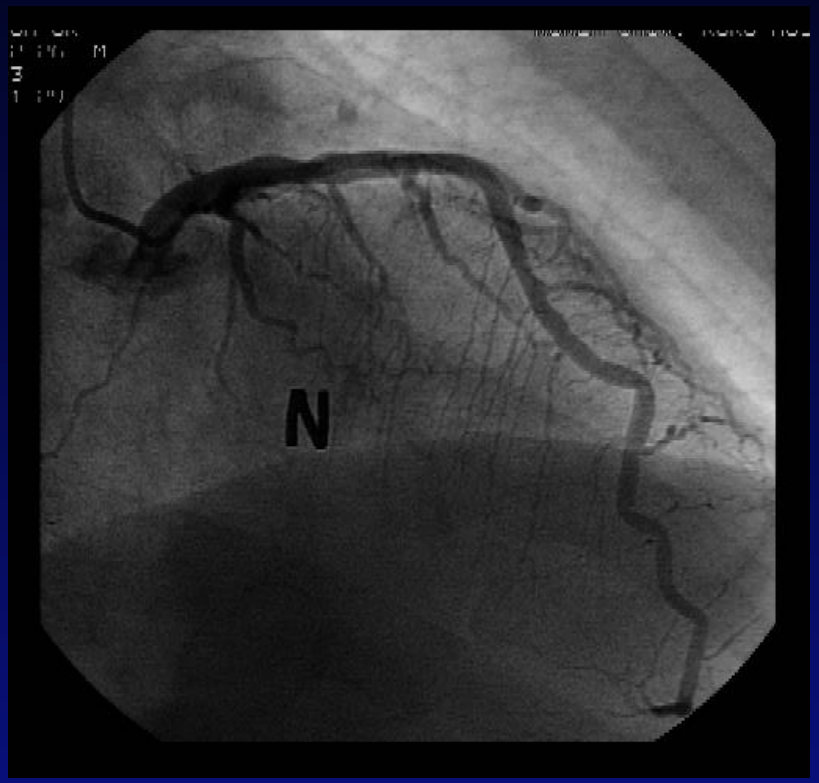
1) Ach was injected by incremental doses of 20μg (A1), 50 μg (A2) and 100 μg (A3) into the left coronary artery.

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

Methods

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





A; Acetylcholine, N; Nitroglycerin

** Total occlusion at mid LAD with A2 injection

Statistics (1)

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 (2)

6. To adjust for potential confounders, *propensity score matched analysis* was performed using the logistic regression model, testing the propensity to have CAS with dyslipidemia rather than without dyslipidemia .

7. We tested all available variables that could be of potential relevance: Age, male, cardiovascular risk factors (hypertension, diabetes, dyslipidemia, current smokers and current alcoholics, coronary fixed lesion) and myocardial bridge.

Statistics (3)

8. The logistic model by which the propensity score was estimated showed well predictive value (*C statistic=0.659*).
9. CAS with dyslipidemia group were then matched to the without dyslipidemia group on the propensity scores with the nearest available pair matching method. Subjects were matched with a caliper width equal to 0.05. The procedure yielded 228 well-matched pairs.
10. Various clinical outcomes at 3-year were estimated with the Kaplan-Meier method, and differences between groups were compared with the log-rank test.

Results

Baseline Clinical Characteristics

Variable. N (%)	Entire Patients			p Value
	Total (n=1609)	Dyslipidemia (n=241)	Normal (n=1368)	
Baseline characteristics				
Gender (Male)	823 (51.1)	120 (49.7)	703 (51.3)	0.648
Age	55.0 ± 11.5	57.0 ± 10.2	54.6 ± 11.7	**0.003**
Body mass index	24.3 ± 3.2	24.9 ± 2.9	24.2 ± 3.2	**0.001**
Left Ventricular ejection fraction(%)	58.8 ± 3.9	58.9 ± 3.6	58.8 ± 3.9	0.611
Hypertension	737 (45.8)	150 (62.2)	587 (42.9)	< 0.001
Diabetes	253 (15.7)	58 (24.0)	195 (14.2)	< 0.001
Insulin	34 (2.1)	8 (3.3)	26 (1.9)	0.158
Medication	133 (8.2)	31 (12.8)	102 (7.4)	0.005
Diet	26 (1.6)	11 (4.5)	15 (1.0)	0.001
New onset diabetes	60 (3.7)	8 (3.3)	52 (3.8)	0.716
Dyslipidemia				
Smoking history	511 (31.7)	76 (31.5)	435 (31.7)	0.936
Current Smoker	395 (24.5)	59 (24.4)	336 (24.5)	0.979
Alcoholic history	635 (39.4)	96 (39.8)	539 (39.4)	0.899
Current alcoholic	556 (34.5)	89 (36.9)	467 (34.1)	0.401
Fixed coronary lesion; FCL	764 (47.4)	129 (53.5)	635 (46.4)	0.042
Mild	696 (43.2)	115 (47.7)	581 (42.4)	0.130
Moderate	68 (4.2)	14 (5.8)	54 (3.9)	0.185

Baseline Laboratory Findings

Variable. N (%)	Entire Patients			
	Total (n=1609)	Dyslipidemia (n=241)	Normal (n=1368)	p Value
Creatinine	0.7 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.210
Total cholesterol	178 ± 40	194 ± 47	176 ± 39	< 0.001
Triglyceride	133 ± 93	167 ± 12	127 ± 89	< 0.001
LDL-C	113 ± 36	123 ± 41	111 ± 35	< 0.001
HDL-C	50 ± 13	51 ± 14	50 ± 13	0.143
Fasting Glucose	101 ± 24	103 ± 23	101 ± 24	0.305
hsCRP	2.5 ± 8.9	1.7 ± 2.61	2.7 ± 9.9	0.009
Fibrinogen	282 ± 102	292 ± 77	280 ± 106	0.368
Uric acid	4.8 ± 1.4	4.9 ± 1.3	4.8 ± 1.4	0.449

Angiographic Characteristics

Variable. N (%)	Entire Patients			
	Total (n=1609)	Dyslipidemia (n=241)	Normal (n=1368)	p Value
Acetylcholin dose				
A1 (20μg)	82 (5.0)	15 (6.2)	67 (4.8)	0.388
A2 (50μg)	542 (33.6)	92 (38.1)	450 (32.8)	0.110
A3 (100μg)	985 (61.2)	134 (55.6)	851 (62.2)	0.052
Reference diameter,mm (after NTG)	2.4 ± 0.8	2.4 ± 0.6	2.4 ± 0.8	0.877
Narrowing diameter,mm (after Ach)	0.7 ± 0.3	0.7 ± 0.38	0.7 ± 0.3	0.247
Narrowing diameter,% (after Ach)	70.4 ± 13.1	69.6 ± 13.9	70.5 ± 13.0	0.315
Baseline spasm (narrowing≥30%)	495 (30.7)	73 (30.2)	422 (30.8)	0.863
Myocardial bridge	434 (26.9)	54 (22.4)	380 (27.7)	0.083
Multi vessle spasm	555 (34.4)	90 (37.3)	465 (33.9)	0.313
Diffuse (≥20mm)	1344 (83.5)	204 (84.6)	1140 (83.3)	0.612
ST-T segment change	100 (6.2)	10 (4.1)	90 (6.5)	0.150
STD	38 (2.3)	7 (2.9)	31 (2.2)	0.547
STE	43 (2.6)	2 (0.8)	41 (2.9)	0.054
T-inversion	19 (1.1)	1 (0.4)	18 (1.3)	0.340
Spasm site				
Left Main	5 (0.3)	2 (0.8)	3 (0.2)	0.164
Left artery desending; LAD	980 (60.9)	142 (58.9)	838 (61.2)	0.493
Left circumflex; LCx	64 (3.9)	9 (3.7)	55 (4.0)	0.834
Left coronary artery; LAD+LCx	541 (33.6)	87 (36)	454 (33.1)	0.378
Narrowing lication				
Proximal to distal	659 (40.9)	110 (45.6)	549 (40.1)	0.109
Mid to distal	592 (36.7)	83 (34.4)	509 (37.2)	0.411
Proximal	120 (7.4)	21 (8.7)	99 (7.2)	0.421
Mid	212 (13.1)	25 (10.3)	187 (13.6)	0.163
Distal	26 (1.6)	2 (0.8)	24 (1.7)	0.411

Baseline Clinical Characteristics

Variable. N (%)	Total (n=456)	Propensity Score-Matched Patients Dyslipidemia (n=228)	Normal (n=228)	p Value
Gender (Male)	223 (48.9)	113 (49.5)	110 (48.2)	0.779
Age	57.3 ± 10.2	56.5 ± 10.2	58.0 ± 10.3	0.142
Body mass index	24.6 ± 2.9	24.8 ± 2.8	24.4 ± 3.0	0.143
Left Ventricular ejection fraction(%)	59.0 ± 3.8	59.0 ± 3.7	59.0 ± 3.8	0.965
Hypertension	272 (59.6)	137 (60.0)	135 (59.2)	0.849
Diabetes	83 (18.2)	46 (20.1)	37 (16.2)	0.275
Insulin	8 (1.7)	4 (1.7)	4 (1.7)	ns
Medication	44 (9.6)	25 (10.9)	19 (8.3)	0.341
Diet	13 (2.8)	9 (3.9)	4 (1.7)	0.159
New onset diabetes	18 (3.9)	8 (3.5)	10 (4.3)	0.631
Dyslipidemia				
Smoking history	146 (32.0)	72 (31.5)	74 (32.4)	0.841
Current Smoker	109 (23.9)	55 (24.1)	54 (23.6)	0.913
Alcoholic history	182 (39.9)	89 (39.0)	93 (40.7)	0.702
Current alcoholic	163 (35.7)	83 (36.4)	80 (35.0)	0.769
Fixed coronary lesion; FCL	245 (53.7)	121 (53.0)	124 (54.3)	0.778
Mild	219 (48.0)	108 (47.3)	111 (48.6)	0.779
Moderate	26 (5.7)	13 (5.7)	13 (5.7)	ns

Baseline Laboratory Findings

Variable. N (%)	Propensity Score-Matched Patients			
	Total (n=456)	Dyslipidemia (n=228)	Normal (n=228)	p Value
Creatinine	0.7 ± 0.1	0.8 ± 0.1	0.7 ± 0.1	0.642
Total cholesterol	186 ± 41	195 ± 47	177 ± 35	< 0.001
Triglyceride	148 ± 10	166 ± 11	129 ± 96	0.001
LDL-C	118 ± 37	124 ± 41	111 ± 34	0.001
HDL-C	51 ± 13	51 ± 13	50 ± 12	0.690
Fasting Glucose	102 ± 24	103 ± 23	102 ± 24	0.807
hsCRP	2.1 ± 4.6	1.7 ± 2.67	2.3 ± 6.1	0.249
Fibrinogen	287 ± 86.	291 ± 76	284 ± 94	0.661
Uric acid	4.9 ± 1.4	4.9 ± 1.3	4.9 ± 1.5	0.861

Angiographic Characteristics

Variable. N (%)	Total (n=456)	Propensity Score-Matched Patients Dyslipidemia (n=228)	Normal (n=228)	p Value
Acetylcholin dose				
A1 (20μg)	26 (5.7)	15 (6.5)	11 (4.8)	0.419
A2 (50μg)	162 (35.5)	84 (36.8)	78 (34.2)	0.557
A3 (100μg)	268 (58.7)	129 (56.5)	139 (60.9)	0.341
Reference diameter,mm (after NTG)	2.4 ± 0.5	2.4 ± 0.6	2.3 ± 0.5	0.250
Narrowing diameter,mm (after Ach)	0.7 ± 0.3	0.7 ± 0.38	0.7 ± 0.3	0.764
Narrowing diameter,% (after Ach)	70.0 ± 13.9	69.8 ± 14.0	70.1 ± 13.7	0.809
Baseline spasm (narrowing≥30%)	151 (33.1)	68 (29.8)	83 (36.4)	0.136
Myocardial bridge	104 (22.8)	52 (22.8)	52 (22.8)	ns
Multi vessle spasm	168 (36.8)	86 (37.7)	82 (35.9)	0.698
Diffuse (≥20mm)	379 (83.1)	193 (84.6)	186 (81.5)	0.382
ST-T segment change	29 (6.3)	10 (4.3)	19 (8.3)	0.084
STD	17 (3.7)	7 (3.0)	10 (4.3)	0.458
STE	10 (2.1)	2 (0.8)	8 (3.5)	0.055
T-inversion	2 (0.4)	1 (0.4)	1 (0.4)	ns
Spasm site				
Left Main	2 (0.4)	2 (0.8)	0 (0.0)	0.499
Left artery desending; LAD	269 (58.9)	134 (58.7)	135 (59.2)	0.924
Left circumflex; LCx	19 (4.1)	8 (3.5)	11 (4.8)	0.482
Left coronary artery; LAD+LCx	163 (35.7)	83 (36.4)	80 (35)	0.769
Narrowing lication				
Proximal to distal	200 (43.8)	106 (46.4)	94 (41.2)	0.257
Mid to distal	159 (34.8)	77 (33.7)	82 (35.9)	0.623
Proximal	36 (7.8)	21 (9.2)	15 (6.5)	0.297
Mid	56 (12.2)	23 (10)	33 (14.4)	0.154
Distal	5 (1.0)	1 (0.4)	4 (1.7)	0.372

Three-year Clinical Outcomes

Variable. N (%)	Entire Patients			
	Total (n=1609)	Dyslipidemia (n=241)	Normal (n=1368)	p Value
Mortality	3 (0.1)	2 (0.8)	1 (0.0)	0.060
Cardiac death	2 (0.1)	1 (0.4)	1 (0.0)	0.277
PTCA	3 (0.1)	0 (0.0)	3 (0.2)	ns
Myocardial infarction; MI	3 (0.1)	2 (0.8)	1 (0.0)	0.060
Cerebrovascular accidents; CVA	3 (0.1)	1 (0.4)	2 (0.1)	0.386
Repeat CAG	102 (6.3)	24 (9.9)	78 (5.7)	**0.012**
MACE ; Mortality, PTCA, MI	9 (0.5)	4 (1.6)	5 (0.3)	**0.033**

Variable. N (%)	Propensity Score-Matched Patients			
	Total (n=456)	Dyslipidemia (n=228)	Normal (n=228)	p Value
Mortality	2 (0.4)	2 (0.8)	0 (0.0)	0.499
Cardiac death	1 (0.2)	1 (0.4)	0 (0.0)	ns
PTCA				
Myocardial infarction; MI	2 (0.4)	2 (0.8)	0 (0.0)	0.499
Cerebrovascular accidents; CVA	2 (0.4)	1 (0.4)	1 (0.4)	ns
Repeat CAG	33 (7.2)	24 (10.5)	9 (3.9)	0.007
MACE ; Mortality, PTCA, MI	4 (0.8)	4 (1.7)	0 (0.0)	0.123

Adjusted by gender, age, myocardial infarction, hypertension, diabetes, chronic kidney disease, current smoker, multivessel disease, collateral vessels(≥grade 2), and failed CTO procedure.

A Predictors of Recurrent Chest Pain (Repeat CAG)

Variable	Entire Patients		PSM Patients	
	Odds Ratio (95% C.I)	p Value	Odds Ratio (95% C.I)	p Value
Age	1.01 (0.99-1.03)	0.221		
Male	1.15 (0.70-1.88)	0.577		
Hypertension	0.94 (0.61-1.43)	0.777		
Diabetes	0.90 (0.48-1.68)	0.759		
Dyslipidemia	1.82 (1.11-2.98)	0.016	2.86 (1.29-6.30)	0.009
Current smoker	1.50 (0.88-2.56)	0.127		
Current alcoholic	0.74 (0.45-1.20)	0.230		
Fixed coronary lesion	1.21 (0.79-1.86)	0.367		

Adjusted by male, age, hypertension, diabetes, dyslipidemia, current smoker, current alcoholic and fixed coronary lesion (stenosis<50%)

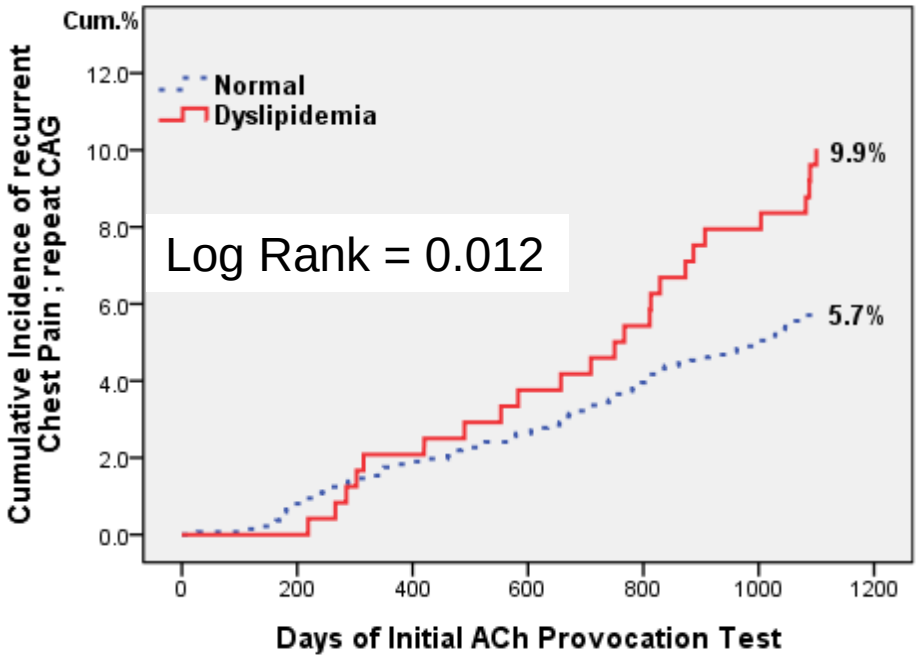
A Predictors of Major Adverse Cardiac Events

Variable	Entire Patients	
	Odds Ratio (95% C.I)	p Value
Age	1.09 (1.01-1.17)	0.019
Male	3.70 (0.76-17.8)	0.103
Hypertension	0.63 (0.16-2.49)	0.520
Diabetes	0.45 (0.05-3.83)	0.472
Dyslipidemia	**5.45 (1.36-21.7)**	**0.016**
Current smoker	0.83 (0.14-4.91)	0.843
Current alcoholic	0.46 (0.08-2.56)	0.376
Fixed coronary lesion	5.56 (0.67-45.6)	0.110

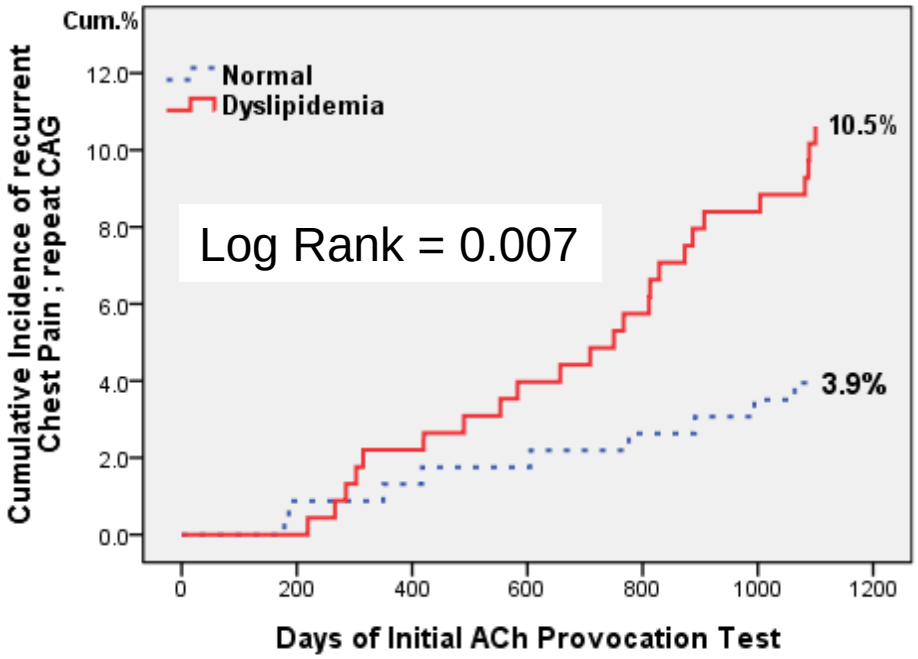
Adjusted by male, age, hypertension, diabetes, dyslipidemia, current smoker, current alcoholic and fixed coronary lesion (stenosis<50%)

Cumulative incidence of recurent chest pain (Kaplan-Meier Curve)

Entire Patients



After PSM Patients



Summary (1)

1. At baseline, pts with dyslipidemia had a higher incidence of elderly, hypertension, diabetes and fixed coronary lesion than pts without dyslipidemia.

2. During Ach provocation test, there was no difference in angiographic and clinical parameters between the two groups.

3. At 3 years, the dyslipidemia group had higher incidence of recurrent chest pain (9.9% vs. 5.7%, p=0.012) and major adverse cardiac events (MACE) including all-cause mortality, myocardial infarction, coronary revascularization (1.6 % vs. 0.3%, p=0.033).

Summary (2)

4. After multivariate analysis, dyslipidemia patients showed a higher risk of recurrent chest pain (HR; 1.82, 95%C.I; 1.11-2.98, p=0.016) and MACE (HR; 5.45, 95%C.I; 1.36-21.7, p=0.016) before propensity score matching analysis.

5. After PSM, dyslipidemia was the only remaining predictor for recurrent chest pain and subsequent follow up coronary angiography (HR; 2.86, 95%C.I; 1.29-6.30, p=0.009).

Conclusion

In this study, pts with dyslipidemia showed significant association with higher incidence of recurrent chest pain and follow up coronary angiography up to 3 years, suggesting higher chance of profound endothelial dysfunction requiring intensive anti-anginal management and close clinical follow up.