Intravascular Imaging–Guided or Angiography-Guided Complex PCI: RENOVATE-COMPLEX-PCI

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Disclosure

- Grant support
  - National Evidence-based Healthcare Collaborating Agency, Ministry of Health & Welfare, Republic of Korea
  - Abbott Vascular, Biosensors, Biotronik, Boston Scientific, Daiichi Sankyo, Donga-ST, Hanmi Pharmaceutical, and Medtronic

- Consulting Fees/Honoraria
  - Abbott Vascular, Amgen, Astra Zeneca, Biosensors, Biotronik, Boston Scientific, Daiichi Sankyo, MSD Korea, Novartis, Pfizer, and Sanofi-Aventis

Background

- Previous trials (CTO-IVUS, AVIO, HOME-DES-IVUS, IVUS-XPL, and ULTIMATE) have shown lower rates of major adverse clinical events after intravascular ultrasound (IVUS)-guided percutaneous coronary intervention (PCI) than after angiography-guided PCI but have not been considered definitive owing to limited sample size, short follow-up duration, or the inclusion of highly selected coronary-lesion subsets.
- Our group has already reported the long-term benefit of the use of IVUS in patients undergoing complex PCI in an observational study.[1]

However, a randomized trial is needed to confirm the benefit of intravascular imaging-guided PCI in patients with complex coronary artery lesions.

1. Choi KH, Song YB, …, Hahn JY. JACC Cardiovasc Interv. 2019

Study Objective

- To investigate whether intravascular imaging-guided PCI using IVUS or optical coherence tomography (OCT) would improve clinical outcomes compared with angiography-guided PCI in patients with complex coronary artery lesions.

Working Hypothesis

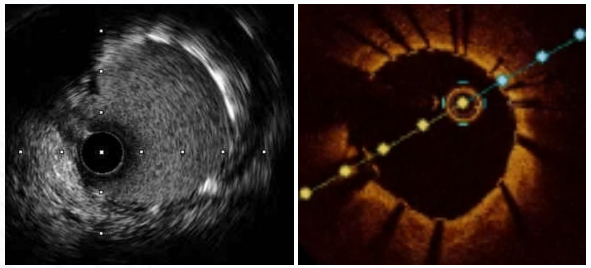
Intravascular imaging-guided PCI would reduce target vessel failure (a composite of cardiac death, target vessel-related myocardial infarction, and target vessel revascularization), compared with angiography-guided PCI in treatment of patients with complex coronary artery lesions.

Study Design

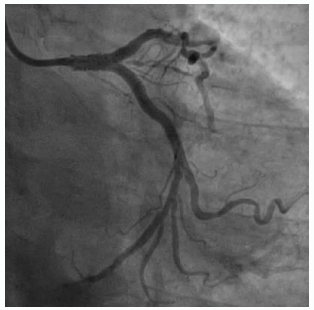
RENOVATE-COMPLEX-PCI (NCT03381872)

An investigator-initiated, prospective, multicenter, randomized, open-label trial at 20 sites in Korea

Patients with Complex Coronary Artery Lesions Undergoing PCI



Randomization (2:1) for Treatment Strategy of Target Lesions



Imaging-Guided Strategy

Angiography-Guided Strategy

Primary end point: target vessel failure
All patients were followed until 1 year after last patient enrollment.

Inclusion and Exclusion Criteria

INCLUSION

1. Patients (≥ 19 years) with coronary artery disease requiring PCI
2. Patients with a **complex coronary artery lesion** defined as:
   - True bifurcation lesion (Medina 1,1,1/1,0,1/0,1,1) with side branch ≥2.5mm
   - Chronic total occlusion (≥3 months) as target lesion
   - Unprotected LM disease PCI (LM ostium, body, distal LM bifurcation including non-true bifurcation)
   - Long coronary lesions (implanted stent ≥38 mm in length)
   - Multi-vessel PCI (≥2 vessels treated at one PCI session)
   - Multiple stents needed (≥3 more stent per patient)
   - In-stent restenosis lesion as target lesion
   - Severely calcified lesion (encircling calcium in angiography)
   - Ostial coronary lesion (LAD, LCX, RCA)

KEY EXCLUSION

1. Target lesions not amenable to PCI by operators' decision
2. Cardiogenic shock (Killip class IV) at presentation
3. Intolerance to Aspirin, Clopidogrel, Prasugrel, Ticagrelor, Heparin, or Everolimus
4. Known true anaphylaxis to contrast medium (not allergic reaction but anaphylactic shock)
5. Pregnancy or breast feeding
6. Non-cardiac co-morbid conditions are present with life expectancy <1 year or that may result in protocol non-compliance (per site investigator's medical judgment)
7. Unwillingness or inability to comply with the procedures described in this protocol.

Randomization and Data Collection

- **Randomization**
  - Via a web-based randomization sequence (S-Soft), in permutated blocks, with block sized of 6
  - Stratified by acute coronary syndrome and by participating centers

- **Data collection and management**
  - Data collected by a web-based electronic case report form.
  - Imaging data and angiograms were analyzed by core laboratories.
  - An independent Data and Safety Monitoring Boards monitored trial.
  - All clinical events were adjudicated by an independent Clinical Events Adjudication Committee.

Study Organization

- ***Principal Investigator***
  Joo-Yong Hahn

- ***Executive Committee***
  Joo-Yong Hahn
  Young Bin Song
  Jeong Hoon Yang
  Joo Myung Lee

- ***Clinical Event Adjudication Committee***
  Hyun-Jong Lee (Chair)
  Dong Ryeol Ryu
  Kyu Tae Park

- ***Data Safety and Monitoring Board***
  Kiyuk Change (Chair)
  Seonwoo Kim (statistician)
  Dong-Yeon Kim

- ***Data Coordination and Management***
  Suyoun Shin
  Jinshil Kim
  Jaeyoung Park
  Seunghyun Lee
  Euna Kim
  Hyein Kang
  Su Jin Hwang
  Yeonhui Lee

- ***Angiography Core Laboratory***
  Hyein Kang
  Hyun Sung Joh
  Ki Hong Choi

- ***Intravascular Imaging Core Laboratory***
  Joo Myung Lee
  Hyein Kang
  Se Young Im

PCI and Intravascular Imaging

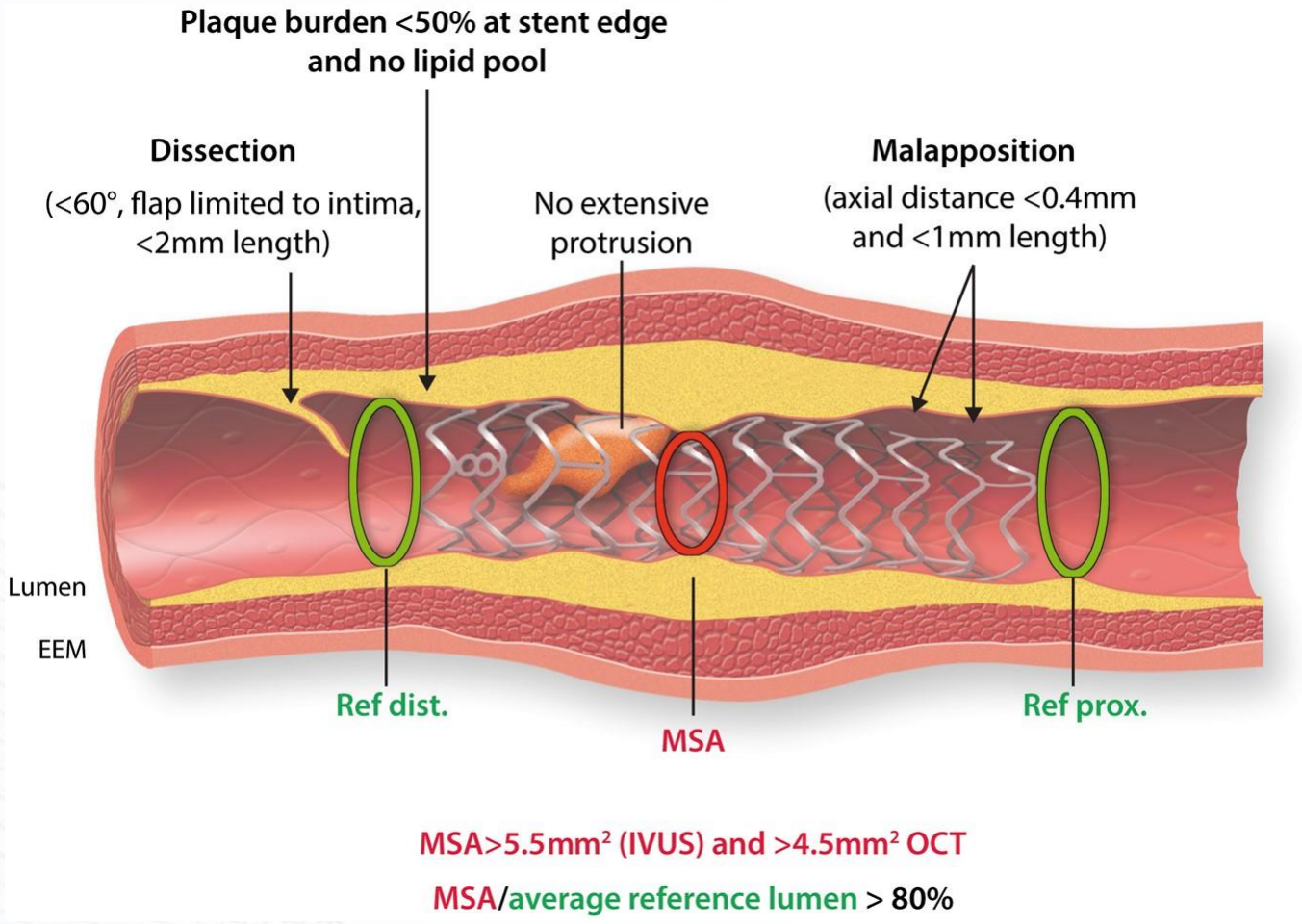
- PCI and Intravascular image acquisition were performed with the use of standard techniques.
  - Intracoronary NG
  - Automatic pullback

- For patients who had been assigned to the intravascular imaging group, the choice of IVUS or OCT was made at the operators' discretion.

- Intravascular imaging could be used at any time during the PCI procedure but was mandated after stent implantation to determine whether the stented segment was optimized.

Criteria of PCI Optimization by Intravascular Imaging

An expert consensus document of the European Association of PCI[1]



- Standardized protocols for selection of reference size, stent size, and length
- In left main lesions, MSA >7 mm^2 for a distal left main coronary artery stenosis and >8 mm^2 for a proximal left main coronary artery stenosis
- If stent optimization did not occur, additional dilation of the stent or additional stent implantation was recommended, and repeat evaluation on intravascular imaging was mandated.

1. Raber L, Mintz GS, Koskinas KC, et al. Eur Heart J 2018;39:3281-300.

Study End Points

Primary End Point

- **Target vessel failure**
  - A composite of cardiac death, target vessel-related MI, or clinically-driven target vessel revascularization.

Secondary End Points

- Target vessel failure without procedure-related MI
- Cardiac death or target vessel-related MI
- Target vessel-related MI with or without procedure-related MI
- Non-target vessel-related MI
- Any MI with or without procedure-related MI
- Target lesion revascularization
- Target vessel revascularization
- Any revascularization (clinically-driven)
- Definite stent thrombosis
- Total amount of contrast
- Incidence of contrast-induced nephropathy
- Total procedural time
- Total medical cost (not reported in this publication)

Definition of Clinical Events

- Spontaneous MI according to 3rd Universal Definition[1]
- Other clinical events according to ARC-2 criteria[3]
- Procedure-related MI according to SCAI Definition[2]

1. Garcia-Garcia HM, McFadden EP, Farb A, et al. Circulation 2018;137:2635-50.
2. Thygesen K, Alpert JS, Jaffe AS, et al. Circulation 2012;126:2020-35.
3. Moussa ID, Klein LW, Shah B, et al. J Am Coll Cardiol 2013;62:1563-70.

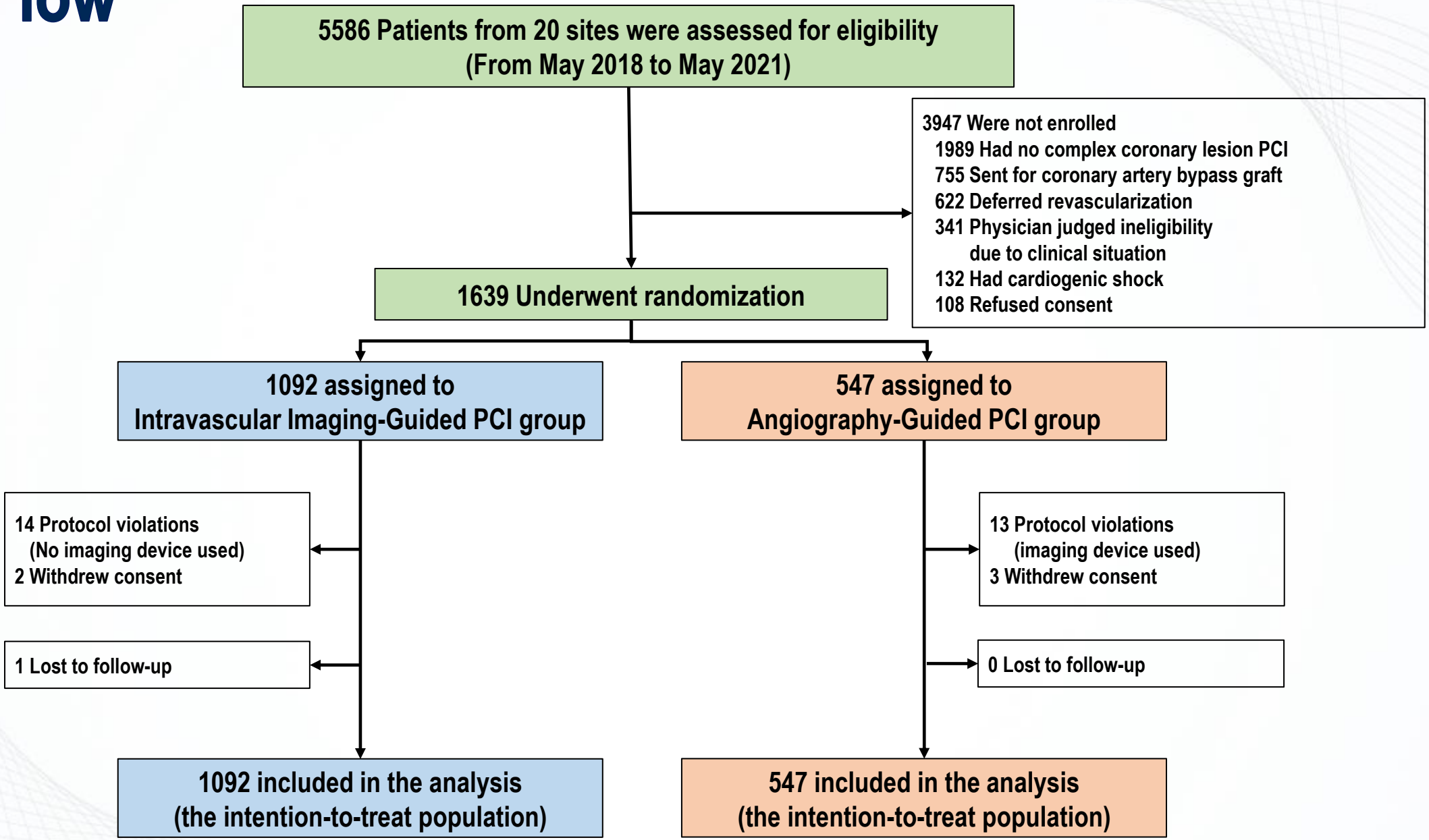
Sample Size Calculation and Statistical Analyses

- Expected annual event rate of the primary end point
  - 6.0% in the angiography-guided PCI group
  - 3.6% in the intravascular imaging-guided PCI group (40% relative risk reduction)
- Accrual time – 3 years
- Additional follow-up time – 1 year after last patient enrollment
- 2:1 randomization
- A total of 1620 patients would provide a statistical power of 90% with significance level of 0.05 (2-sided).

- The main analysis were performed according to the intention-to-treat principle and adjusted for the potential competing risk of non-cardiac death.

1. Witzenbichler B, Maehara A, Weisz G, et al. Circulation 2014;129:463-70.
2. Chieffo A, Latib A, Caussin C, et al. Am Heart J 2013;165:65-72.
3. Jakabcin J, Spacek R, Bystron M, et al. Catheter Cardiovasc Interv 2010;75:578-83.
4. Kim JS, Kang TS, Mintz GS, et al. JACC Cardiovasc Interv 2013;6:369-76.
5. Kim BK, Shin DH, Hong MK, et al. Circ Cardiovasc Interv 2015;8:e002592.
6. Hong SJ, Kim BK, Shin DH, et al. JAMA 2015;314:2155-63.

Study Flow


5586 Patients from 20 sites were assessed for eligibility
(From May 2018 to May 2021)
3947 Were not enrolled
1989 Had no complex coronary lesion PCI
755 Sent for coronary artery bypass graft
622 Deferred revascularization
341 Physician judged ineligibility due to clinical situation
132 Had cardiogenic shock
108 Refused consent
1639 Underwent randomization
1092 assigned to Intravascular Imaging-Guided PCI group
547 assigned to Angiography-Guided PCI group
14 Protocol violations
(No imaging device used)
2 Withdrew consent
1 Lost to follow-up
13 Protocol violations
(imaging device used)
3 Withdrew consent
0 Lost to follow-up
1092 included in the analysis
(the intention-to-treat population)
547 included in the analysis
(the intention-to-treat population)

Baseline Clinical Characteristics

Characteristics	Total (N=1639)	Imaging-guided PCI (N=1092)	Angio-guided PCI (N=547)
Age — yr	65.6±10.2	65.3±10.3	66.0±10.0
Male — n (%)	1300 (79.3)	869 (79.6)	431 (78.8)
Initial presentation — no. (%)			
Stable ischemic heart disease	807 (49.2)	532 (48.7)	275 (50.3)
Acute coronary syndrome	832 (50.8)	560 (51.3)	272 (49.7)
Unstable angina	534 (32.6)	361 (33.1)	173 (31.6)
Acute myocardial infarction	298 (18.2)	199 (18.2)	99 (18.1)
Non-ST-segment elevation myocardial infarction	258 (15.7)	171 (15.7)	87 (15.9)
ST-segment elevation myocardial infarction	40 (2.4)	28 (2.6)	12 (2.2)
Medical history — no. (%)			
Hypertension	1005 (61.3)	682 (62.5)	323 (59.0)
Diabetes mellitus	617 (37.6)	394 (36.1)	223 (40.8)
Dyslipidemia	840 (51.3)	560 (51.3)	280 (51.2)
Current smoking	307 (18.7)	212 (19.4)	95 (17.4)
Chronic renal insufficiency	296 (18.1)	203 (18.6)	93 (17.0)
Previous PCI	395 (24.1)	268 (24.5)	127 (23.2)
Previous myocardial infarction	117 (7.1)	75 (6.9)	42 (7.7)
LV ejection fraction —(%)	58.7±11.6	58.4±11.9	59.3±11.0

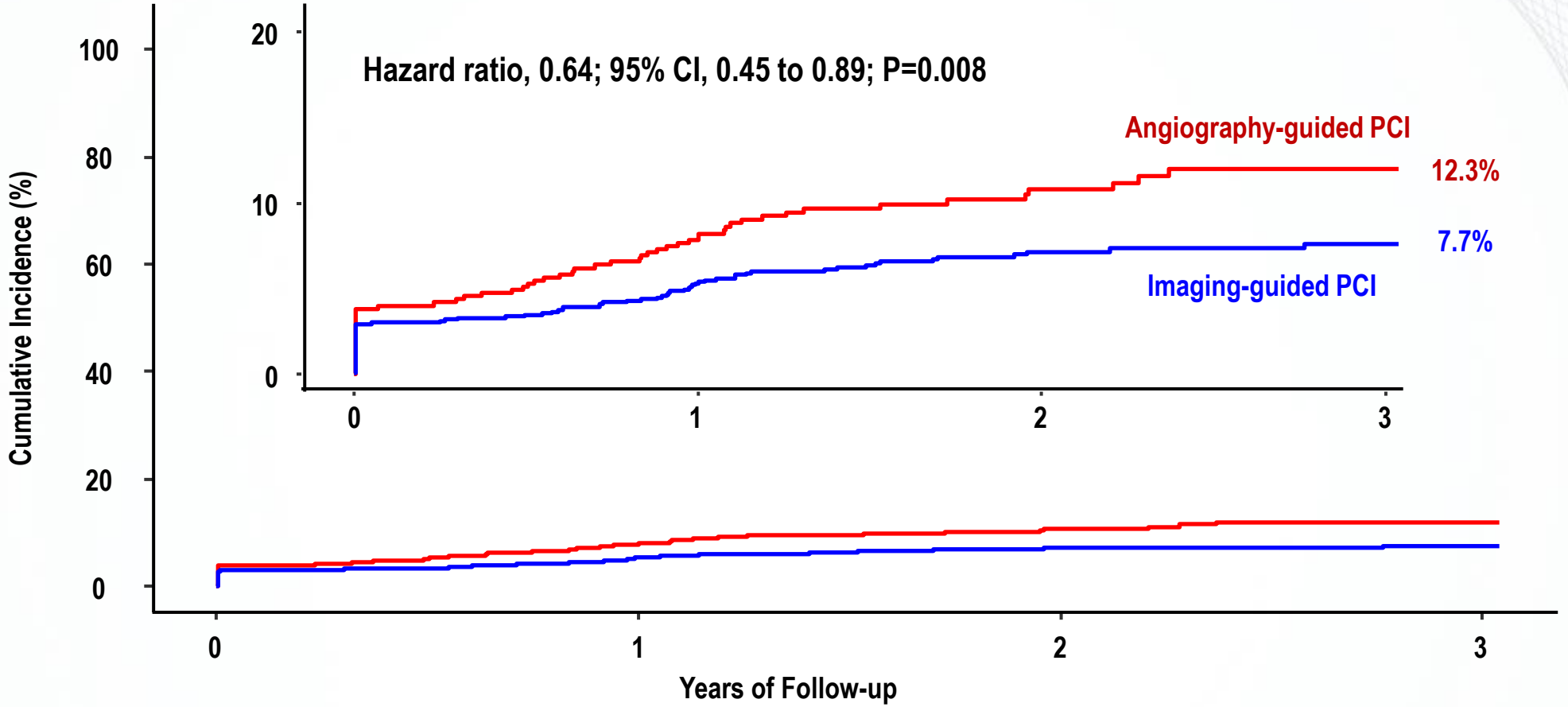
Baseline Angiographic and Procedural Characteristics

Characteristics	Total (N=1639)	Imaging-guided PCI (N=1092)	Angio-guided PCI (N=547)
Complex coronary lesions — no. (%)			
True bifurcation lesion with side branch ≥2.5mm	359 (21.9)	233 (21.3)	126 (23.0)
Chronic total occlusion (≥3 months)	319 (19.5)	220 (20.1)	99 (18.1)
Unprotected left main coronary artery disease	192 (11.7)	138 (12.6)	54 (9.9)
Long coronary lesion (implanted stent ≥38 mm in length)	898 (54.8)	617 (56.5)	281 (51.4)
Multivessel PCI (≥2 vessels treated at one PCI session)	622 (37.9)	409 (37.5)	213 (38.9)
Multiple stents (≥3 more stent per patient)	305 (18.6)	208 (19.0)	97 (17.7)
In-stent restenosis	236 (14.4)	158 (14.5)	78 (14.3)
Severely calcified (encircling calcium in angiography)	231 (14.1)	157 (14.4)	74 (13.5)
Ostial coronary lesion (LAD, LCX, RCA)	251 (15.3)	182 (16.7)	69 (12.6)
Number of vessels with disease — no. (%)			
1-vessel disease	526 (32.1)	342 (31.3)	184 (33.6)
2-vessel disease	621 (37.9)	420 (38.5)	201 (36.7)
3-vessel disease	492 (30.0)	330 (30.2)	162 (29.6)
Procedural characteristics			
Radial artery access — no. (%)	1253 (76.4%)	827 (75.7%)	426 (77.9%)
Intravascular imaging devices used — no./total no. (%) †	1091/1639 (66.6)	1078/1092 (98.7)	13/547 (2.4)
Intravascular ultrasound	813/1091 (74.5)	800/1078 (74.2)	13/13 (100.0)
Optical coherence tomography	278/1091 (25.5)	278/1078 (25.8)	0/13 (0.0)
Volume of contrast media used — ml	207.3±116.5	214.2±118.5	193.7±111.3
Procedural time — min	65.0 (47.0-89.0)	70.0 (51.0-95.0)	53.5 (40.0-75.0)
Procedural success — no. (%)	1613 (98.4)	1073 (98.3)	540 (98.7)

Lesion-level Analysis

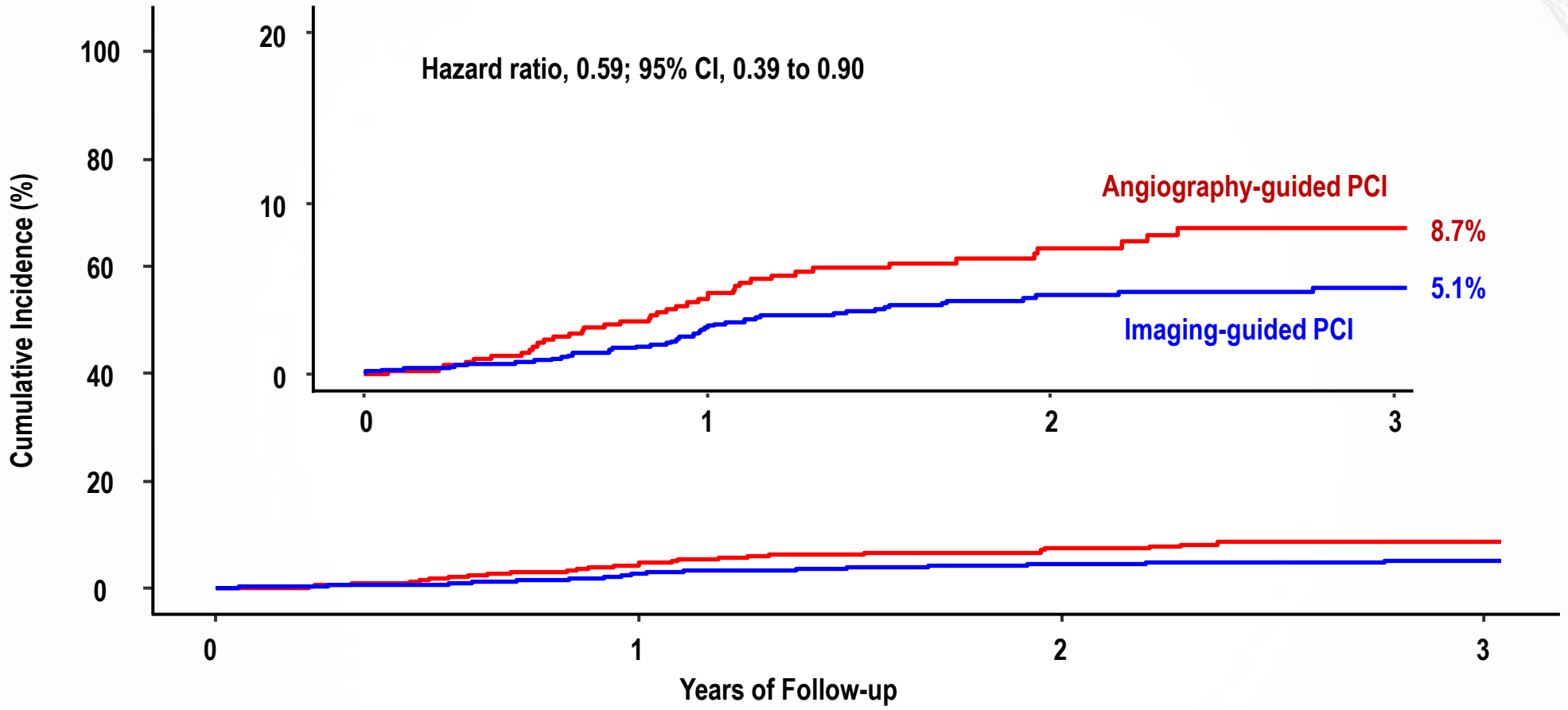
Characteristic	Total (N=2438)	Imaging-guided PCI (N=1623)	Angiography-guided PCI (N=815)
Quantitative coronary angiography			
Pre-PCI QCA			
Proximal reference vessel diameter — mm	3.2±0.5	3.2±0.5	3.1±0.5
Distal reference vessel diameter — mm	2.7±0.5	2.7±0.5	2.7±0.4
Minimum lumen diameter — mm	0.44±0.37	0.44±0.37	0.44±0.36
Diameter stenosis — %	85.4±11.6	85.4±11.5	85.2±11.7
Lesion length — mm	27.9±15.6	28.4±15.9	26.8±14.8
Post-PCI QCA			
Minimum lumen diameter — mm	2.8±0.5	2.8±0.5	2.7±0.5
Diameter stenosis — %	9.8±8.8	9.8±8.9	10.0±8.6
Post-PCI residual stenosis<10% — no. (%)	1638/2346 (69.8)	1098/1560 (70.4)	540/786 (68.7)
Profile of intravascular imaging use — no./total no. (%)			
Pre-PCI evaluation only	18/1569 (1.1)	16/1549 (1.0)	2/20 (10.0)
Post-PCI evaluation only	371/1569 (23.6)	366/1549 (23.6)	5/20 (25.0)
Both pre- and post-PCI evaluation	1180/1569 (75.2)	1167/1549 (75.3)	13/20 (65.0)
Adjunctive non-compliant balloon used — no. (%)	1351 (55.4)	980 (60.4)	371 (45.5)
Size of adjunctive balloon — mm	3.5±0.6	3.5±0.6	3.5±0.5
Maximum inflation pressure — atm	18.9±4.6	18.7±4.6	19.2±4.6

Primary End Point



Number at risk				
Angiography-guided PCI	547	496	280	120
Imaging-guided PCI	1092	1023	591	255

Target Vessel Failure excluding Procedural MI



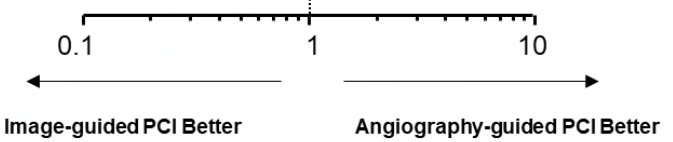
Number at risk				
Angiography-guided PCI	547	516	284	121
Imaging-guided PCI	1092	1051	596	256

Primary and Secondary End Points

End Point	Total (N=1639)	Imaging-guided PCI (N=1092)	Angiography-guided PCI (N=547)	Hazard Ratio (95% CI)*	P Value
Primary end point — no. (%)					
Target vessel failure	**136 (9.2)**	**76 (7.7)**	**60 (12.3)**	**0.64 (0.45-0.89)**	**0.008**
Secondary end points — no. (%)					
Target vessel failure without procedure-related MI	88 (6.3)	48 (5.1)	40 (8.7)	0.59 (0.39-0.90)	
Cardiac death or target-vessel related MI	96 (6.4)	53 (5.3)	43 (8.5)	0.63 (0.42-0.93)	
All-cause death	70 (5.6)	42 (5.3)	28 (6.4)	0.71 (0.44–1.15)	
Cardiac death	33 (2.4)	16 (1.7)	17 (3.8)	0.47 (0.24-0.93)	
Myocardial infarction	75 (5.0)	43 (4.4)	32 (6.2)	0.78 (0.48-1.25)	
Target-vessel related MI	68 (4.3)	38 (3.7)	30 (5.6)	0.74 (0.45-1.22)	
Spontaneous MI	17 (1.2)	8 (0.9)	9 (1.8)	0.66 (0.23-1.90)	
Procedure-related MI	52 (3.2)	30 (2.7)	22 (4.0)	0.77 (0.43-1.35)	
Non-target vessel related MI	8 (0.8)	5 (0.8)	3 (0.8)	1.24 (0.24-6.40)	
Repeat revascularization	87 (6.6)	55 (6.3)	32 (7.1)	0.95 (0.60-1.48)	
Target vessel revascularization	57 (4.1)	32 (3.4)	25 (5.5)	0.69 (0.40-1.18)	
Target lesion revascularization	44 (3.2)	24 (2.6)	20 (4.4)	0.66 (0.36-1.22)	
Definite stent thrombosis	5 (0.3)	1 (0.1)	4 (0.7)	0.25 (0.02-2.75)	
Contrast induced nephropathy†	40 (2.4)	26 (2.4)	14 (2.6)	0.99 (0.51-1.92)	

Prespecified Subgroup Analysis

Subgroup	Imaging-guided PCI No. of events / total no. of patients (cumulative incidence, %)	Angiography-guided PCI No. of events / total no. of patients (cumulative incidence, %)	Hazard ratio (95% CI)
Overall	76/1092 (7.7%)	60/547 (12.3%)	0.64 (0.45-0.89)
Type of imaging devices			
IVUS	59/800 (8.0%)	60/547 (12.3%)	0.66 (0.46-0.95)
OCT	15/278 (5.8%)	60/547 (12.3%)	0.47 (0.27-0.83)
Initial Presentation			
Stable ischemic heart disease	25/532 (5.0%)	27/275 (10.4%)	0.46 (0.27-0.80)
Acute coronary syndrome	51/560 (10.4%)	33/272 (14.6%)	0.74 (0.48-1.15)
Age			
<65 years	36/517 (7.8%)	23/238 (10.6%)	0.72 (0.42-1.21)
≥65 years	40/575 (7.4%)	37/309 (13.6%)	0.57 (0.36-0.88)
Sex			
Male	66/869 (8.3%)	46/431 (11.7%)	0.70 (0.48-1.02)
Female	10/223 (5.2%)	14/116 (14.5%)	0.35 (0.16-0.80)
Diabetes mellitus			
Presence	45/394 (12.9%)	26/223 (12.3%)	0.97 (0.60-1.57)
Absence	31/698 (4.7%)	34/324 (12.2%)	0.41 (0.25-0.67)
Chronic kidney disease			
Presence	22/203 (13.3%)	19/93 (23.3%)	0.51 (0.27-0.93)
Absence	54/889 (6.4%)	41/454 (9.9%)	0.66 (0.44-0.99)
Left ventricular ejection fraction			
<50%	22/210 (12.0%)	12/84 (15.0%)	0.72 (0.35-1.45)
≥50%	54/882 (6.7%)	48/463 (11.8%)	0.58 (0.39-0.85)



Limitations

- The trial was unblinded, and it was not possible for the operators to be unaware of the patient's assigned trial group. However, we minimized the risk of bias by using an end-point analysis with precisely defined criteria, by having angiographic and imaging analyses performed at the core laboratories, and by having clinical events adjudicated by a committee.
- Intravascular imaging-defined stent optimization was achieved in only 45.4% of patients. One possible explanation may be that we focused our trial only on complex coronary artery lesions.
- Given patients in the angiography-guided PCI group did not undergo intravascular imaging, we could assess stent optimization in this group only by means of QCA.

Conclusion

- ***Among patients with complex coronary artery lesions,*** **intravascular imaging-guided PCI reduced a composite of cardiac death, target vessel-related myocardial infarction, or clinically driven target vessel revascularization** compared with **angiography-guided PCI.**
- The **RENOVATE-COMPLEX-PCI** supports the intravascular imaging-guided PCI in patients with complex coronary lesions.