Clinical Update of Resolute Integrity with DAPT

Pooled RESOLUTE Clinical Program

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Author Disclosures

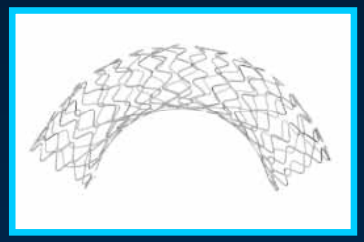
- I am a full-time employee of Medtroinc CardioVascular
- I currently own stock or other investments in Medtronic in excess of >$10,000

Resolute Integrity™ DES

System Components

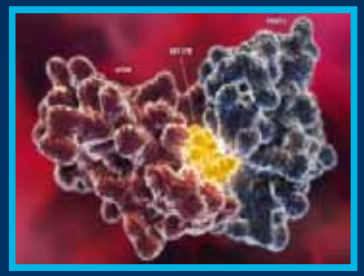
Established Components

- Integrity™ cobalt alloy stent



- MicroTrac™ delivery system

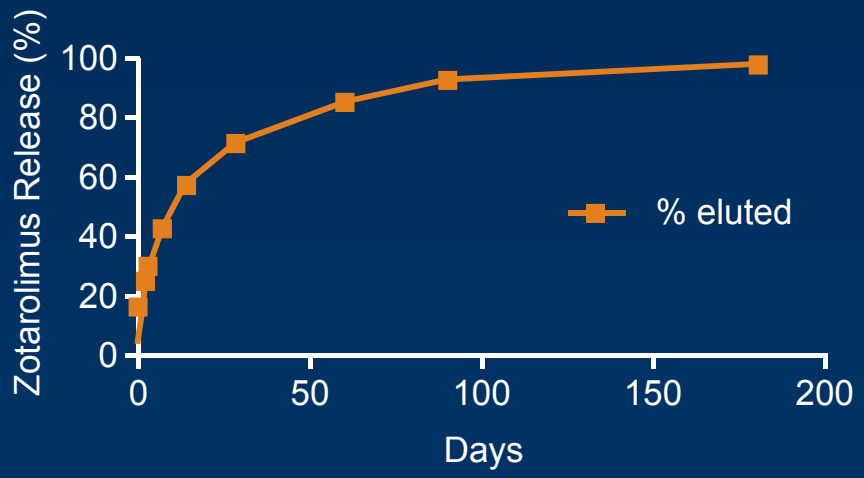
- Zotarolimus antiproliferative drug



Unique Polymer Technology

- BioLinx™ polymer is a unique blend of three polymers to control drug release, support biocompatibility and enhance elution rate

- Drug-release kinetics: complete elution by 180 days



Udipi K, et al. *EuroIntervention.* 2007; 3:137-9
Meredith IT, et al. *J Am Coll Cardiol Intv*. 2009; 2:977-85
Meredith IT, et al. *EuroIntervention*. 2007; 3:50-53

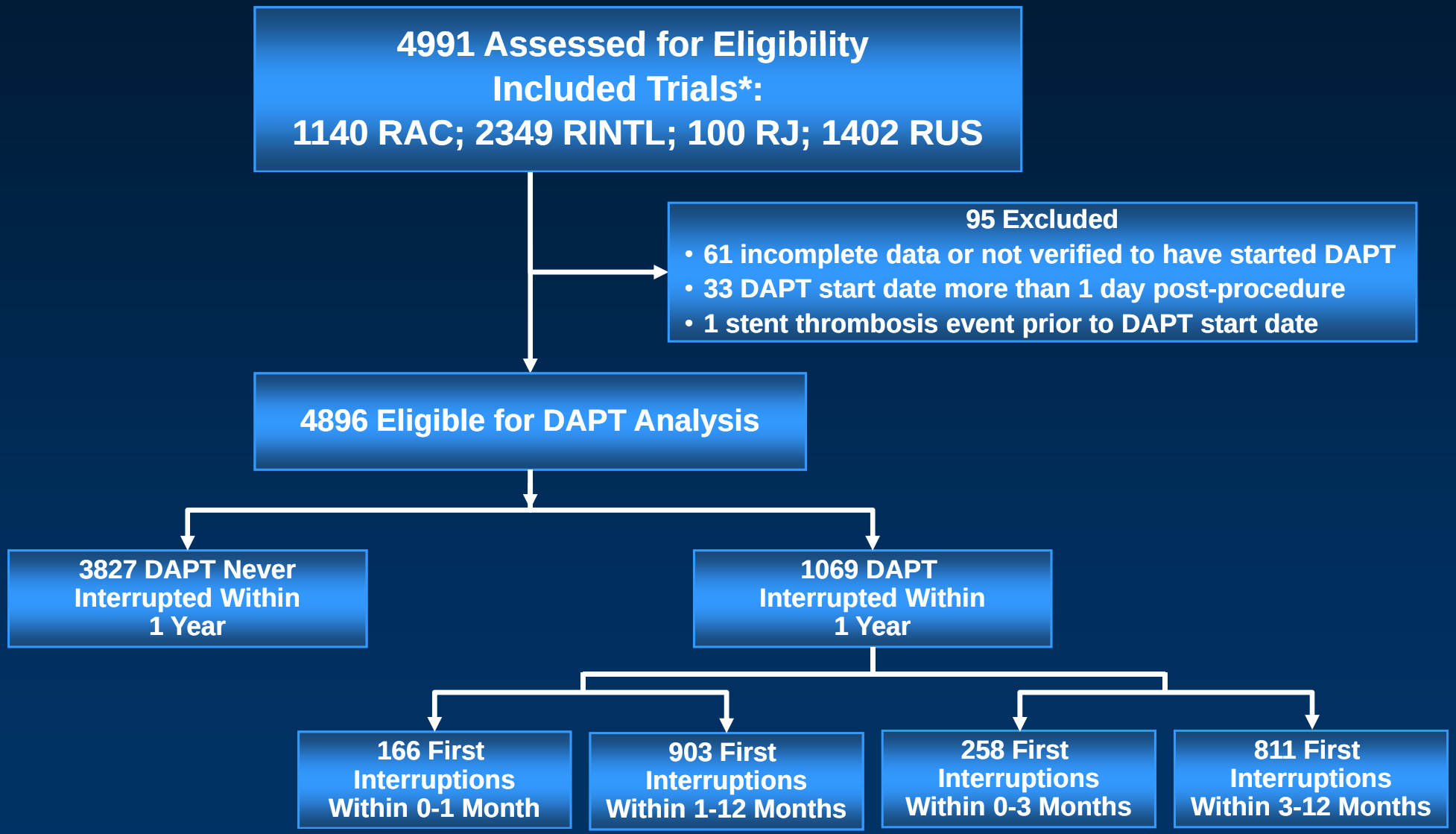
Background

- Continuation of dual antiplatelet therapy (DAPT), consisting of aspirin plus a P2Y12 receptor antagonist, is currently recommended for 12 months following drug-eluting stent (DES) implantation.
- Observational data suggest that a significant proportion of patients either interrupt or are unable to tolerate DAPT in this period.
- It is unclear if earlier interruption and/or discontinuation of DAPT is associated with a higher risk of stent thrombosis (ST), particularly with newer generation DES.

Methods

- One-year ST data from 4896 patients treated with a Resolute™ Zotarolimus-eluting stent (R-ZES) in the global RESOLUTE Clinical Program were analyzed according to DAPT status.
- ST was assessed based on the timing of first DAPT interruption (0-3 vs >3-12 months; 0-1 vs >1-12 months), and was further categorized by the type of interruption (permanent, all interruptions >1 day and interruptions >14 days).

Patient Flow and Stent Thrombosis Through 1 Year



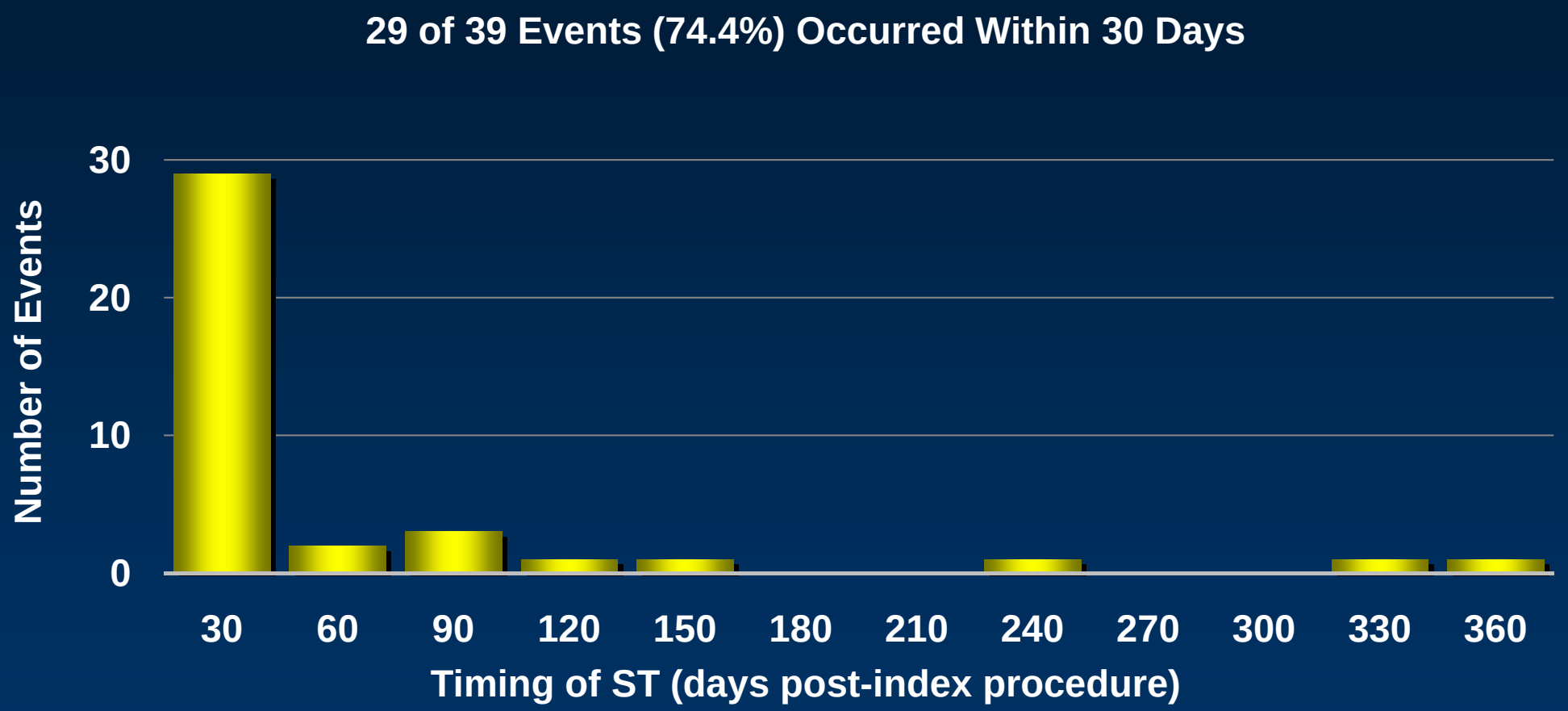
*All trials within the Pooled RESOLUTE Program were included in this analysis with the exception of RESOLUTE FIM. The RESOLUTE FIM protocol did not require DAPT data collection.

Baseline Patient and Lesion Characteristics From the Pooled RESOLUTE Program

Baseline Characteristics (%)	*All Patients Included in the Analysis N = 4896*
Age (years) Mean ± SD (N)	63.9 ± 11.0
History of Smoking	58.7
Prior Percutaneous Coronary Revascularization	31.0
Diabetes Mellitus	30.1
Insulin Dependent	8.9
Prior MI	25.8
ACS	41.9
STEMI	8.2
NSTEMI	7.9
Unstable Angina	25.8
Lesion Class ACC/AHA - B2/C	66.6
Pre-procedure RVD (mm) Mean ± SD (N)	2.78 ± 0.51
Lesion Length (mm) Mean ± SD (N)	15.74 ± 9.50
No. of stents per patient	1.5 ± 0.9
Total Length of stents per patient	29.0 ±19.5
Implanted stent diameter per lesion	3.0 ± 0.4

Timing of Stent Thrombosis

N = 4896 Resolute™ ZES Patients



Timing of Stent Thrombosis

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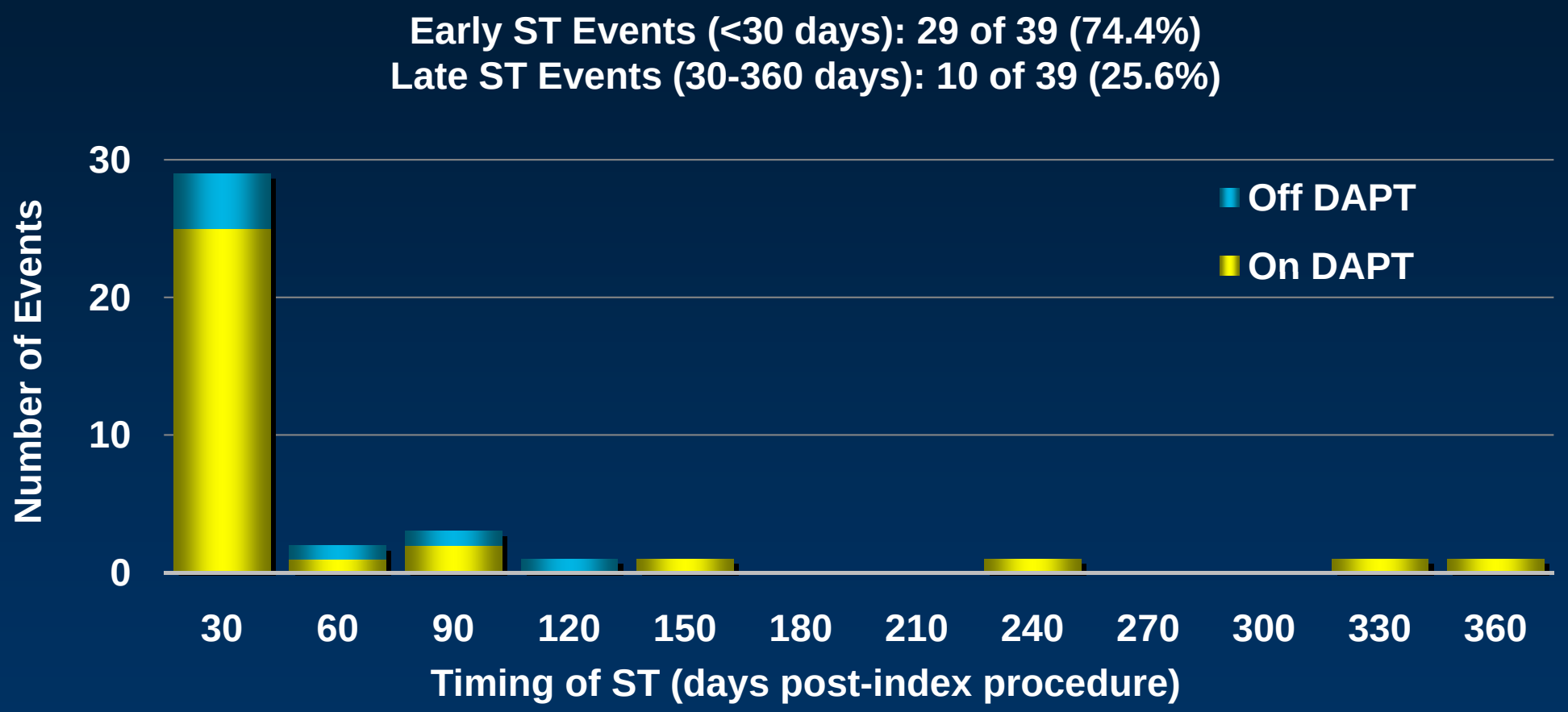
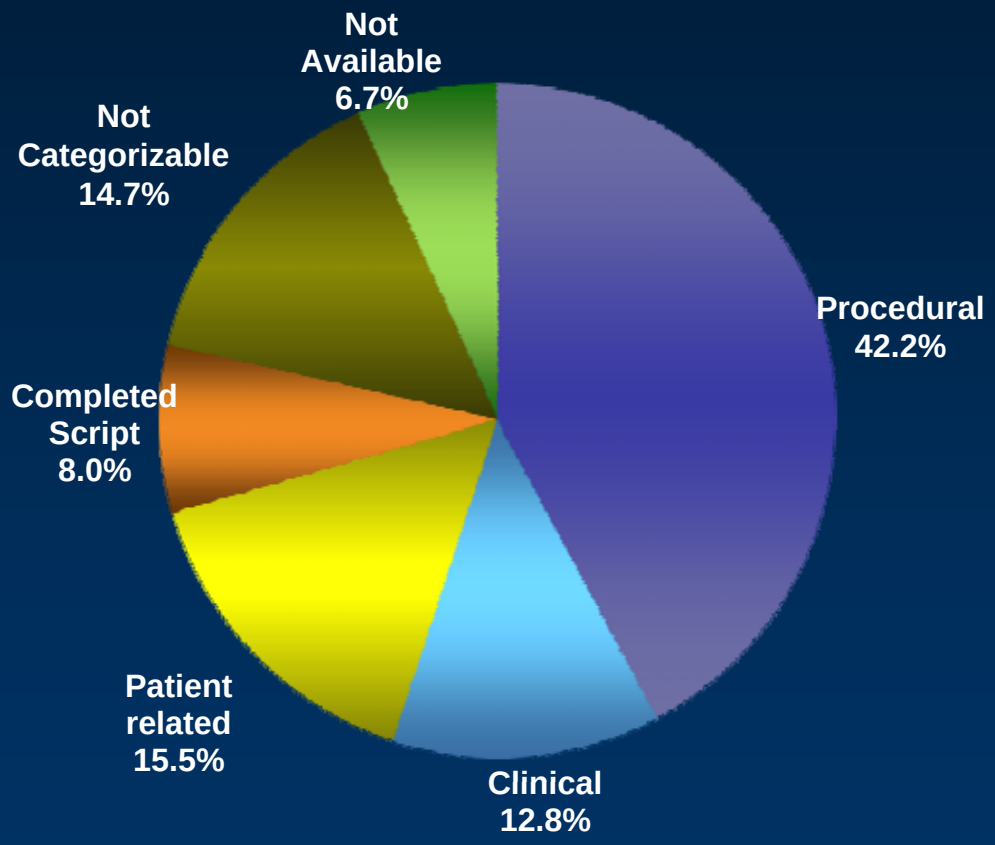
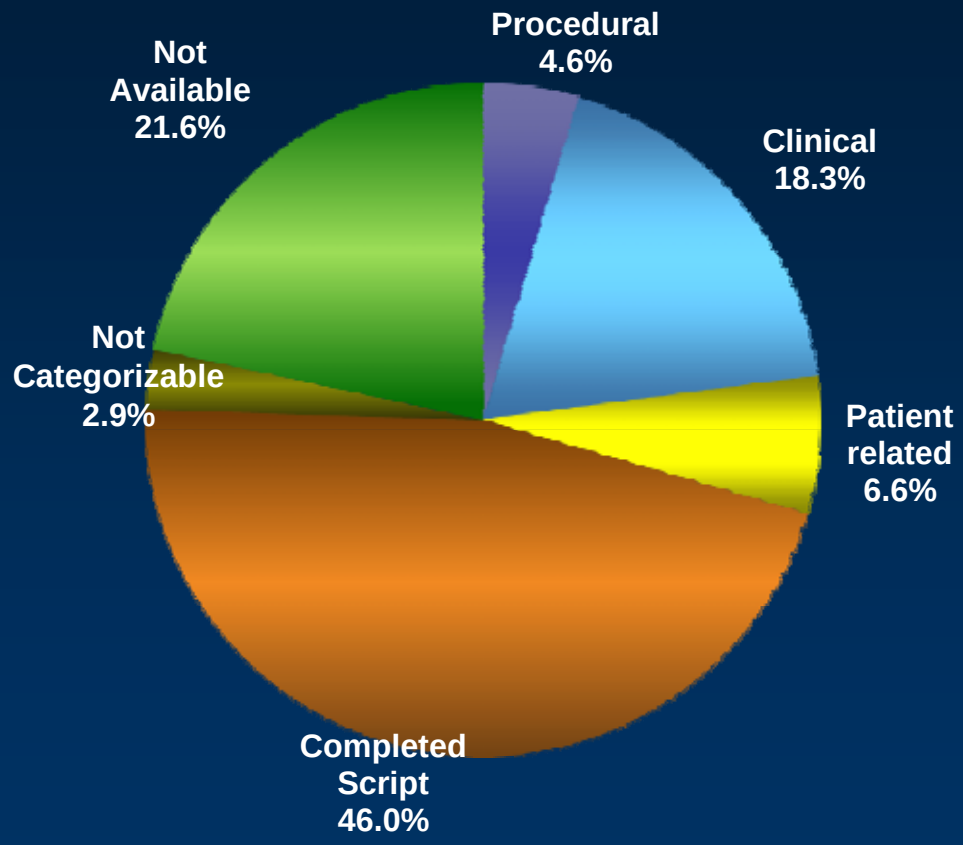


Reasons Given for DAPT Temporary Interruption and Permanent Discontinuation

Reasons Given for DAPT Temporary Interruption



Reasons Given for DAPT Permanent Discontinuation



Procedural = surgical, medical, dental procedures including screening and diagnostic tests
Clinical = clinical status such as allergies or bleeding
Patient related = inadvertently not taken or change of dose

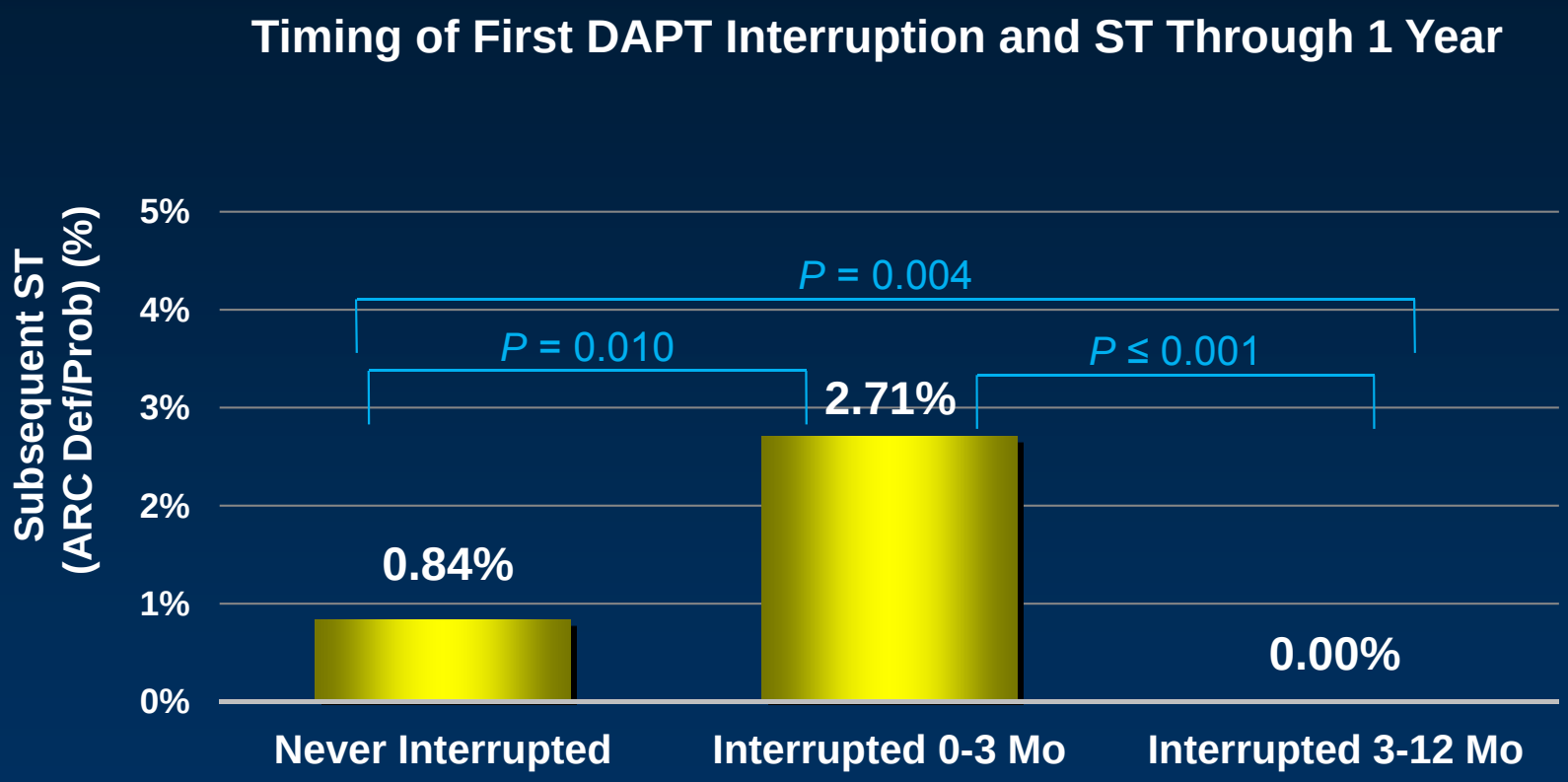
Baseline Demographic and Lesion Characteristics

Never Interrupted vs All Interruptions

Baseline Characteristics (%)	*Never Interrupted N = 3827 Patients*	*All Interruptions N = 1069 Patients*	*P-value*
Age (years) Mean ± SD (N)	63.4 ± 10.8	65.7 ± 11.4	<0.001
History of Smoking	59.1	57.5	0.380
Prior Percutaneous Coronary Revascularization	30.7	32.2	0.370
Diabetes Mellitus	29.6	31.9	0.163
Insulin Dependent	8.5	10.3	0.079
Prior MI	25.6	26.4	0.605
ACS	42.4	40.3	0.234
STEMI	8.5	7.1	0.148
NSTEMI	7.8	8.2	0.607
Unstable Angina	26.1	25.0	0.502
Lesion Class ACC/AHA B2/C	65.9	69.2	0.025
Pre-procedure RVD (mm) Mean ± SD (N)	2.79 ± 0.51	2.75 ± 0.53	0.010
Lesion Length (mm) Mean ± SD (N)	15.93 ± 9.66	15.04 ± 8.85	0.002

Pooled RESOLUTE: 3 Months

All Interruptions



# of pts at risk at baseline	3827	258	811
# of events	32	7	0
# of days to interruption (median)	NA	15	275
95% CI	(0.57, 1.18)	(1.10, 5.51)	(0.00, 0.37)

Baseline Demographic and Lesion Characteristics

Temporary Interruptions and Interruptions >14 Days

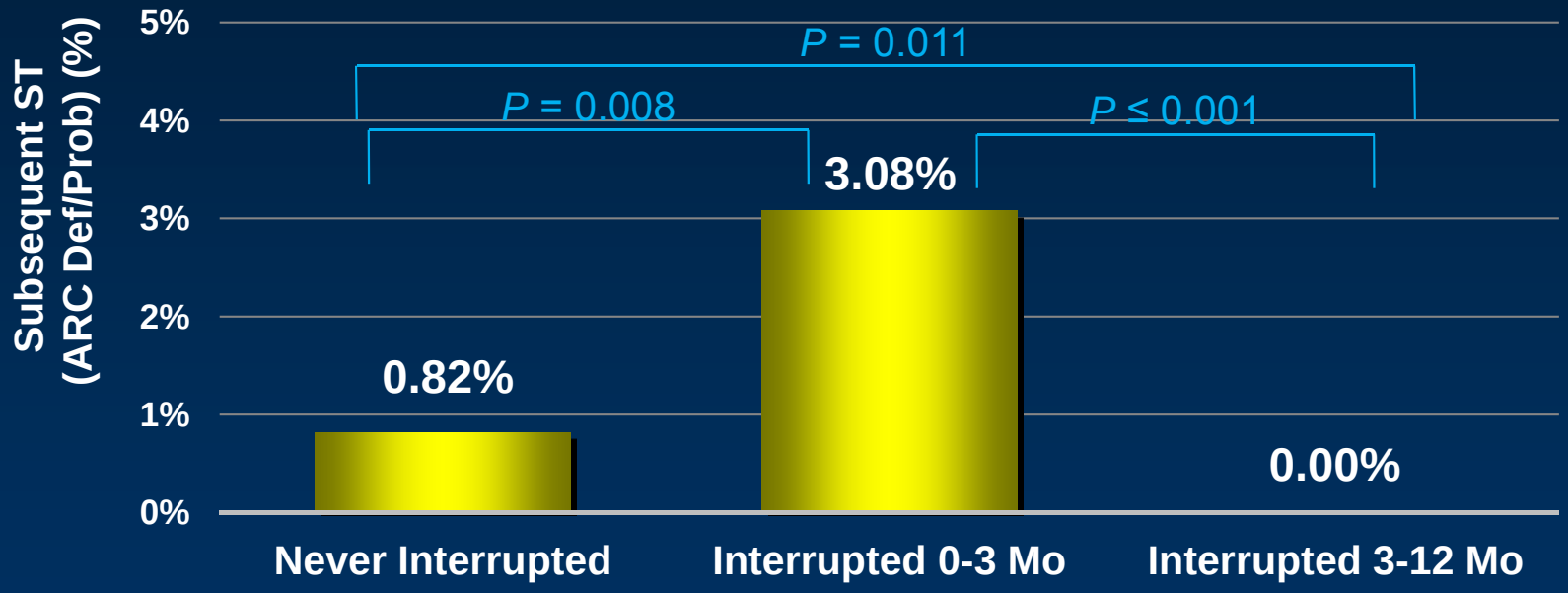
Baseline Characteristics (%)	*Temporary Interruptions N = 374 Patients*	*Interruptions >14 Days N = 874 Patients*
Age (years) Mean ± SD (N)	65.9 ± 11.3	65.7 ± 11.3
History of Smoking	61.2	56.6
Prior Percutaneous Coronary Revascularization	35.0	31.8
Diabetes Mellitus	34.5	31.5
Insulin Dependent	10.2	10.4
Prior MI	24.8	27.6
ACS	37.7	40.4
STEMI	4.5	7.4
NSTEMI	5.3	8.9
Unstable Angina	27.8	24.0
Lesion Class ACC/AHA		
B2/C	71.6	67.9
Pre-procedure RVD (mm) Mean ± SD (N)	2.66 ± 0.53	2.77 ± 0.53
Lesion Length (mm) Mean ± SD (N)	14.80 ± 8.41	14.91 ± 8.78

Pooled RESOLUTE: 3 Months

>14 Days Of Interruption Or Discontinuation Only

Interruption duration >14 days, chosen to define compliance in the Dual Antiplatelet Therapy (DAPT) Study.

Timing of First DAPT Interruption (>14 Days) and ST Through 1 Year



	Never Interrupted	Interrupted 0-3 Mo	Interrupted 3-12 Mo
# of pts at risk at baseline	4022	195	679
# of events	33	6	0
# of days to interruption (median)	NA	15	296
95% CI	(0.57, 1.15)	(1.14, 6.58)	(0.00, 0.44)

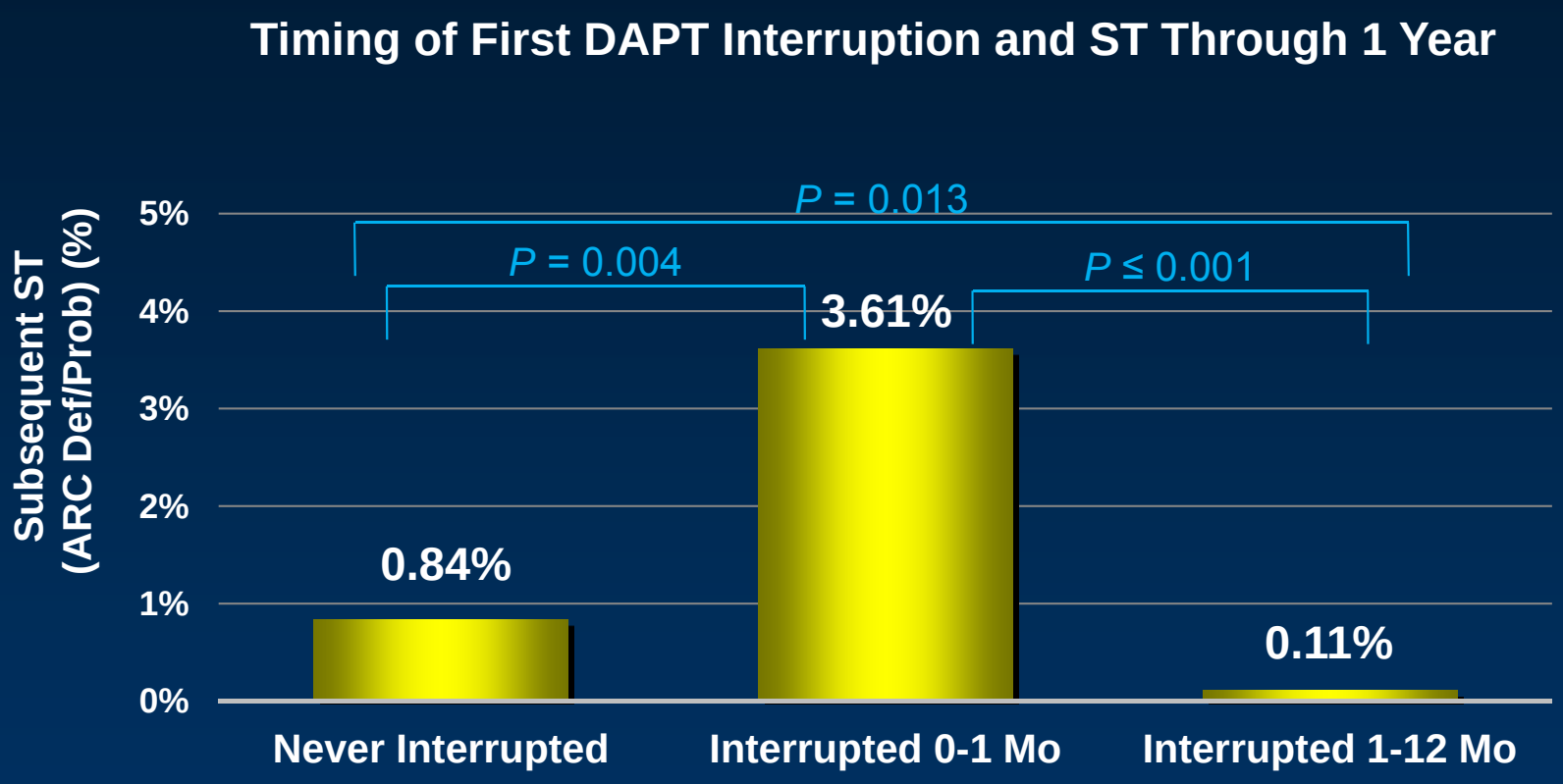
Baseline Demographic and Lesion Characteristics

Interrupted 0-1 Month vs Interrupted 1-12 Months

Baseline Characteristics (%)	*Interrupted 0-1 Month N = 166 Patients*	*Interrupted 1-12 Months N = 903 Patients*	*P-value*
Age (years) Mean ± SD (N)	66.6 ± 12.0	65.5 ± 11.3	0.236
History of Smoking	53.0	58.4	0.201
Prior Percutaneous Coronary Revascularization	27.1	33.1	0.148
Diabetes Mellitus	32.5	31.8	0.857
Insulin Dependent	10.8	10.2	0.782
Prior MI	22.7	27.1	0.288
ACS	42.2	40.0	0.606
STEMI	8.4	6.9	0.510
NSTEMI	7.8	8.3	1.000
Unstable Angina	25.9	24.8	0.770
Lesion Class ACC/AHA			
B2/C	72.7	68.5	0.254
Pre-procedure RVD (mm) Mean ± SD (N)	2.70 ± 0.56	2.76 ± 0.53	0.149
Lesion Length (mm) Mean ± SD (N)	14.77 ± 8.33	15.09 ± 8.95	0.645

Pooled RESOLUTE: 1 Month

All Interruptions

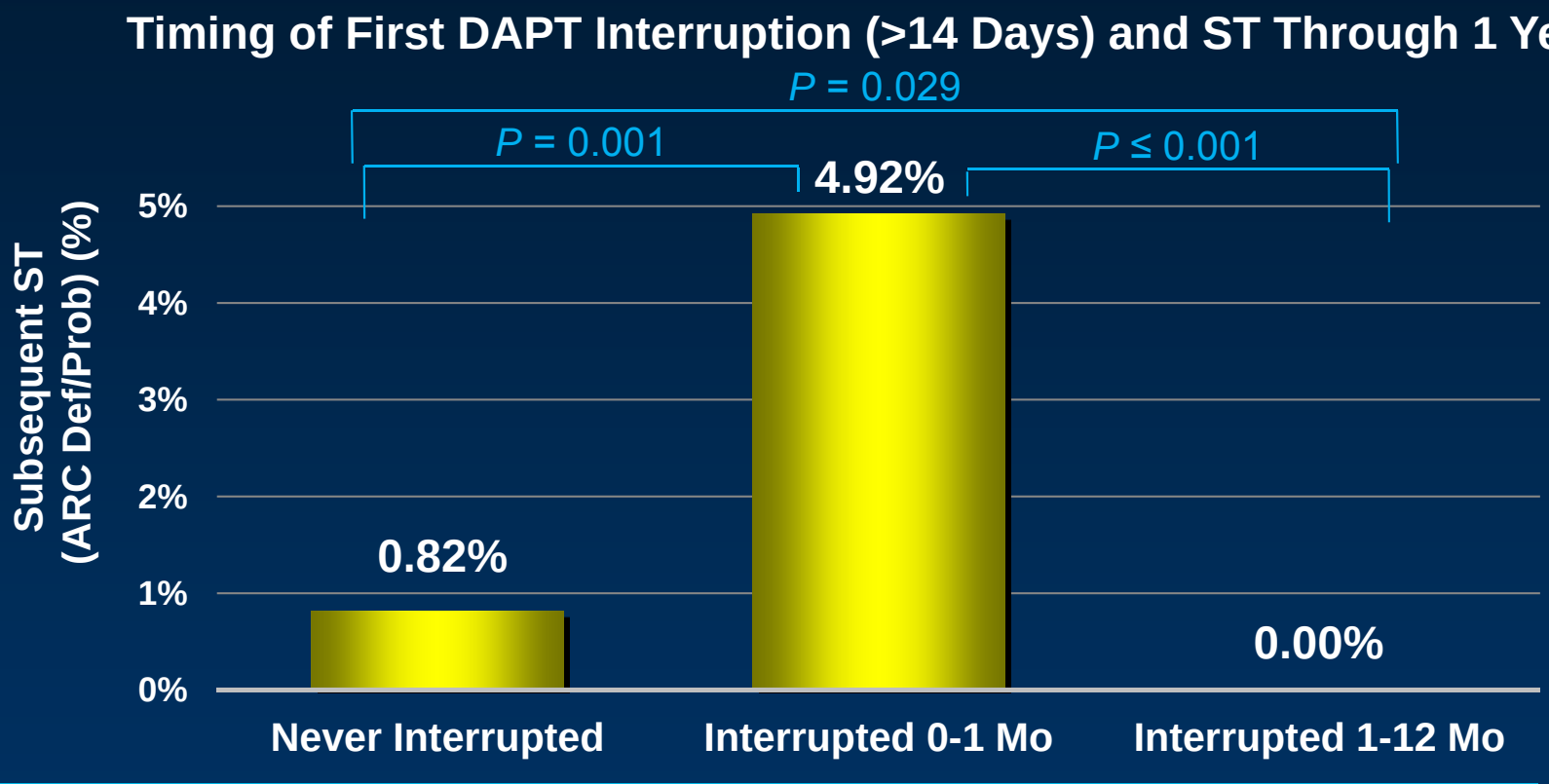


# of pts at risk at baseline	3827	166	903
# of events	32	6	1
# of days to interruption (median)	NA	3	249
95% CI	(0.57, 1.18)	(1.34, 7.70)	(0.00, 0.62)

Pooled RESOLUTE: 1 Month

>14 Days of Interruption or Discontinuation Only

Interruption duration >14 days, chosen to define compliance in the Dual Antiplatelet Therapy (DAPT) Study.

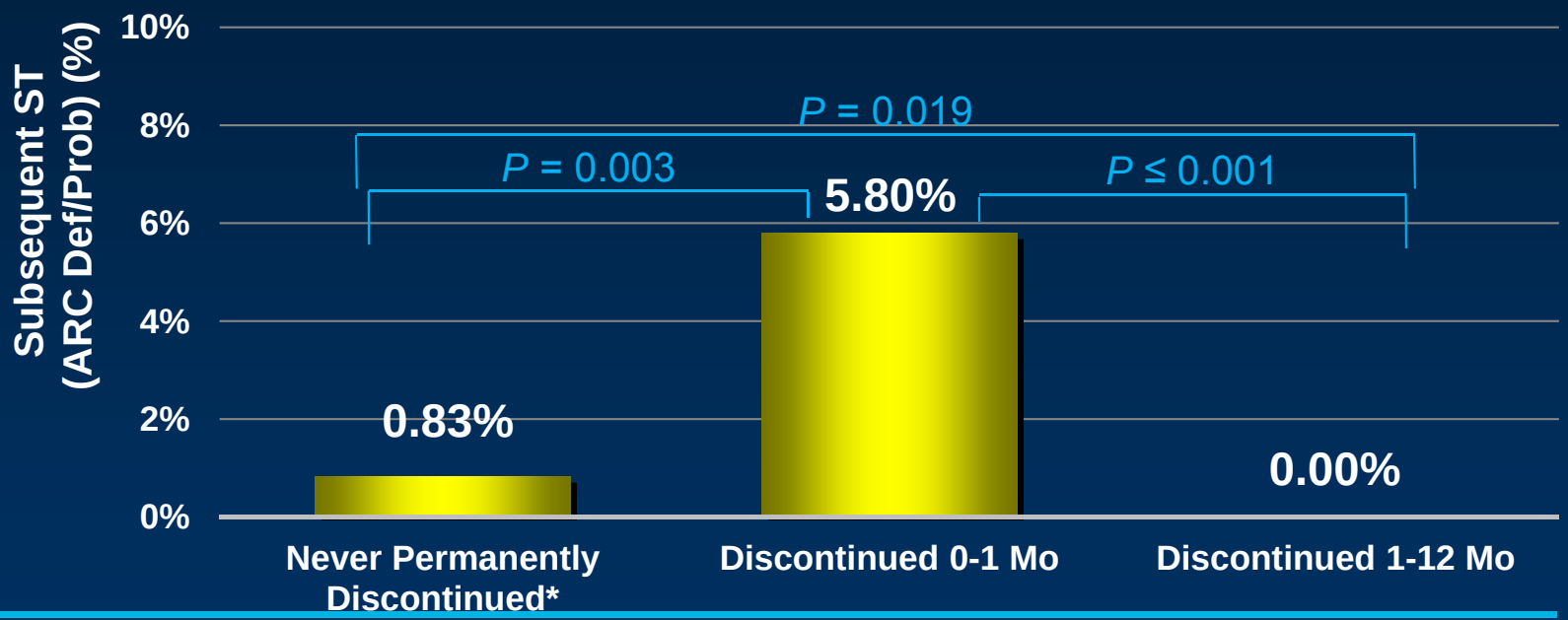


# of pts at risk at baseline	4022	122	752
# of events	33	6	0
# of days to interruption (median)	NA	3	266
95% CI	(0.57, 1.15)	(1.83, 10.40)	(0.00, 1.12)

Pooled RESOLUTE: 1 Month

1ST Interruption Was Permanent Discontinuation

Timing of DAPT Permanent Discontinuation and ST Through 1 Year

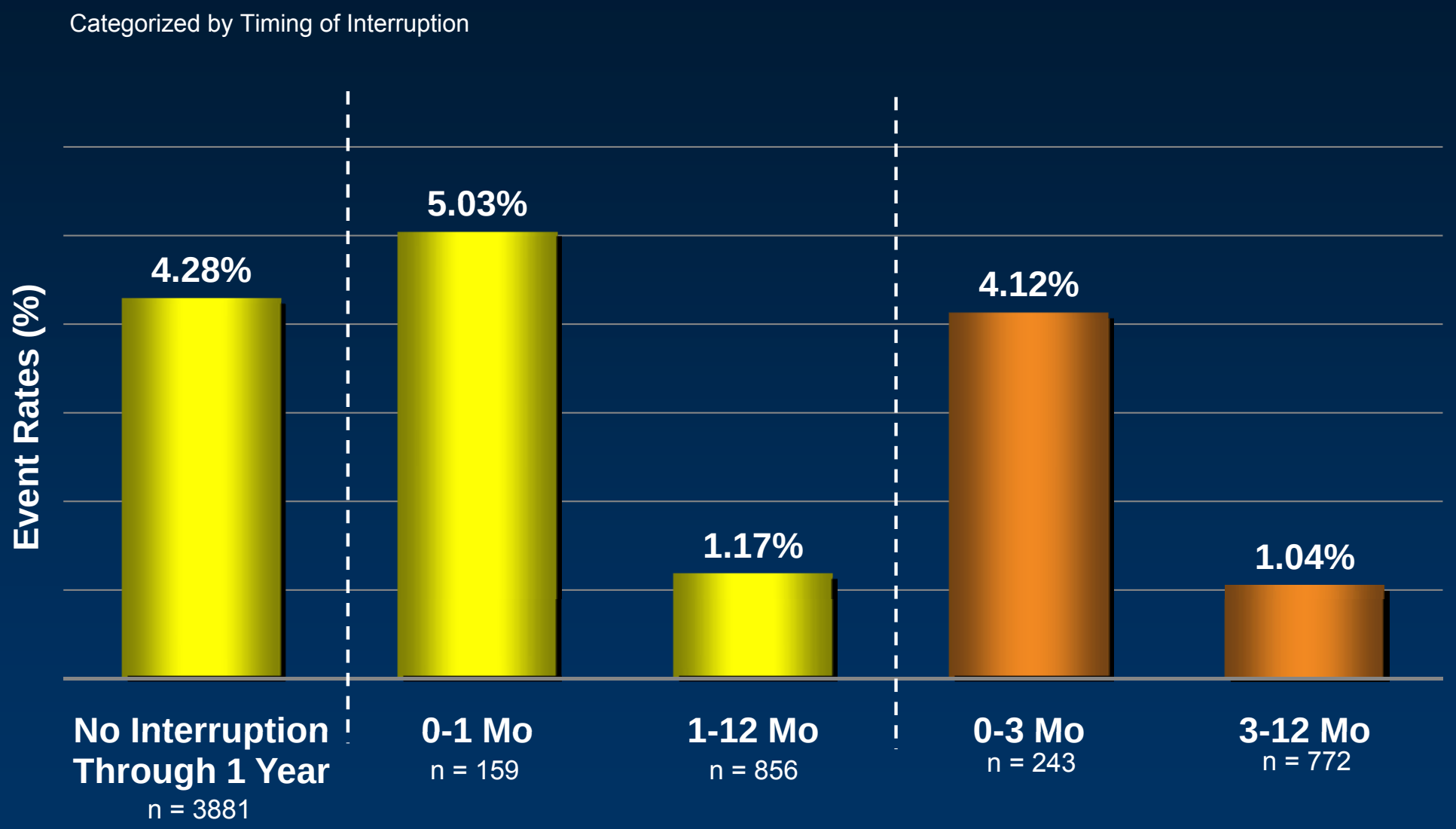


	Never Permanently Discontinued*	Discontinued 0-1 Mo	Discontinued 1-12 Mo
# of pts at risk at baseline	4201	69	626
# of events	35	4	0
# of days to interruption (median)	NA	1	295
95% CI	(0.58, 1.16)	(1.60, 14.18)	(0.00, 0.48)

*Including patients with no DAPT interruption except for ST while on DAPT through 12 months.

RESOLUTE Pooled

Risk of Cardiac Death/Target Vessel MI



Risk of CD/TVMI during the first year after with and without DAPT interruption.

DAPT Language in Updated CE Mark IFU

- **Significant Statement of Finding**

> One year data from the RESOLUTE Clinical Program indicates low stent thrombosis rates for those that interrupted or discontinued DAPT any time after one month. While physicians should adhere to current ESC or ACC/AHA/SCAI Guidelines for PCI, patients who interrupt or discontinue DAPT medication one month or more after stent implantation are considered at low risk and showed no increased risk for stent thrombosis.

Strengths and Limitations

Strengths:

- **All data were collected from regulatory trials with 100% monitoring (except for RESOLUTE International with 25% randomly assigned monitoring) and high rates of follow-up.**

Limitations:

- **This is a post-hoc analysis of pooled datasets, the generalized application of these results to the entire population demands careful attention given that a larger sample size might be required to provide a definite answer regarding low frequency events such as ST.**

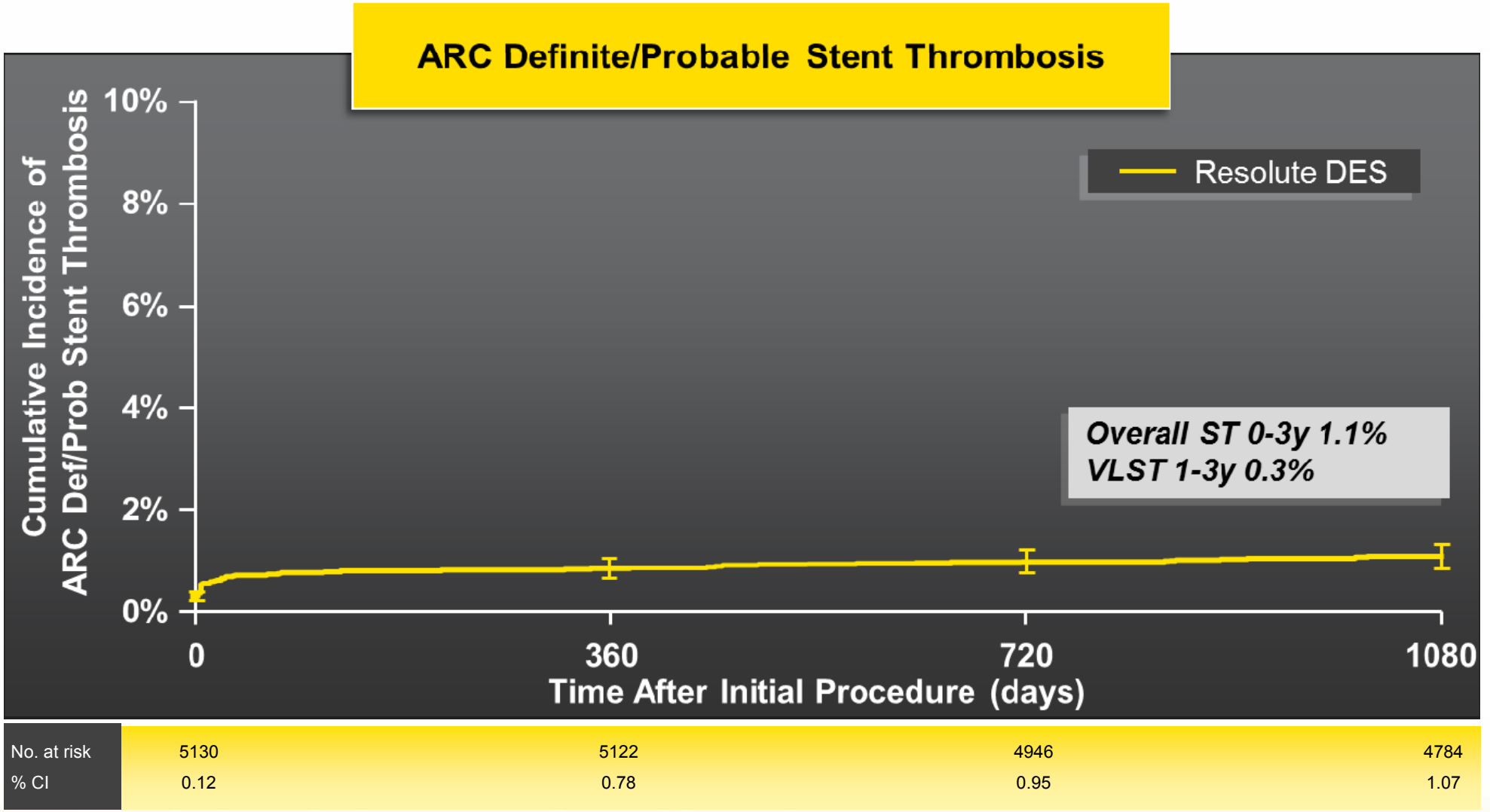
Medtronic Notification on Dual Antiplatelet Therapy

- **Medtronic fully supports the clinical guidelines and understands that the physician is the ultimate DAPT decision-maker.**

- **Medtronic recommends that you follow the recommendations for the Resolute DES as set forth in the IFU.**

Resolute™ DES Showed Low 1.1% ST Rate in More Than 5000 Patients

RESOLUTE Pooled* Stent Thrombosis Rate to Three Years

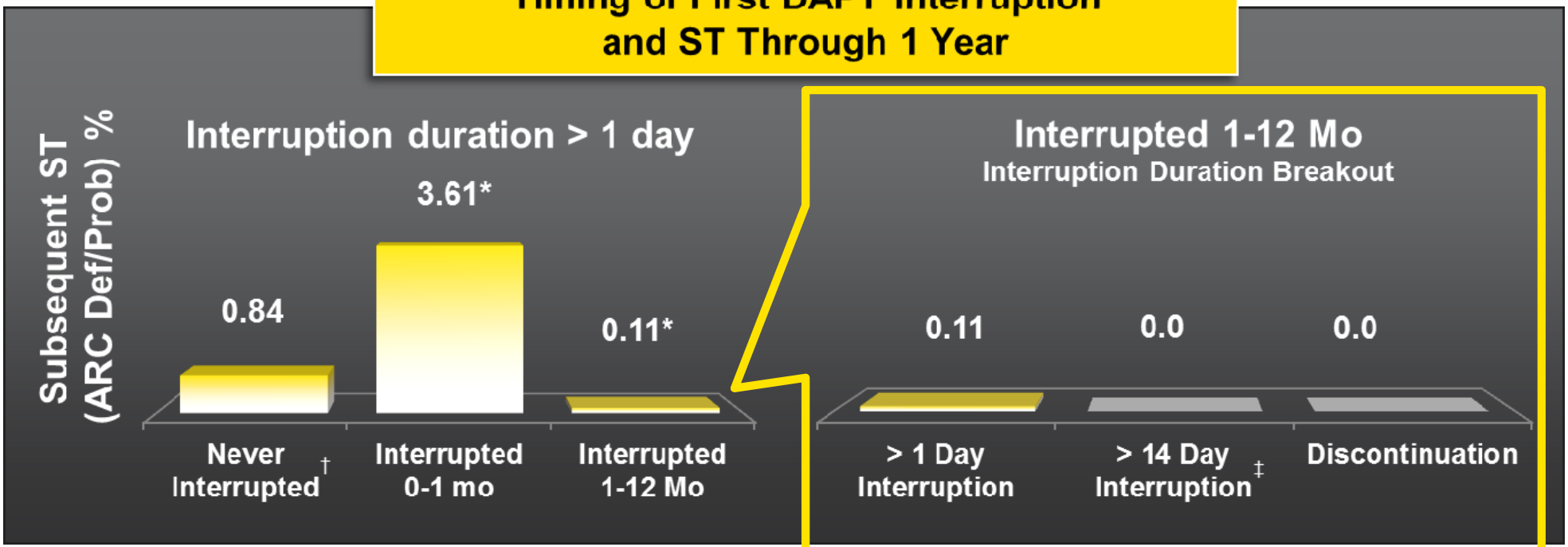


No. at risk	5130	5122	4946	4784
% CI	0.12	0.78	0.95	1.07

Manoharan, G. Pooled analysis of clinical events from prospective trials of the Resolute zotarolimus-eluting stent: three year outcomes of 5130 patients. ACC. 2013.
Post-hoc RESOLUTE Pooled analysis was not powered for the analysis shown.
Outcomes remain consistent when adjusted for duration of DAPT and other variables.
*RESOLUTE FIM, RESOLUTE All-Comers, RESOLUTE International, RESOLUTE US, RESOLUTE Japan

No Increased Risk of ST in Resolute™ DES Patients Interrupting DAPT Beyond One Month

Timing of First DAPT Interruption and ST Through 1 Year



Patients at risk	3827	166	903	903	752	626
No. of Events	32	6	1§	1§	0	0
Median days to interruption	NA	3	249	249	266	295

14-day cutoff selected because studies have shown that it takes up to 14 days for the platelet function to recover after DAPT withdrawal‡.

* $p < 0.05$ for comparison to Never Interrupted group. Post-hoc RESOLUTE Pooled DAPT analysis was not powered for the analysis shown.
† Including patients with no DAPT interruption except for ST while on DAPT through 12 months
§ Patient with a history of thrombosis was on DAPT at the time of ST event but had interrupted DAPT for 2 consecutive days prior to the event
‡ Anaesthesia, 2003, 58, pages 28–35
ESC guidelines recommend a DAPT duration of 6–12 months after DES implantation in all patients and 1 year after ACS, irrespective of the type of implanted stent.

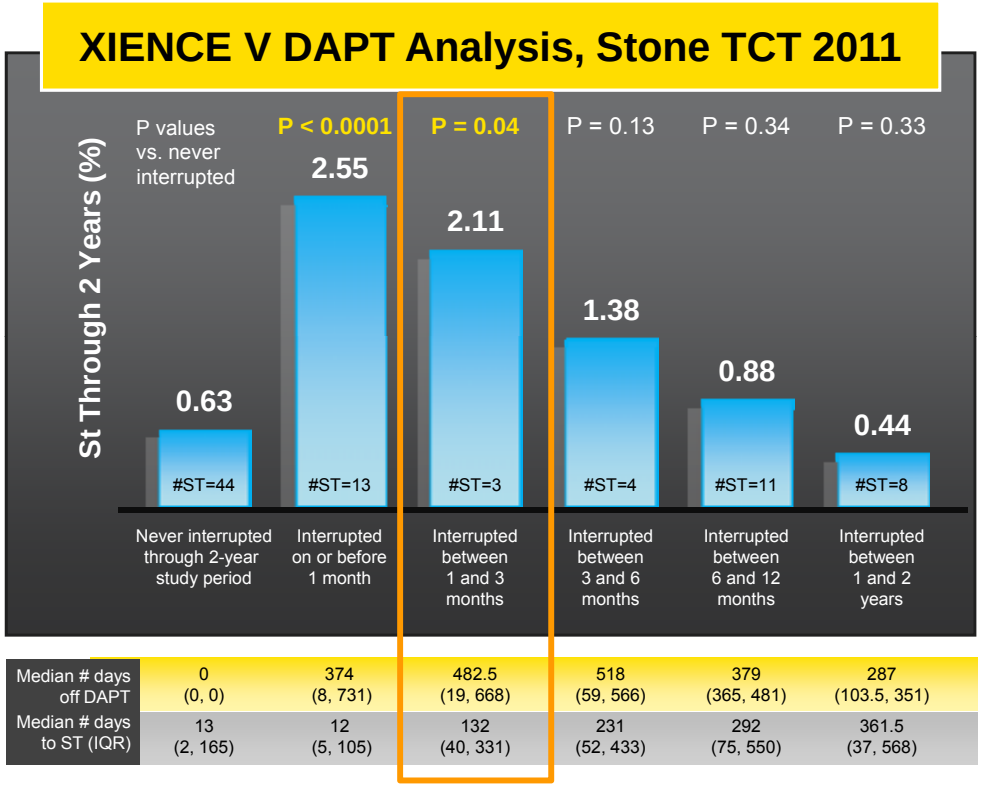
Resolute Integrity™

Xience™ V DAPT Analysis

Timing of First DAPT Interruption and Any Stent Thrombosis Through 2 Years

Xience V DAPT Analysis: G Stone, TCT 2011

- The Stone analysis, based on the SPIRIT randomized trials and subsequent post-market registries
- 70% of patients in this analysis come from post-market registries with little or no monitoring – could result in under-reporting of ST events



Patients who received a Xience V DES were at a **significant increased risk** for **stent thrombosis** if they interrupt DAPT between 1-3 months

Rates are KM estimates. Note: DAPT may have been interrupted before or after an ST event.