No DAPT is the way to go after DES implantation ?

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STOPDAPT-3

Disclosures

Name of Author : Takeshi Kimura

ABBOTT Vascular, and Boston Scientific.

STOPDAPT-2 Total cohort

STOPDAPT-2 Total Cohort

STOPDAPT-2 and STOPDAPT-2 ACS

Cardiovascular Endpoint

CV death/MI/ST/Stroke

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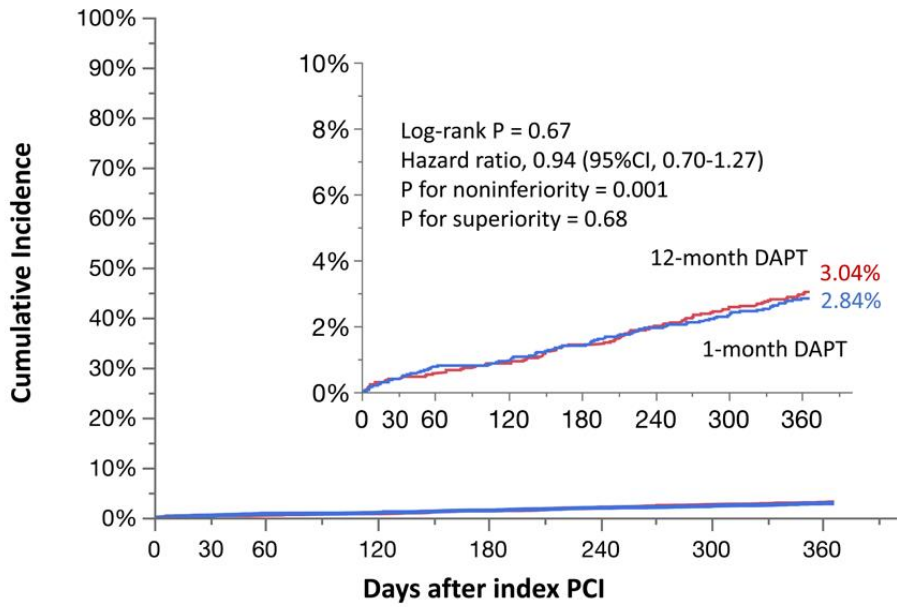
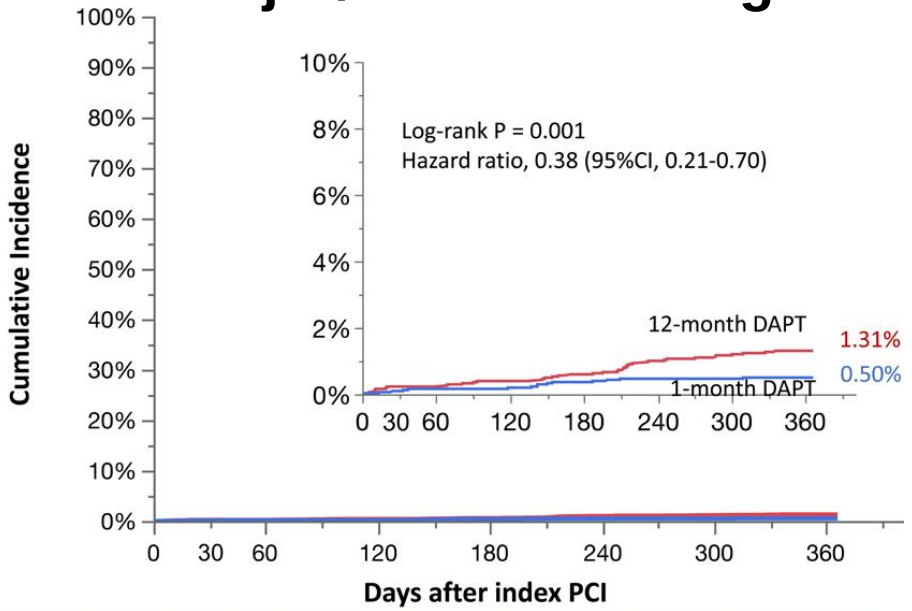


1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		13	23	29	42	58	70	84
Number of patients at risk	2993	2980	2956	2946	2928	2905	2885	2357
Cumulative incidence (%)		0.43	0.77	0.97	1.41	1.95	2.35	2.84
12-month DAPT	**0**	**30**	**60**	**120**	**180**	**240**	**300**	**365**
Number of patients with event		12	18	26	43	60	77	90
Number of patients at risk	3004	2991	2970	2959	2941	2922	2902	2327
Cumulative incidence (%)		0.40	0.60	0.87	1.44	2.01	2.58	3.04

Major Bleeding Endpoint

TIMI major/minor bleeding



1-month DAPT	0	30	60	120	180	240	300	365
Number of patients with event		3	5	6	11	14	14	15
Number of patients at risk	2993	2985	2970	2965	2955	2941	2927	2400
Cumulative incidence (%)		0.10	0.17	0.20	0.37	0.47	0.47	0.50
12-month DAPT	**0**	**30**	**60**	**120**	**180**	**240**	**300**	**365**
Number of patients with event		7	8	12	18	30	36	39
Number of patients at risk	3004	2995	2977	2968	2957	2941	2929	2360
Cumulative incidence (%)		0.23	0.27	0.40	0.60	1.01	1.21	1.31

Clopidogrel monotherapy after 1-month DAPT compared to 12-month DAPT with aspirin and clopidogrel:

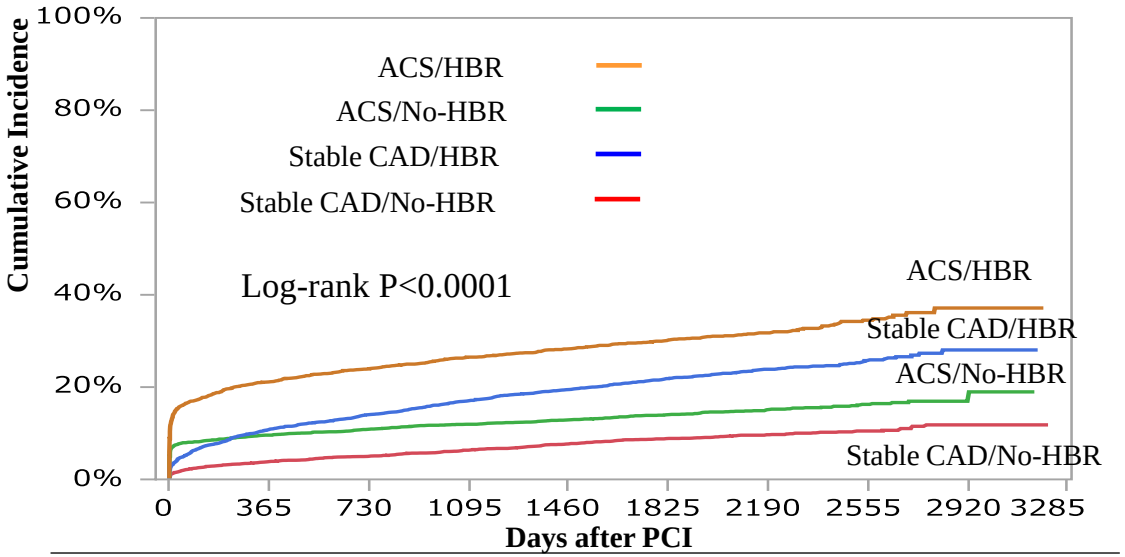
Significant reduction in major bleeding without increase in CV events!!

Obayashi Y, et al. Circ cardiovasc Interv. 2022.

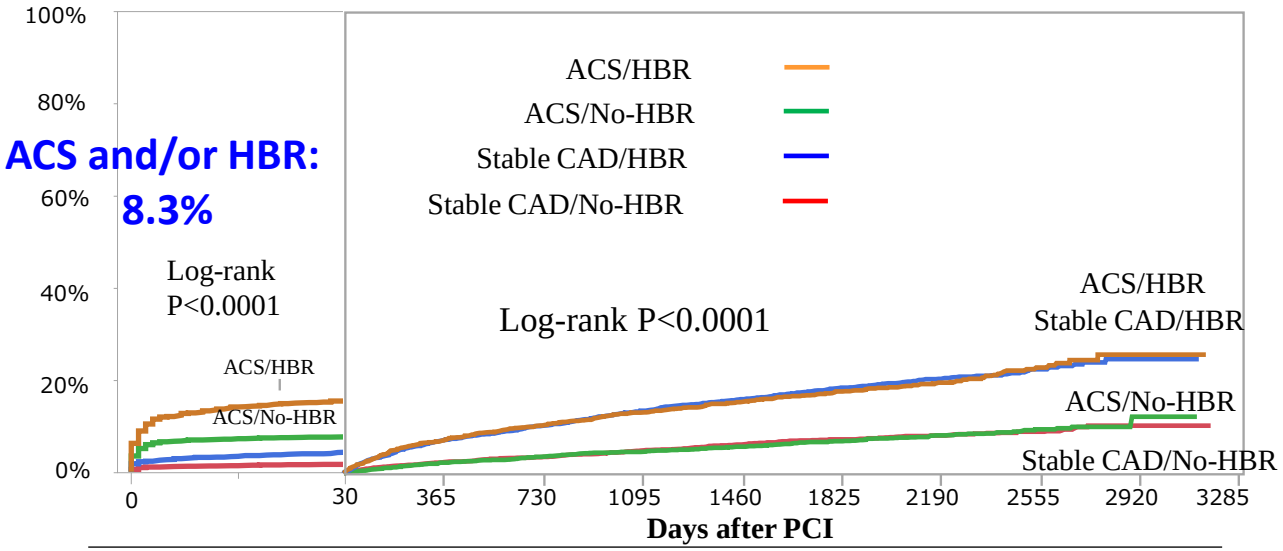
What are the remaining issues beyond very short DAPT?

CREDO-Kyoto PCI/CABG Registry Cohort-3 ACS/HBR Analysis

Major Bleeding (BARC type 3 or 5)



Interval	0-day	30-day	1-year	3-year	5-year
ACS/HBR group					
N of patients with event		377	504	608	668
N of patients at risk	2502	1965	1639	1339	973
Cumulative incidence		15.4%	21.2%	26.5%	30.1%
ACS/No-HBR group					
N of patients with event		230	287	354	408
N of patients at risk	3019	2738	2616	2445	2007
Cumulative incidence		7.7%	9.6%	12.0%	14.0%
Stable CAD/HBR group					
N of patients with event		168	415	628	770
N of patients at risk	3905	3692	3246	2691	1952
Cumulative incidence		4.3%	10.9%	17.1%	21.9%
Stable/No-HBR group					
N of patients with event		62	148	239	326
N of patients at risk	3832	3760	3606	3394	2784
Cumulative incidence		1.6%	3.9%	6.4%	8.8%

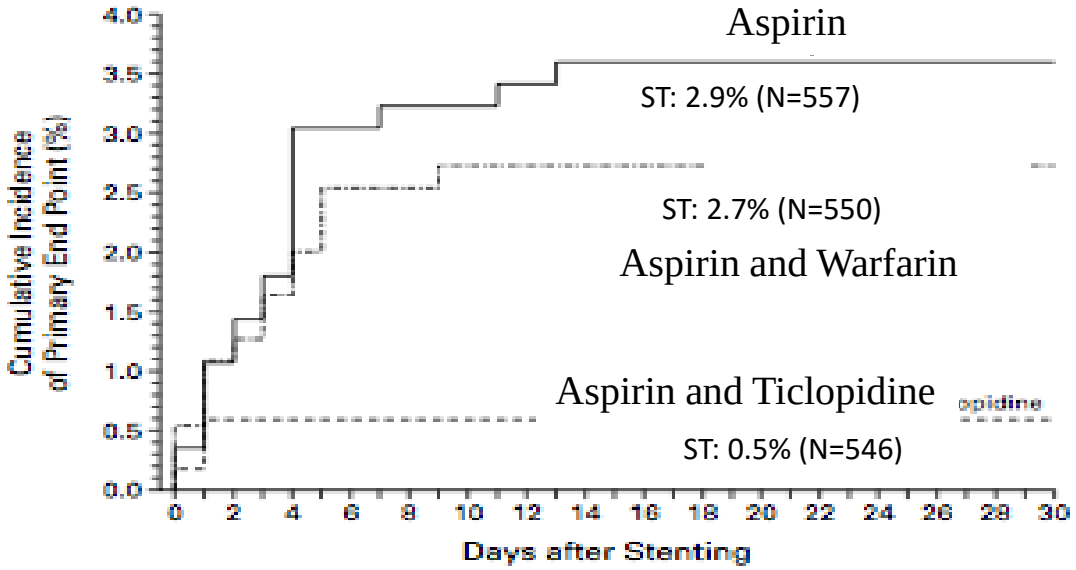


Interval	0-day	7-day	30-day	1-year	3-year	5-year
ACS/HBR group						
N of patients with event		313	377	127	231	291
N of patients at risk	2502	2088	1965	1639	1339	973
Cumulative incidence		12.7%	15.4%	6.9%	13.2%	17.4%
ACS/No-HBR group						
N of patients with event		206	230	57	124	178
N of patients at risk	3019	2783	2738	2616	2445	2007
Cumulative incidence		6.8%	7.7%	2.1%	4.7%	6.9%
Stable CAD/HBR group						
N of patients with event		116	168	247	460	602
N of patients at risk	3905	3768	3692	3246	2691	1952
Cumulative incidence		3.0%	4.3%	6.9%	13.3%	18.3%
Stable/No-HBR group						
N of patients with event		45	62	86	177	264
N of patients at risk	3832	3782	3760	3606	3394	2784
Cumulative incidence		1.2%	1.6%	2.3%	4.8%	7.3%

Natsuaki M, et al. Circ J. 2021

Stent Anticoagulation Restenosis Study (STARS)

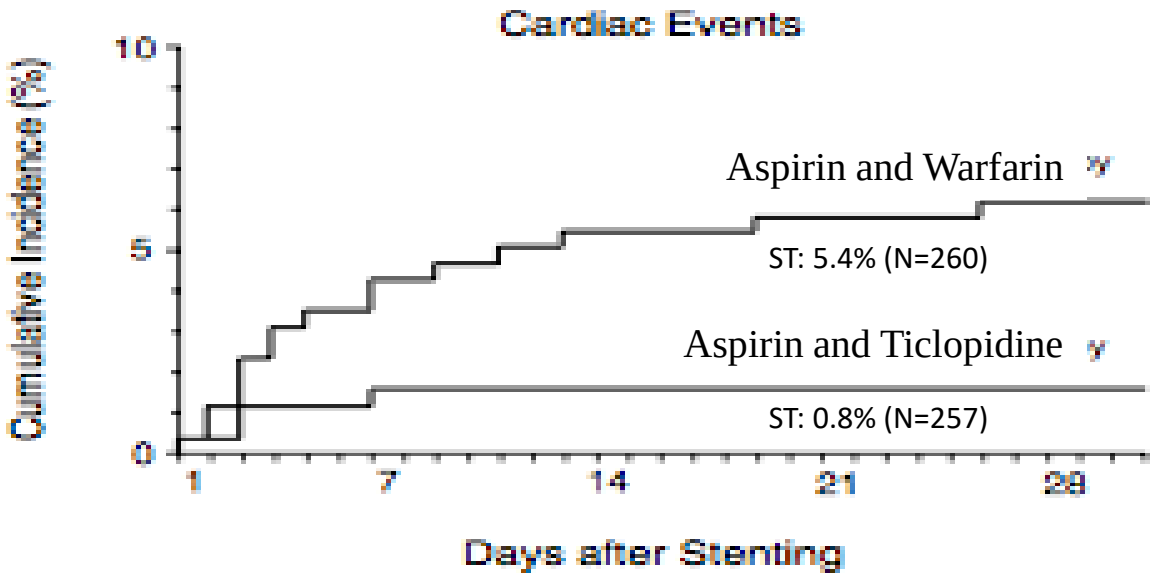
Death/TLR/ST/MI



Leon MB, et al. NEJM 1998.

Intracoronary Stenting and Antithrombotic Regimen Trial (ISAR)

Cardiac death/CABG/PCI/MI



Schomig A, et al. NEJM 1996.

STARS and ISAR trials have established the role of DAPT after coronary stent implantation.
Addition of a $P2Y_{12}$ inhibitor (ticlopidine) demonstrated >80% relative risk reduction in ischemic cardiac event within 30 days with a background of aspirin in all groups.
We might reasonably speculate that a $P2Y_{12}$ inhibitor would be the major component of DAPT in preventing ischemic cardiac event, stent thrombosis in particular.

Addressing the Remaining Issues beyond Very Short DAPT

ASET Trial Exploring Aspirin-free Strategy after PCI

ASET

Study Design

ClinicalTrial.gov NCT03469856

Target population of 200 patients

Enrollment

3-month
Primary EPs assessment

4-month
Last clinical assessment

ASA discontinued

Loading 60 mg prasugrel immediately after PCI (only for those naïve to prasugrel)

Prasugrel 10 mg/d
(monotherapy)

Antithrombotics at investigator`s discretion

Scheduled for elective PCI
(DAPT standard of care)

Successful PCI
(based on local judgment) with Synergy EES

Screening

Co-primary EP (at 3-month)
- **Ischemic**: Adjudicated composite of cardiac death, TV-MI (>48 hours) or def ST
- **Bleeding**: Adjudicated BARC type 3 or 5

Stopping rule ➡ enrollment would be terminated if > 3 patients with **definite stent thrombosis**

tct2019

Kogame N, et al. EuroIntervention. 2019 Aug 9;15(6):e547-e550

Cardiovascular® Research Foundation

ASET

Primary endpoint at 3 months

	n = 201
Primary ischemic endpoint	0.5% (1)*
Cardiac death	0.5% (1)*
TV-spontaneous MI (48 hours after PCI)	0% (0)
Definite stent thrombosis	0% (0)
Primary bleeding endpoint	0.5% (1)*
BARC type 3a	0% (0)
BARC type 3b	0% (0)
BARC type 5a	0% (0)
BARC type 5b	0.5% (1)*

*The patient died 3 days after index procedure due to hemorrhagic stroke. Uncontrollable hypertension was observed during index procedure and hemorrhagic stroke occurred a few hours after index procedure. Prasugrel 60mg was loaded immediately after procedure according to the protocol.
This event was adjudicated as cardiac death, since it was probably related to index procedure.

Research Foundation

Kogame N, et al. JACC Cardiovasc Interv. 2020.

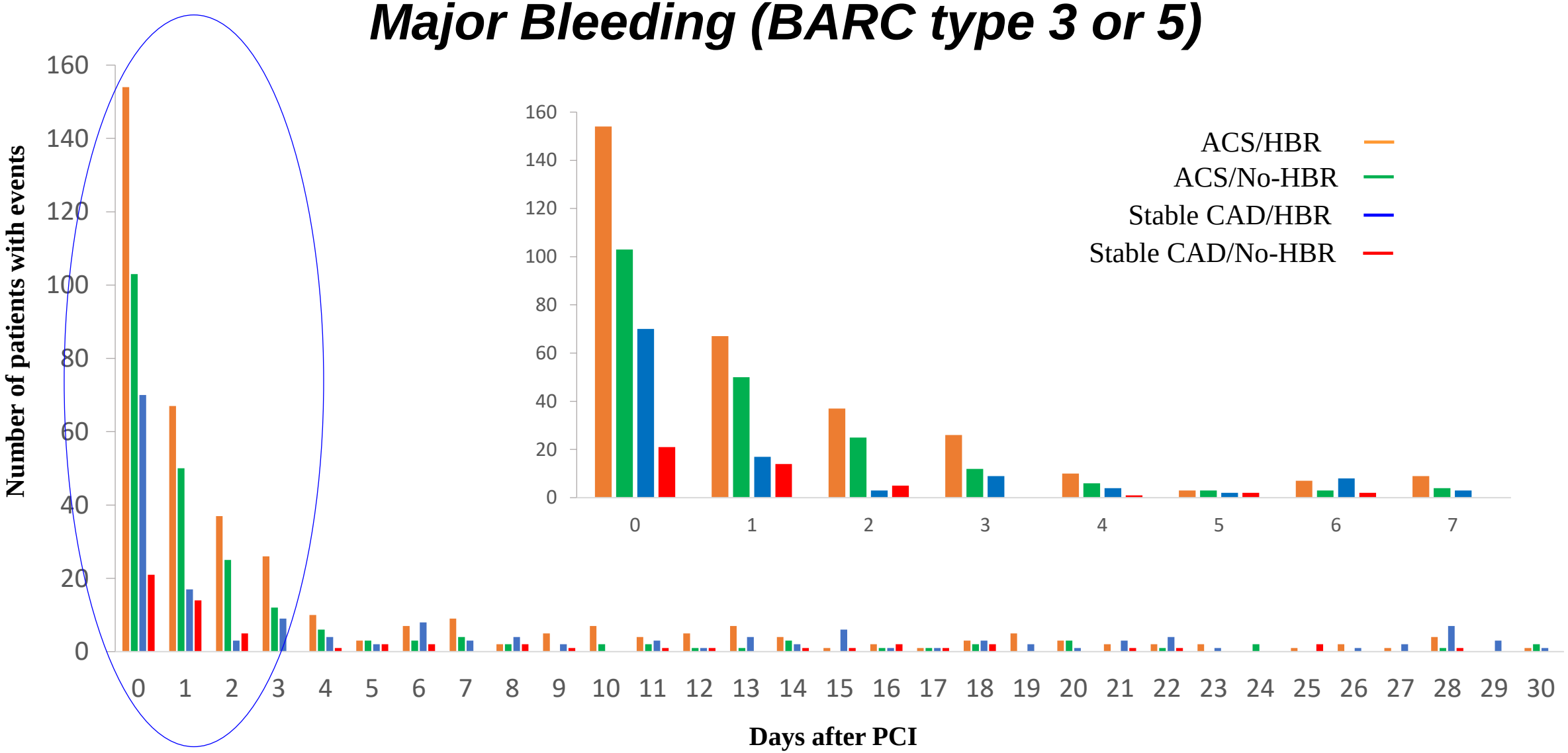
STOPDAPT-3

Ongoing Trials Exploring Aspirin-free Strategy in Patients Undergoing DES Implantation

	Region	N	Population	Monotherapy	Timing of Monotherapy
ISAR-REACT 6	Europe	9,200	CCS or NSTE-ACS	Prasugrel or Ticagrelor	**After discharge**
LEGACY NCT05125276; 2025/5	Netherlands	3,090	NSTE-ACS	Prasugrel or Ticagrelor	**After PCI**
Neo-MINDSET NCT04360720; 2024/1	Brazil	3,400	ACS	Prasugrel or Ticagrelor	**After PCI**
STOPDAPT-3 NCT04609111; 2023/6	Japan	6,000	ACS or HBR	Prasugrel	**Before PCI**
PREMIUM NCT05709626; 2026/3	Japan	2,258	STEMI	Prasugrel	**Before PCI**

CREDO-Kyoto Registry Cohort 3

Major Bleeding (BARC type 3 or 5)



Completely aspirin-free strategy even before PCI might be important to reduce bleeding early after PCI!!

Natsuaki M, et al. Circ J. 2021

STOPDAPT-3 Trial Exploring Completely Aspirin-free Strategy

＜Inclusion Criteria＞

1. **PCI with planned exclusive use of CoCr-EES (XIENCE)**
2. **ACS presentation or ARC-HBR**
3. **Eligible for DAPT (Aspirin/$P2Y_{12}$ inhibitor) for 1 month**

No Exclusion Criteria

Informed Consent Before Angiography

Randomization After Angiography, but Before PCI

Loading: Prasugrel 20 mg

Loading Aspirin also, if Aspirin naïve

No aspirin Group
3001 Patients

Prasugrel 3.75 mg Monotherapy for 1 Month

1-month DAPT Group
3001 Patients

DAPT (Aspirin 81-100 mg and Prasugrel 3.75 mg) for 1 Month

Primary Analysis at 1-Month

Co-primary Bleeding Endpoint：BARC 3 or 5 bleeding at 1M (Superiority)

Co-primary Cardiovascular Endpoint : CV death/MI/Ischemic Stroke/ST at 1M (Non-inferiority)

Clopidogrel Monotherapy
Between 1M and 12 M

Exploratory Analysis

Aspirin Monotherapy
Between 1M and 12 M

STOPDAPT-3: Event rates at 30-day in the initial 1200 patients

(Blinded evaluation, Adjudicated)

Outcome	N (%)	Assumed event rate
Co-primary bleeding endpoint (BARC 3 or 5 Bleeding)	50 (4.2%)	5.8%
Co-primary CV endpoint (CVD, MI, Definite ST, Ischemic Stroke)	39 (3.3%)	6.2%
Death	23 (1.9%)	
CV death	23 (1.9%)	
MI	9 (0.8%)	
Definite ST	3 (0.3%)	
Stroke	9 (0.8%)	
Ischemic	7 (0.6%)	
Hemorrhagic	2 (0.2%)	
BARC 3	45 (3.8%)	
BARC 5	5 (0.4%)	

Original target sample size: 3000 patients

Revised sample size calculation based on the actual event rates in the initial 1200 patients

STOPDAPT-3

- **Sample size for the co-primary bleeding endpoint on superiority basis**

Event rate at 30 days 4.0% (Observed event rate from cumulative 1200 case: 4.2% * 0.95 conservative discount)
Relative risk reduction 38% (STOPDAPT-2 ACS provided 54% * 0.7 conservative discount)
Power 90%, One-sided alpha 0.025, Randomization ratio 1:1

Sample size with survival 5860 (If binary 5700), Dropout rate 2%: 5860/0.98 =5980

- **Power for the co-primary cardiovascular endpoint on non-inferiority basis**

Event rate at 30 days 3.0% (Observed event rate from cumulative 1200 case: 3.2% * 0.95 conservative discount)
Non inferiority margin on HR 1.5, One-sided alpha 0.025, Randomization ratio 1:1
Total sample size 5980

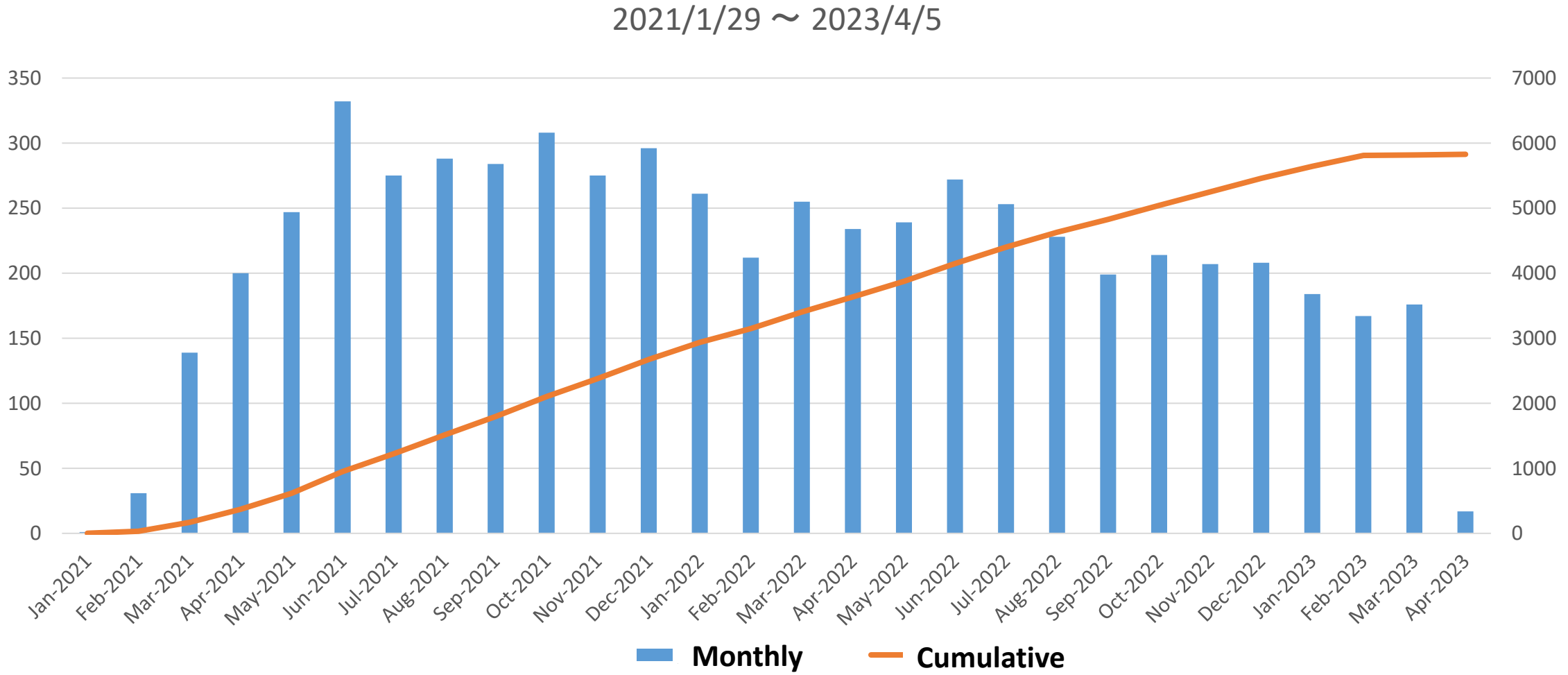
Power with survival 0.85 (if binary 0.92)

Due to the event rates lower than anticipated,
we have decided to double the sample size to maintain adequate statistical power!!

Because we assess the two co-primary endpoints simultaneously, this study is deemed positive when both the bleeding and cardiovascular endpoints meet for superiority and for non-inferiority, respectively.

STOPDAPT-3 Enrollment Status (Target: 5980 patients)

2023. 4. 5 **6002 patients (ACS N=4401, Non-ACS HBR N=1601)**



A challenging clinical trial in the midst of Covid-19 pandemic!!

STOPDAPT-3

Baseline Clinical Characteristics

	All N=6002	ACS N=4535	CCS N=1467
Age, years	71.7±11.7	69.9±12.0	76.9±8.8
Men	76%	78%	72%
Acute coronary syndrome	76%	100%	-
STEMI	39%	52%	-
NSTEMI	17%	22%	-
Unstable angina	13%	18%	-
Unknown	6%	8%	-
Cardiac arrest	1.3%	1.7%	-
Cardiogenic shock	4.4%	5.8%	-
Current heart failure	12%	16%	-

STOPDAPT-3

Baseline Clinical Characteristics

	All N=6002	ACS N=4535	CCS N=1467
Prior PCI	16%	11%	31%
Prior MI	8%	6%	14%
Prior stroke	9%	7%	17%
Prior heart failure	19%	16%	30%
LVEF (%)	54.5±12.1	53.7±11.7	56.6±12.7
Atrial fibrillation	9%	6%	19%
Peripheral artery disease	6%	3%	14%
Hypertension	77%	73%	88%
Diabetes	40%	36%	50%
Current smoker	24%	28%	12%
Hemodialysis	6%	3%	16%
Cancer	10%	8%	17%

Conclusions

We are currently conducting the STOPDAPT-3 trial, which would be an adequately powered trial exploring completely aspirin-free strategy without any DAPT background in an attempt to reduce major bleeding early after PCI in ACS and/or HBR patients.

Main results of the STOPDAPT-3 trial will be presented at ESC 2023!!