Increased Risk of Ischemic Events Upon Discontinuation of Prasugrel After 12 or 30 Months of Therapy Following Placement of the TAXUS Liberté Paclitaxel- Eluting Coronary Stent

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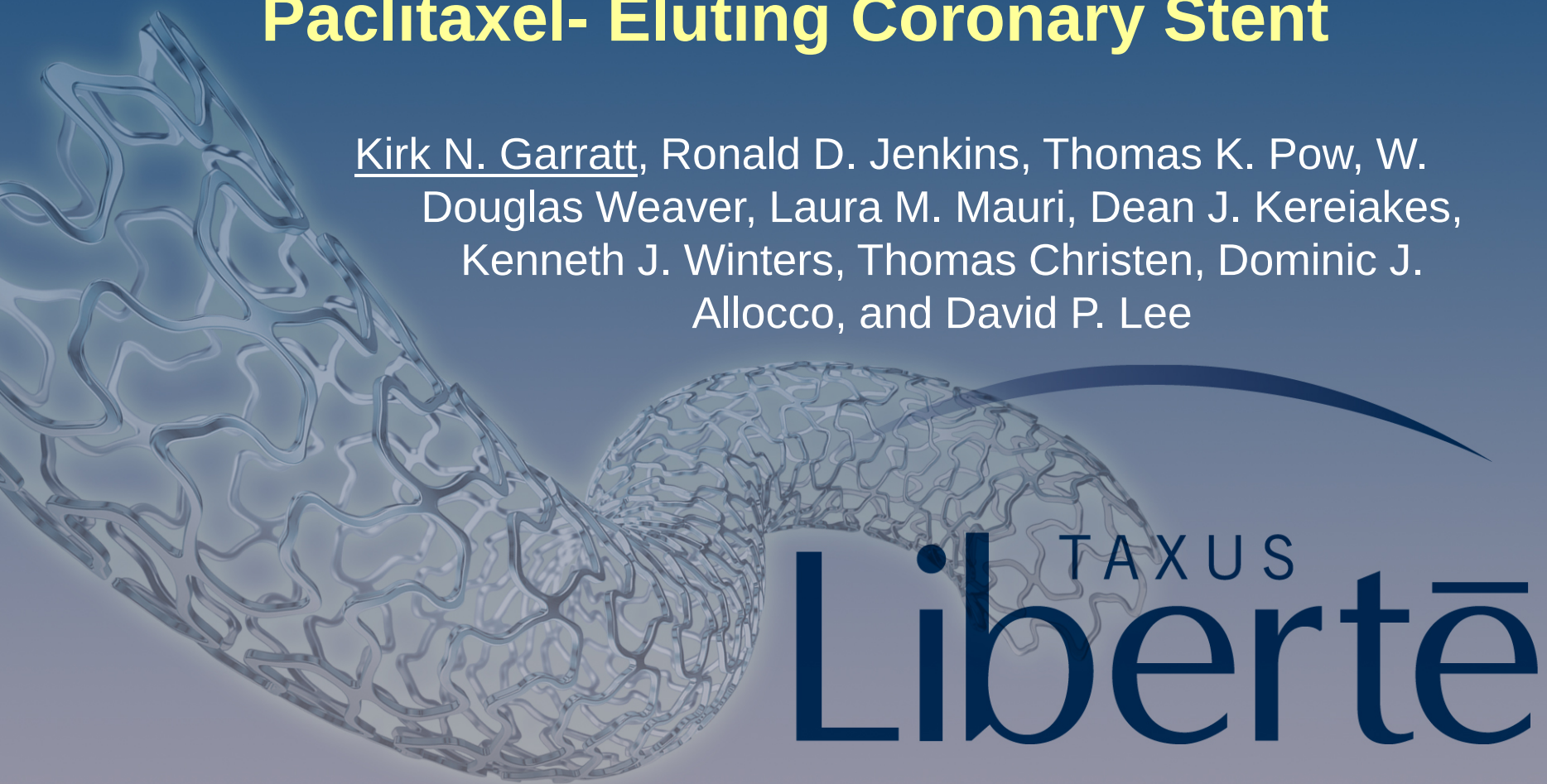

Background

- TAXUS Libertē Post-Approval Study (TL-PAS) was designed to provide long-term safety and efficacy data on the TAXUS Liberté paclitaxel-eluting coronary stent (PES) with concomitant prasugrel and ASA in a broad spectrum of patients
- TL-PAS contributed to the Dual Antiplatelet Therapy (DAPT) Study by randomizing TAXUS Liberté stent patients to blinded thienopyridine treatment, using prasugrel or matched placebo, from 12 through 30 months after the index procedure
- The TL-PAS data are being presented separately following guidance from the TL-PAS Data Monitoring Committee (DMC)

TL-PAS and DAPT

- TL-PAS represented 1 of 4 manufacturer sponsored studies that contributed subjects to the DAPT Study
- Each contributing study was required to employ the same randomization criteria, end point definitions, and follow-up specified by the DAPT Study
- The overall DAPT Study, but not the individual contributing studies, was designed with sufficient power to compare the endpoints

DAPT Study Endpoints

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Two co-primary effectiveness endpoints

- MACCE (all-cause death, MI or stroke) occurring between 12-30 months post-procedure
- Definite or probable stent thrombosis (ST) occurring between 12-30 months post-procedure

Primary safety endpoint

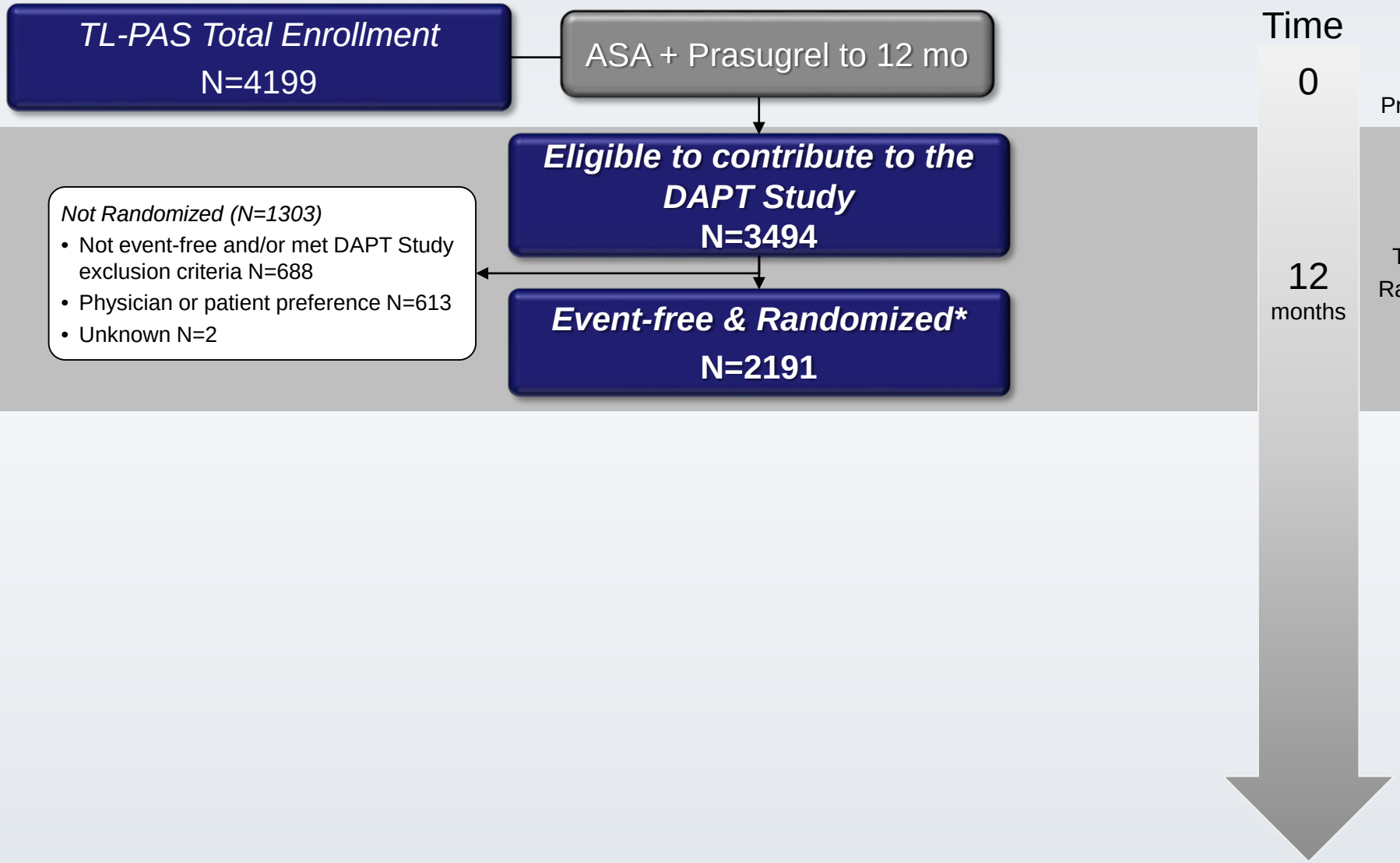
- Major bleeding, defined as moderate or severe by GUSTO classification, occurring between 12-30 months post-procedure

For MI and ST (definite or probable), Academic Research Consortium (ARC) definitions were used: Cutlip et al *Circulation* 2007
For moderate or severe bleeding, Global Utilization of Streptokinase and TPA for Occluded Arteries (GUSTO) definitions were used: GUSTO investigators *N Engl J Med* 1993

Study Oversight

- Potential endpoint events were adjudicated by the TL-PAS Clinical Events Committee (CEC) using uniform definitions; the CEC was blinded to treatment assignment
- Safety within TL-PAS was monitored by the TL-PAS Data Monitoring Committee (DMC)
- Overall DAPT Study data were monitored by the DAPT Study DMC

TL-PAS Patient Flow



Randomization at 12 months permitted only for consenting patients free of death, CABG, stroke, stent thrombosis or major bleeding event at any time after stent placement, and free of MI and any PCI beyond 6 weeks after initial stent placement, and who has been compliant with antiplatelet therapy.

TL-PAS Patient Flow

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Baseline Characteristics

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Characteristic (%, unless noted)	12-month Prasugrel + ASA N=1093 patients	30-month Prasugrel + ASA N=1098 patients	Characteristic (%, unless noted)	12-month Prasugrel + ASA N=1093 patients	30-month Prasugrel + ASA N=1098 patients
Male	74.6	76.3	PCI History	30.9	28.1
Age (years)	59.2 ± 9.5	59.6 ± 9.7	CABG History	12.8	12.0
Age >75 years	2.7	3.8	Bleeding disorder	0.3	0.5
Weight <60 kg	3.5	3.2	Stable angina	30.6	29.4
Diabetes*	27.3	31.4	Unstable angina	32.6	34.5
Metabolic Syndrome	12.5	15.7	Silent ischemia	8.0	8.3
Hyperlipidemia*	69.7	68.1	MI	28.2	27.3
Hypertension*	71.0	71.9	NSTEMI	17.9	15.5
MI History	20.3	20.3	STEMI	9.5	10.7

Numbers are % or mean ± SD; *Medically-treated; MI=myocardial infarction; PCI=percutaneous coronary intervention; CABG=coronary artery bypass graft

Baseline Characteristics

Characteristic	12-month Prasugrel + ASA	30-month Prasugrel + ASA	Characteristic	12-month Prasugrel + ASA	30-month Prasugrel + ASA
Emergent procedure‡	22.7	22.6	Lesions treated* (mean ± SD)	1.3 ± 0.7	1.4 ± 0.7
RVD† (mm)	3.0 ± 0.5	3.0 ± 0.50	Vessels treated* (mean ± SD)	1.2 ± 0.4	1.1 ± 0.4
Length† (mm)	15.8 ± 9.9	15.3 ± 8.7	Stents Implanted* (mean ± SD)	1.4 ± 0.8	1.5 ± 0.8
DS† (%)	85.6 ± 12.0	85.5 ± 11.6	Stent length per patient* (mean ± SD)	28.3±19.0	28.4±18.3
De novo lesions† (%)	96.2	96.4	B2 lesion† (%)	20.1	21.6
Pre-dilatation performed‡ (%)	54.1	53.7	C lesion† (%)	19.4	18.5

RVD=reference vessel diameter; DS=diameter stenosis; SD=standard deviation
12-month Prasugrel + ASA: N=1093 Patients*, N=1465 Lesions†, N=1142 Procedures‡
30-month Prasugrel + ASA: N=1098 Patients*, N=1492 Lesions†, N=1138 Procedures‡

Co-Primary Endpoint: MACCE at 540 days

All Death, ARC MI, Stroke

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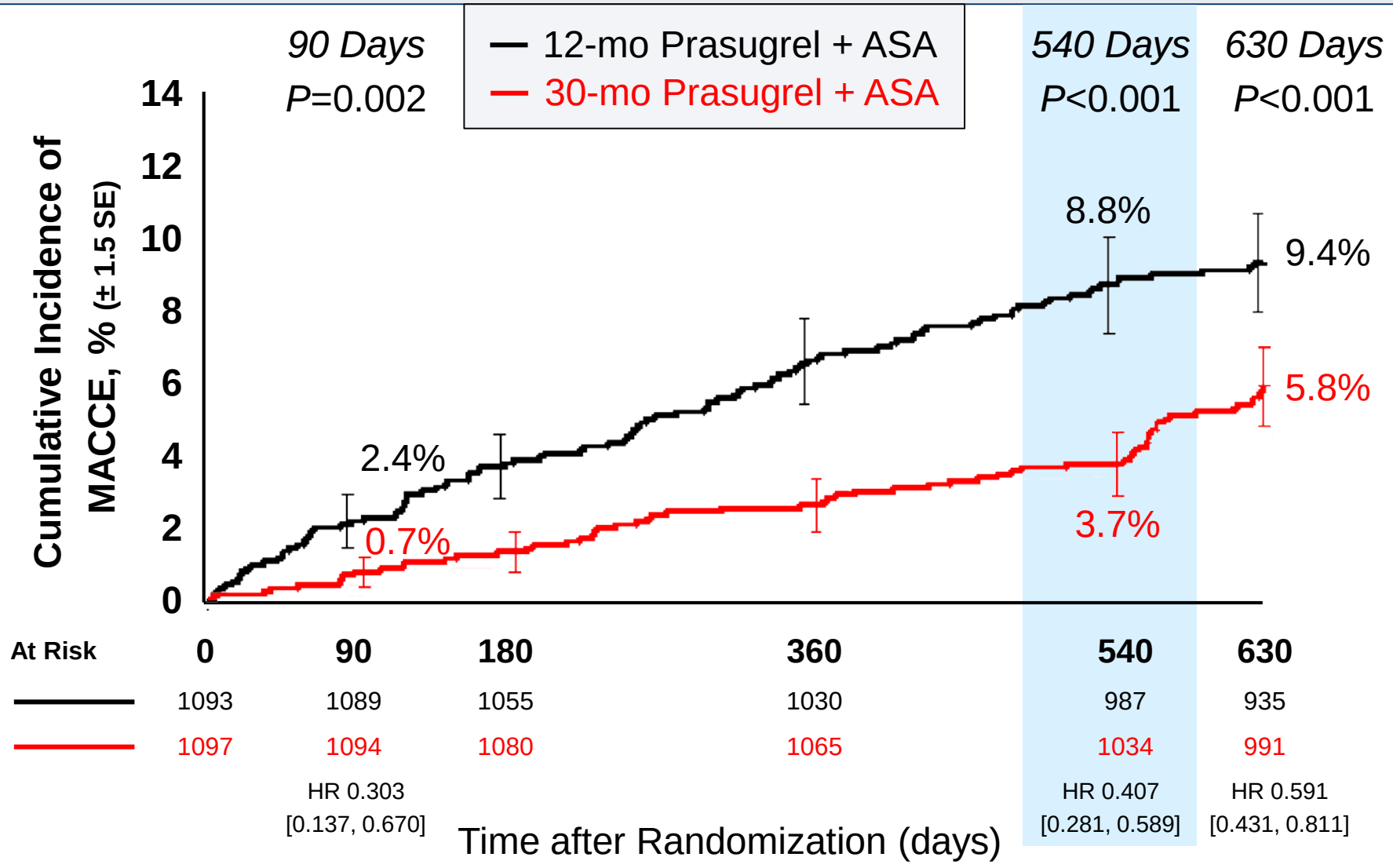

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; HR=Hazard Ratio [95% confidence interval]

Results:
MACCE – All Death, Stroke, and MI

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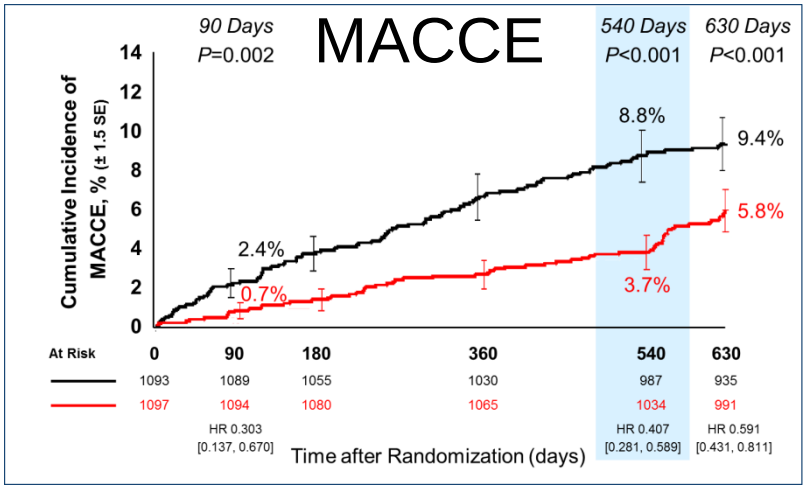
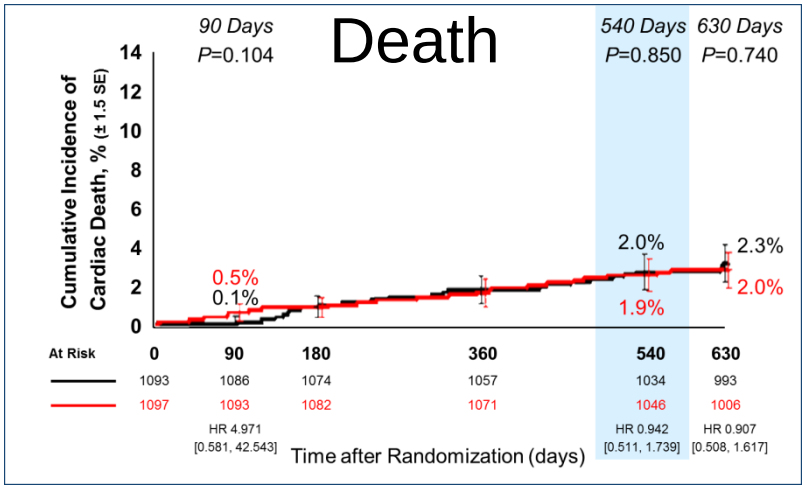
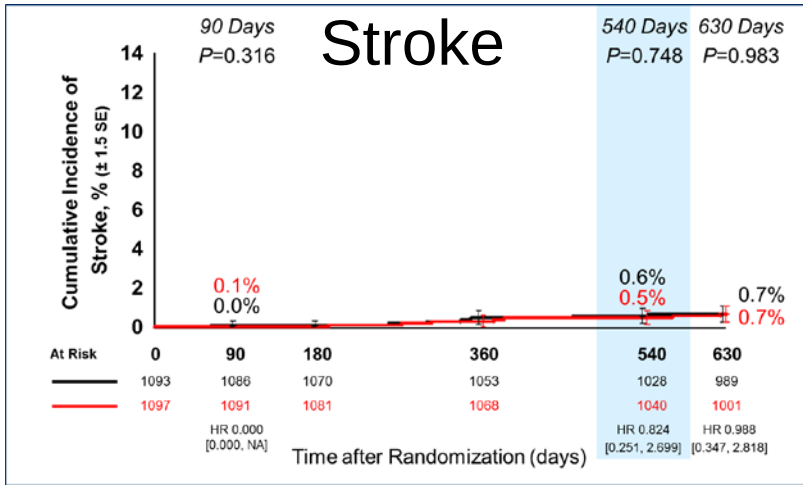
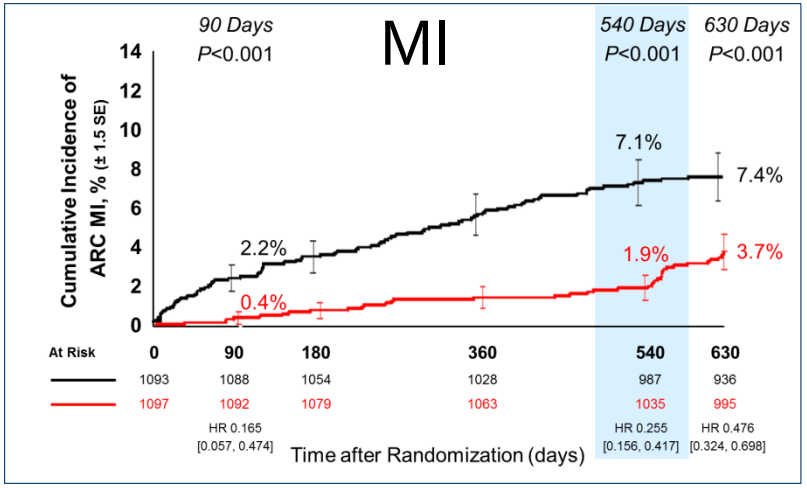
— 12-mo Prasugrel + ASA — 30-mo Prasugrel + ASA









Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; HR=Hazard Ratio [95% confidence interval]

Results: ARC MI

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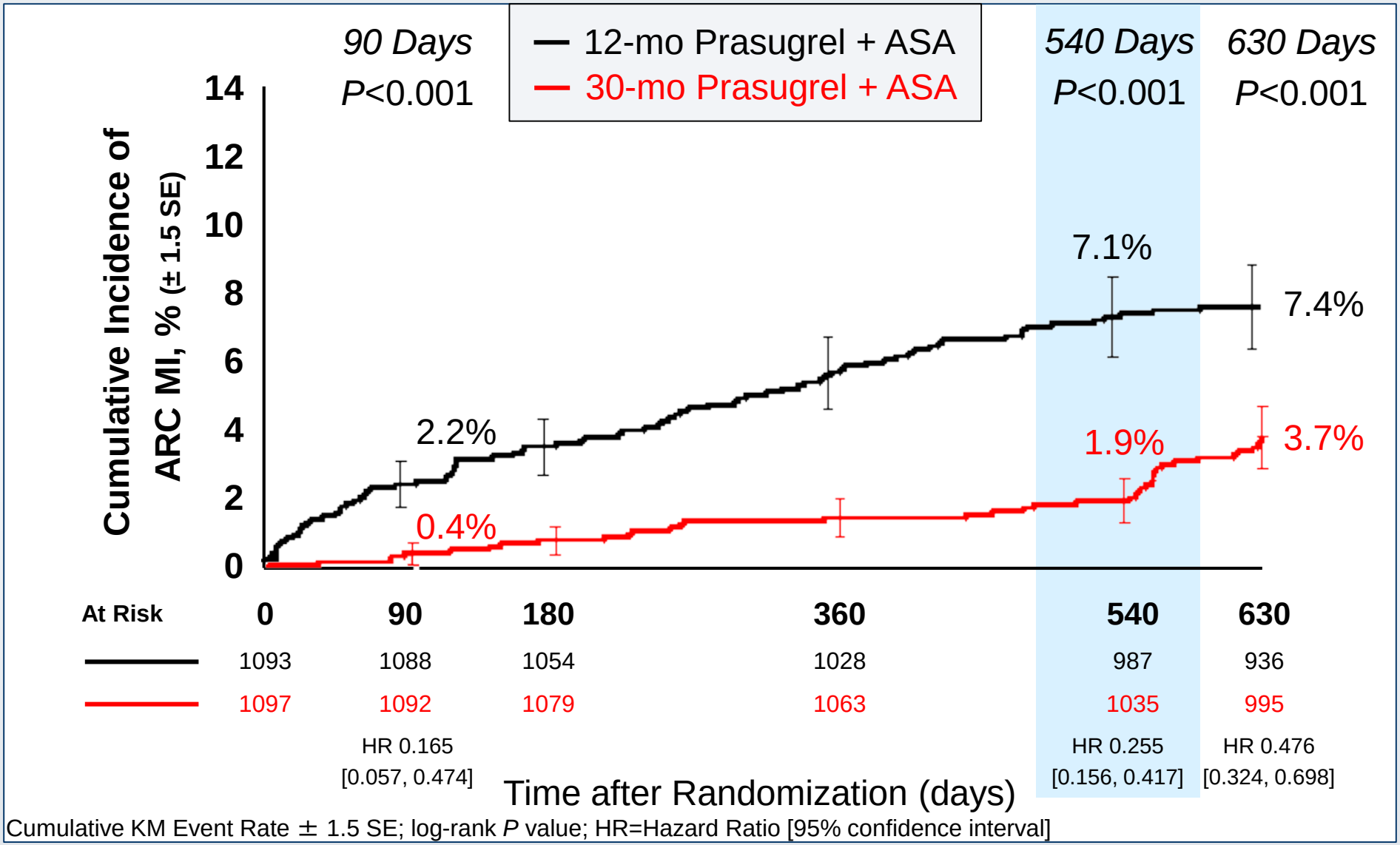

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Co-Primary Endpoint: Definite or Probable ARC Stent Thrombosis at 540 days

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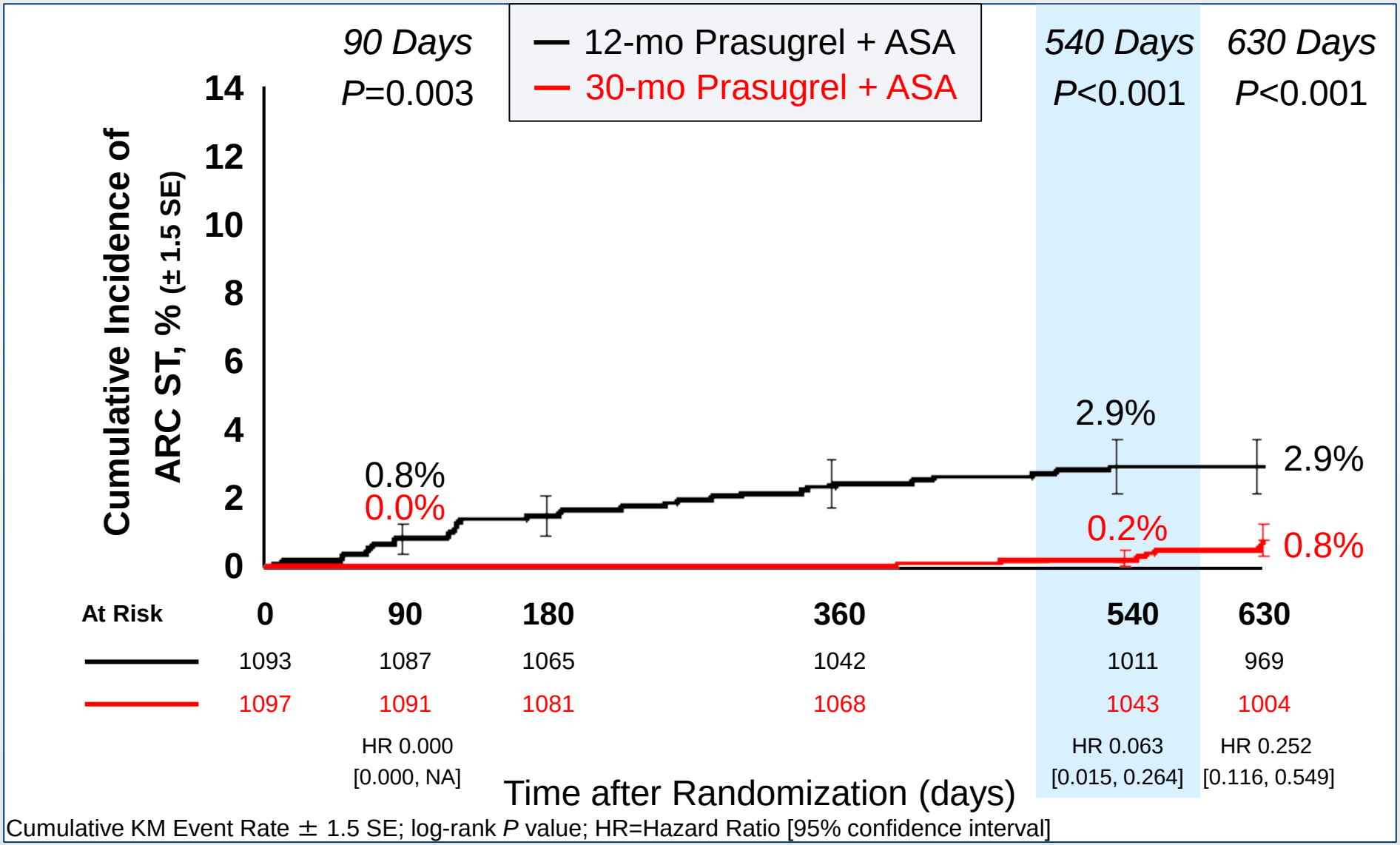
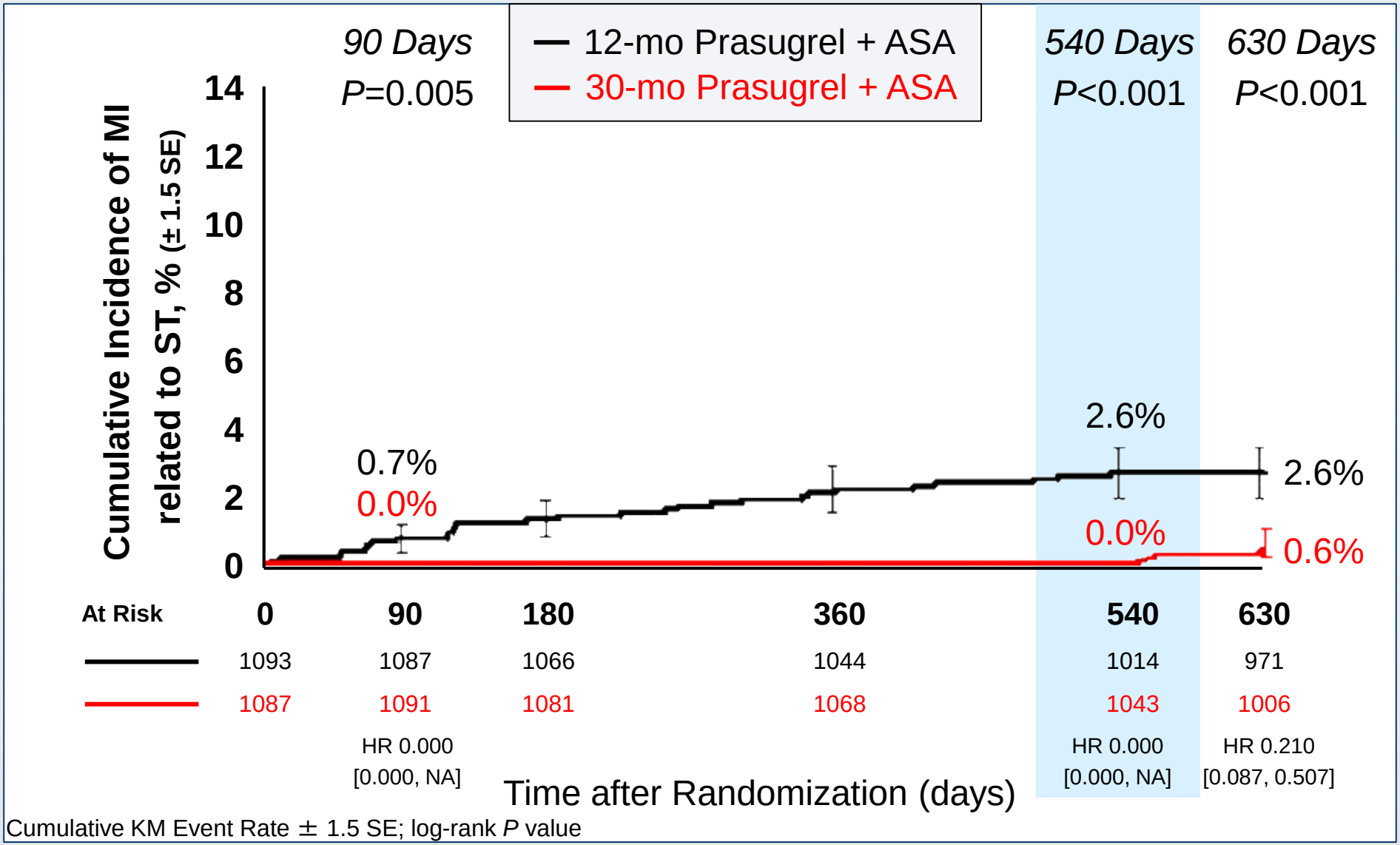


Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; HR=Hazard Ratio [95% confidence interval]

Results: ARC MI related to ST



Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Results: ARC MI not related to ST

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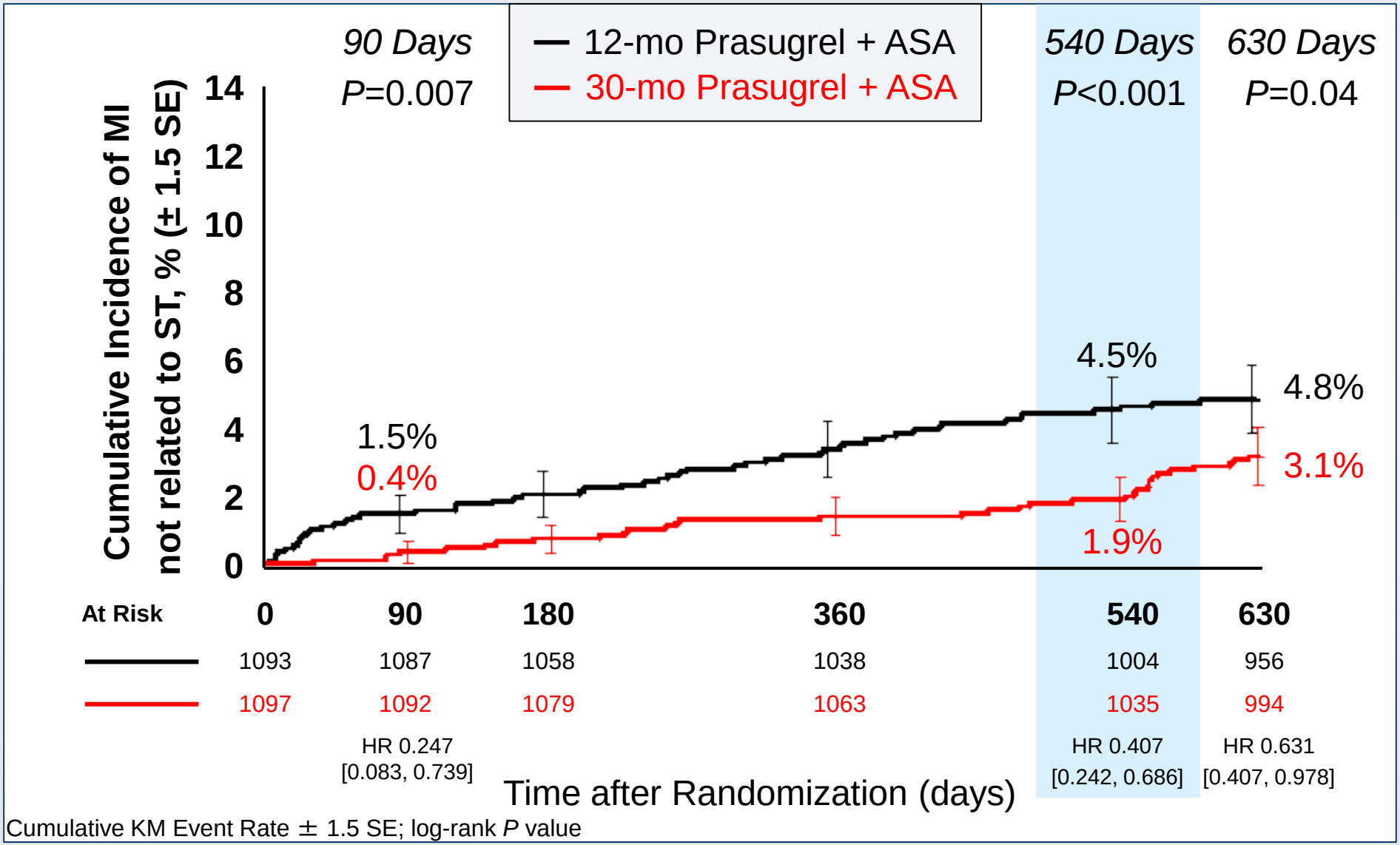

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value

Interim DMC Review

- In mid-2013, TL-PAS DMC noted the early increase in spontaneous ischemic events following withdrawal of active prasugrel therapy in patients randomized to 12 month and 30 month prasugrel + aspirin
- TL-PAS DMC recommended that randomized treatment be unblinded for TL-PAS patients who had not yet completed 30 month follow-up to allow discussion of continuing open-label prasugrel
- Unblinding affected a very small number of patients (N=27) and was conducted at the 30 month time point, after study drug treatment was completed

Results: Major Bleeding
GUSTO Moderate or Severe

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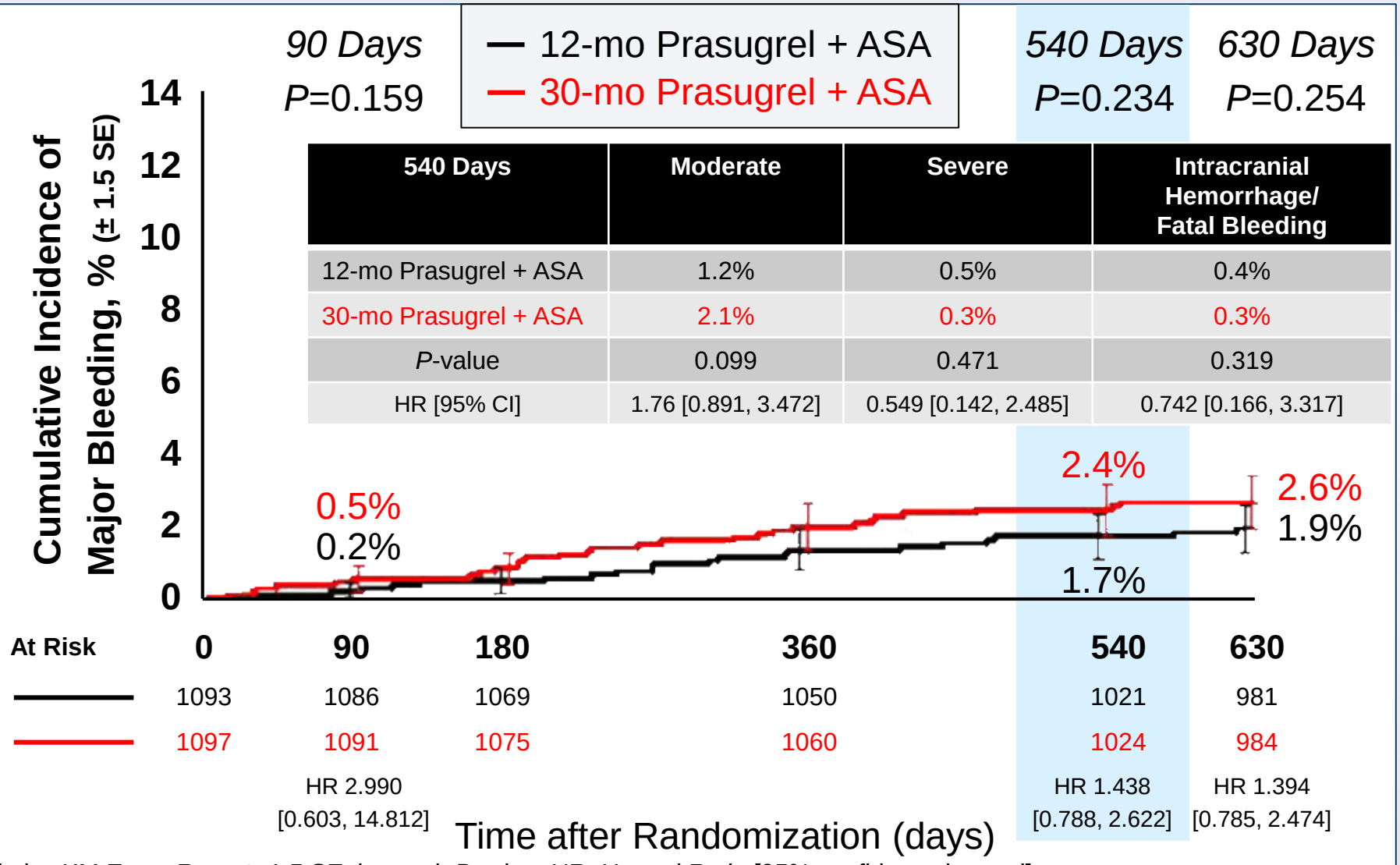


540 Days	Moderate	Severe	Intracranial Hemorrhage/ Fatal Bleeding
12-mo Prasugrel + ASA	1.2%	0.5%	0.4%
30-mo Prasugrel + ASA	2.1%	0.3%	0.3%
P-value	0.099	0.471	0.319
HR [95% CI]	1.76 [0.891, 3.472]	0.549 [0.142, 2.485]	0.742 [0.166, 3.317]

Cumulative KM Event Rate ± 1.5 SE; log-rank *P* value; HR=Hazard Ratio [95% confidence interval]

Limitations

- Analysis of TAXUS Liberté patients from TL-PAS was prespecified but not powered for DAPT Study endpoints
- TL-PAS exclusion criteria included a history of prior cerebrovascular or active pathological bleeding events
- Subjects with very low body mass or advanced age may have been underrepresented
- Randomized subjects tolerated 12 months prasugrel plus aspirin without major bleeding before randomization

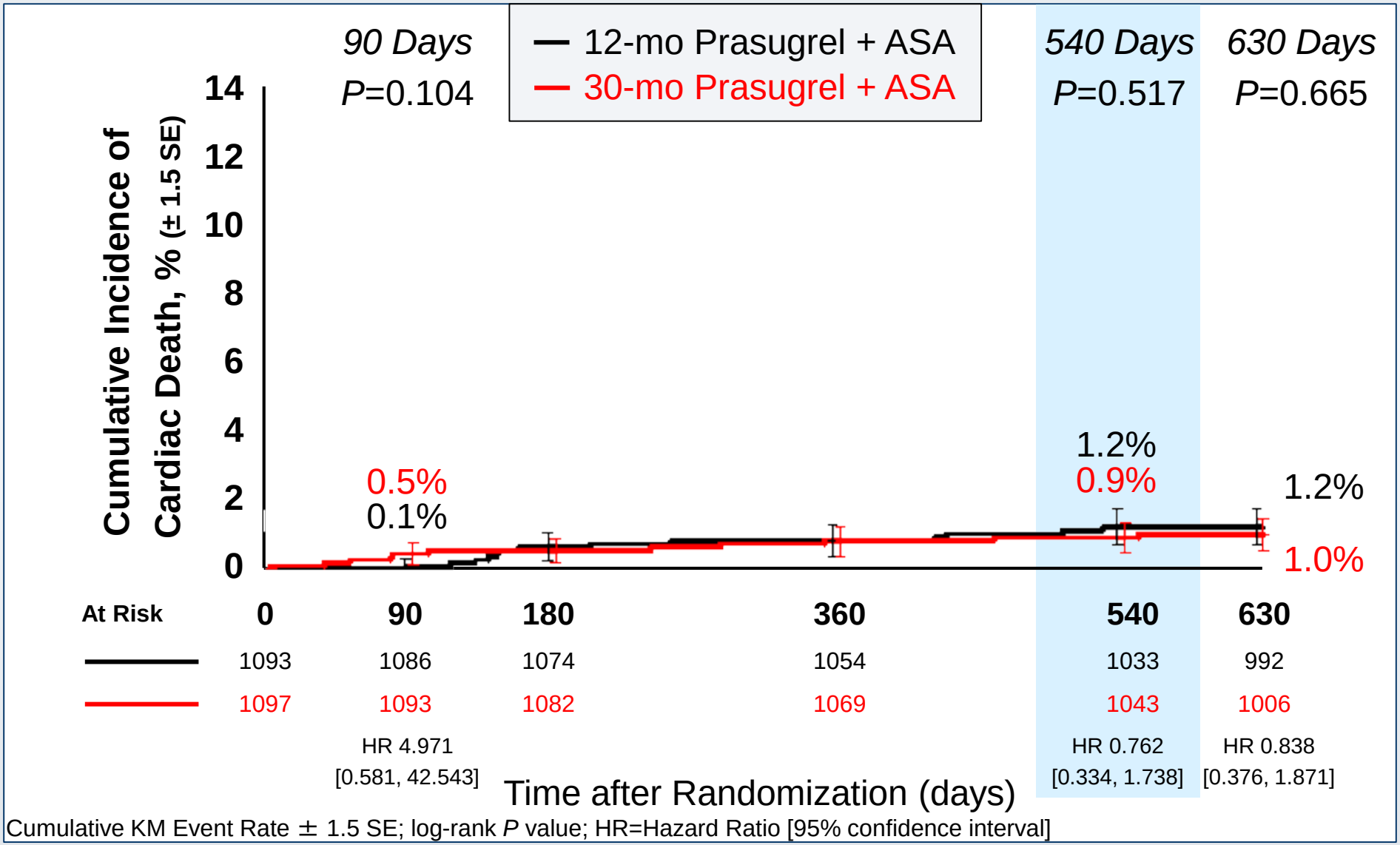
Summary (1)

- **In patients receiving the TAXUS Liberté paclitaxel-eluting stent, 30-month prasugrel + ASA was associated with:**
  - Significant reduction in MACCE (HR = 0.407) primarily related to a reduction in ARC MI (HR = 0.255)
    - ARC MI related to ST (0.0% vs 2.6%)
    - ARC MI not related to ST (1.9% vs 4.5%)
  - Significant reduction in ARC definite or probable ST (HR = 0.063)
  - A modest increase in GUSTO moderate or severe bleeding (HR = 1.438) without an increase in intracranial hemorrhage or fatal bleeding

Summary (2)

- **Withdrawal of prasugrel resulted in apparent loss of protection, with an early increase in ischemic events, when stopped after 12 months or 30 months**
  - Principal risk was increased MI
  - Difference significant within 90 days of prasugrel cessation
- **Whether the reduction in late ischemic events demonstrated with prasugrel + ASA and the TAXUS Liberté paclitaxel-eluting coronary stent would be observed with other dual anti-platelet regimens and/or other drug-eluting stents will require further study including insights from the larger DAPT Study**

Results: Cardiac Death



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