Primary Outcomes of a Pivotal Multicenter Randomized Trial Comparing the AGENT Paclitaxel-Coated Balloon with Conventional Balloon Angioplasty for In-Stent Restenosis

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Disclosure of Relevant Financial Relationships

Within the prior 24 months, I have had a relevant financial relationships with ineligible companies listed below.

Nature of Financial Relationship	**Ineligible Company**
Grant/Research Support	Abbott Vascular, BD Bard, Boston Scientific, Cook Medical, Philips Medical and Medtronic
Consulting	Abbott Vascular, Boston Scientific, CathWorks, Elixir Medical, Infraredx, Medtronic, Shockwave Medical and Zoll

All relevant financial relationships have been mitigated.

Faculty disclosure information can be found on the app

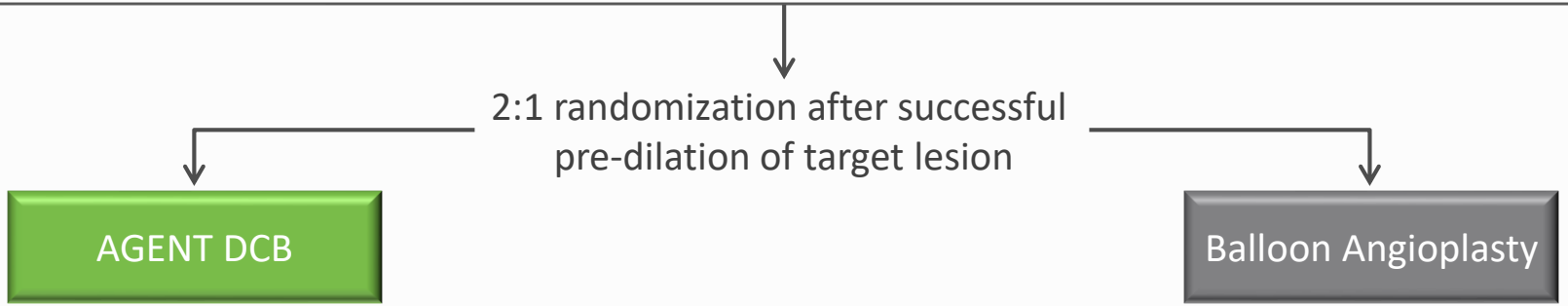
Introduction

- Treatment of in-stent restenosis (ISR) is commonly encountered and clinically challenging.
- Drug coated balloons (DCBs) transfer a therapeutic dose of an anti-restenotic agent to the vessel wall without introducing another layer of metal
- No coronary DCBs are currently approved in the United States
- The AGENT DCB delivers a targeted low-dose formulation of paclitaxel (2 $\mu g/mm^2$) to the treated vessel
- **AGENT IDE is a pivotal randomized trial comparing the safety and efficacy of the AGENT DCB to conventional balloon angioplasty in patients with ISR**

AGENT IDE Study Design

Prospective, randomized, multicenter, superiority trial across 40 US sites (N=480 patients*)

- Key Inclusion Criteria: Patients with ISR of a lesion previously treated with BMS or DES; lesion length <26 mm, RVD >2.0 - ≤4.0 mm, and %DS >70 - <100% (asymptomatic) or %DS >50 - <100% (symptomatic)
- Key Exclusion Criteria: Recent STEMI, bifurcation, LM, SVG or arterial graft, thrombus in target vessel



Primary Endpoint: Target Lesion Failure at 1-year (composite of TLR, TV-MI, or cardiac death)
Clinical follow-up: In-hospital, 30 days, 6 months, 1-year and annually between 2 and 5 years

DAPT required for at least a month; Antiplatelet monotherapy through the duration of the study
*Based on an adaptive trial design (interim analysis with pre-specified sample size readjustment plan); Yeh et al. Am Heart J. 2021;241:101-107

AGENT IDE Study Leadership Team

Principal Investigator	Robert W. Yeh Beth Israel Deaconess Medical Center Boston, MA
Study Chair	Ajay J. Kirtane Columbia University/NewYork-Presbyterian Hospital New York, NY
Steering Committee	J. Dawn Abbott, Cinthia Bateman, Wayne Batchelor Suhail Dohad, J Aaron Grantham, William Bachinsky Robert Stoler, Jennifer Tremmel
Angiographic Core Laboratory	Dr. Charles Michael Gibson Baim Institute for Clinical Research, Inc Boston, MA

AGENT IDE Centers – Top Enrolling Sites

Richard Shlofmitz (79) St. Francis Hospital	Cinthia Tjan Bateman (15) South Denver Cardiology Associates, PC
Jeffrey Moses (49) Columbia University Medical Center	Amar Krishnaswamy (15) Cleveland Clinic Foundation
William Bachinsky (41) Pinnacle Health Cardiovascular Institute	J. Aaron Grantham (14) St. Luke's Hospital of Kansas City
Suhail Dohad (34) Cedars - Sinai Medical Center	Francis J. Zidar (13) Austin Heart
Steven Rudick (31) Lindner Center at Christ Hospital	Rajendran Sabapathy (13) Overland Park Regional Medical Center
Robert Stoler (30) Baylor Heart & Vascular Hospital	Jennifer Tremmel (12) Stanford University Medical Center
Brian Jefferson (30) Centennial Medical Center	Cindy Grines (12) Northside Hospital
William Nicholson (28) Emory University Hospital	Mustafa Ahmed (11) University of Alabama at Birmingham
John Altman (20) St. Anthony Hospital	Azeem Latib (11) Montefiore Medical Center
Robert Yeh (16) Beth Israel Deaconess Medical Center	Behnam Tehrani (10) Inova Fairfax Hospital

Sample Size Calculation

Hypothesis: AGENT DCB superior to balloon angioplasty (BA) in ISR lesions for the primary endpoint of 1-year TLF

Expected rates*: AGENT DCB = 10.6%; BA = 21.2%

Randomization ratio = 2 DCB: 1 BA

Test significance level (α) = 0.025 (1-sided)

Power = 85%

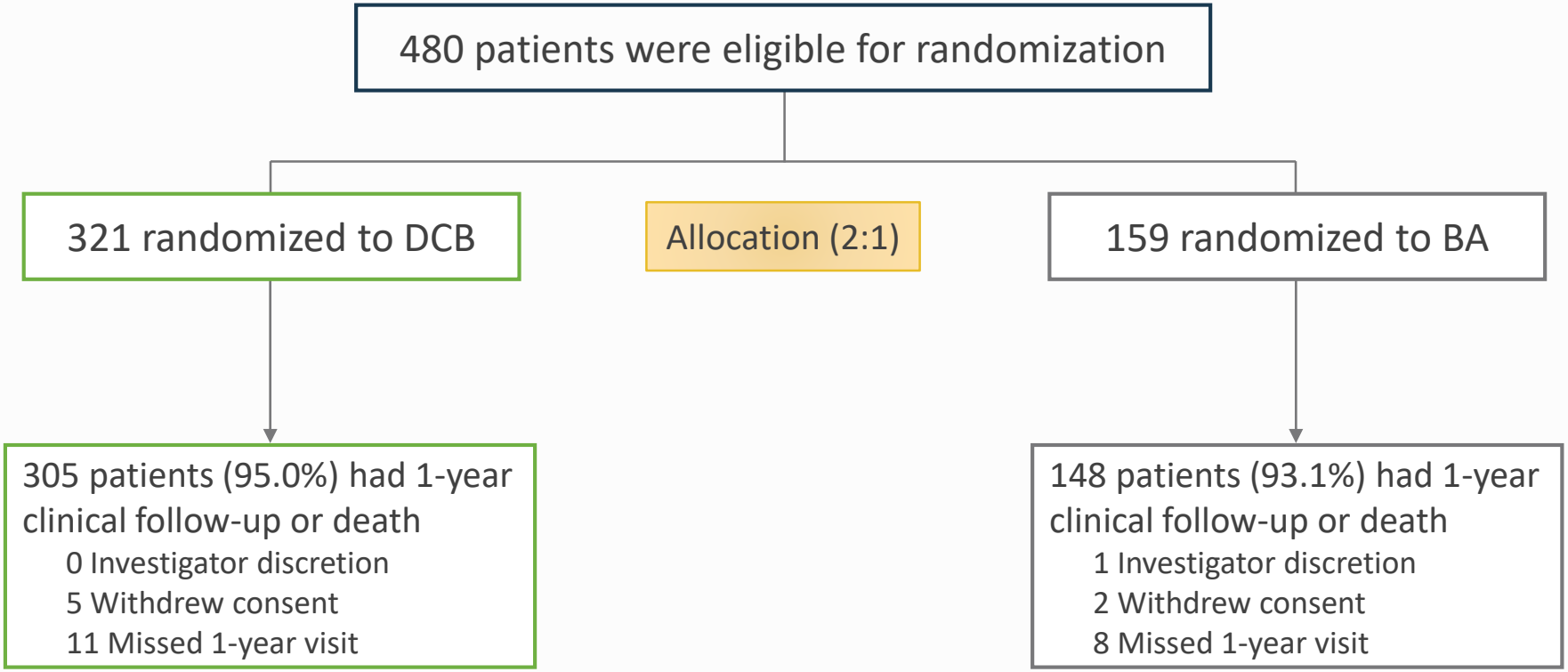
Expected rate of attrition = 3%

Planned enrollment = 480 patients**

The study primary endpoint will be considered met if the P-value from the z-test is <0.025 and the TLF rate in the DCB arm is less than the BA arm

*Based on meta-analysis of historical trials and including an adjustment to account for the oculo-stenotic reflex; Yeh et al. Am Heart J. 2021;241:101-107;
**Based on an adaptive trial design; final sample size increased to 600 patients; primary endpoint analysis conducted on the first 480 patients enrolled

Patient Disposition



Baseline Clinical Characteristics

	AGENT DCB N=321	Balloon Angioplasty N=159
Age (years)	68.6±9.8	67.5±9.9
Female	26.8%	27.0%
Caucasian	73.8%	76.1%
Diabetes	50.5%	50.9%
Prior CABG	32.1%	27.8%
Prior Myocardial Infarction	47.8%	48.7%
Previous Congestive Heart Failure	22.4%	20.3%
History of Renal Disease	18.2%	16.4%
History of Multivessel Disease	79.4%	77.1%
History of Left Main Disease	22.4%	20.9%
Indication for Index Procedure		
NSTE-ACS	37.4%	39.6%
Stable Angina	54.2%	52.8%
Silent Ischemia	1.9%	1.3%
Other Indication	6.5%	6.3%

Baseline Restenosis Pattern

	AGENT DCB N=321	Balloon Angioplasty N=159
Single stent layer	56.4%	56.6%
Multiple stent layers	43.6%	43.4%
Mehran ISR pattern*		
0	0.0%	0.0%
1A (articulation)	0.0%	0.0%
1B (margin)	1.3%	1.3%
1C (focal)	35.8%	44.2%
1D (multifocal)	0.3%	0.6%
2 (intrastent)	57.5%	48.1%
3 (proliferative)	4.4%	5.2%
4 (total occlusion)	0.6%	0.6%

*Quantified by the angiographic core laboratory

Angiographic Lesion Characteristics

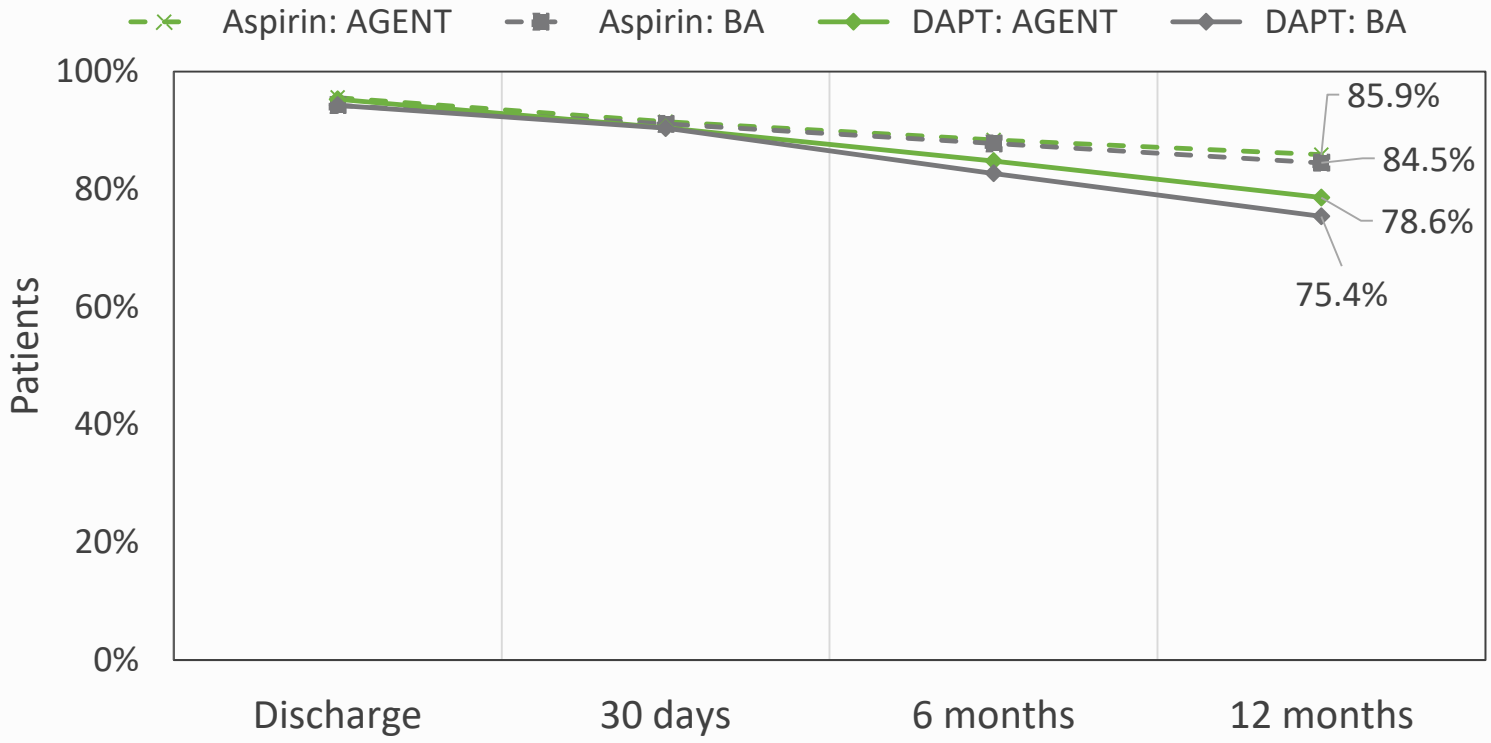
		AGENT DCB N=322 Lesions[†]	Balloon Angioplasty N=159 Lesions
Pre-Procedure			
Target vessel treated	LAD	34.9%	35.2%
	LCx	24.6%	26.4%
	RCA	37.7%	33.3%
	LMCA	2.8%	5.0%
Lesion Length, mm		12.97±6.33	11.88±6.51
<10 mm		37.0%	46.5%
10 – 20 mm		48.0%	43.9%
>20 mm		15.0%	9.7%
MLD[*], mm		0.95±0.38	0.94±0.38
Diameter Stenosis[*], %		64.86±12.63	65.52±12.19
Post-Procedure			
MLD[*], mm		2.13±0.45	2.15±0.51
Diameter Stenosis[*], %		22.09±10.66	21.90±10.56
Acute Gain[*], mm		1.17±0.47	1.21±0.52

*in-lesion values; [†]One patient in the AGENT arm had two target lesions treated with DCB that was counted as a protocol deviation

Procedural Characteristics

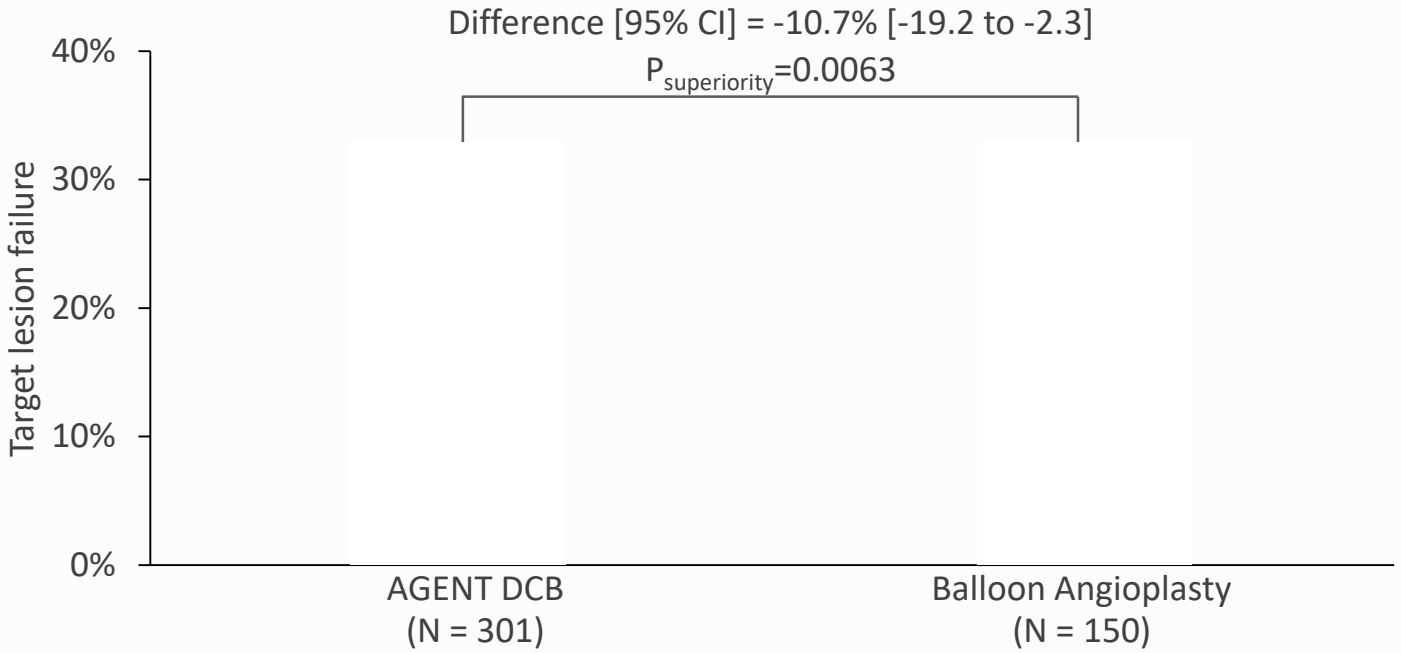
	AGENT DCB N=321	Balloon Angioplasty N=159
Technical success (Post-procedure diameter stenosis of <30% in 2 near-orthogonal projections with TIMI 3 flow)	92.9%	89.3%
Clinical procedural success (Technical success with no in-hospital MI, TVR, or cardiac death)	91.9%	88.7%
Procedure time (min)	56.9±31.0	52.7±27.3
Patients with only target lesion treated	87.2%	87.4%
Patients with both target & non-target lesion treated	12.8%	12.6%
Intravascular imaging use during procedure	72.3%	76.7%

Antiplatelet Medication Usage



DAPT required for at least a month; Antiplatelet monotherapy through the duration of the study

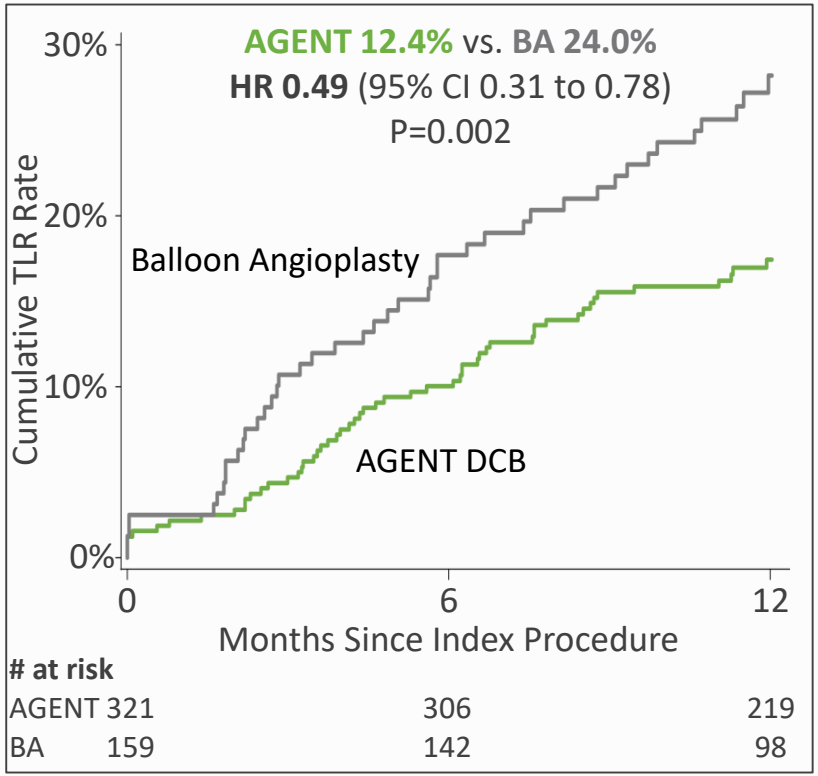
Primary Endpoint: TLF at 1-Year

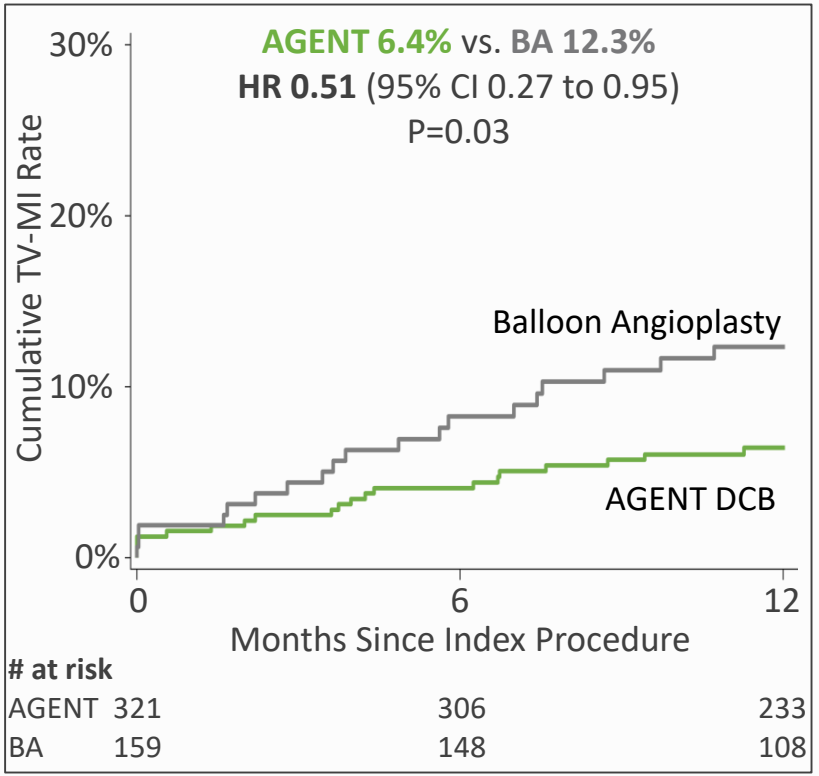


AGENT DCB demonstrated superior outcomes compared to BA for 1-year TLF

Binary event rates; A z-test with unpooled variance for the difference of two proportions was used

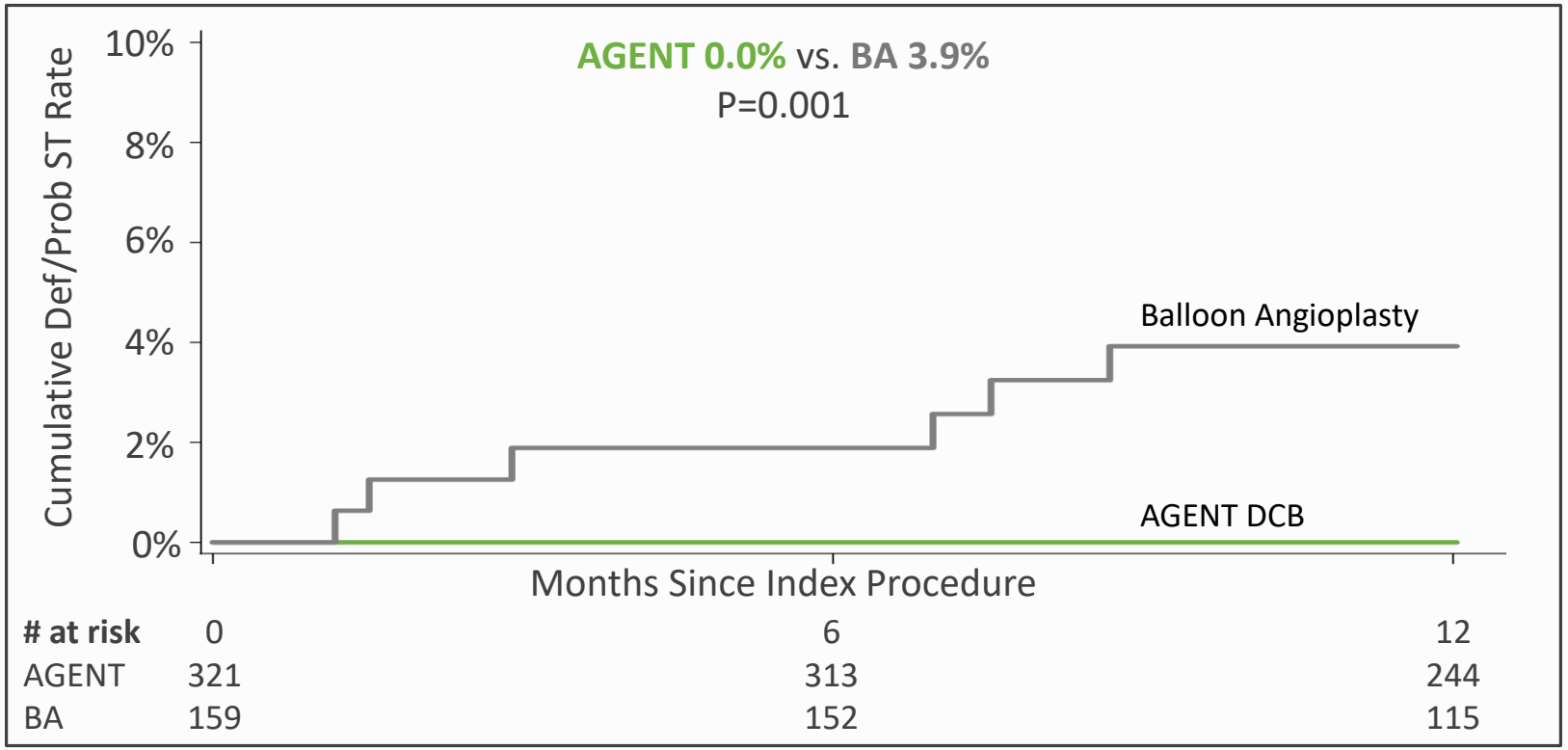
TLR and Target Vessel Related MI at 1-Year





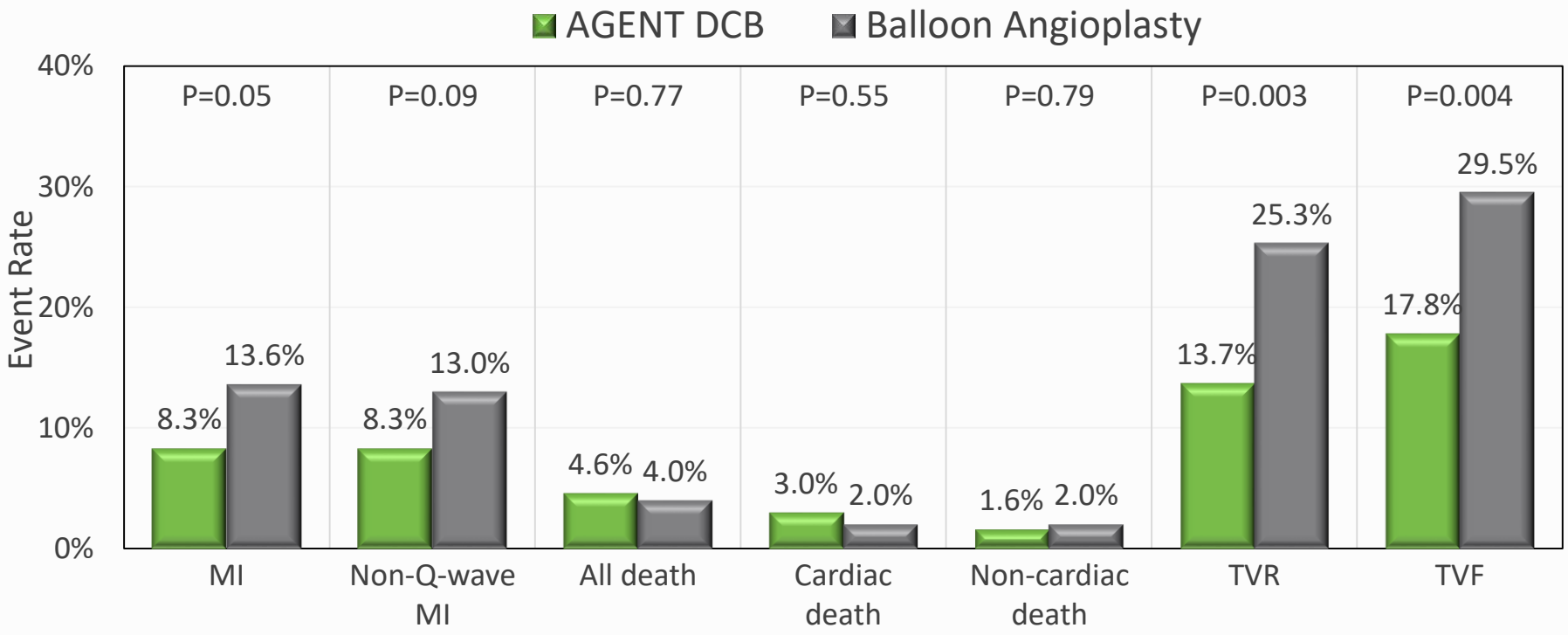
Log-rank P values; Periprocedural MI occurring within 48 hours of the index procedure adjudicated by the SCAI definition, and spontaneous MI occurring 48 hours after the index procedure was adjudicated according to the 4th Universal MI definition

Definite/Probable ST at 1-Year



KM Event Rate; Log-rank P values; All definite ST in the BA arm (6 patients)

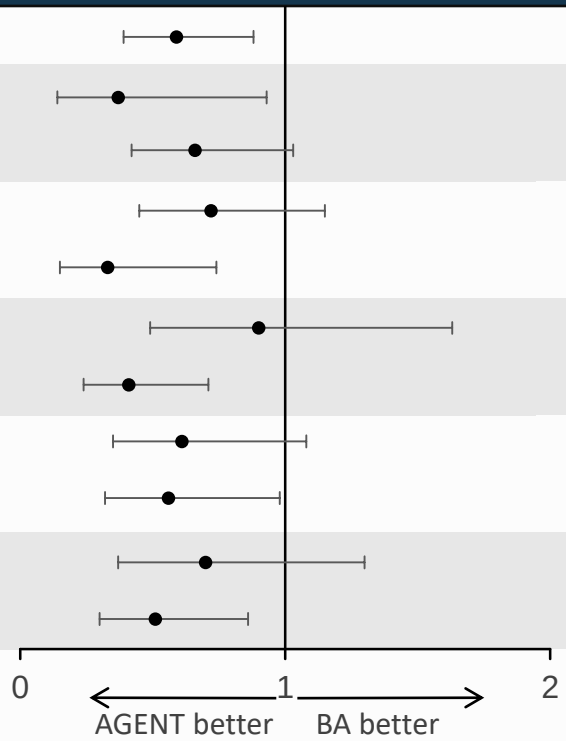
Additional Endpoints at 1-Year



KM Event Rate; Log-rank P values

Subgroup Analyses of the Primary Outcome

Subgroup		AGENT DCB	BA	Hazard Ratio [95% CI]	P-Interaction
All Patients		**17.4%**	**28.2%**		
Sex	Female (N=129)	10.6%	24.1%		0.26
	Male (N=351)	20.0%	29.8%		
Age	<75 years (N=349)	19.2%	26.4%		0.10
	≥75 years (N=131)	12.9%	32.6%		
Diabetes	Yes* (N=213)	21.3%	23.4%		0.06
	No† (N=265)	14.7%	32.3%		
Vessel size‡	Small (RVD< 2.75 mm) (N=259)	16.8%	25.5%		0.83
	Large (RVD≥2.75 mm) (N=218)	18.4%	31.5%		
Stent Layer§	Single (N=270)	14.0%	19.7%		0.45
	Multiple (N=209)	21.9%	39.3%		



*Diabetic patients requiring medical treatment; †Diabetic patients treated with diet only or patients without diabetes;
‡RVD based on angiographic core lab data.

Discussion Points - Sample Size

- Sample Size
  - Interim analysis was planned after 90% of patients enrolled, expecting 40% achieving 1-year endpoint at that time.
  - Due to rapid enrollment, very limited 1-year follow-up available after 90% enrollment -> DMC recommended continuing enrollment to 600.
  - **FDA recommended performing interim analysis when 40% had achieved 1-year follow up. Analysis demonstrated 480 to be adequately powered.**
  - 600 patient full sample will be included in the final manuscript.

Discussion Points – Control Group

- Study designed for superiority over balloon angioplasty rather than non-inferiority vs. DES.
- Trial enrolled high number of patients with multiple-stent layers, for whom additional DES are often avoided.
- The design incorporated practical considerations necessary for conducting a successful trial to support regulatory approval.

Conclusions

- AGENT IDE is the first RCT conducted in the US examining the efficacy and safety of DCB in patients with coronary ISR
- AGENT DCB was superior to conventional balloon angioplasty for the primary endpoint of TLF at 1-year (17.9% vs. 28.7%; P=0.006)
  - These differences were driven by ~50% reductions in rates of TLR and TV-MI after treatment with AGENT DCB compared with BA
- No thromboses occured in the AGENT arm (0.0% vs. 3.9%; P=0.001)
- These data support the use of AGENT DCB for the treatment of coronary in-stent restenosis

THANK YOU