

Conservative versus Aggressive Revascularization in Patients with Intermediate Lesions Undergoing Percutaneous Coronary Intervention with Angiography Guidance Alone :SMART-CASE Trial

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

- Grant/Research Support
- Consulting Fees/Honoraria

Company

- Abbott vascular Korea
- Medtronic Korea
- Medtronic Asia-Pacific

Background

- Coronary angiography is the most widely used technique for guiding percutaneous coronary intervention (PCI) in daily practice.
- The diameter stenosis (DS) $> 50\%$ was determined as significant in an animal experiment¹. However, the DS between 50 to 70% has been considered as intermediate by many operators.
- In the literatures, the indication of PCI was
 - DS $> 50\%$ in SYNTAX trial², FAME trial³, 2011 ACC/AHA/SCAI guideline for PCI⁴
 - DS $> 70\%$ in COURAGE trial⁵, 2010 ESC guideline for revascularization⁶
- The clinical outcome of PCI based on the criteria of DS $>50\%$ vs. $>70\%$ has never been studied.

1) Gould KL, Am J Cardiol 1974;33:87-94, 2) Serruys PW, N Engl J Med 2009;360:961-72

3) Tonino PA, N Engl J Med 2009;360:213-24 4) Circulation 2011;124:e574-e651

5) Boden WE, N Engl J Med 2007;356:1503-16, 6) Eur Heart J 2010;31:2501-2555

Study Objective

- Objective
 - To find the optimal strategy of PCI for the angiographically intermediate lesion

Hypothesis

The *conservative* revascularization using criteria of 70% diameter stenosis would be *non-inferior* to the *aggressive* revascularization using criteria of 50% diameter stenosis.

Subjects

- Inclusion criteria

- Intermediate coronary lesion(s): a diameter stenosis 50-70% by QCA
- Target lesion(s) located in a native coronary artery with a diameter of 2.25- 4.25 mm and amenable for PCI

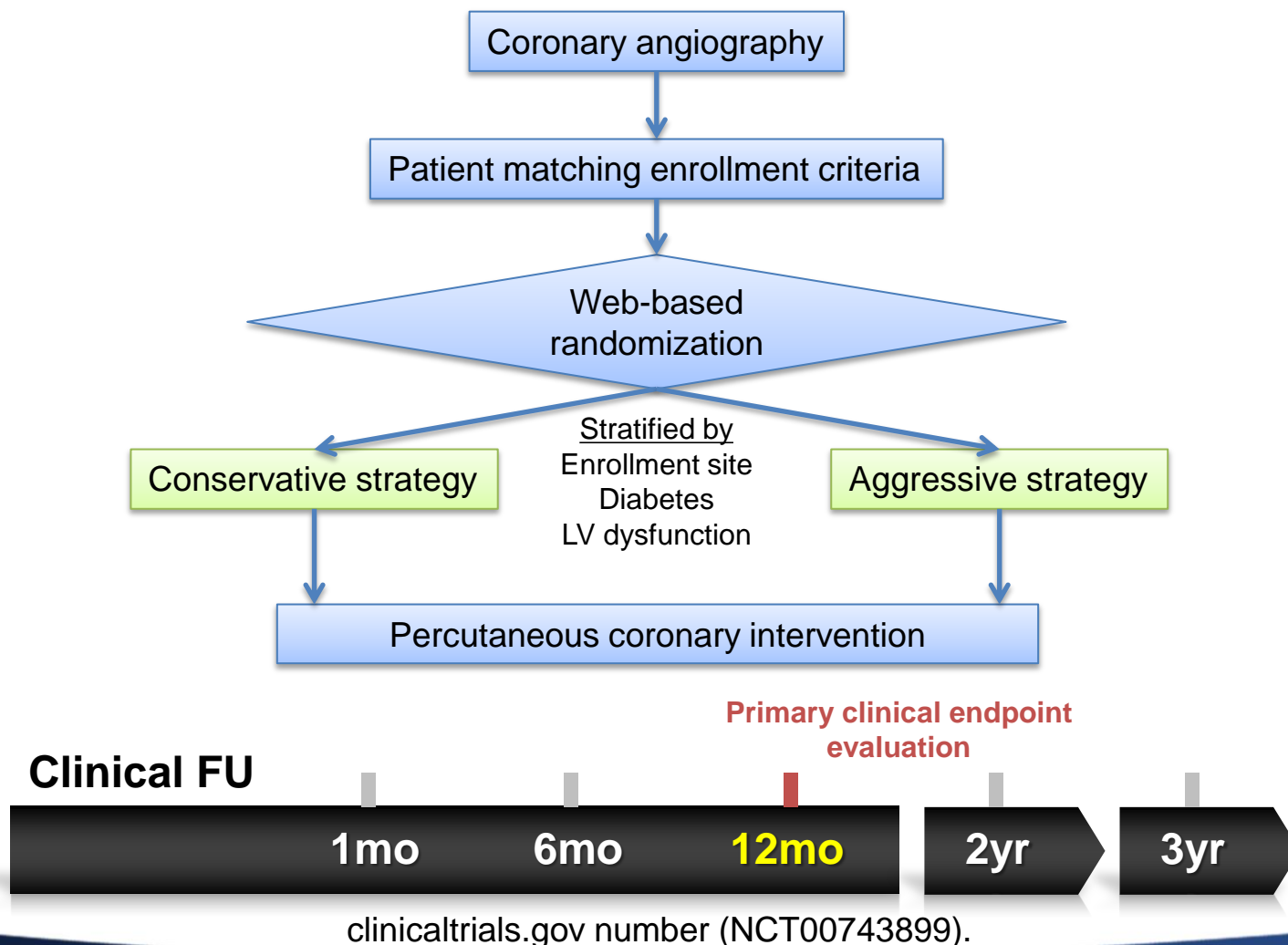
- Exclusion criteria

- Cardiogenic shock
- Left main lesion
- ≥ 2 CTOs in major coronary arteries
- GI or GU within 3 months
- Platelet count $< 100,000$ cells/mm³
- Life expectancy < 1 year
- MI within 48 hours
- Prior DES implantation in target vessel
- Bleeding diathesis or coagulopathy;
- Major surgery within 2 months
- Planned surgery within 6 months

QCA = quantitative coronary angiography, MI = myocardial infarction, DES = drug-eluting stent
CTO = chronic total occlusion, GI = gastrointestinal, GU = genitorurinary

Trial Design

Investigator-initiated, multi-center, open label, prospective randomized trial



PCI procedure

- In the conservative group
 - Stenting only in lesions with DS >70% and RD \geq 2.25 mm
- In the aggressive group
 - Stenting in lesions with DS >50% and RD \geq 2.25 mm

- Cobalt-chromium everolimus-eluting stents used for all lesions.
- No restriction in terms of number or total length of stents
- Balloon angioplasty for small vessel disease was discouraged in the conservative group.
- Uses of IVUS, GP IIb/IIIa inhibitors were at the operator's discretion.
- Staged PCI was allowed within 7 days of randomization.

DS = diameter stenosis, RD = reference diameter

Study Endpoints

- **Primary Endpoint**

- Composite outcome of all cause death, MI*, and any revascularization at 12 months

- **Secondary Endpoints**

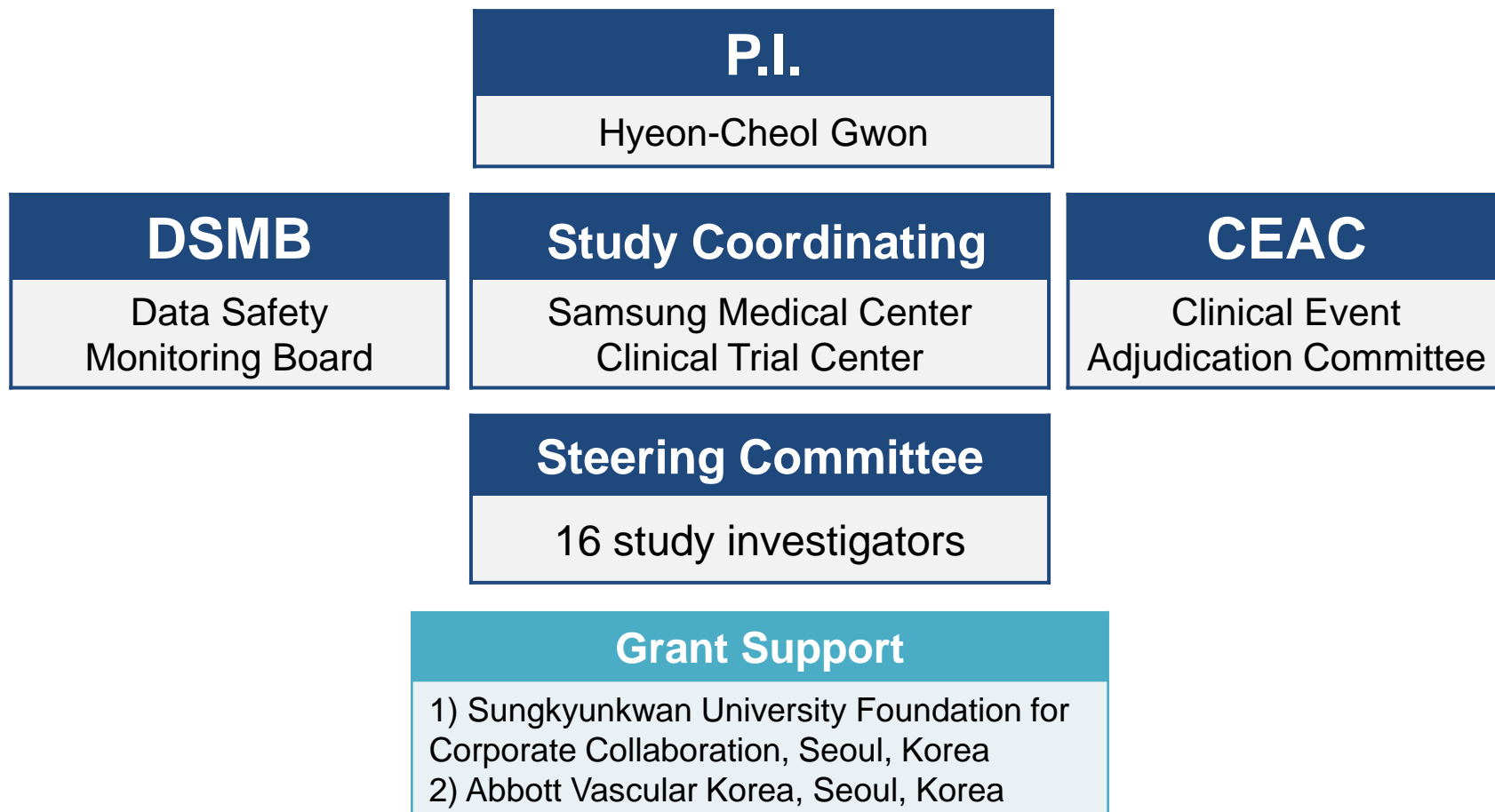
- All cause death
- Myocardial infarction
- Death or myocardial infarction
- Any revascularization
- Revascularization of target intermediate lesion
- Stent thrombosis

* an elevation of CK-MB or troponin > UNL with concomitant ischemic symptoms or ECG change

Sample size calculation

- Non-inferiority design
- Type I (α) error was set at 0.05
- One-sided test
- Sampling ratio is 1:1
- The incidence of the primary end point with aggressive strategy for 1 year was assumed to be 8.0%
 - SPIRIT III trial: 1-year TVF 8.6% with everolimus-eluting stent
- Non-inferiority margin: absolute difference 5.0 percentage points
- With a total of 900 patients (450 per group), the power of the study would be 86.5%

Independence in Trial Coordination



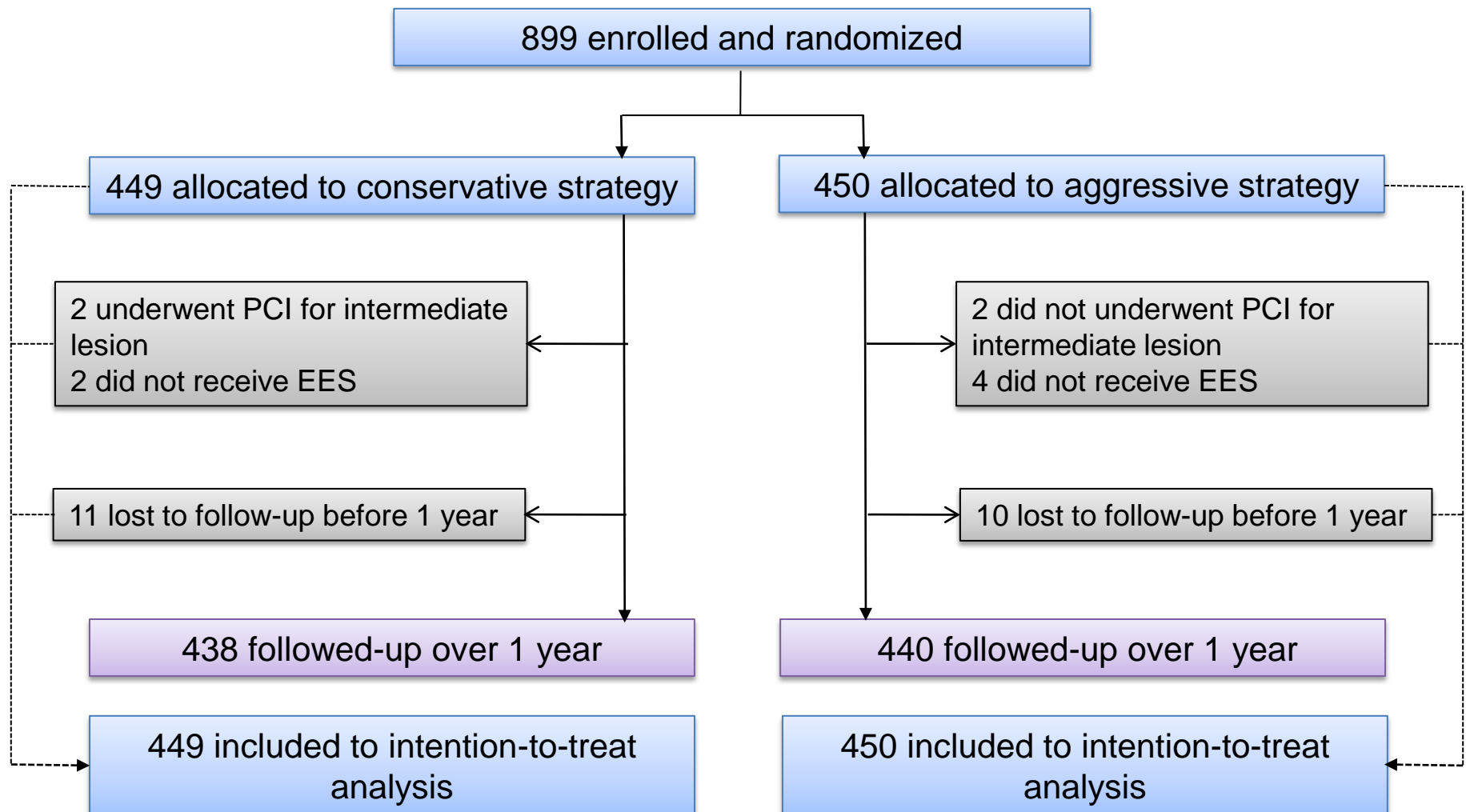
The sponsor were not involved with the protocol development or the study process, including site selection, management, data collection, and analysis.

Participating Centers

16 Hospitals in South Korea

- Sungkyunkwan University Samsung Medical Center
- Sungkyunkwan University Samsung Changwon Hospital
- Chungnam University Hospital
- Inje University Ilsan Baik Hospital
- Dongsuwon Hospital
- Dankuk University Hospital
- Hanmaeum Hospital
- Chungang University Yonsan Hospital
- Eulji University Hospital
- Seoul Medical Center
- Hanjeon Hospital
- Kyunghee University Hospital
- Kangwon University Hospital
- Sungkyunkwan University Samsung Kangbuk Hospital
- Inje University Seoul Baik Hospital
- Kyungpook University Hospital

Patient Flow



(1Y FU rate 98%)

Clinical characteristics

	Conservative Group (n=449)	Aggressive Group (n=450)	p Value
Age, y	64.1±9.4	65.3±9.9	0.07
Male sex	289 (64.4)	305 (67.8)	0.28
Body mass index*	24.7±2.9	24.5±3.0	0.43
Diabetes mellitus	145 (32.3)	151 (33.6)	0.69
Hypertension	293 (65.3)	295 (65.6)	0.93
Dyslipidemia	114 (25.4)	125 (27.8)	0.42
Current smoker	93 (20.7)	116 (25.8)	0.07
Previous myocardial infarction	25 (5.6)	16 (3.6)	0.15
Previous revascularization	56 (12.5)	46 (10.2)	0.29
Clinical presentation			0.46
Stable ischemic heart disease	298 (66.4)	282 (62.7)	
Unstable angina	122 (27.2)	139 (30.9)	
Myocardial infarction	29 (6.5)	29 (6.4)	
Ejection fraction (%)	62.1±9.3	62.4±9.5	0.64

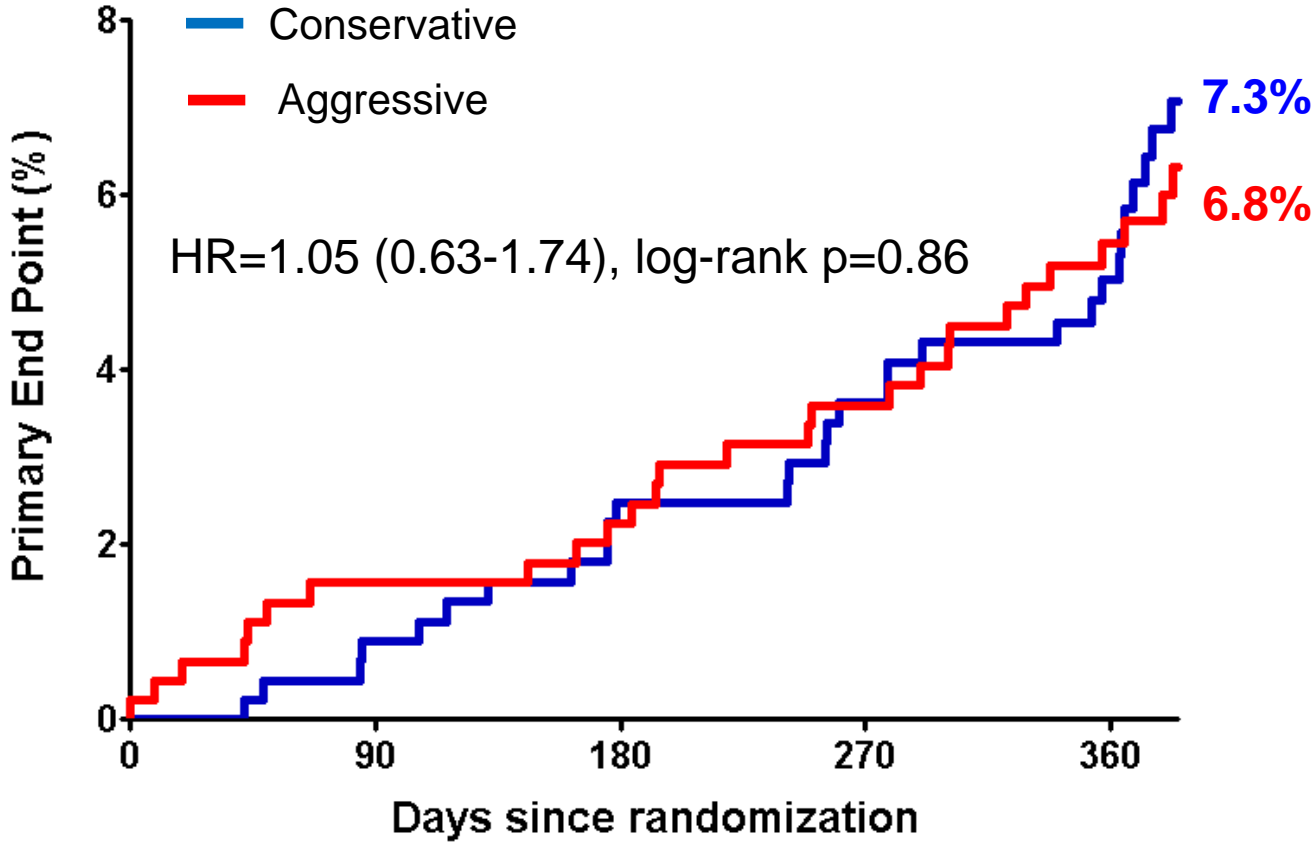
Data are n (%) or mean±SD

Lesion and procedural characteristics

	Conservative Group (n=449)	Aggressive Group (n=450)	p Value
Target intermediate lesion			
Location			0.25
Left anterior descending artery	197 (43.9)	218 (48.4)	
Left circumflex artery	106 (23.6)	88 (19.6)	
Right coronary artery	146 (32.5)	144 (32.0)	
Quantitative coronary analysis (core-lab)			
Reference diameter (mm)	3.1±0.6	3.0±0.5	0.68
Lesion length (mm)	13.4±5.1	13.1±4.4	0.39
Diameter stenosis (%)	55.6±6.3	55.6±6.0	0.97
< 50%	29 (6.5)	35 (7.8)	
50 - 60%	321 (72.5)	322 (72.0)	
61 - 70%	91 (20.5)	85 (19.0)	
> 70%	2 (0.5)	5 (1.1)	
Multivessel disease	253 (56.3)	237 (52.7)	0.27
Number of stents per patient	0.7±0.9*	1.8±1.0	<0.001
Total stent length per patient (mm)	15.6±21.5	39.3±24.7	<0.001
Average stent diameter per patient (mm)	3.0±0.9	3.1±0.7	0.21

* No stent was implanted in 213 patients (47.4%)

All cause death, MI, or any revascularization



No. at Risk
 Conservative
 Aggressive

	0	90	180	270	360
Conservative	449	439	429	420	369
Aggressive	450	436	433	427	361

Test of non-inferiority

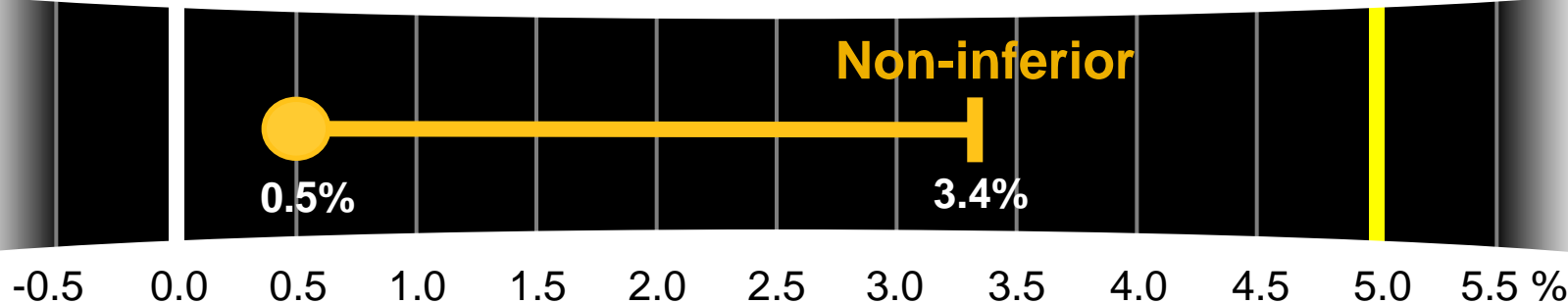
Cumulative proportional primary endpoint estimate at 1 year

<p>Conservative (N=449) 7.3±1.3%</p>	<p>Aggressive (N=450) 6.8±1.2%</p>	<p>Pre-specified non-inferiority margin 5.0%</p>	<p>Difference p=0.86</p>	<p>Non-inferiority p=0.0055</p>
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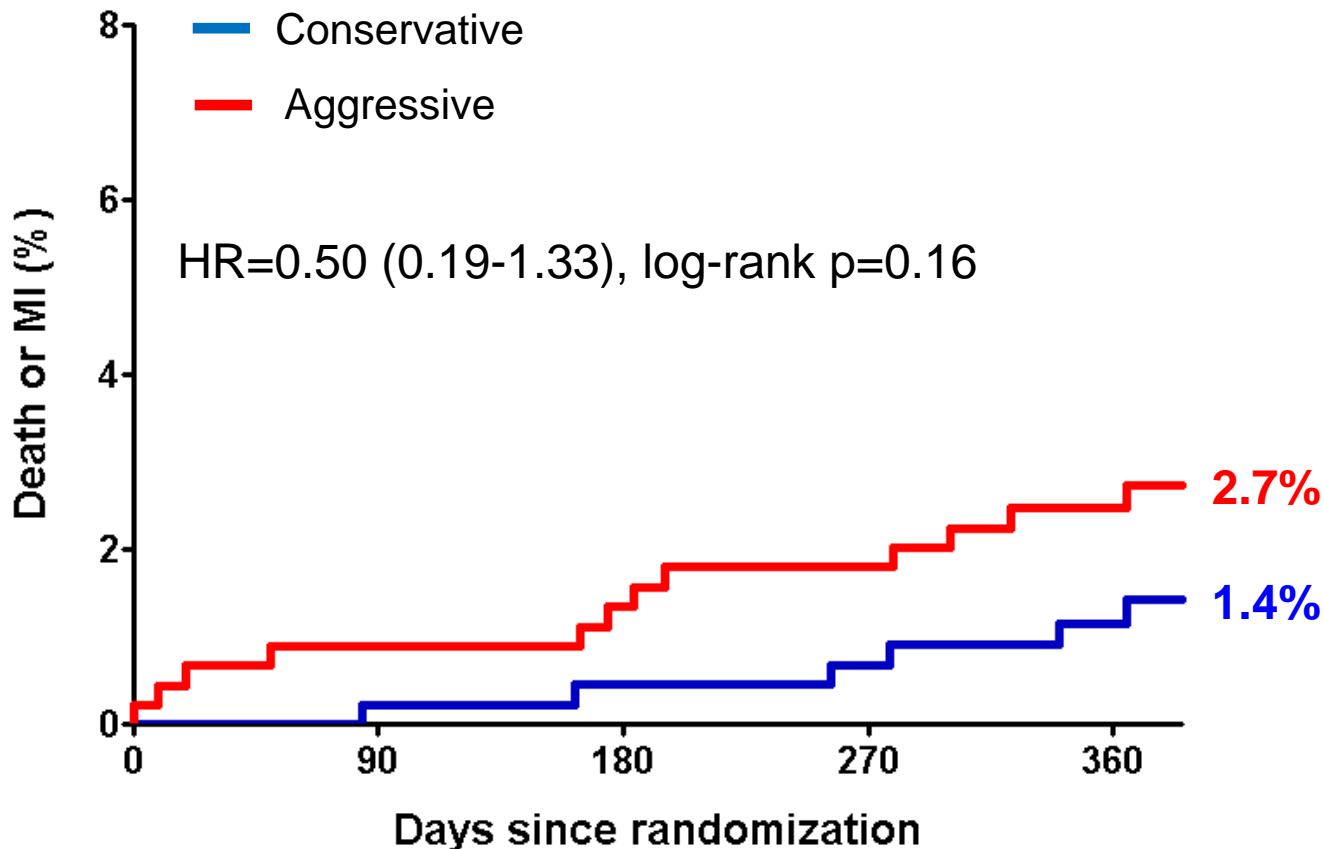
Difference ● — Upper 1-sided 95% CI

Pre-specified non-inferiority margin

Non-inferior



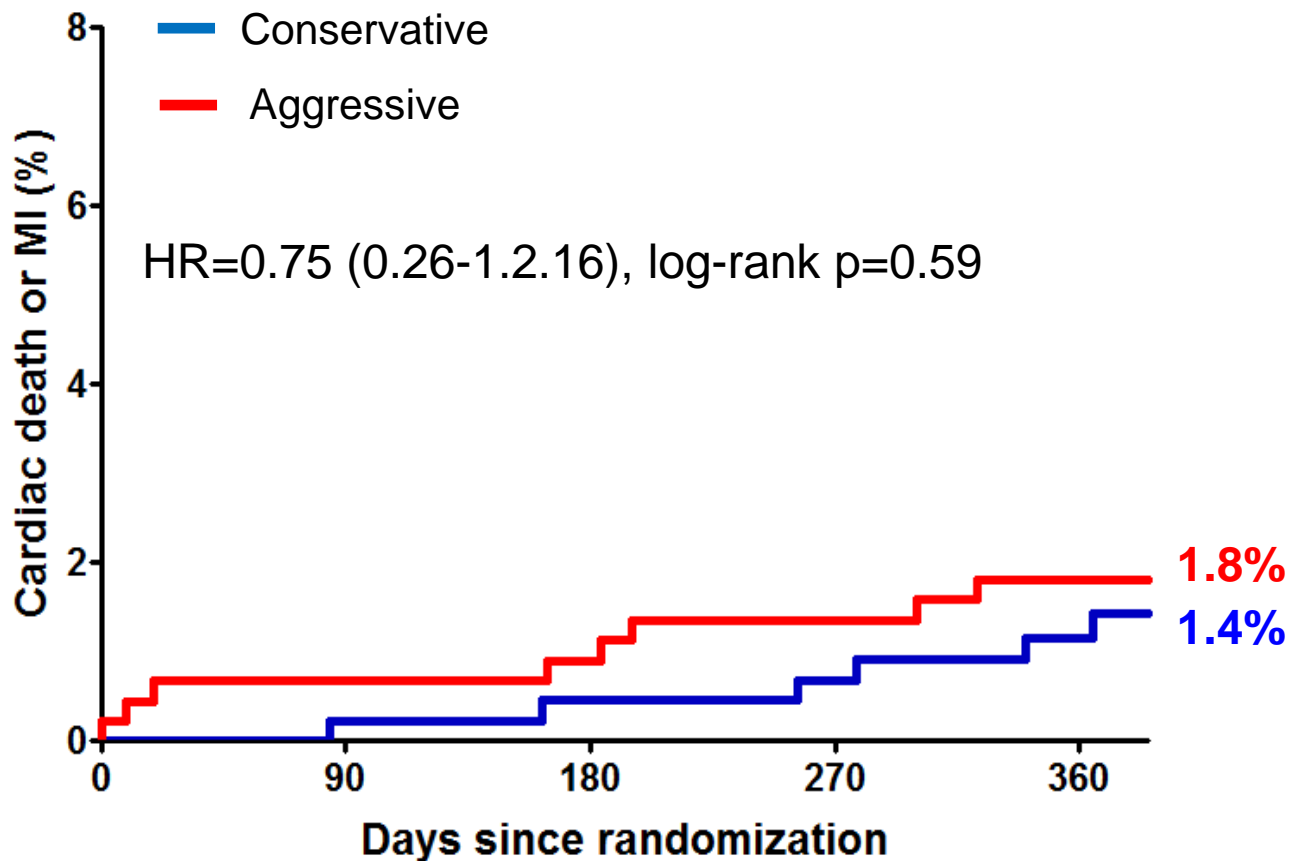
Death or MI



No. at Risk

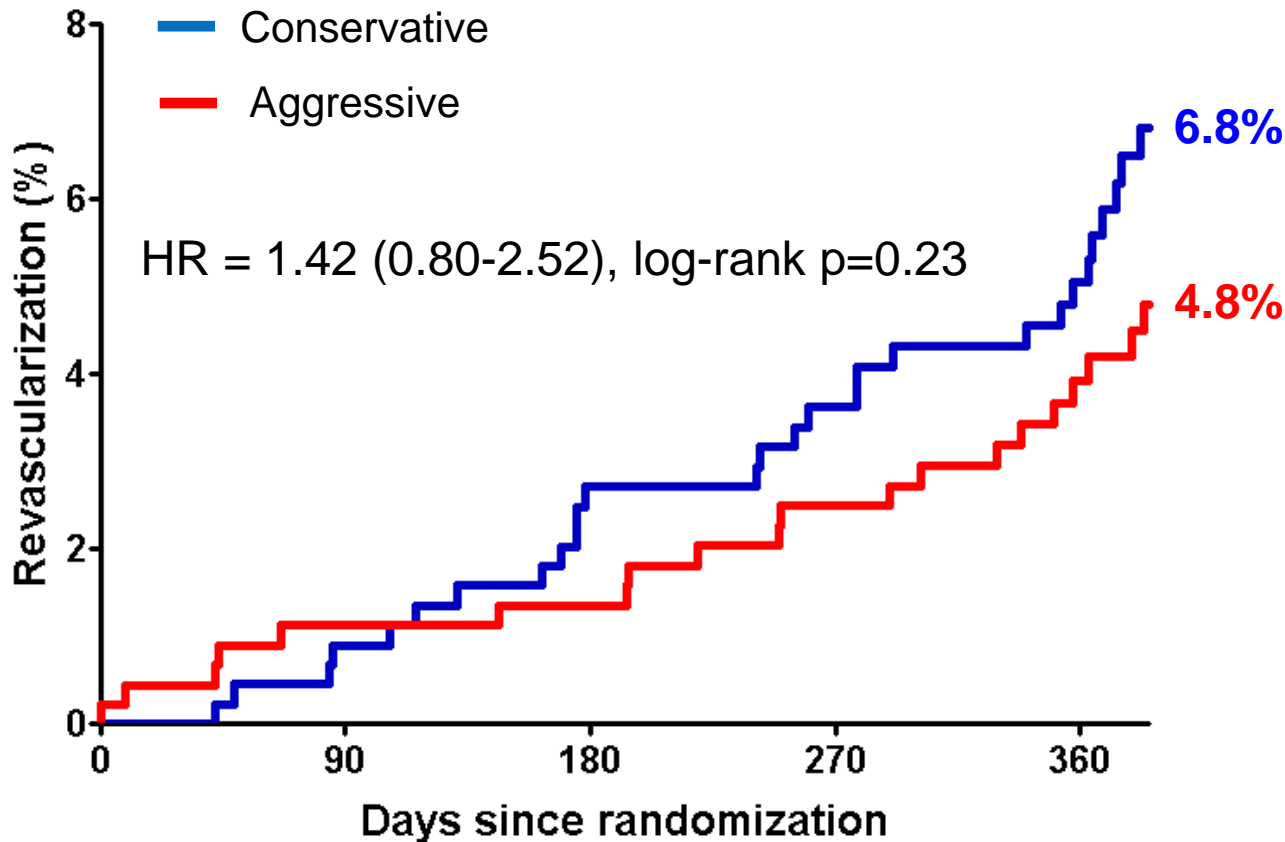
	0	90	180	270	360
Conservative	449	442	439	434	383
Aggressive	450	439	437	435	374

Cardiac death or MI


No. at Risk

	0	90	180	270	360
Conservative	449	442	439	434	383
Aggressive	450	439	437	435	374

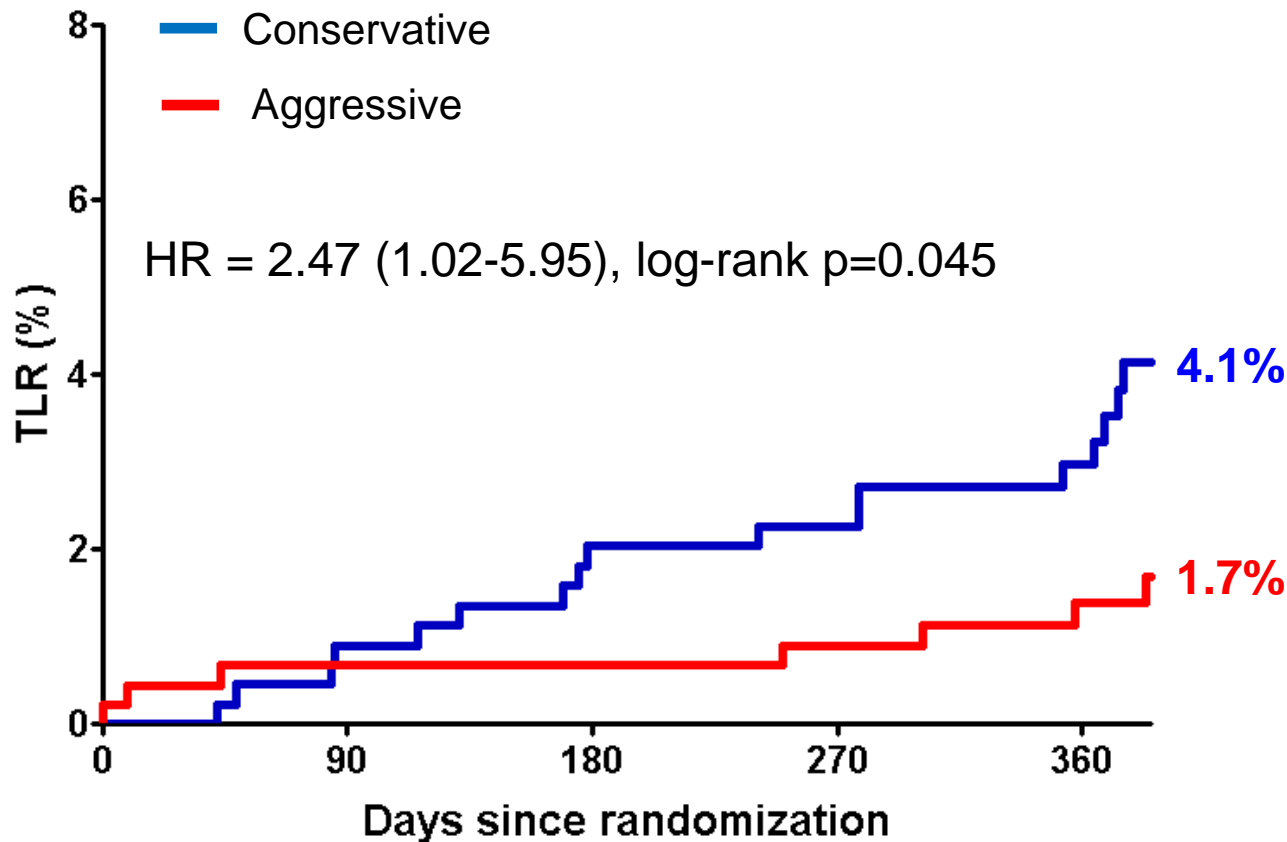
Any revascularization



No. at Risk

Conservative	449	439	429	420	369
Aggressive	450	436	434	427	362

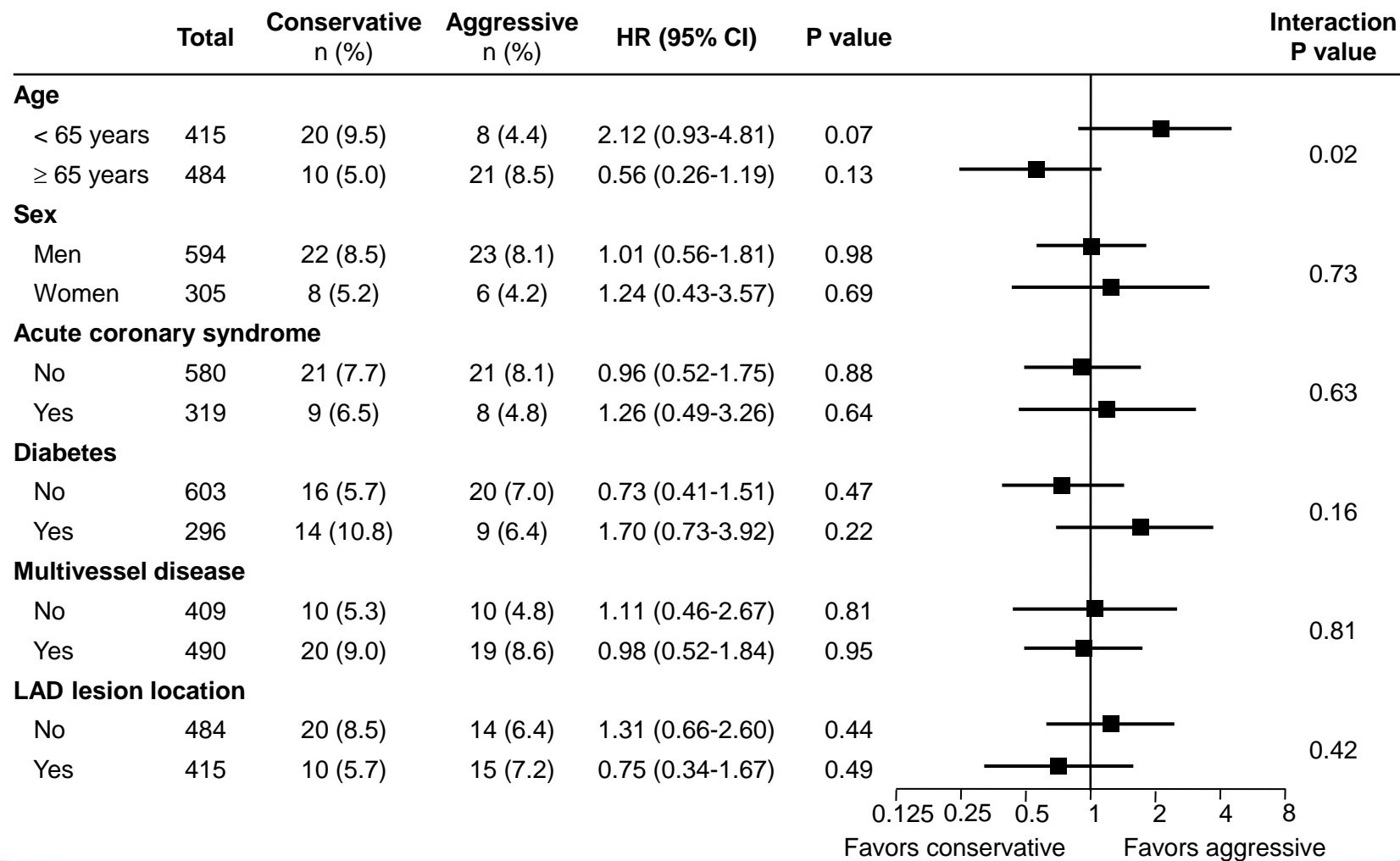
Revascularization of the target intermediate lesion



No. at Risk

Conservative	449	439	432	426	377
Aggressive	450	438	437	434	372

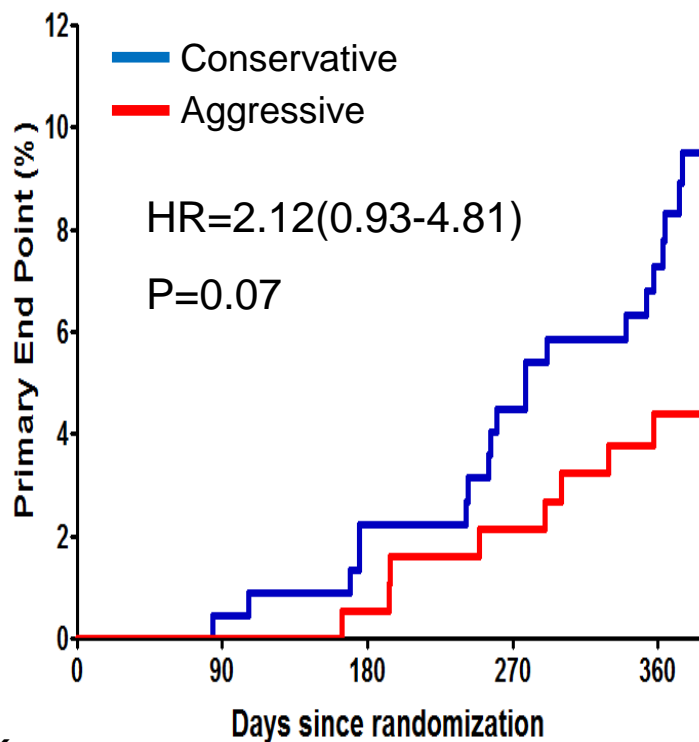
Subgroup Analysis



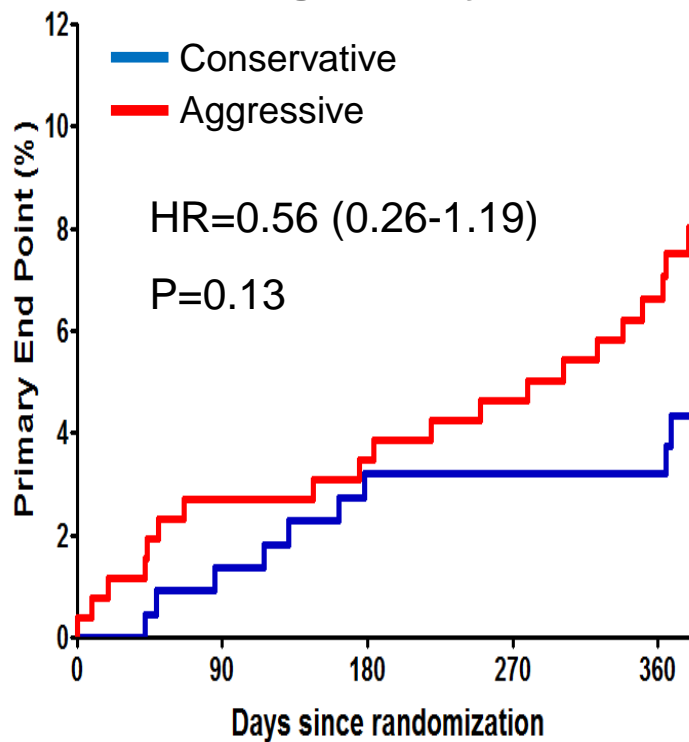
Subgroup-analysis: Age

Primary Endpoint

Age < 65 yr



Age ≥ 65 yr



No. at Risk

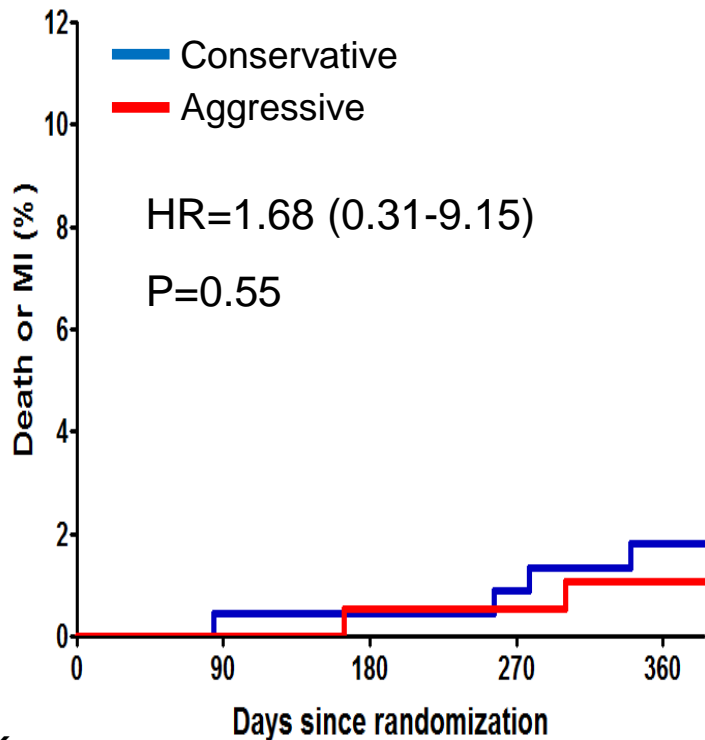
	0	90	180	270	360
Conservative	226	223	218	211	187
Aggressive	189	186	185	182	151

	0	90	180	270	360
Conservative	223	216	211	209	182
Aggressive	261	250	248	243	210

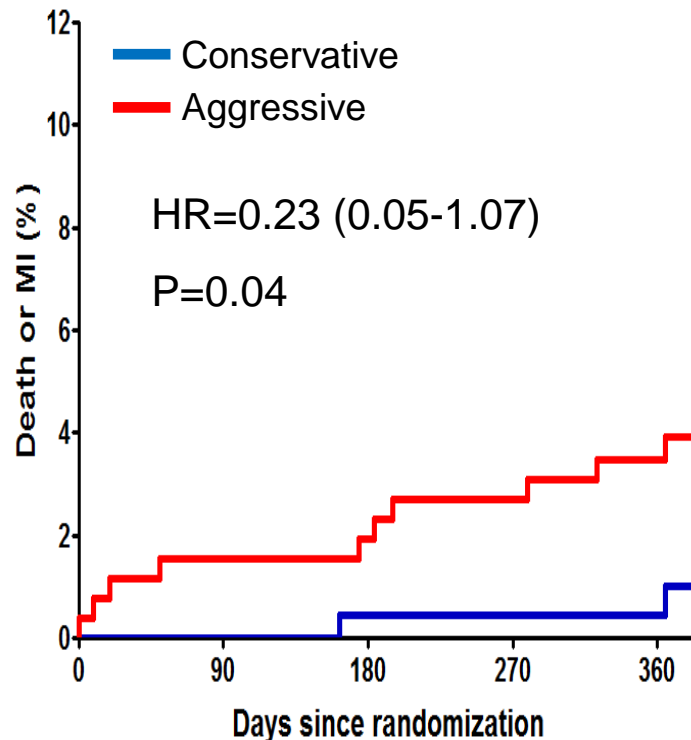
Subgroup-analysis: Age

Death or MI

Age < 65 yr



Age ≥ 65 yr



No. at Risk

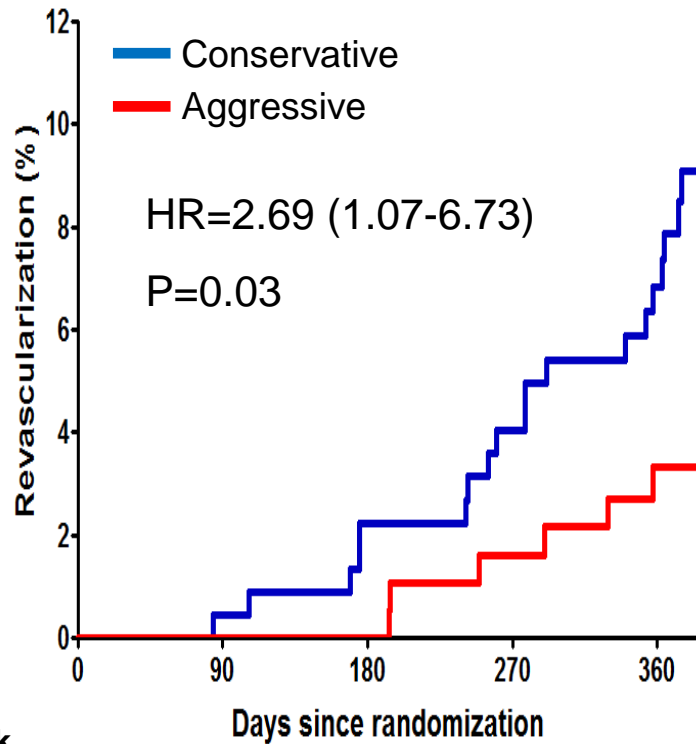
	0	90	180	270	360
Conservative	226	223	222	219	196
Aggressive	189	186	185	185	157

	0	90	180	270	360
Conservative	223	219	217	215	187
Aggressive	261	253	252	250	217

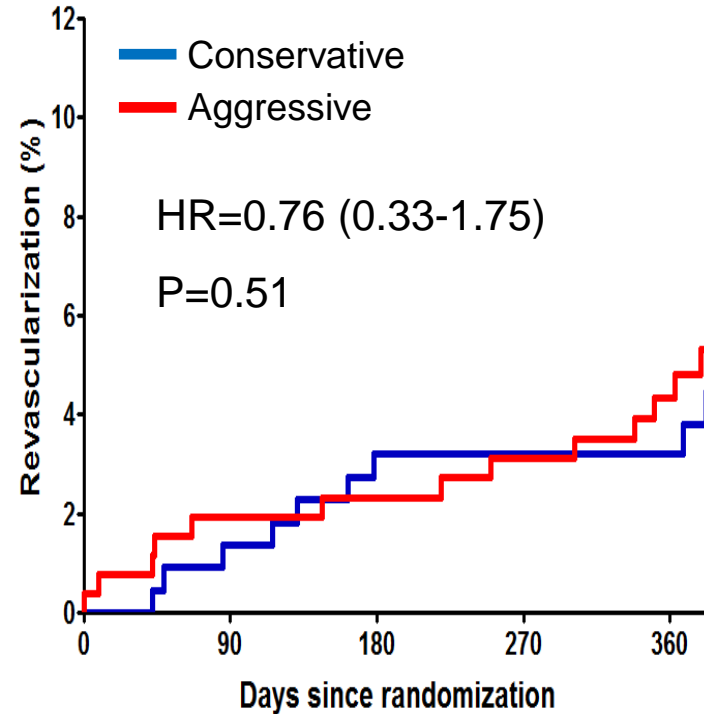
Subgroup-analysis: Age

Any revascularization

Age < 65 yr



Age ≥ 65 yr



No. at Risk

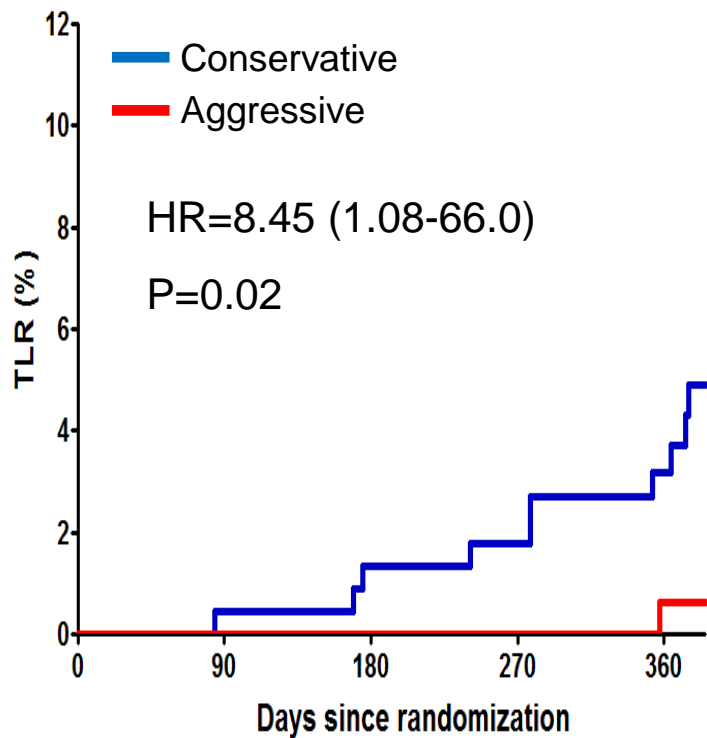
	0	90	180	270	360
Conservative	226	223	218	211	187
Aggressive	189	186	185	182	152

	0	90	180	270	360
Conservative	223	216	211	209	182
Aggressive	261	250	249	245	210

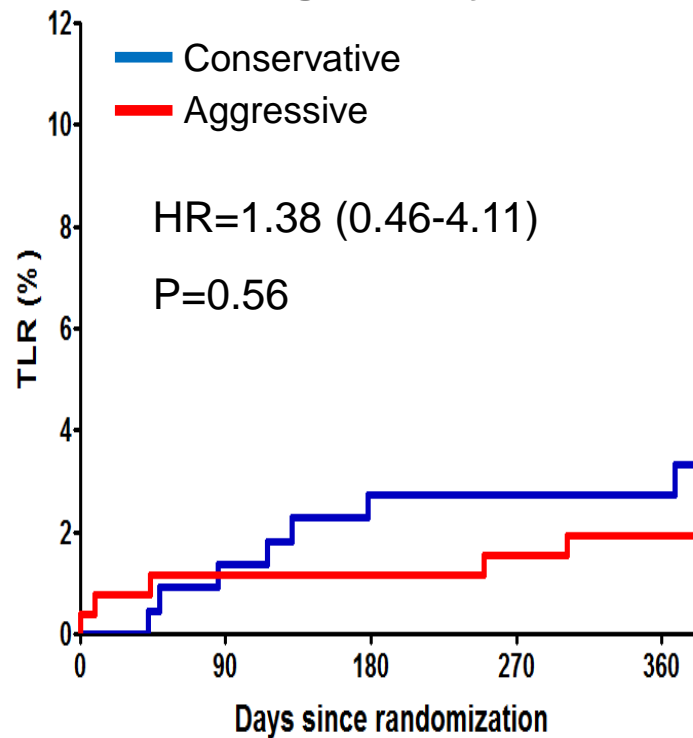
Subgroup-analysis: Age

Revascularization of target intermediate lesion

Age < 65 yr



Age ≥ 65 yr



No. at Risk

Conservative	226	223	220	216	194
Aggressive	189	186	185	185	157

Conservative	223	216	212	210	183
Aggressive	261	252	252	249	215

Study limitations and strengths

- Limitations
 - Wide non-inferiority margin
 - Underpowered to test hard endpoints
 - Short follow-up duration
 - No coronary physiology data (e.g. FFR)
- Strengths
 - Enrollment based on QCA measurement
 - The use of currently popular drug-eluting stent
 - Power of the study was more than 80% (84%)

Conclusions

- Conservative revascularization using criteria of diameter stenosis $> 70\%$ was found to be non-inferior to aggressive revascularization.
- The revascularization of angiographically intermediate lesion can be deferred safely.

Thank you for your attention



Clinical outcomes

	Conservative Group (n=449)	Aggressive Group (n=450)	HR (95% CI)*	p
All cause death, MI, or any revascularization (1° EP)	30 (7.3)	29 (6.8)	1.05 (0.63-1.74)	0.86
All cause death	2 (0.5)	9 (2.1)	0.22 (0.05-1.03)	0.06
Cardiac death	2 (0.5)	5 (1.1)	0.40 (0.08-2.07)	0.28
Myocardial infarction	4 (0.9)	4 (0.9)	1.00 (0.25-3.99)	0.99
Death or myocardial infarction	6 (1.4)	12 (2.7)	0.50 (0.19-1.33)	0.17
Any revascularization	28 (6.8)	20 (4.8)	1.42 (0.80-2.52)	0.23
Revascularization of target intermediate lesion	17 (4.1)	7 (1.7)	2.47 (1.02-5.95)	0.045
Stent thrombosis	1 (0.2)	2 (0.4)	0.50 (0.05-5.48)	0.57

Data are n (%). The percentages shown are Kaplan–Meier estimates from the intention-to-treat analysis.

*Hazard ratios (HR) are for the conservative group as compared with the aggressive group.