1-Year Outcomes of Patients with Residual Physiologic Ischemia After Percutaneous Coronary Intervention: The DEFINE PCI Trial

Manesh Patel, Allen Jeremias, Justin Davies, Akiko Maehara, Mitsuaki Matsumura, Arnold Seto, Habib Samady, Andrew Sharp, Joel Schneider, Kare Tang, Ziad Ali, Suneel Talwar, and Gregg W. Stone on behalf of the DEFINE PCI Investigators

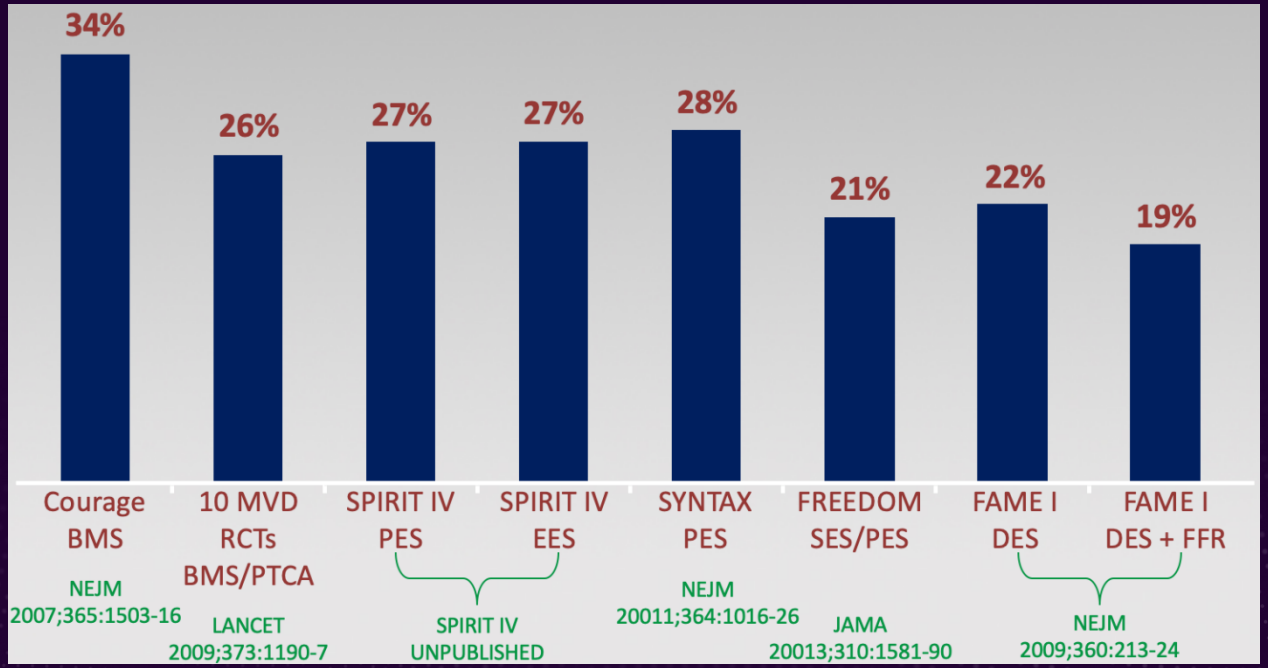
Disclosure Statement of Financial Interest

- **Research Grants:** Phillips, AstraZeneca, Bayer, Janssen, HeartFlow, NHLBI,
- **Advisory Board:** Bayer, Janssen, HeartFlow

Faculty disclosure information can be found on the app

Background

- Recurrent angina at 1 year after PCI is present in 20-30% of patients



Courtesy of Dr. Gregg Stone

DEFINE PCI

International Multicenter Trial of 500 Pts

Inclusion Criteria

- Pts with stable or unstable angina
- Lesions of ≥40% angiographic severity
- Single vessel CAD with long lesion (≥20 mm), multi-lesion CAD of a single vessel or multi-vessel CAD
- Pre-PCI iFR performed in all vessels with angiographic lesion severity of ≥40%

iFR < 0.9 in 1 or more vessel

↓

PCI of all vessels with abnormal baseline iFR

↓

Angiographic confirmation of PCI result

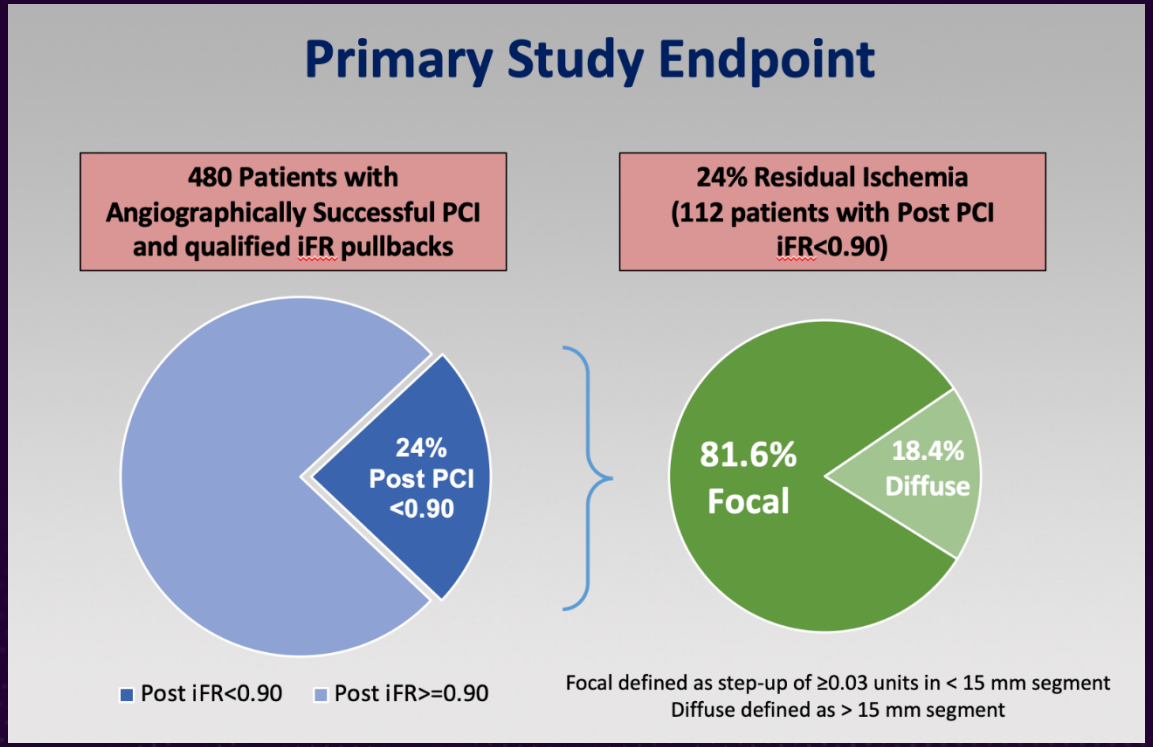
↓

Blinded iFR and blinded iFR pullback at end of procedure

Exclusion Criteria

- STEMI within past 7 days
- Cardiogenic shock
- Ventricular arrhythmias
- Prior CABG
- CTO
- LVEF <30%
- Severe valvular heart disease
- TIMI flow <3 at baseline or post PCI
- Intra-coronary thrombus on baseline angiography
- Procedural complications

Principal Findings from DEFINE PCI



Jeremias A et al. JACC Cardiovasc Interv. 2019 Oct 28;12:1991-2001.

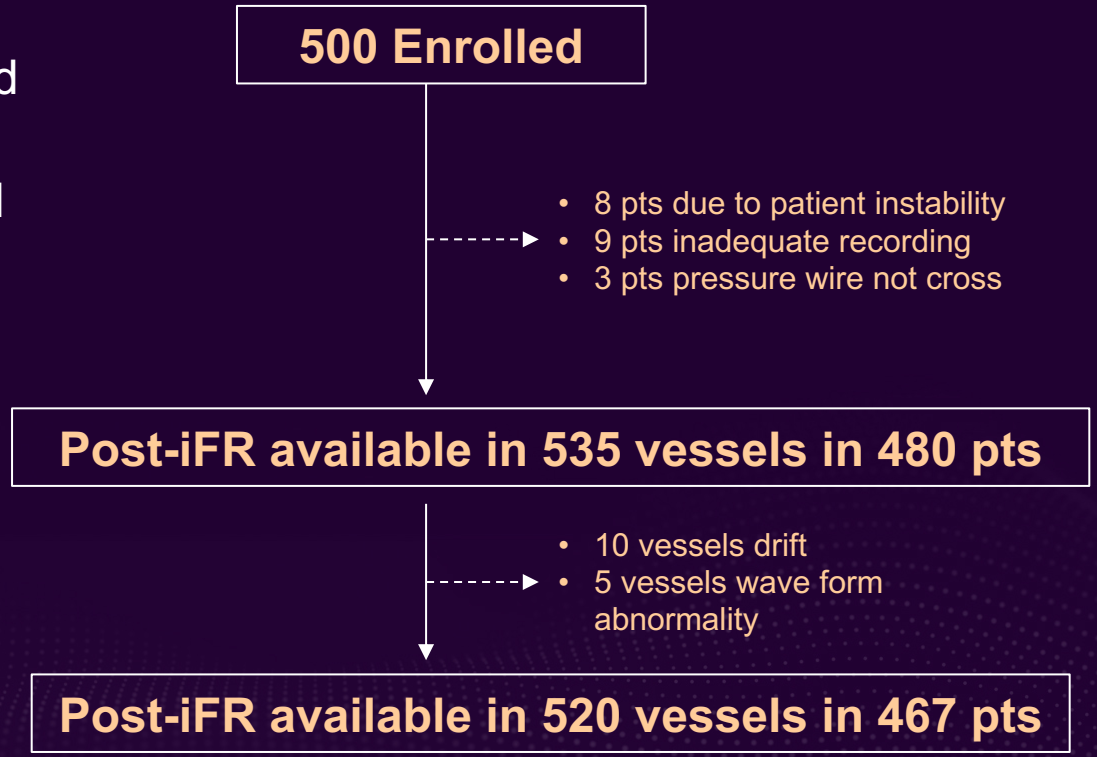
1. Significant residual ischemia after angiographically successful PCI was not uncommon, occurring in 24% of patients
2. Post-PCI angiography poorly correlated with physiologic measures
3. In a large majority of cases residual pressure gradients were focal and thus potentially amenable to treatment with additional PCI

DEFINE – PCI: 1-Year Follow-Up Objectives

- To assess the change in the Seattle Angina Questionnaire Angina Frequency (SAQ-AF) score during 1-year follow-up
- To assess clinical events (CV death, MI, and target vessel revascularization) at 1-year
- Perform post-hoc analysis to determine if there is a target post-PCI iFR value associated with improved outcomes

Methods

- Patients were followed 1-year for clinical events – blindly adjudicated
  - CV death, MI, and target vessel revascularization
- SAQ was assessed at baseline, 6 months and 12 months
- Post-hoc analysis identified achieving a post-PCI iFR value ≥0.95 to optimally discriminate clinical events

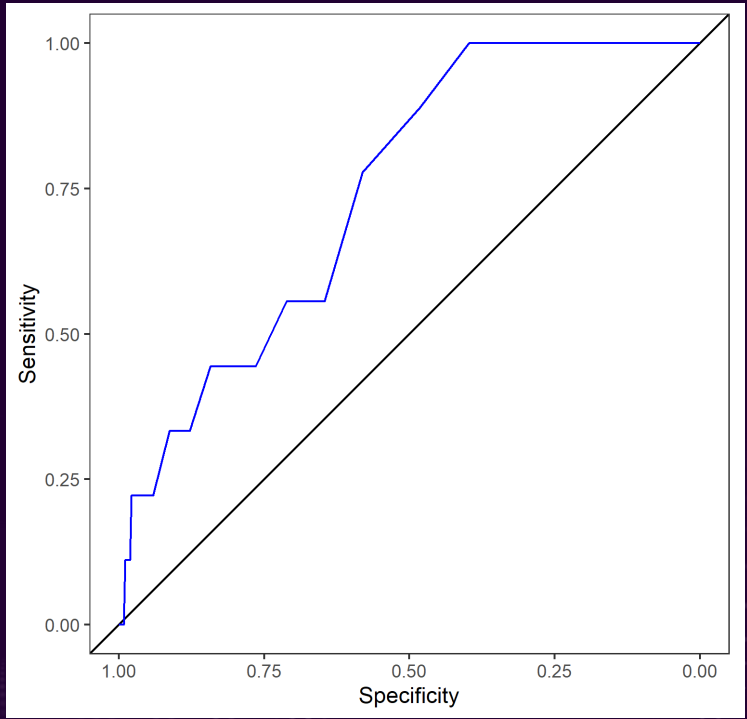


Identification of Post PCI iFR Target

Cardiac Death or Spontaneous MI

Cut-off value < 0.95

AUC (95%CI)=0.74 (0.61, 0.88)



Baseline Demographic and Medical History

Demographics	iFR <0.95 (N=285)	iFR ≥0.95 (N=182)	Total	P value
Sex, female	22.8%	25.8%	24.0%	0.46
Age, median (Q1, Q3)	67.0 (60.0, 74.0)	67.0 (59.0, 72.0)	67.0 (60.0, 73.0)	0.30
BMI, kg/m^2, median (Q1, Q3)	30.1 (26.2, 34.6)	29.1 (25.4, 32.9)	29.7 (25.9, 33.7)	0.045*

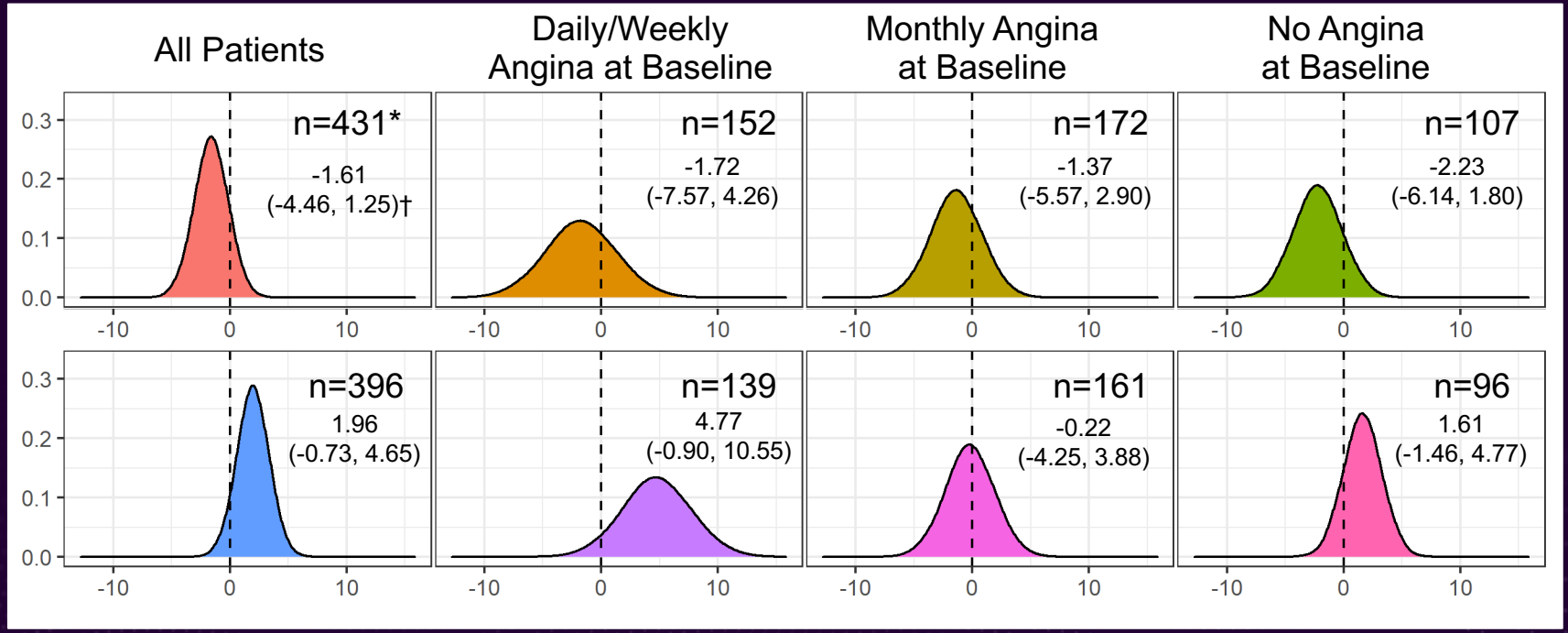
Baseline Demographic and Medical History

Demographics	iFR <0.95 (N=285)	iFR ≥0.95 (N=182)	Total	P value
Current smoker	13.3%	20.3%	16.1%	0.04
Diabetes	34.4%	30.8%	33.0%	0.42
Insulin-treated diabetes	30.6%	23.2%	27.9%	0.32
Hypertension	76.1%	76.4%	76.2%	0.95
Hyperlipidemia	70.2%	68.1%	69.4%	0.64
Renal disease	8.1%	6.6%	7.5%	0.55
Prior PCI	47.7%	39.6%	44.5%	0.08
Prior MI	28.1%	25.8%	27.2%	0.59

Baseline Demographic and Medical History

Demographics	iFR <0.95 (N=285)	iFR ≥0.95 (N=182)	Total	P value
Clinical presentation				
Stable angina	44.2%	39.0%	42.2%	0.27
Silent ischemia	4.6%	7.1%	5.6%	0.24
Unstable angina	31.2%	30.2%	30.8%	0.82
NSTEMI	15.1%	19.8%	16.9%	0.19
Recent MI, including STEMI (>7 days)	4.9%	3.8%	4.5%	0.59

Distributions of Differences Between post-iFR <0.95 vs ≥0.95 in SAQ Angina Scores Compared to Baseline by Bayesian Analysis



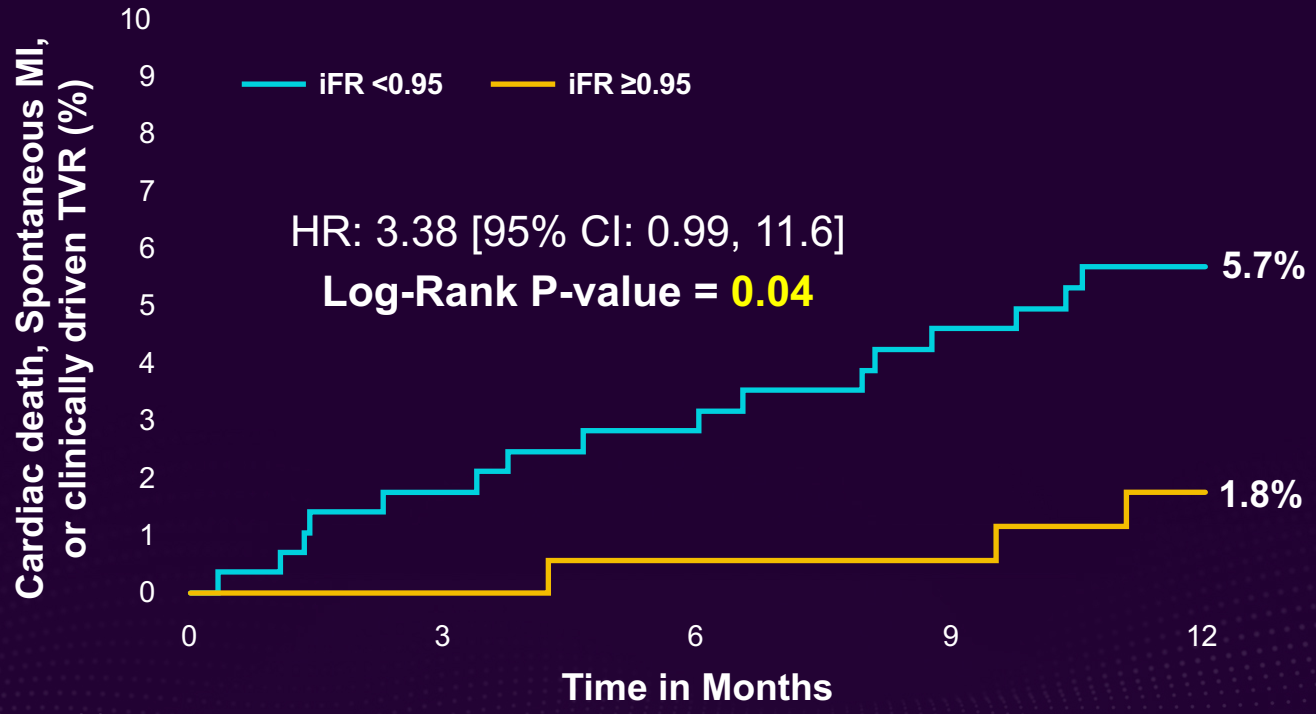
Positive values in x-axis indicate magnitude of benefit for pts with post-iFR ≥0.95

* indicates number of patients, † indicates posterior estimate (95% CI)

Quality of Life: Seattle Angina Questionnaire (12-Month)

Angina Frequency Score	iFR <0.95 (N=285)	iFR ≥0.95 (N=182)	Total (N=467)	P-value
Absolute change from Baseline				
N	246	150	396	
Mean ± SD	21.4 ± 25.0	20.7 ± 21.8	21.2 ± 23.8	
Absolute change from baseline ≥10	67.1%	68.7%	67.7%	0.74
Absolute change from baseline ≥10 in patients with SAQ ≤60 at baseline	88.5%	100.0%	92.8%	0.01

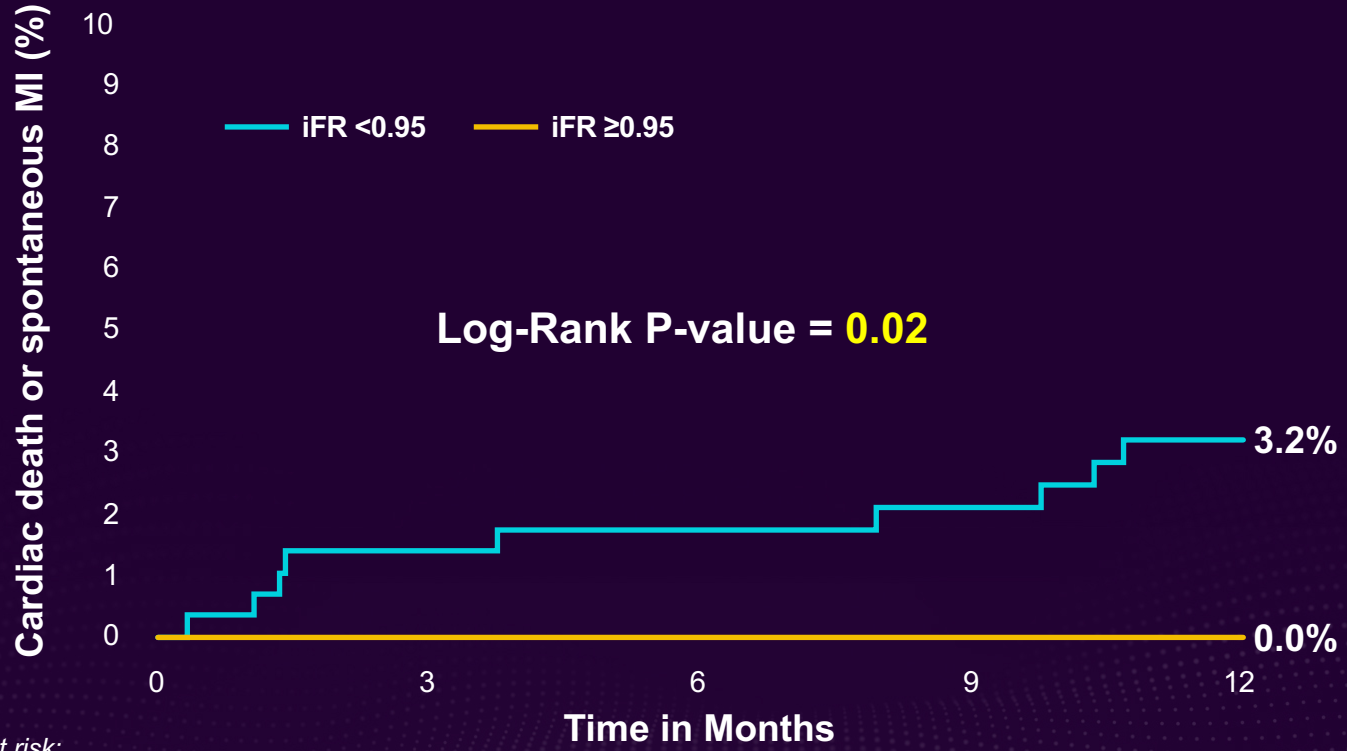
Cardiac Death, Spontaneous MI, or Clinically Driven TVR



Number at risk:

iFR <0.95	285	279	275	264	252
iFR ≥0.95	182	179	175	166	162

Cardiac Death or Spontaneous MI (%)



Number at risk:

iFR <0.95	285	280	278	271	259
iFR ≥0.95	182	179	176	167	165

Adjudicated Clinical Events at 12 Months

	iFR <0.95 (N=285)	iFR ≥0.95 (N=182)	Total (N=467)	P value
Death	1.4% (4)	1.1% (2)	1.3% (6)	0.81
Cardiac	0.4% (1)	0.0% (0)	0.2% (1)	0.44
Non-cardiovascular	1.1% (3)	1.1% (2)	1.1% (5)	0.93
MI	3.9% (11)	1.1% (2)	2.8% (13)	0.08
Peri-procedural MI	1.1% (3)	1.1% (2)	1.1% (5)	0.96
Spontaneous MI	2.8% (8)	0.0% (0)	1.8% (8)	0.02
Target Vessel MI	2.1% (6)	1.1% (2)	1.7% (8)	0.42

Adjudicated Clinical Events at 12 Months (cont.)

	iFR <0.95 (N=285)	iFR ≥0.95 (N=182)	Total (N=467)	P value
Clinically-driven revascularization	7.4% (21)	7.4% (13)	7.4% (34)	0.98
Target vessel revascularization	3.6% (10)	1.8% (3)	2.9% (13)	0.25
Target lesion revascularization	3.2% (9)	1.8% (3)	2.7% (12)	0.34
Non-target lesion revascularization	1.8% (5)	0.6% (1)	1.3% (6)	0.28
Non-target vessel revascularization	5.0% (14)	6.3% (11)	5.5% (25)	0.56

Multivariable Cox Regression Model for Cardiac Death, Spontaneous MI, or Clinically Driven TVR

	Hazard Ratio (95% CI)	p-value
Post-iFR <0.95	3.35 (0.97, 11.49)	0.055
Age, year	1.01 (0.96, 1.06)	0.74
Diabetes Mellitus	1.47 (0.59, 3.70)	0.41
Acute Coronary Syndrome Presentation	1.33 (0.53, 3.31)	0.54

Conclusions

- In DEFINE-PCI, despite angiographically successful PCI, pts who were highly symptomatic at baseline without residual ischemia by post-PCI iFR (iFR ≥0.95) tended to have greater improvements in anginal symptoms at 12 months compared with pts with residual ischemia
- A post-PCI iFR ≥0.95 was associated with less cardiac death, spontaneous MI, or clinically-driven TVR compared with a post-PCI iFR <0.95 (1.8% vs. 5.7% respectively, p=0.04)
- The clinical effectiveness of iFR guidance (target iFR ≥0.95) to identify and eliminate post-PCI ischemia will be studied in the prospective randomized DEFINE-GPS trial

Implications

- Well studied physiologic indices (FFR / iFR) have provided evidence as to:
  - When to revascularize (FFR ≤0.80 and iFR of ≤0.89)
- DEFINE PCI leading to DEFINE GPS aims to determine:
  - How to optimally revascularize (testing iFR target of ≥0.95)

Thank You

Study Chairman
- Gregg W. Stone, Mount Sinai Heart Health System, NY

Principal Investigators
- Allen Jeremias, St. Francis Hospital, Roslyn, NY
- Justin Davies, Imperial College London
- Manesh Patel, Duke Health Care System

Steering Committee
- Habib Samady, Emory University
- Andrew Sharp, Royal Devon and Exeter
- Arnold Seto, VAMC, Long Beach, CA

Clinical Events Committee
- Cardiovascular Research Foundation, New York, NY; Steven O. Marx, MD, chair

Physiology Core Laboratory
- Allen Jeremias, Cardiovascular Research Foundation, New York, NY
- Akiko Maehara, Cardiovascular Research Foundation, New York, NY
- Mitsuaki Matsumura, Cardiovascular Research Foundation, New York, NY

Angiography Core Laboratory
- Ziad Ali, Cardiovascular Research Foundation, New York, NY

Sponsor
- Philips/Volcano, Amsterdam, The Netherlands

Participants and Enrolling Sites

Top 15 Enrolling Centers
- North Carolina Heart & Vascular (J. Schneider)
- Essex Cardiothoracic Centre (K. Tang)
- Royal Bournemouth Hospital (S. Talwar)
- VU University Medical Center (K. Marques)
- Midwest Cardiovascular Research Foundation (N. Shammas)
- Northwell Health (L. Gruberg)
- Colorado Heart & Vascular (J. Altman)
- Dartmouth Hitchcock (J. Jayne)
- VAMC Long Beach (A. Seto)
- VAMC Atlanta (G. Kumar)
- AMC Amsterfdam (J. Piek)
- St. Francis Hospital (R. Schlofmitz)
- Minneapolis Heart Institute (E. Brilakis)
- Royal Devon & Exeter (A. Sharp)
- Stony Brook University Hospital (W. Lawson)