Off-Label and Untested Use of Drug Eluting Stents: Frequency, Efficacy and Safety From the Drug Eluting Stent (D.E.S. cover) Registry

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Conflict of Interest Statement

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Physician Name	Company/Relationship
Nirat Beohar	J & J Cordis / Sponsor

Background

- To date, the safety and efficacy of DES use in ***off-label*** and ***untested*** lesion subtypes has not been systematically evaluated by **either** the **pivotal DES trials or from any large United States or outside US registries**.

Hypothesis

- We evaluated the frequency, efficacy and safety of *Off-label* and *Untested* use of DES in the D.E.S.cover PCI Registry; a large, prospective, observational, contemporary, multi-center US registry.

Patient Population

- This study was conducted at 140 U.S. sites and consists of 7,752 patients who underwent PCI between January to June, 2005.

Study Cohort

7,752 PCI-treated patients, 140 US hospitals

↓

6,706 DES only and no bare metal stent

↓

5,851 DES only no other device

↓

In 5,543 *Off-label* and *Untested* use determine constituting the study cohort

Group Definition

Standard Use

- *Standard* DES use was defined by the device label in the IFU.
- This definition is based on the results of the pivotal DES trials

Off-Label Use

- *Off-label* DES use was based on the manufacturer's IFU.
- Cypher® stent:
  - previously treated lesions
  - lesion in bypass graft
  - lesion length > 30 mm
  - reference vessel diameter (RVD) <2.5 mm or >3.5 mm
- Taxus™ stent:
  - Criteria were identical except for:

  lesion length >28 mm and RVD <2.5 mm or >3.75 mm.

Untested **Use**

- For both Cypher® and Taxus™ DES, ***Untested*** use was also defined by the IFU :

  - *left main*
  - *ostial*
  - *bifurcation*
  - *total occlusion*

- Patients that met the definition for both *Off-label* and *Untested* DES were classified as ***Off-label***.

Primary Outcomes

- To assess the ***"Efficacy"*** of DES use in *Off-label* and *Untested* groups:

➢ the primary outcome was 6-month target lesion repeat revascularization (TLR) with PCI.

➢ However, for subgroup analyses, target vessel repeat revascularization (TVR) with PCI or CABG was used instead of TLR with PCI to increase statistical power.

Primary Outcomes

- To assess the ***"Safety"*** of DES use in *Off-label* and *Untested* groups:

➢ the primary outcome was the composite endpoint of death, MI, or stent thrombosis at both 30 days and 6 months.

Definition of Adverse Events

Stent Thrombosis

- Definite stent thrombosis: angiographic thrombus in a successfully deployed stent accompanied by an acute coronary syndrome.
  - Angiographic thrombus is defined as complete occlusion (TIMI 0 or I flow) with a stent diameter stenosis <30% or evidence of flow limiting thrombus (ovoid or linear filling defect) within or immediately adjacent to the stent.

- Probable stent thrombosis : unexplained sudden cardiac death or Q-wave MI in the distribution of the stented artery.

Myocardial Infarction

- **Myocardial infarction** is defined as the occurrence of either a Q-wave MI or a non-Q wave MI.

  Q-wave MI is defined as the development of new pathologic Q waves on the ECG *and* the presence of CK-MB greater than normal.

  Non-Q wave MI is defined as an event associated with elevation of CK-MB in excess of 3 times normal *or* total CK in excess of 2 times normal.

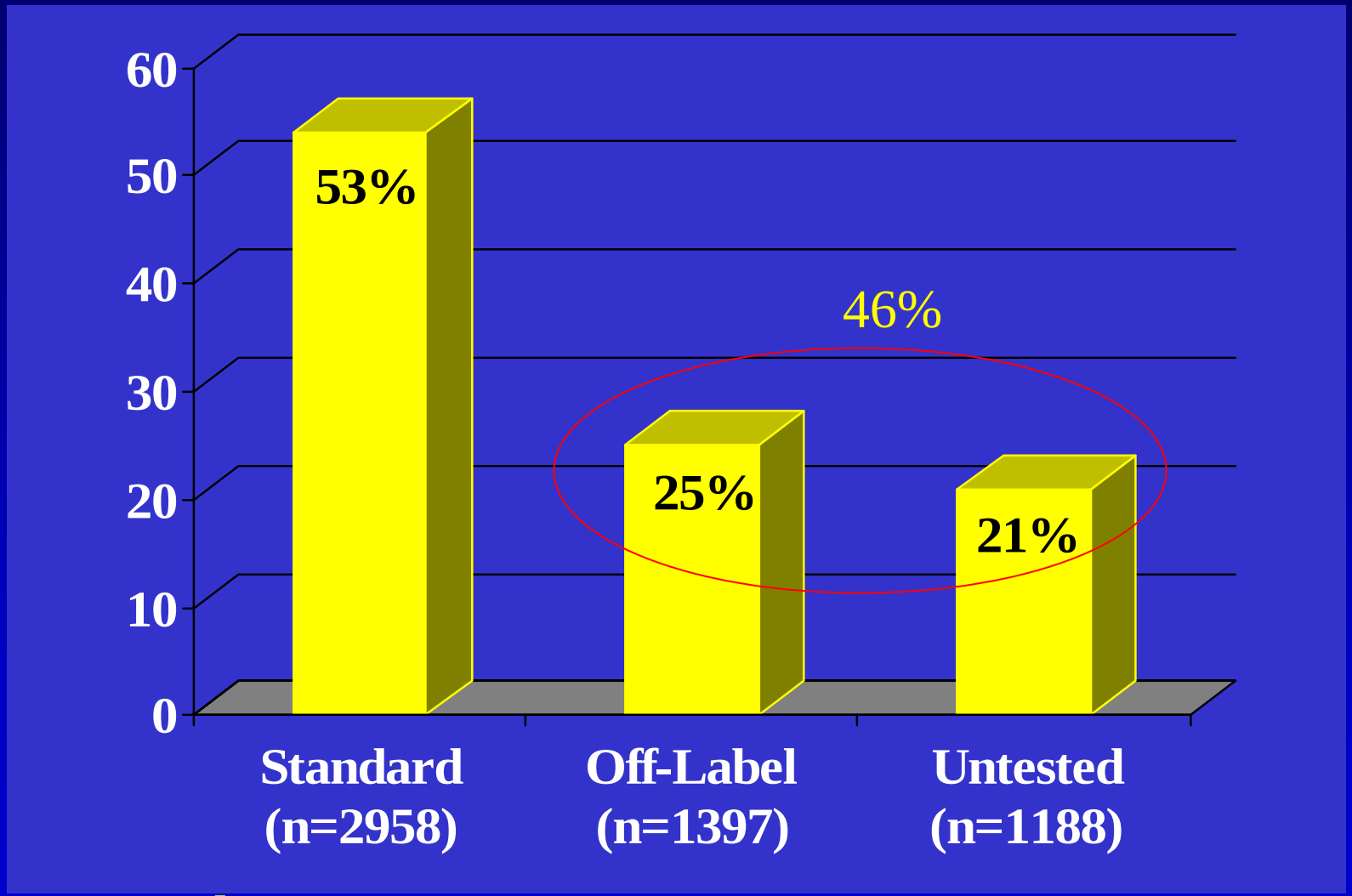
Adjudication of Events

- An independent committee adjudicated clinical outcomes.
- For this analysis, adjudicated data were available for 91% of reported stent thrombosis

Statistical Analysis

- To assess the independent effect of DES treatment strategy, multivariable Cox proportional hazards regression was used with *Standard* DES use as the referent category and separate indicator variables for *Untested* and *Off-label* DES use.

Frequency of DES Usage



Total n=5,543

Baseline Characteristics by DES Stent Use

	Standard (n=2958)	Off-label (n=1397)	Untested (n=1188)	P-value
Age (years)	64.1 ± 11.8	64.5 ±11.4	62.4 ± 12.0	
Male gender	65.7	71.3	68.3	
History of:				
PCI	34.1	50.9	26.3	<0.0001
CABG	11.7	36.9	13.9	<0.0001
MI	24.2	38.2	20.7	<0.0001
Diabetes	31.1	35.8	27.1	<0.0001
Left anterior descending disease	58.7	62.7	61.0	0.04

Primary indication for index procedure

	Standard (n=2958)	Off-label (n=1397)	Untested (n=1188)	P-value
Primary indication				<0.0001
▪ Acute MI	17	16.5	35.8	
▪ Unstable angina	32.2	37.5	26.5	
▪ Stable angina	15.2	15.2	13.4	
▪ Positive ischemia	27.4	23.0	18.4	

Index Procedure Characteristics by DES Stent Use

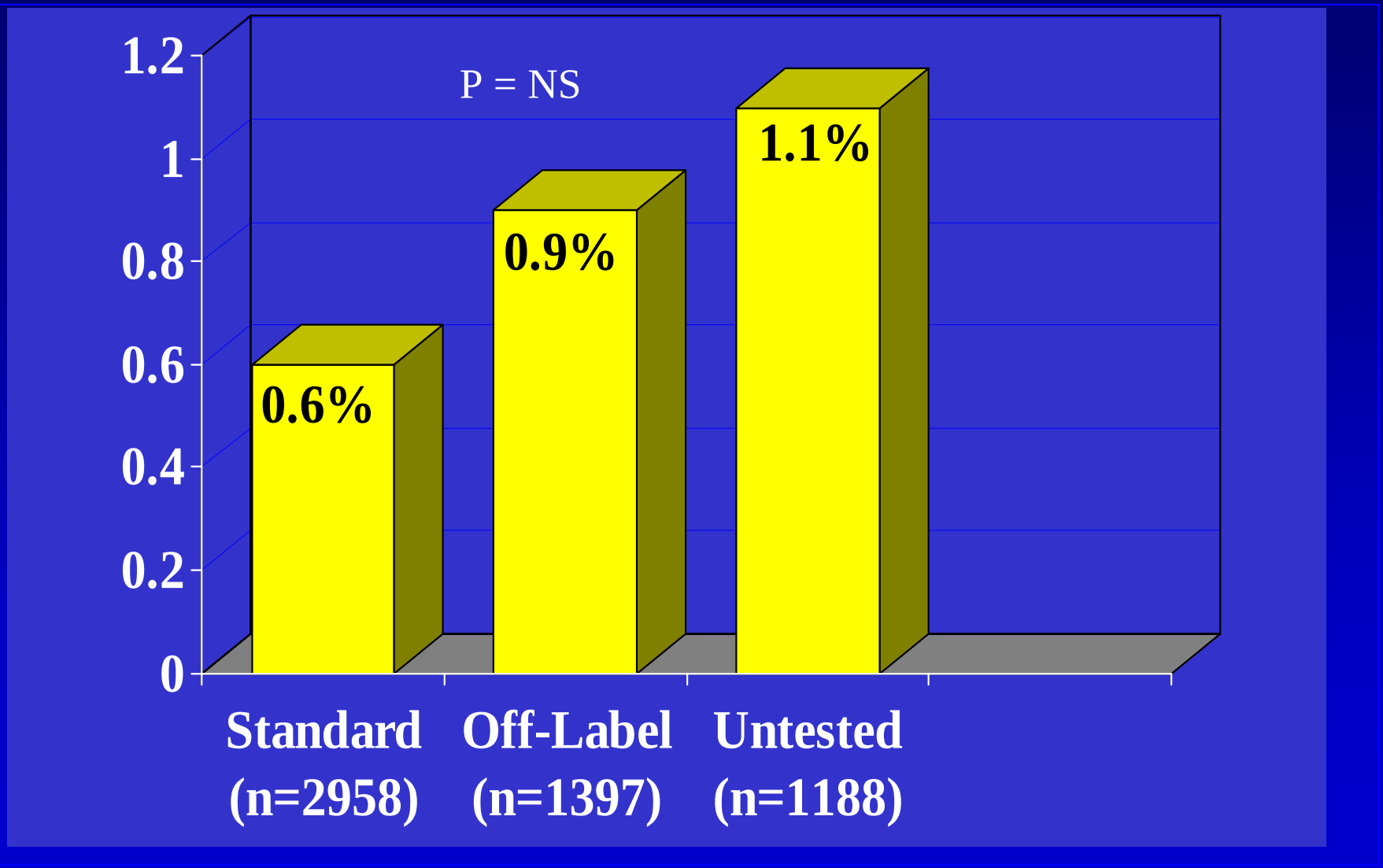
Lesion Level Analysis	Standard (N=4427)	Off-label (N=1580)	Untested (N=1512)	P-value
▪Lesion length	14.3 ± 6.3	22.4 ± 14.9	14.61 ± 6.6	
▪Reference vessel diameter	3.0 ± 0.4	3.2 ± 0.6	2.9 ± 0.4	
▪Maximum length of stent	18.4 ± 6.6	21.8 ± 8.0	18.8 ±7.0	<0.0001
▪2 or more lesions attempted	21.8	34.4	38.3	<0.0001
▪Procedural planned use of IIb/IIIa GP inhibitors	41.3	43.0	57.1	<0.0001
▪Angiographic success	99.5	98.5	98.0	<0.0001

Lesion Complications by DES Stent Use

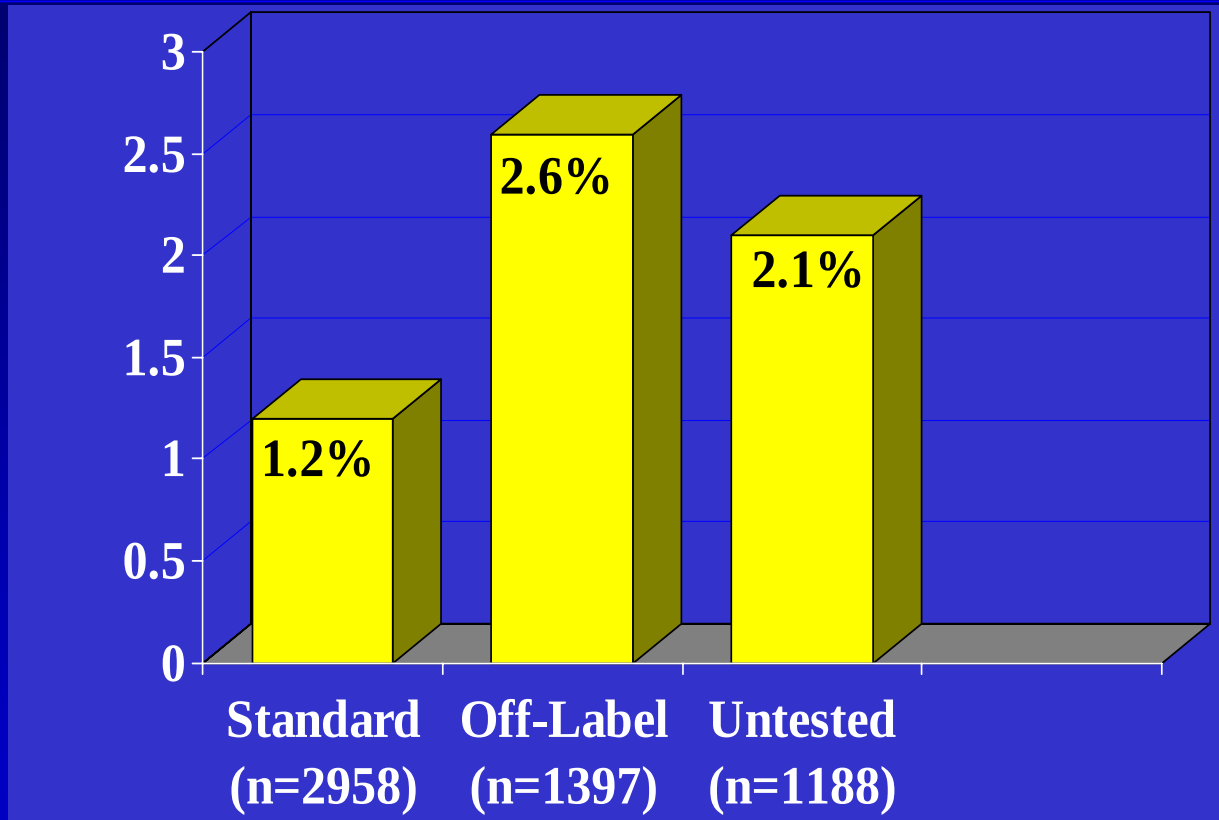
	Standard (n=4404)	Off-label (n=1575)	Untested (n=1512)	P-value
Any Lesion Complication	2.9 %	4.0 %	5.6 %	<0.0001
Abrupt closure	0.2 %	0.2 %	0.6 %	0.06
Lesion dissection	1.7 %	2.0 %	2.6 %	0.12
Persistent flow reduction	0.3 %	0.3 %	0.5 %	0.45
Side branch occlusion	0.4 %	0.9 %	1.8 %	<0.0001
Lesion device malfunction	0.1 %	0.0 %	0.2 %	0.19

In-Hospital Events

Death/MI/Stent Thrombosis

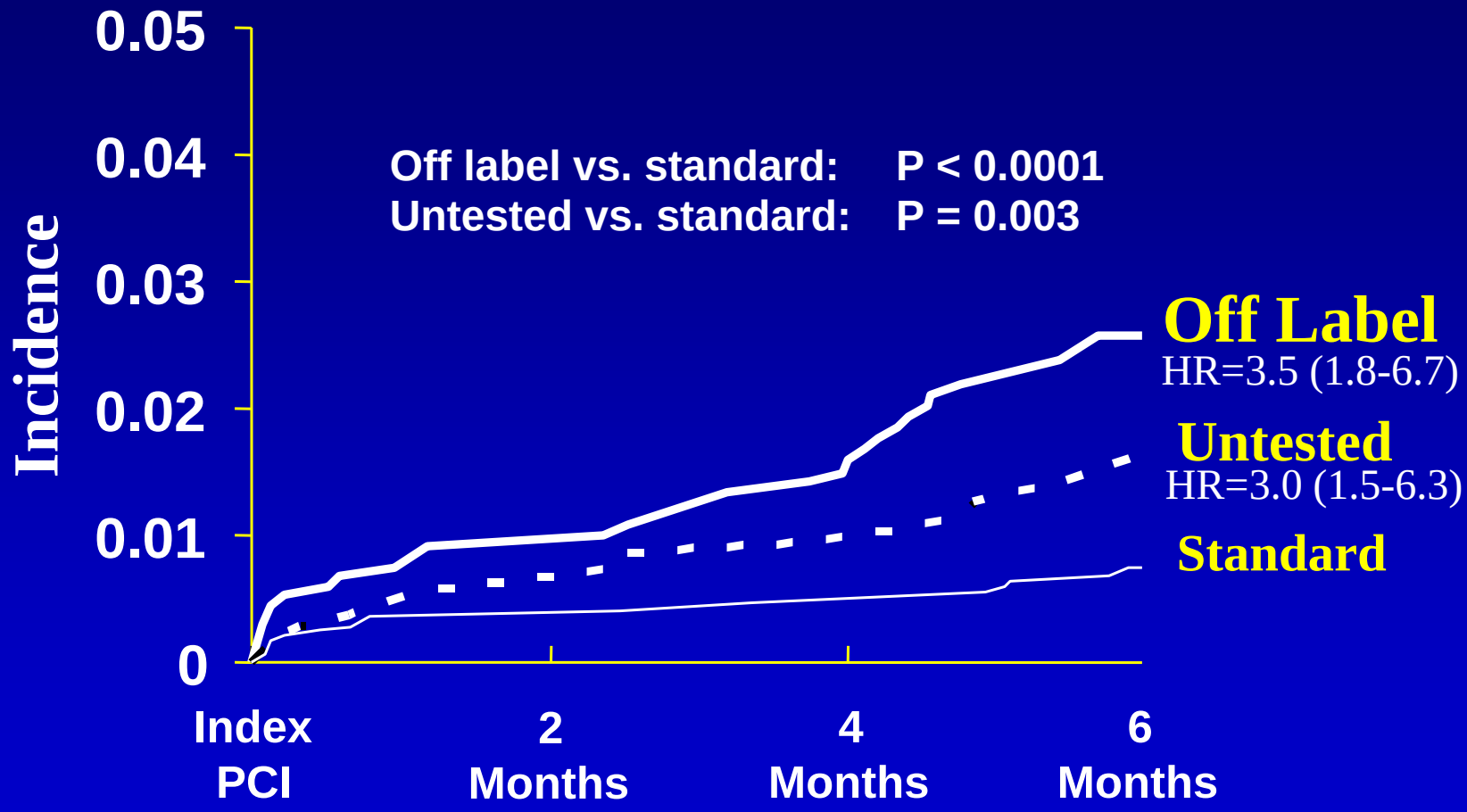


30 Day Events
Death/MI/Stent Thrombosis



	HR (95% C.I)	P-value
Standard	1.0	
Off-label	1.83 (1.13-2.9)	0.01
Untested	1.81 (1.05-3.11)	0.03

6 Month Repeat PCI: TLR



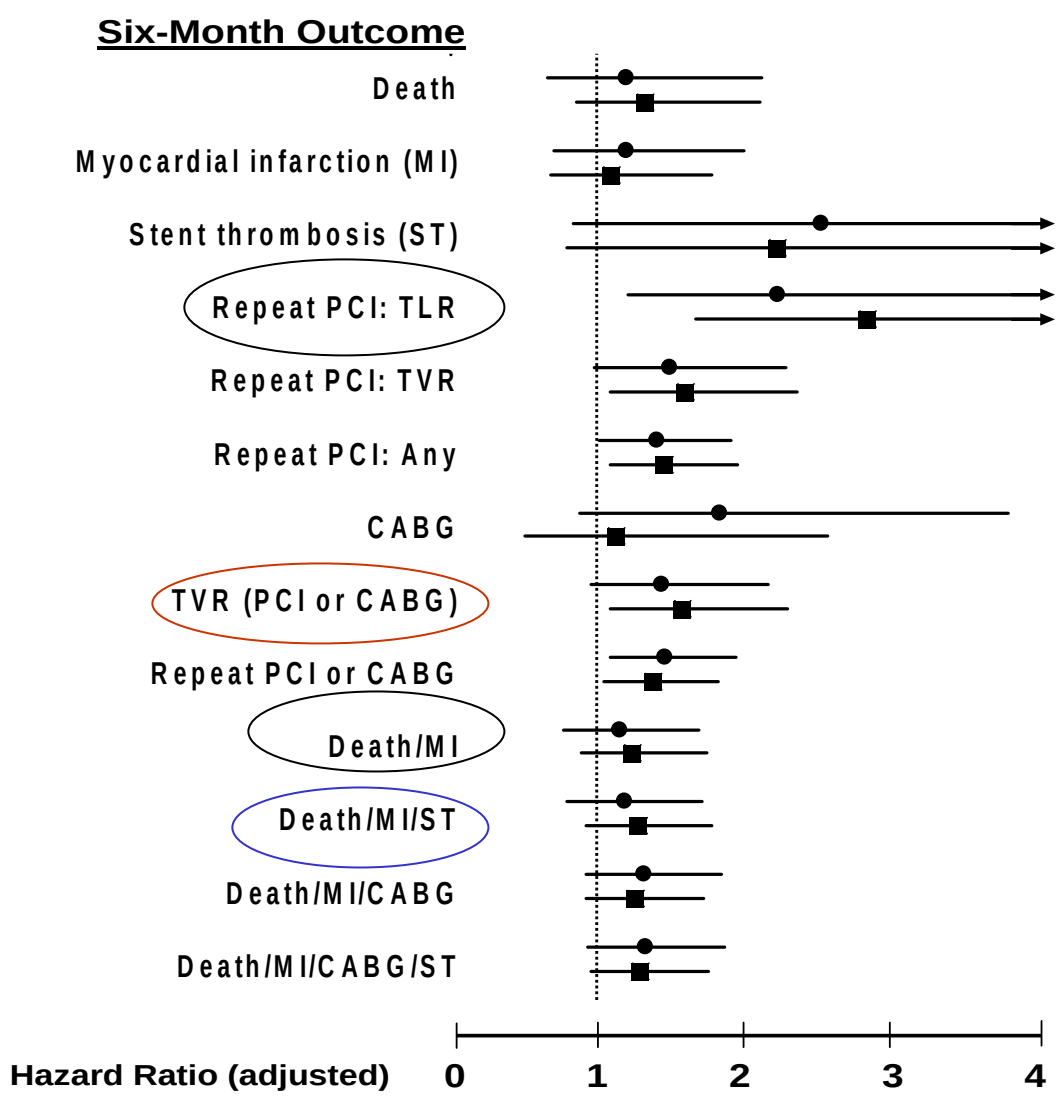
6 Month Hazard of TVR (PCI or CABG)

(Excluding Early Events)

	Hazard Ratio (95% CI)	P-value
Standard use	1	----
Untested lesions	1.69 (1.03-2.78)	0.04
Off-label lesions	2.00 (1.28-3.10)	0.002

6 Month Outcomes: Summary Data

- Untested
- Off-label



	HR	95% C.I	P-value
Death	1.18	(0.66-2.11)	0.58
	1.33	(0.85-2.10)	0.22
Myocardial infarction (MI)	1.18	(0.70-1.99)	0.54
	1.10	(0.68-1.77)	0.69
Stent thrombosis (ST)	2.51	(0.83-7.56)	0.10
	2.22	(0.79-6.25)	0.13
Repeat PCI: TLR	2.21	(1.21-4.03)	0.01
	2.84	(1.67-4.82)	0.001
Repeat PCI: TVR	1.48	(0.97-2.28)	0.07
	1.60	(1.09-2.36)	0.02
Repeat PCI: Any	1.39	(1.01-1.91)	0.04
	1.46	(1.09-1.95)	0.01
CABG	1.82	(0.88-3.79)	0.11
	1.13	(0.50-2.56)	0.76
TVR (PCI or CABG)	1.43	(0.95-2.16)	0.09
	1.58	(1.09-2.29)	0.02
Repeat PCI or CABG	1.45	(1.08-1.94)	0.01
	1.38	(1.04-1.82)	0.02
Death/MI	1.14	(0.77-1.69)	0.51
	1.24	(0.89-1.74)	0.20
Death/MI/ST	1.17	(0.79-1.71)	0.43
	1.28	(0.92-1.78)	0.14
Death/MI/CABG	1.30	(0.92-1.84)	0.14
	1.26	(0.92-1.72)	0.15
Death/MI/CABG/ST	1.32	(0.93-1.86)	0.11
	1.29	(0.95-1.75)	0.11

Conclusions

- ***Off-label*** **and** ***Untested*** **use of DES in contemporary PCI is widespread in the US.**

- **Despite overall low absolute risk, relative short-term safety and long-term efficacy appear to be compromised when DES are used in** ***Off-label*** **and** ***Untested*** **circumstances**

Thank you for your attention

Index Procedure Characteristics by DES Stent Use

Characteristic	Off-label (n=1397)	Untested (n=1188)
Off label indications		
▪ Restenotic lesion	26.0	
▪ Graft lesion treated	25.3	
▪ Reference vessel diameter		
< 2.5 mm	9.9	
> 3.5 mm or > 3.75 mm	24.9	
▪ Lesion length > 28 mm or > 30 mm	29.4	
Any off-label indication	100.0	
Untested indications		
▪ Left main lesion treated	2.8	5.8
▪ Ostial lesion	13.1	38.6
▪ Bifurcation lesion	8.9	39.1
▪ Total occlusion	11.2	39.4
▪ Any untested indication	29.6	100.0

Index Procedure Characteristics by DES Stent Use

Lesion Level Analysis	Standard (N=4427)	Off-label (N=1580)	Untested (N=1512)	P-value
▪Lesion length	14.3 ± 6.3	22.4 ± 14.9	14.61 ± 6.6	
▪Reference vessel diameter	3.0 ± 0.4	3.2 ± 0.6	2.9 ± 0.4	
▪Lesion location				
Right coronary artery	35.1	38.1	27.7	
Left anterior descending	38.8	25.4	42.7	
Circumflex	24.7	13.8	22.9	
Left main	0.0	1.4	5.7	
Graft	0.0	27.0	0.0	
▪Maximum length of stent	18.4 ± 6.6	21.8 ± 8.0	18.8 ±7.0	<0.0001
▪Angiographic success	99.5	98.5	98.0	<0.0001

In-Hospital MACE by DES Stent Use

Clinical Event	Standard Use (n=2958)	Off-label use (n=1397)	Untested Use (n=1188)
Death	0.1 %	0.2 %	0.3 %
Myocardial infarction (MI)	0.5 %	0.7 %	0.7 %
Stent thrombosis	0.03%	0.0 %	0.2 %
Repeat PCI: TLR	0.1 %	0.1 %	0.1 %
Repeat PCI: TVR	0.2 %	0.2 %	0.3 %
Repeat PCI: Any	0.2 %	0.3 %	0.5 %
CABG	0.1 %	0.0 %	0.3 %
TVR (via PCI/CABG)	0.2 %	0.2 %	0.3 %
Repeat PCI/CABG: Any	0.3 %	0.3 %	0.8 %
Death/MI	0.6 %	0.9 %	0.9 %
Death/MI/Stent Thrombosis	0.6 %	0.9 %	1.1 %
Death/MI/CABG	0.6 %	0.9 %	1.2 %
Death/MI/CABG/Stent Thrombosis	0.7 %	0.9 %	(1.3 %)

30-Day MACE by DES Stent Use

Clinical Event	Standard Use (n=2958)	Off-label Use (n=1397)	Untested Use (n=1188)
Death	0.2 %	{0.7 %}	(0.6 %)
Myocardial infarction (MI)	0.8 %	(1.7 %)	1.3 %
Stent thrombosis	0.2 %	0.5 %	0.5 %
Repeat PCI: TLR	0.4 %	0.8 %	0.5 %
Repeat PCI: TVR	0.8 %	0.9 %	1.0 %
Repeat PCI: Any	1.4 %	1.7 %	2.2 %
CABG	0.2 %	0.0 %	(0.7 %)
TVR (via PCI/CABG)	0.9 %	0.9 %	1.1 %
Repeat PCI/CABG: Any	1.6 %	1.7 %	(2.8 %)
Death/MI	1.1 %	[2.4%]	(1.9 %)
Death/MI/Stent Thrombosis	1.2 %	[2.6 %]	(2.1 %)
Death/MI/CABG	1.2 %	{2.4 %}	{2.4 %}
Death/MI/CABG/Stent Thrombosis	1.3 %	{2.6 %}	{2.6 %}

6-Month MACE by DES Stent Use

Clinical Event	Standard Use (n=2958)	Off-label use (n=1397)	Untested Use (n=1188)
Death	1.2 %	(2.8 %)	1.5 %
Myocardial infarction (MI)	1.5 %	2.3 %	2.0 %
Stent thrombosis	0.2%	0.6 %	0.6 %
Repeat PCI: TLR	0.7 %	[2.6 %]	{1.6 %}
Repeat PCI: TVR	1.8 %	[3.7 %]	(3.1 %)
Repeat PCI: Any	3.7 %	[6.0 %]	(5.5 %)
CABG	0.5 %	0.8 %	{1.6 %}
TVR (via PCI/CABG)	2.0 %	[4.1 %]	{3.4 %}
Repeat PCI/CABG: Any	4.1 %	{6.5 %}	[6.9 %]
Death/MI	2.6 %	{5.0 %}	3.4 %
Death/MI/Stent Thrombosis	2.7 %	{5.2 %}	3.6 %
Death/MI/CABG	3.0 %	{5.6 %}	(4.8 %)
Death/MI/CABG/Stent Thrombosis	3.1 %	{5.8 %}	(4.9 %)

Crude and Adjusted Hazard Ratios of Primary Outcomes by PCI Treatment Strategy

Unadjusted **Adjusted Hazard Ratios**

PCI Treatment Strategy	N	Hazard Ratio			Model 3	Model 4	95% C.I.	P-value
Outcome: Death/MI/Stent Thrombosis								
30- Day Risk								
Standard use	2958	1			1	----	----	----
Untested lesions	1188	1.83			1.81	----	1.05-3.11	0.03
Off-label lesions	1397	2.24			1.83	----	1.13-2.98	0.01
6-Month Risk								
Standard use	2958	1			1	1	----	----
Untested lesions	1188	1.23			1.27	1.17	0.79-1.71	0.43
Off-label lesions	1397	1.61			1.32	1.28	0.92-1.78	0.14
6- Month Risk (no early event)								
Standard use	2925	1			1	1	----	----
Untested lesions	1164	0.87			0.95	0.90	0.52-1.56	0.70
Off-label lesions	1362	1.24			1.04	1.01	0.64-1.57	0.97

Crude and Adjusted Hazard Ratios of Primary Outcomes by PCI Treatment Strategy

		Unadjusted	Adjusted Hazard Ratios					
PCI Treatment Strategy	N	Hazard Ratio	Model 1	Model 2	Model 3	Model 4	95% C.I.	P-value
Outcome: Repeat PCI: TLR								
30- Day Risk								
Standard use	2958	1	1	1	1	----	----	----
Untested lesions	1188	1.26	1.09	1.10	1.09	----	0.36-3.27	0.88
Off-label lesions	1397	2.11	2.08	1.96	1.96	----	0.79-4.87	0.14
6-Month Risk								
Standard use	2958	1	1	1	1	1	----	----
Untested lesions	1188	2.34	2.17	2.31	2.30	2.21	1.21-4.03	0.01
Off-label lesions	1397	3.43	3.35	2.90	2.91	2.84	1.67-4.82	0.0001
6- Month Risk (no early event)								
Standard use	2948	1	1	1	1	1	----	----
Untested lesions	1183	3.12	2.98	3.27	3.25	3.03	1.46-6.30	0.003
Off-label lesions	1387	4.37	4.28	3.58	3.59	3.47	1.79-6.71	0.0002

Crude and Adjusted Hazard Ratios of Primary Outcomes by PCI Treatment Strategy

		Unadjusted	Adjusted Hazard Ratios					
PCI Treatment Strategy	N	Hazard Ratio	Model 1	Model 2	Model 3	Model 4	95% C.I.	P-value
Outcome: TVR (via PCI/CABG)								
30- Day Risk								
Standard use	2958	1	1	1	1	----	----	----
Untested lesions	1188	1.26	1.22	1.13	1.11	----	0.54-2.27	0.78
Off-label lesions	1397	1.05	1.05	0.93	0.94	----	0.46-1.92	0.87
6-Month Risk								
Standard use	2958	1	1	1	1	1	----	----
Untested lesions	1188	1.67	1.63	1.65	1.64	1.43	0.95-2.16	0.09
Off-label lesions	1397	1.92	1.92	1.71	1.71	1.58	1.09-2.29	0.02
6-Month Risk (no early event)								
Standard use	2934	1	1	1	1	1	----	----
Untested lesions	1176	1.92	1.87	1.97	1.97	1.69	1.03-2.78	0.04
Off-label lesions	1385	2.45	2.45	2.18	2.17	2.00	1.28-3.10	0.002