One-Month Dual Antiplatelet Therapy Followed by Clopidogrel Monotherapy versus Standard 12-Month Dual Antiplatelet Therapy with Clopidogrel After Drug-Eluting Stent Implantation:

Hirotoshi Watanabe

Takenori Domei, Takeshi Morimoto, Hiroki Shiomi, Masahiro Natsuaki, Toshiaki Toyota, Kensuke Takagi, Yoshiki Hata, Satoru Suwa, Mamoru Nanasato, Masanobu Ohya, Masahiro Yagi, Takafumi Yokomatsu, Mitsuru Abe, Kenji Ando, Kazushige Kadota, Ken Kozuma, Yoshihiro Morino, Yuji Ikari, Kengo Tanabe, Koichi Nakao, Kazuya Kawai, Yoshihisa Nakagawa, and Takeshi Kimura,
on behalf of STOPDAPT-2 investigators

STOPDAPT-2

Background

- Mandatory 1-month DAPT had been the standard care after BMS implantation.
- DAPT duration was prolonged after introduction of DES without firm scientific evidence.
- New generation DES has substantially reduced stent thrombosis.
- Prolonged DAPT is inevitably associated with increase in bleeding.
- Bleeding is associated with subsequent mortality risk at least comparable to that of MI.

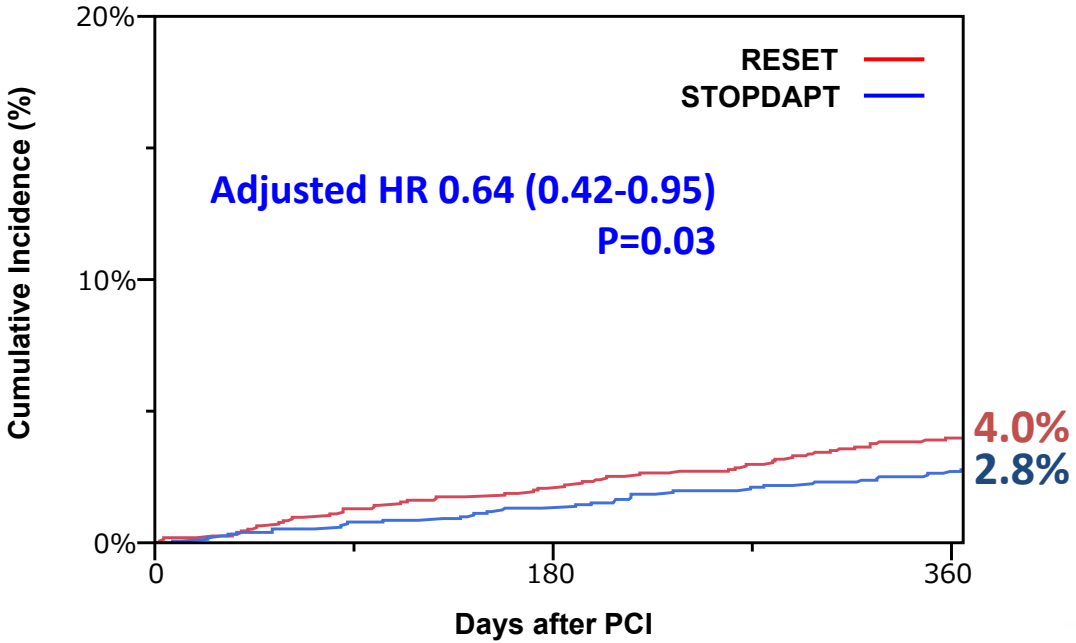
- Therefore, very short mandatory DAPT duration after DES might be an attractive option, if not associated with increase in ischemic events disproportionate to the reduction in bleeding events.

STOPDAPT

Prospective multicenter open-label single arm trial evaluating 3-month DAPT after CoCr-EES implantation

Primary Endpoint

Cardiovascular death, MI, Stroke, Definite ST, and Bleeding



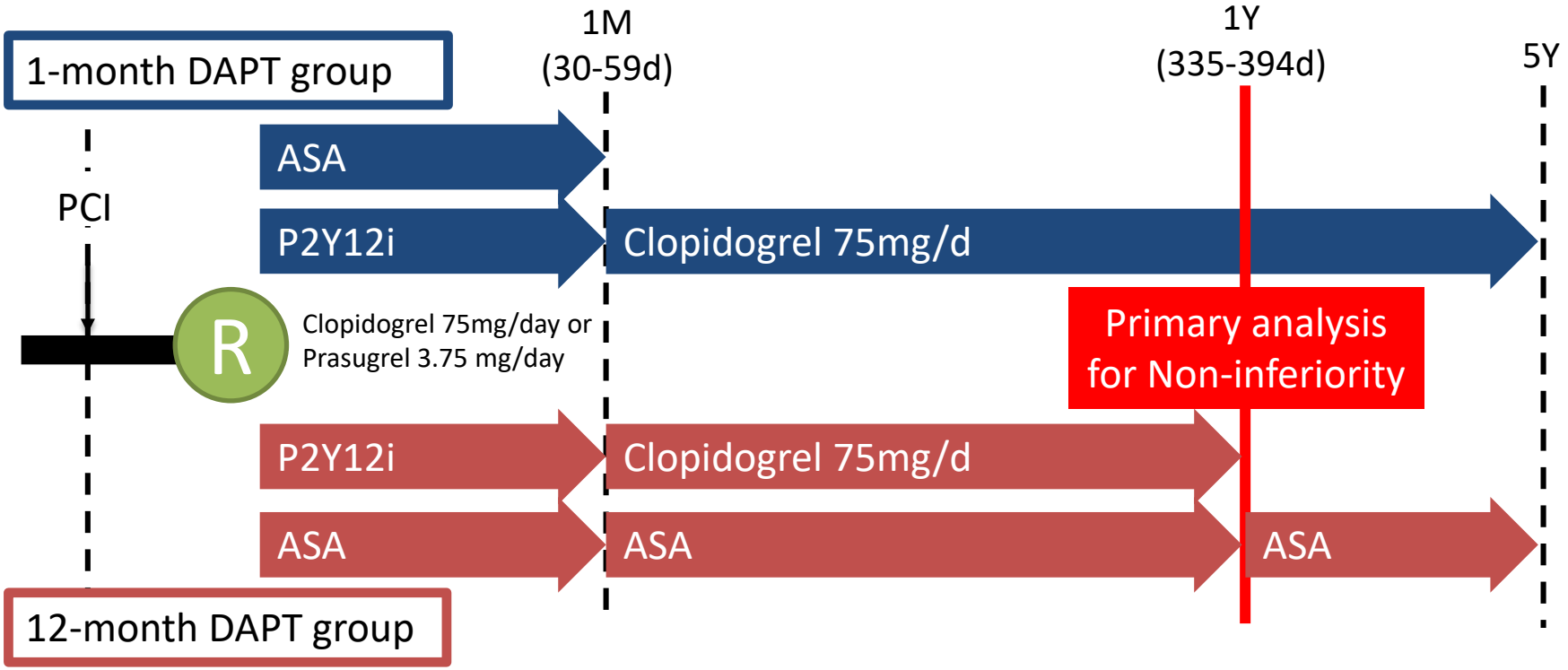
Cardiovasc Interv Ther 2016; 31: 196–209.

Objective

The objective of the STOPDAPT-2 trial is to explore the safety and efficacy of the experimental regimen of 1-month DAPT followed by clopidogrel monotherapy as compared with the standard 12-month DAPT with aspirin and clopidogrel after implantation of cobalt-chromium everolimus-eluting stents (CoCr-EES).

STOPDAPT-2:

Prospective multicenter open-label randomized trial comparing 1-month versus 12-month DAPT after CoCr-EES implantation with limited exclusion criteria.



Study Organization

Steering Committee

Takeshi Kimura (PI)
Kazushige Kadota
Ken Kozuma
Yoshihiro Morino
Keiichi Igarashi-Hanaoka
Yuji Ikari
Kengo Tanabe
Kenji Ando
Koichi Nakao
Kazuya Kawai
Mitsuru Abe

Trial Statistician

Takeshi Morimoto

Clinical Event Committee

Yoshihisa Nakagawa
Yutaka Furukawa
Masahiro Natsuaki
Hiroki Shiomi
Toshiaki Toyota

Safety Evaluation Committee

Shunichi Miyazaki
Ryuji Nohara

Coordinating Center

Research Institute for Production Development, Kyoto, Japan
Saori Tezuka
Yumika Fujino

Angiography Core Laboratory

Cardio Core Japan, Tokyo, Japan

Study administrative staff

Masahiro Natsuaki
Hirotoshi Watanabe
Toshiaki Toyota
Toshikazu Jinnai

Funded by

Abbott Vascular Japan, Co., Ltd.

90 Participating Centers

Teine Keijinkai Hospital
Hokko Memorial Hospital
Hirosaki University Hospital
Iwate Medical University Hospital
Sendai Kousei Hospital
Sendai Cardiovascular Center
Tohoku Medical and Pharmaceutical University Hospital
Nakadori General Hospital
Nihonkai General Hospital
Hoshi General Hospital
Jichi Medical University Hospital
Mashiko Hospital
Mitsui Memorial Hospital
Juntendo University Hospital
The Fraternity Memorial Hospital
Edogawa Hospital
Showa University Koto Toyosu Hospital
Tokyo Women's Medical University Hospital
Tokyo General Hospital
Juntendo University Nerima Hospital
Kawakita General Hospital
Sakakibara Heart Institute
Tokyo Metropolitan Tama Medical Center
Minamino Cardiovascular Hospital
Higashiyamato Hospital
St.Marianna University School of Medicine Hospital
Yokohama Rosai Hospital
Showa University Fujigaoka Hospital
Saiseikai Yokohamashi Tobu Hospital
Yokohama City University Medical Center

Kitasato University Hospital
Hiratsuka Kyosai Hospital
Tokai University Hospital
Kimitsu Chuo Hospital
Kanazawa Cardiovascular Hospital
University of Fukui Hospital
Municipal Tsuruga Hospital
University of Yamanashi Hospital
Gifu Prefectural General Medical Center
Ogaki Municipal Hospital
Juntendo University Shizuoka Hospital
Shizuoka General Hospital
Japanese Red Cross Nagoya Daini Hospital
Handa City Hospital
Tosei General Hospital
Ichinomiyanishi Hospital
Yokkaichi Hazu Medical Center
Matsusaka Central General Hospital
Nabari City Hospital
Otsu Red Cross Hospital
Hikone Municipal Hospital
Kyoto University Hospital
Kyoto Medical Center
Mitsubishi Kyoto Hospital
Kitano Hospital
Osaka Red Cross Hospital
National Cerebral and Cardiovascular Center
Kindai University Hospital
Mimihara General Hospital
Bell Land General Hospital

Kobe City Medical Center General Hospital
Kindai University Nara Hospital
Tenri Hospital
Japanese Red Cross Wakayama Medical Center
Wakayama Medical University Hospital
Shimane University Hospital
Japanese Red Cross Okayama Hospital
Kurashiki Central Hospital
Hiroshima University Hospital
Iwakuni Medical Center
Tokuyama Central Hospital
Shimonoseki City Hospital
Tokushima University Hospital
Tokushima Red Cross Hospital
Kagawa Prefectural Central Hospital
Ehime Prefectural Central Hospital
Matsuyama Red Cross Hospital
Chikamori Hospital
Kokura Memorial Hospital
Hospital of University of Occupational and Environmental Health Japan
Saiseikai Fukuoka General Hospital
Fukuoka Tokushukai Hospital
Kumamoto University Hospital
Saiseikai Kumamoto Hospital
Japanese Red Cross Kumamoto Hospital
Miyazaki Prefectural Nobeoka Hospital
Ibusuki Medical Center
Izumi Regional Medical Center
Urasoe General Hospital
Nakagami Hospital

Inclusion Criteria

- PCI with exclusive use of CoCr-EES (Xience™ series)
- No major complications during hospitalization for index PCI
- No plan for staged PCI
- Patients who could take DAPT with aspirin and $P2Y_{12}$ inhibitors

Key Exclusion Criteria

- Needs for oral anticoagulants
- History of intracranial hemorrhage

STOPDAPT-2

Endpoints

Primary endpoint:

Net adverse cardiovascular events (NACE: Ischemia and Bleeding)

- A composite of cardiovascular death, MI, Definite ST, Stroke, or TIMI major/minor bleeding

Major secondary endpoints:

Ischemic composite endpoint

- A composite of cardiovascular death, MI, Definite ST, or Stroke

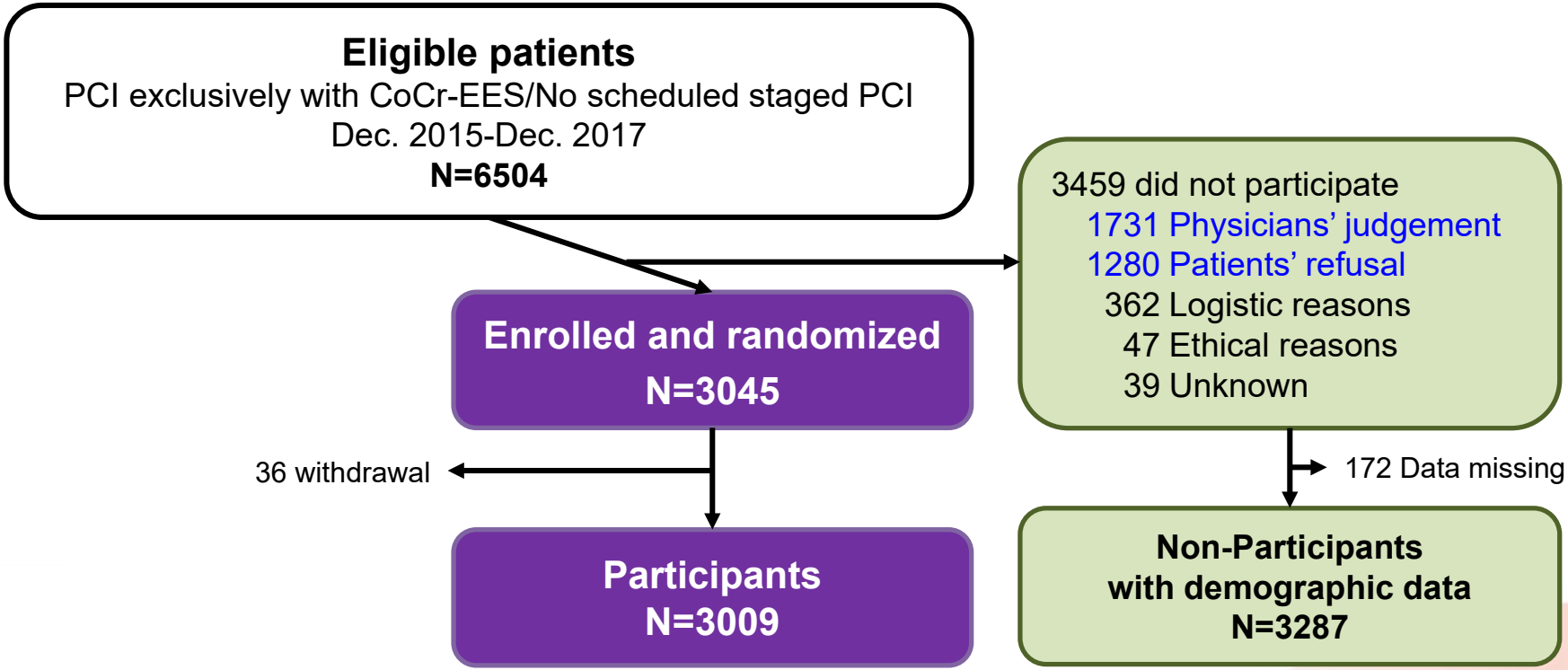
Bleeding endpoint

- TIMI major/minor bleeding

Sample Size Calculation

- Hypothesis: Non-inferiority of 1-month DAPT to 12-month DAPT for the primary endpoint at 1-year
- Assumption: Event rate at 1-year: 4.6% (Based on RESET study).
- Non-inferiority margin; 50% on the hazard ratio scale
- Randomization ratio: 1:1
- One-sided alpha: 0.025
- Power: 85%
- Sample size: 3000 patients (1500 in each arm)

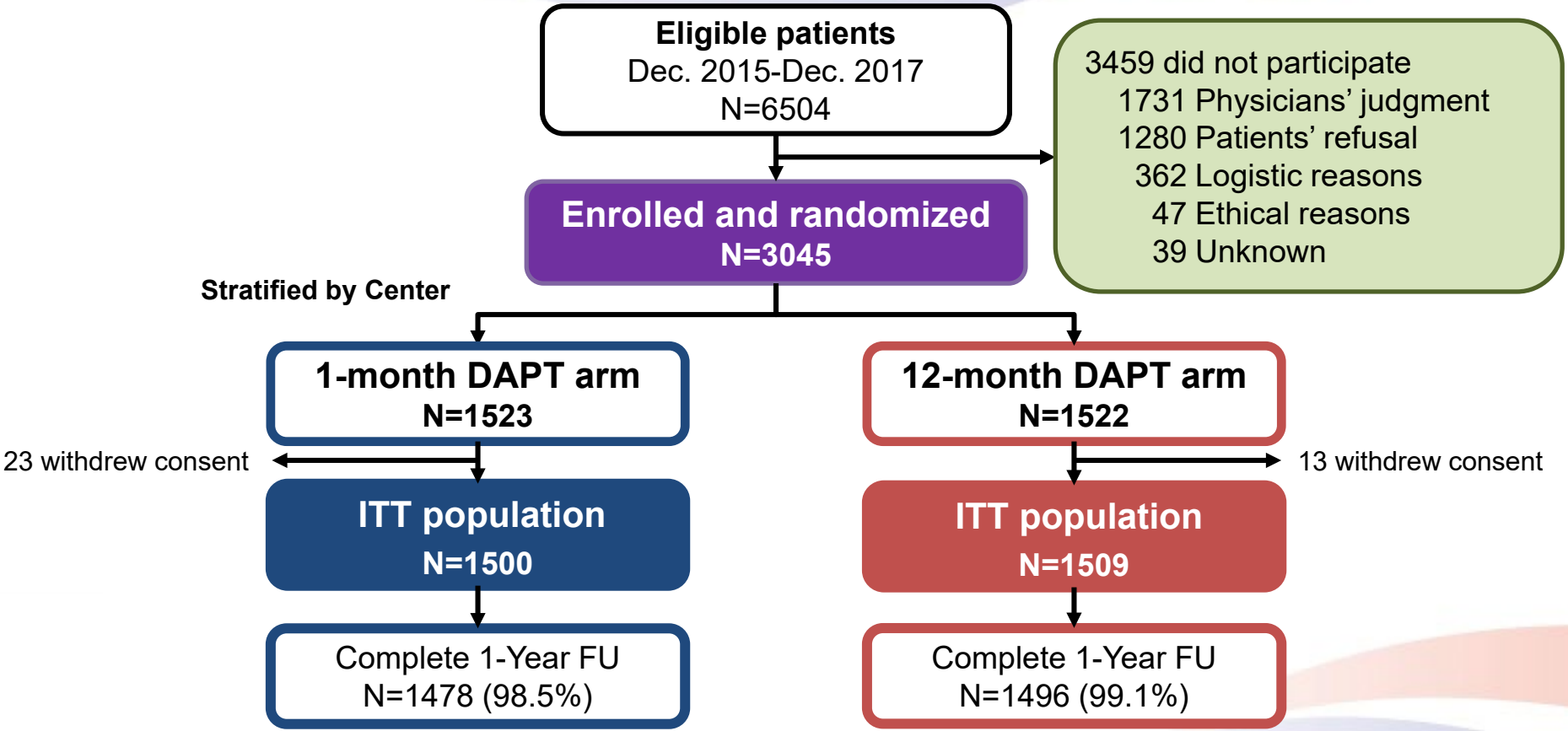
Study Flow


Eligible patients
PCI exclusively with CoCr-EES/No scheduled staged PCI
Dec. 2015-Dec. 2017
N=6504
3459 did not participate
1731 Physicians' judgement
1280 Patients' refusal
362 Logistic reasons
47 Ethical reasons
39 Unknown
Enrolled and randomized
N=3045
36 withdrawal
172 Data missing
Participants
N=3009
Non-Participants
with demographic data
N=3287

Participants vs Non-participants

	Participants N=3009	Non-participants N=3287	P value
Age, y	68.6±10.7	70.0±11.7	<0.001
ACS	38%	39%	0.61
STEMI	19%	22%	0.003
Prior MI	14%	23%	<0.001
Prior 1st-generation DES implantation	4%	6%	<0.001
Diabetes	39%	39%	0.47
Severe CKD	6%	9%	<0.001
Dialysis	3%	5%	<0.001
Target of LMCA	3%	5%	<0.001
Two or more target vessels	7%	9%	0.003

Study Flow


Eligible patients
Dec. 2015-Dec. 2017
N=6504
3459 did not participate
1731 Physicians' judgment
1280 Patients' refusal
362 Logistic reasons
47 Ethical reasons
39 Unknown
Enrolled and randomized
N=3045
Stratified by Center
1-month DAPT arm
N=1523
12-month DAPT arm
N=1522
23 withdrew consent
13 withdrew consent
ITT population
N=1500
ITT population
N=1509
Complete 1-Year FU
N=1478 (98.5%)
Complete 1-Year FU
N=1496 (99.1%)

STOPDAPT-2

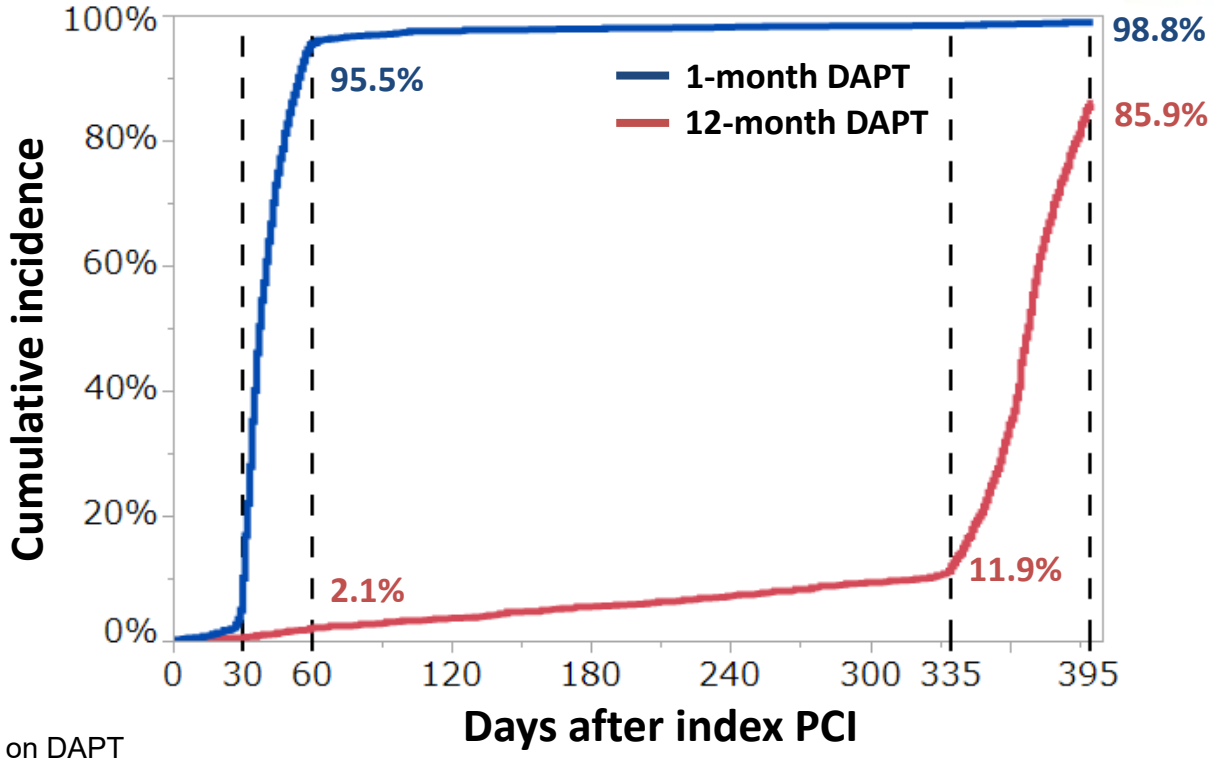
Baseline Clinical Characteristics

	1-month DAPT N=1500	12-month DAPT N=1509
Age, years	68.1±10.9	69.1±10.4
Men	79%	77%
ACS	38%	39%
STEMI	19%	18%
Stable CAD	62%	61%
Diabetes	39%	38%
Severe CKD (eGFR<30ml/min/m^2)	6%	6%
Prior MI	14%	13%
Prior PCI	34%	35%
CREDO-Kyoto thrombotic risk score		
High; Intermediate; Low	8%; 21%; 71%	8%; 24%; 68%
CREDO-Kyoto bleeding risk score		
High; Intermediate; Low	7%; 27%; 66%	7%; 27%; 66%

Procedural Characteristics and Medications

	1-month DAPT N=1500	12-month DAPT N=1509
Transradial approach	82%	84%
N of target lesions	1.12 ± 0.35	1.14 ± 0.39
Minimal stent diameter, mm	2.98 ± 0.49	2.96 ± 0.48
Total stent length, mm	30.3 ± 16.7	30.5 ± 16.8
SYNTAX Score	8 (5-14)	9 (6-15)
Target of LMCA	3%	3%
CTO	4%	4%
IVUS or OCT	97%	98%
ASA	99.8%	100%
Clopidogrel	60%	63%
Prasugrel (3.75mg/day)	40%	37%
Statin	88%	87%
PPI	79%	79%

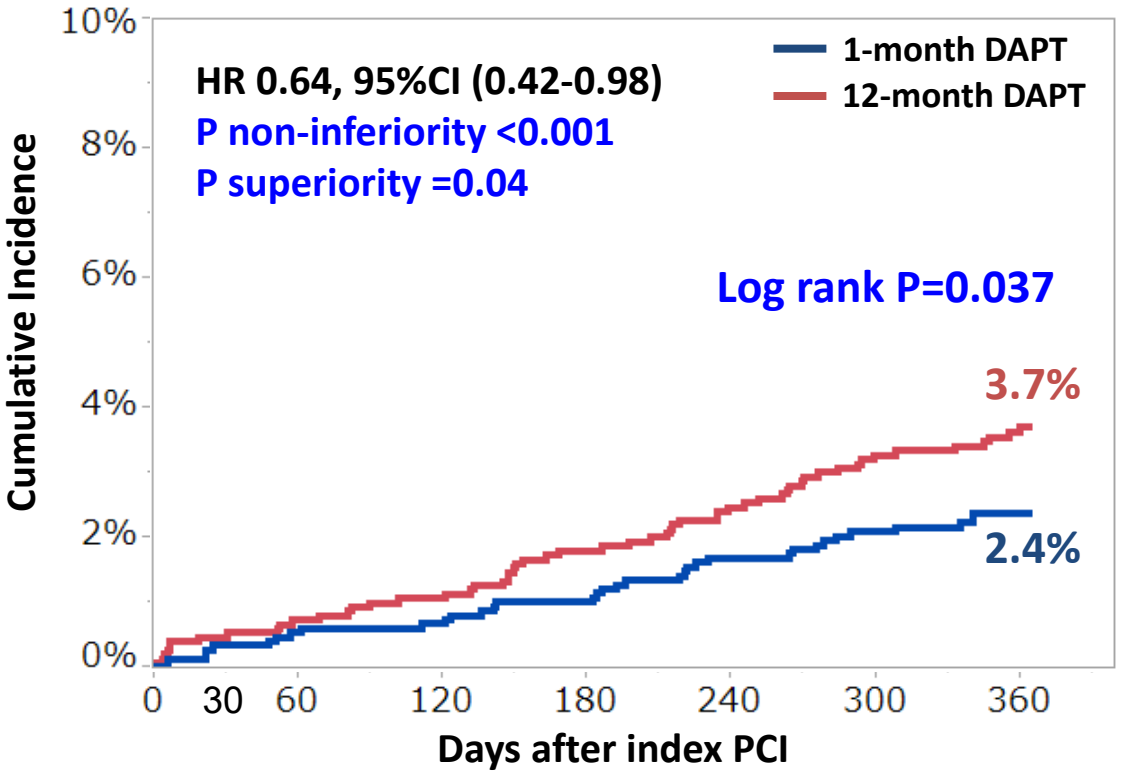
Persistent DAPT discontinuation rate



Number of patients on DAPT									
1-month DAPT	1500	1346	67	38	32	28	25	23	9
12-month DAPT	1509	1499	1467	1442	1412	1387	1352	1314	178

Primary Endpoint: Net clinical benefit

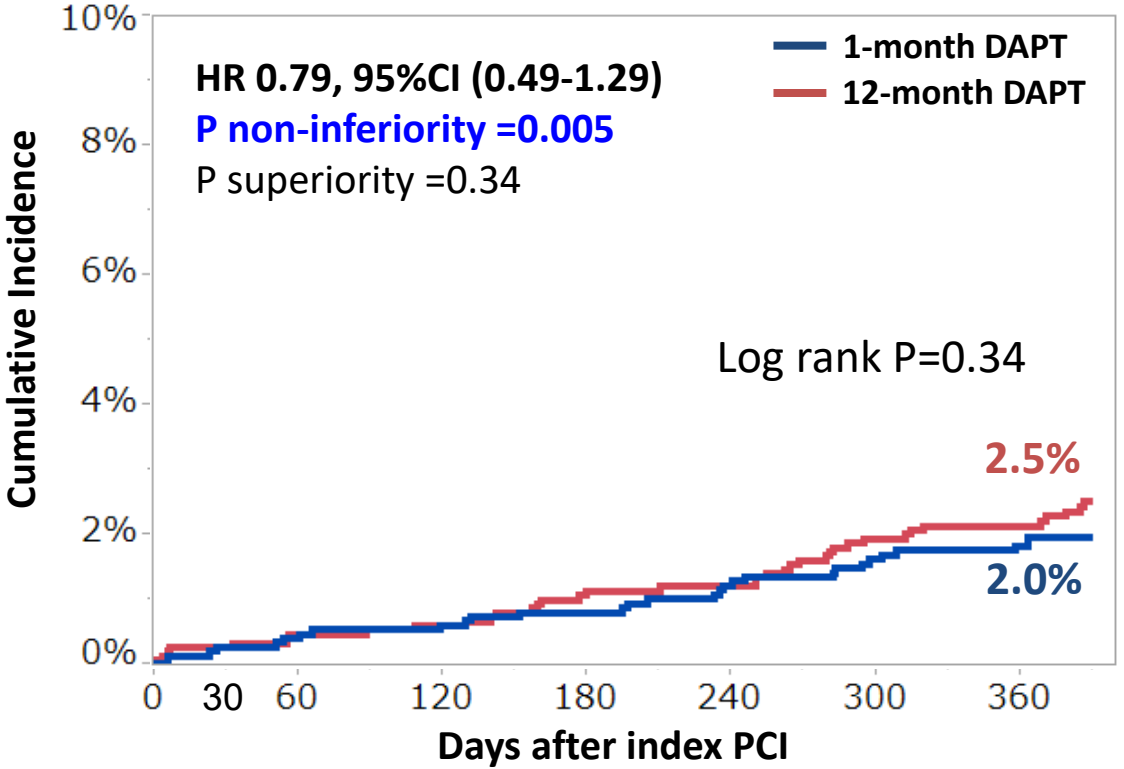
CV death/MI/ST/Stroke/TIMI major/minor bleeding



No. at risk								
12-month DAPT	1509	1501	1486	1481	1469	1458	1442	1159
1-month DAPT	1500	1494	1479	1475	1468	1453	1441	1151

Major secondary ischemic endpoint

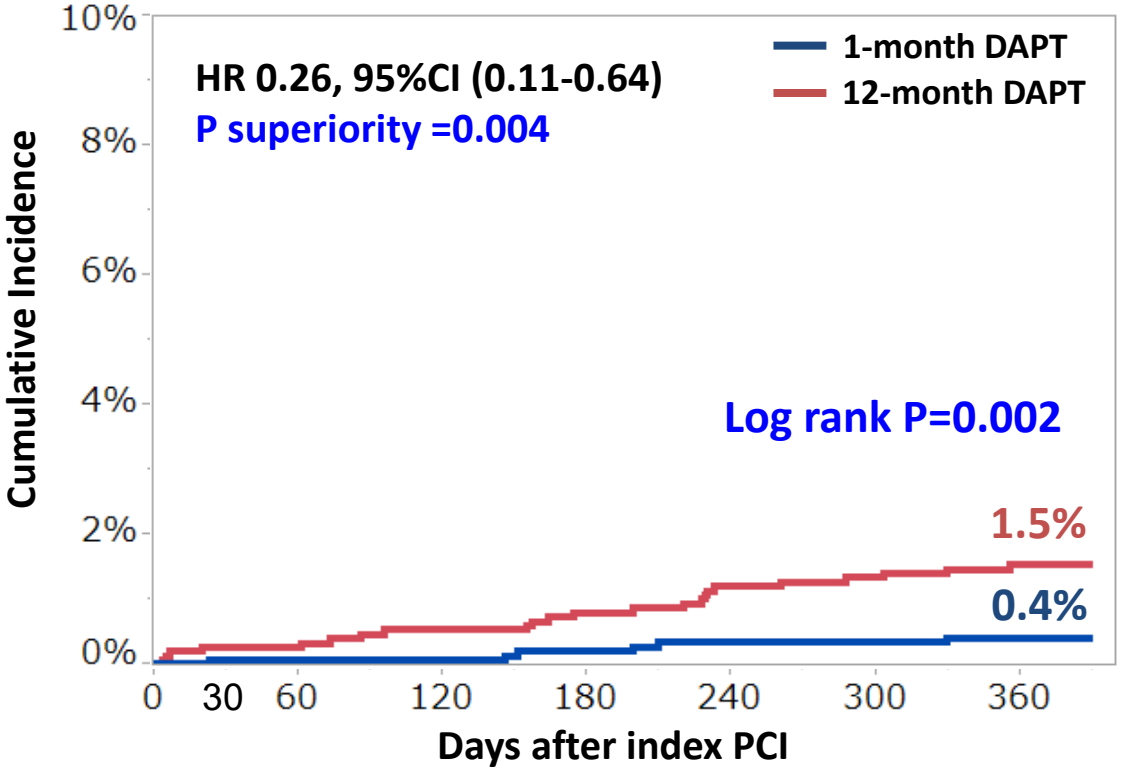
CV death/MI/ST/Stroke



No. at risk								
12-month DAPT	1509	1504	1490	1488	1479	1473	1458	1172
1-month DAPT	1500	1495	1480	1476	1471	1458	1446	1157

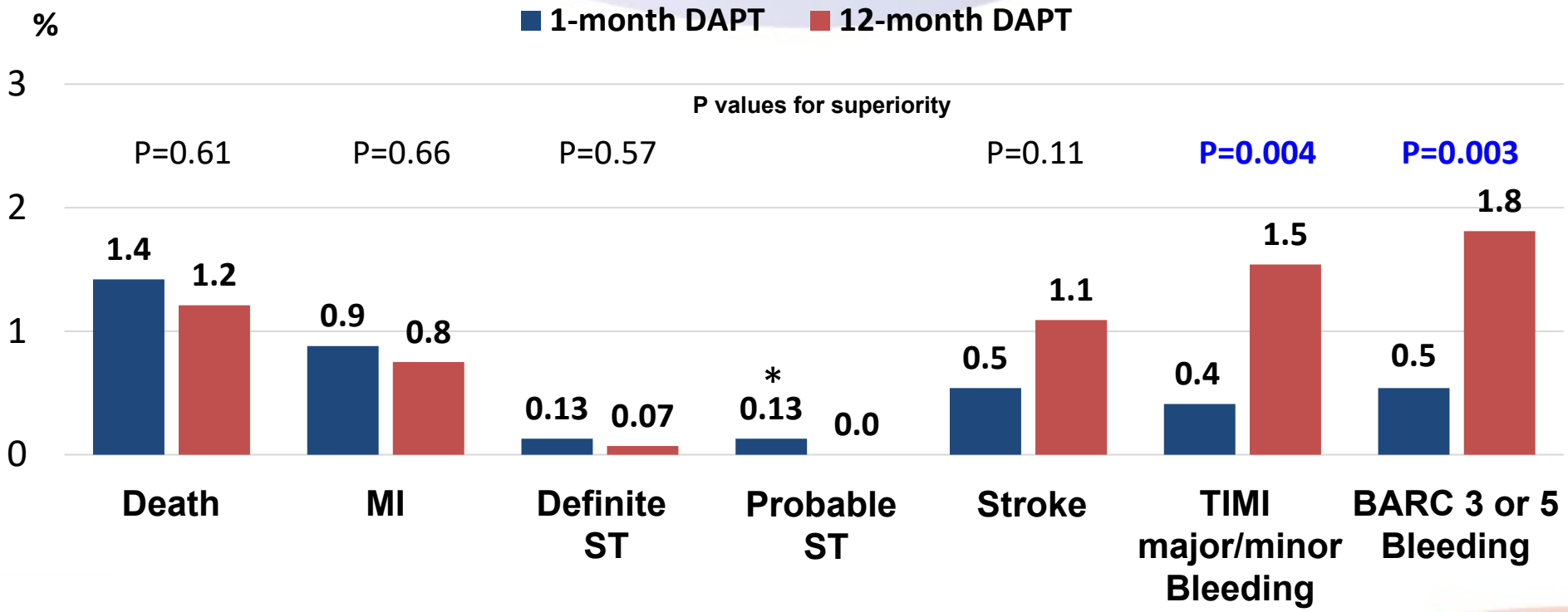
Major secondary bleeding endpoint

TIMI major/minor bleeding



No. at risk								
12-month DAPT	1509	1504	1491	1487	1480	1471	1462	1180
1-month DAPT	1500	1495	1483	1481	1477	1467	1457	1166

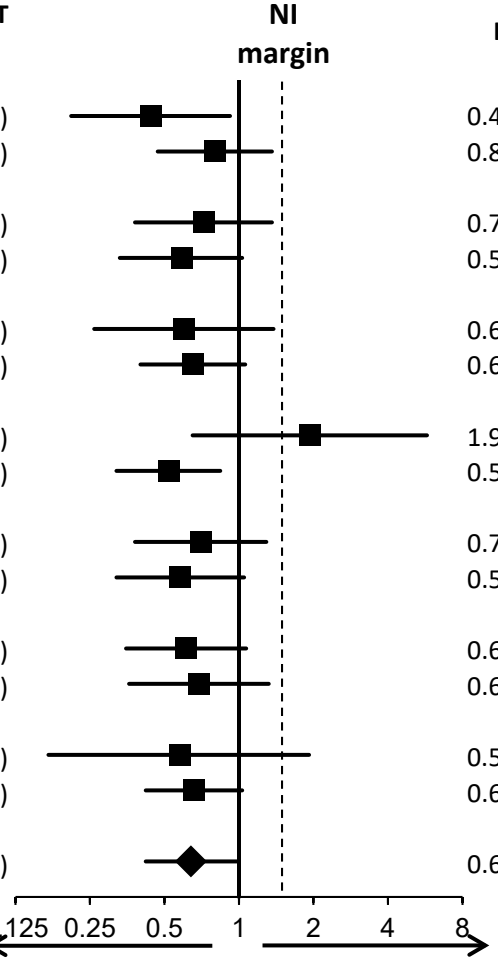
Clinical Outcomes at 1 year



* 2 cases of probable ST (undefined death) in the 1-month DAPT group occurred before discontinuing DAPT at 1-month

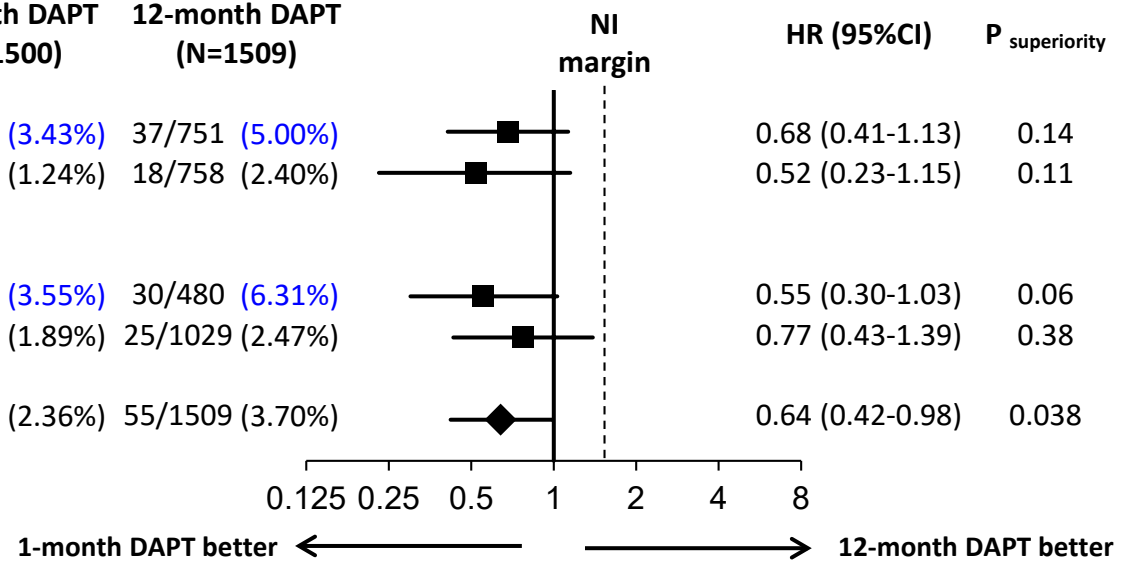
Subgroup analysis for the primary endpoint (1)

	1-month DAPT (N=1500)	12-month DAPT (N=1509)	HR (95%CI)	P superiority	P interaction
Age					
>=75 years	10/448 (2.26%)	25/499 (5.08%)	0.44 (0.21-0.92)	0.03	0.20
<75 years	25/1052 (2.41%)	30/1010 (3.02%)	0.80 (0.47-1.36)	0.41	
ACS					
Yes	16/565 (2.88%)	23/583 (4.02%)	0.72 (0.38-1.36)	0.44	0.64
No	19/935 (2.05%)	32/926 (3.49%)	0.59 (0.33-1.03)	0.06	
STEMI					
Yes	9/291 (3.15%)	14/270 (5.26%)	0.60 (0.26-1.38)	0.23	0.87
No	26/1209 (2.18%)	41/1239 (3.36%)	0.65 (0.40-1.06)	0.08	
Severe CKD					
Yes	9/82 (11.22%)	5/84 (5.97%)	1.93 (0.65-5.75)	0.24	0.03
No	26/1418 (1.86%)	50/1425 (3.56%)	0.52 (0.32-0.84)	0.007	
Diabetes					
Yes	18/585 (3.12%)	25/574 (4.45%)	0.70 (0.38-1.29)	0.26	0.65
No	17/915 (1.88%)	30/935 (3.24%)	0.58 (0.32-1.05)	0.07	
Total stent length >=28mm					
Yes	19/742 (2.60%)	33/787 (4.23%)	0.61 (0.35-1.07)	0.08	0.76
No	16/758 (2.14%)	22/722 (3.12%)	0.69 (0.36-1.32)	0.26	
Two or more target vessels					
Yes	4/100 (4.14%)	8/116 (6.94%)	0.58 (0.17-1.92)	0.37	0.85
No	31/1400 (2.24%)	47/1393 (3.43%)	0.66 (0.42-1.03)	0.07	
Overall	35/1500 (2.36%)	55/1509 (3.70%)	0.64 (0.42-0.98)	0.038	



Subgroup analysis for the primary endpoint (2)

	1-month DAPT (N=1500)	12-month DAPT (N=1509)	HR (95%CI)	$P_{superiority}$	$P_{interaction}$
PARIS thrombotic risk score					
Intermediate/High	26/771 (3.43%)	37/751 (5.00%)	0.68 (0.41-1.13)	0.14	0.56
Low	9/729 (1.24%)	18/758 (2.40%)	0.52 (0.23-1.15)	0.11	
CREDO-Kyoto thrombotic risk score					
Intermediate/High	15/431 (3.55%)	30/480 (6.31%)	0.55 (0.30-1.03)	0.06	0.45
Low	20/1069 (1.89%)	25/1029 (2.47%)	0.77 (0.43-1.39)	0.38	
Overall	35/1500 (2.36%)	55/1509 (3.70%)	0.64 (0.42-0.98)	0.038	



Limitations

- Lack of consensus on the use of the NACE as primary endpoint
- Open label design with its inherent limitations
- Limited enrollment of high ischemic risk patients
- Lower ischemic risk of Japanese versus US/European CAD patients
- Ticagrelor / Prasugrel (standard dose) not available in Japan
- No assessment of aspirin monotherapy after 1-month DAPT

Conclusions

One-month DAPT followed by clopidogrel monotherapy provided a net clinical benefit for ischemic and bleeding events over 12-month DAPT with aspirin and clopidogrel after CoCr-EES implantation.

The benefit was driven by significant reduction in bleeding events without increase in ischemic events.