The XIENCE Short DAPT Program:

XIENCE 90/28

Evaluating the Safety of 3-month and 1-month DAPT in HBR Patients

Roxana Mehran, MD and Marco Valgimigli, MD, PhD

on Behalf of the XIENCE 90/28 Investigators

ClinicalTrials.gov: NCT03218787, NCT03815175, NCT03355742

Roxana Mehran, MD

**Mount Sinai Professor of Cardiovascular Clinical Research and Outcomes,
Director of Interventional Cardiovascular Research and Clinical Trials,
Icahn School of Medicine at Mount Sinai, New York, NY, USA**

@Drroxmehran

Marco Valgimigli, MD, PhD

Deputy Chief, CardioCentro Ticino, Lugano, Switzerland

Professor of Cardiology, University of Bern, Bern, Switzerland

@vlgmrc

Disclosure Statement of Financial Interest

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

Affiliation/Financial Relationship	Company
Consultant / Advisory / Speaking Engagements	Abbott Laboratories (to institution), Abiomed (spouse), Boston Scientific, Idorsia Pharmaceuticals Ltd. (no fee), Janssen, Medscape/WebMD, Medtelligence (Janssen Scientific Affairs), Roivant Sciences Inc, Sanofi, Siemens Medical Solutions, Regeneron Pharmaceuticals (no fee), Spectranetics/Philips/Volcano Corp (to institution), The Medicines Company (spouse)
Research Funding to Institution	Abbott Laboratories, Abiomed, AstraZeneca, Bayer, Beth Israel Deaconess, BMS, CERC, Chiesi, Concept Medical, CSL Behring, DSI, Medtronic, Novartis, OrbusNeich
Scientific Advisory Board	Bristol-Myers Squibb (to institute), Medtelligence (Janssen Scientific Affairs), Merck (spouse)
Equity, <1%	Claret Medical, Elixir Medical
DSMB Membership Paid to Institution	Watermark Research Partners
Associate Editor	ACC, AMA

Disclosure Statement of Financial Interest

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

Affiliation/Financial Relationship	Company
Grant/Research Support	Daiichi Sankyo, Medicure, Terumo, CoreFLOW
Consulting Fees/Honoraria	Abbott, Alvimedica/CID, Astra Zeneca, Bayer, CoreFLOW, Chiesi, IDORSIA, Bristol Myers Squib SA, Medscape, Vesalio, Universität Basel Dept. Klinische Forschung
Major Stock Shareholder/Equity	None
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

Background

Xience short DAPT

- DAPT is essential for the prevention of ischemic events after PCI but inevitably increases the risk of bleeding
- Patients at high bleeding risk (HBR) constitute up to 40% of subjects undergoing PCI[1]
- As hemorrhagic events following PCI have substantial prognostic implications[2,3], bleeding-avoidance strategies are vital to improve patient outcomes[4]
- Recent trials on next-generation DES have shown an acceptable safety profile with a short course of DAPT[5-8]; however, the optimal DAPT duration in HBR patients remains unknown

1. Capodanno et al. J Am Coll Cardiol. 2020;76(12):1468–83
2. Mehran et al. Eur Heart J. 2009;30(12):1457-66
3. Valgimigli et al. Eur Heart J. 2017;38(11):804-10
4. Mehran et al. N Engl J Med. 2019 Nov 21;381(21):2032-2042
5. Urban et al. N Engl J Med 2015;373:2038–47
6. Ariotti et al. J Am Coll Cardiol Intv 2016;9:426–36
7. Varenne et al. Lancet 2018;391:41–50
8. Windecker et al. N Engl J Med. 2020 Mar 26;382(13):1208-1218

XIENCE

Xience short DAPT

Stent Platform

Multilink Stent Design
CoCr L-605 Alloy

Strut thickness:
81 µm

Polymer Coating

Durable Fluoropolymer Coating

Fluoropassivation properties selectively retain albumin and minimize platelet adhesion

Drug

Everolimus

Average drug concentration:
100 µg/cm^2

Study Hypotheses

In HBR patients who have undergone successful PCI with the XIENCE stent and completed a short DAPT regimen of 1 month (XIENCE 28) or 3 months (XIENCE 90) without experiencing adverse ischemic events, continued treatment with aspirin monotherapy would be *non-inferior* to DAPT for up to 12 months with respect to ischemic events and *superior* with respect to bleeding.

Trial Objectives

Among HBR patients who have undergone successful PCI with the XIENCE stent:

Primary Objective:

- To evaluate the *safety (all death or MI)* of a short DAPT regimen (1 or 3 months) versus DAPT for up to 12 months

Secondary Objectives:

- To determine the impact of short DAPT (1 or 3 months) versus DAPT for up to 12 months on *clinically relevant bleeding (BARC 2-5)*
- To evaluate *stent thrombosis (definite/probable)* against a performance goal*

* Only for XIENCE 90

XIENCE Short DAPT Program

Xience short DAPT

Xience short DAPT

Xience short DAPT XIENCE 90

3-month DAPT

101 sites in USA

2,047 patients

Xience short DAPT XIENCE 28

1-month DAPT

Global

52 sites

963 patients

USA

58 sites

642 patients

TOTAL OF ~3,600 PATIENTS WITH 1-MONTH OR 3-MONTH DAPT

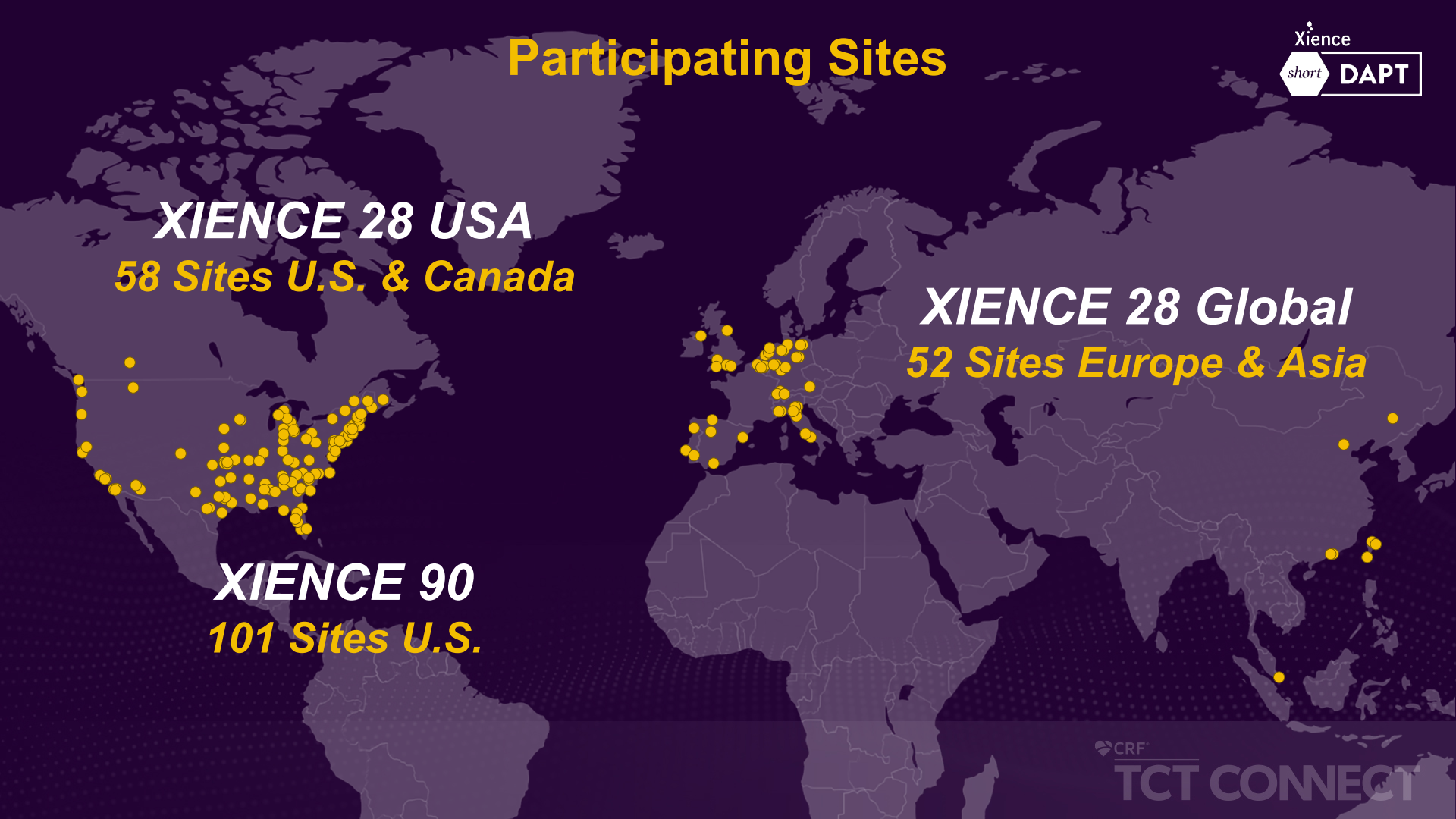
Short DAPT Program Organization

Xience short DAPT

PIs	Dr. Roxana Mehran Dr. Marco Valgimigli
Executive Committee	Drs. Dominick J. Angiolillo, Sripal Bangalore, Deepak L. Bhatt, Junbo Ge, James Hermiller, Rajendra R. Makkar, Franz-Josef Neumann, Shigeru Saito, Marco Valgimigli, Roxana Mehran
Steering Committee	Drs. Jose M De La Torre Hernandez, Vijay Kunadian, Gennaro Sardella, Holger Thiele, Olivier Varenne, Pascal Vranckx, Stephan Windecker, Yujie Zhou
Independent Biostatistician	Dr. Joseph Massaro (Boston University)
DSMB	Axio Research
CEC	Cardiovascular Research Foundation
Sponsor	Abbott

Participating Sites

Xience short DAPT



Key Inclusion Criteria

HBR Criteria

- Age ≥75 years
- Chronic OAC therapy
- CKD (creatinine ≥ 2.0 mg/dl or dialysis)
- Anemia (hemoglobin <11 g/dl)
- Hematological disorders (platelet count <100,000/mm^3 or any coagulation disorder)
- Major bleeding in the last 12 months
- History of stroke

Angiographic Criteria

- Successful PCI
- Exclusive use of XIENCE stents
- Target vessel diameter of 2.25 - 4.25 mm
- Target lesion ≤32 mm in length*
- ≤3 target lesions with ≤2 target lesions per vessel

* Only for XIENCE 90

Key Exclusion Criteria

Xience short DAPT

Clinical Criteria

- STEMI presentation
- LVEF <30%
- Planned surgery within 1 or 3 months* of PCI

Angiographic Criteria

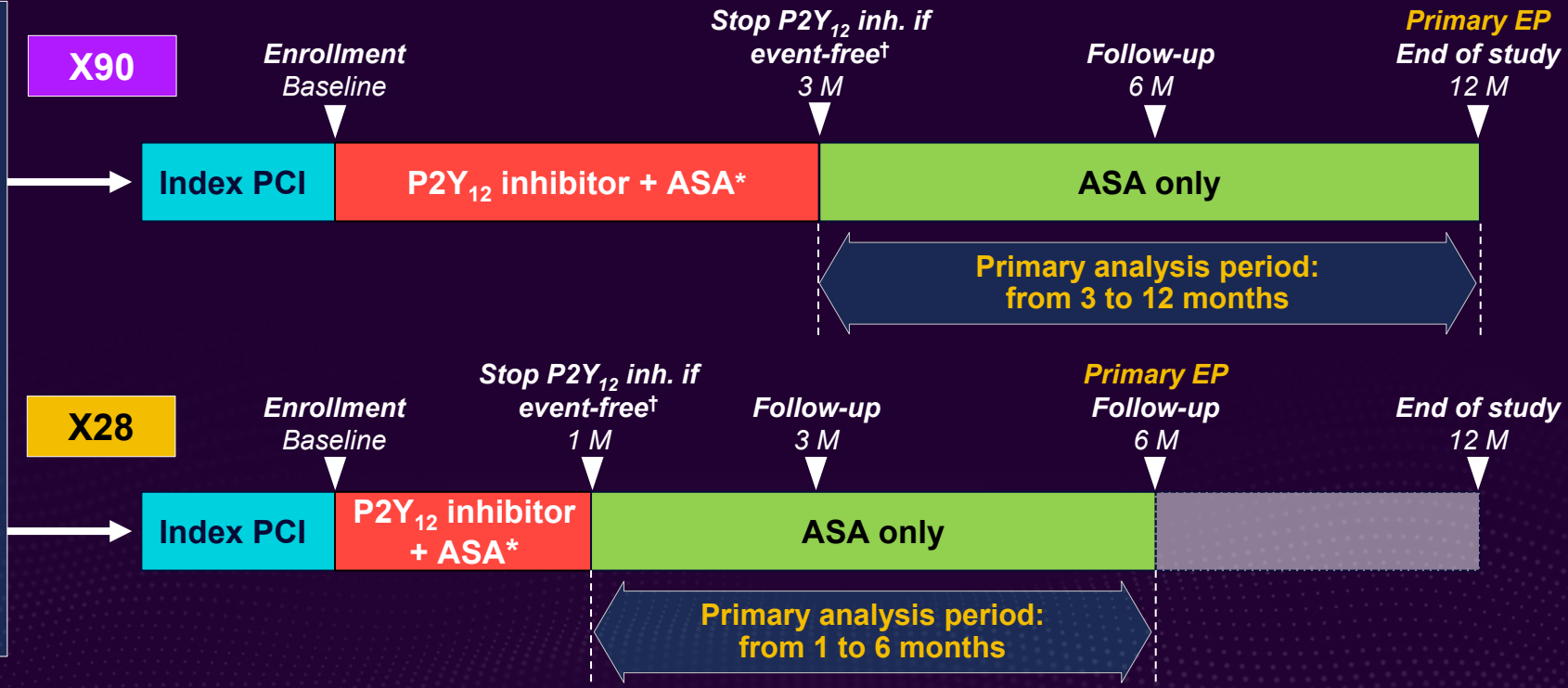
- Target lesion containing thrombus†
- PCI with overlapping stents
- Target lesion in one of the following:
  - × left main coronary artery
  - × arterial or saphenous vein graft
  - × in-stent restenosis
  - × chronic total occlusion

* 1 month in XIENCE 28; 3 months in XIENCE 90
† Only for XIENCE 90

Trial Design

Xience short DAPT

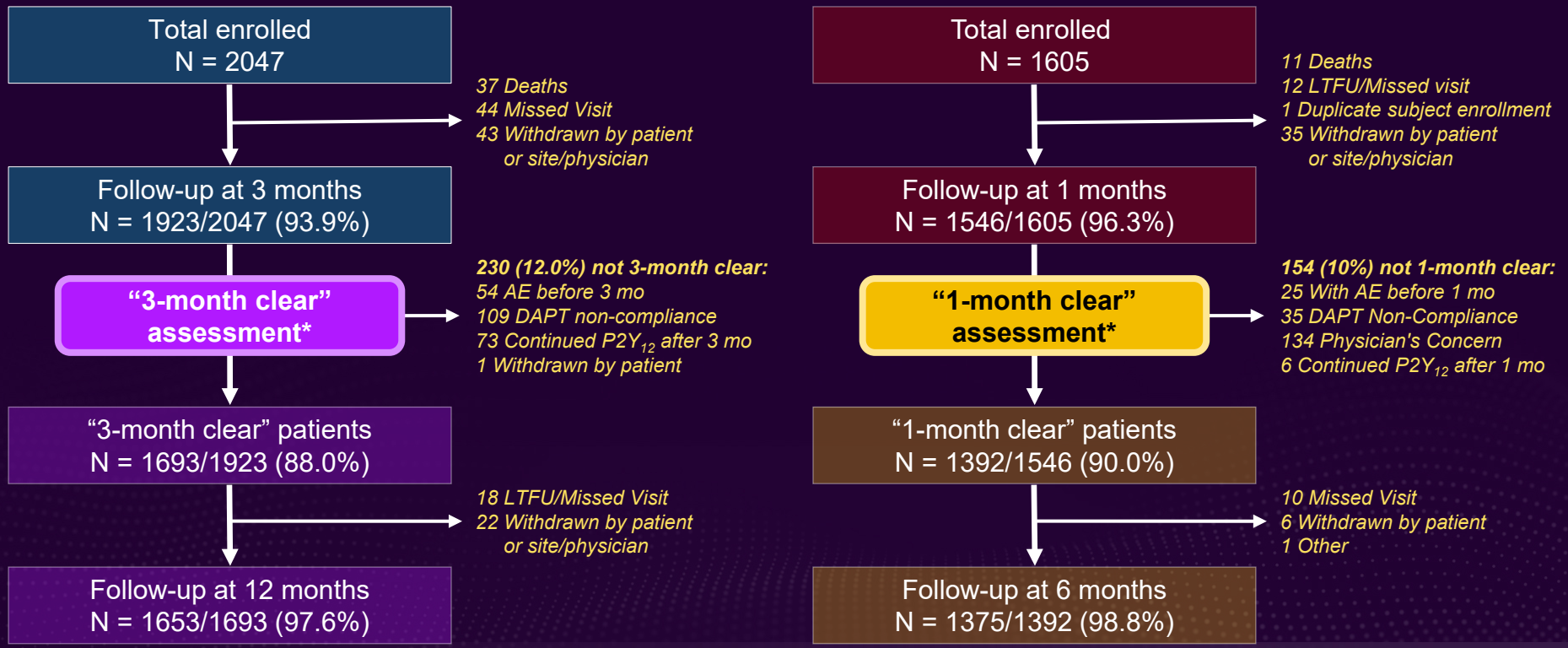
A prospective, single-arm, multicenter, open-label, non-randomized trial



* For patients on chronic OAC, dual therapy (OAC plus $P2Y_{12}$ inhibitor) might be considered for the first 1 or 3 months

† "Event-free" defined as free from MI, repeat revascularization, stroke, or ST and compliant with DAPT in the first 1 or 3 months

Patient Disposition



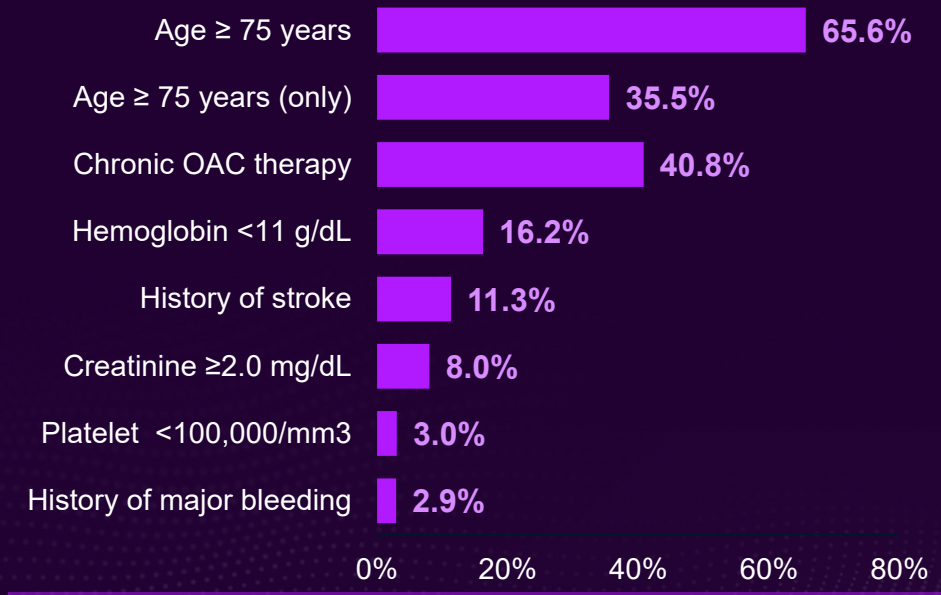
* "Clear" defines patients who are event free (MI, repeat revascularization, stroke, or ST) and compliant with DAPT within 1 month (XIENCE 28) or 3 months (XIENCE 90) of index PCI

HBR Criteria Distribution

Xience short DAPT

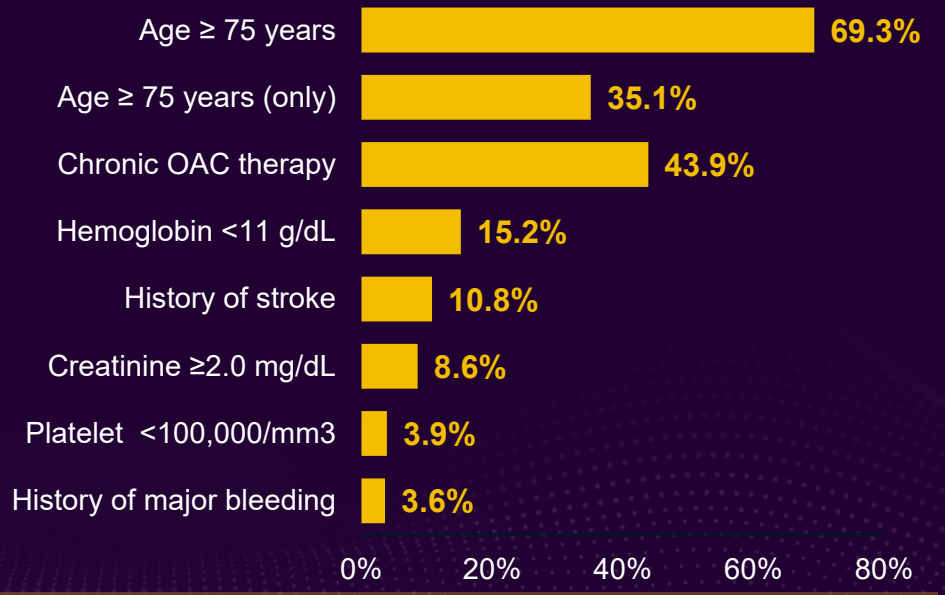
All Registered Patients

XIENCE 90



AVERAGE NUMBER OF CRITERIA MET: *1.5 ± 0.7*

XIENCE 28



AVERAGE NUMBER OF CRITERIA MET: *1.6 ± 0.8*

Baseline Characteristics

Xience short DAPT

"Clear" Patients

Variable	XIENCE 90 (N = 1693)	XIENCE 28 (N = 1392)
Age, years (Mean ± SD)	75.25 ± 9.29 (1693)	75.97 ± 8.37 (1392)
Female	35.2% (596/1693)	32.5% (453/1392)
Hypertension	89.5% (1516/1693)	84.7% (1179/1392)
Dyslipidemia	82.8% (1401/1693)	67.5% (939/1392)
Diabetes	39.2% (663/1692)	37.0% (512/1382)
CKD (eGFR < 60 mL/min)	40.2% (677/1682)	47.4% (631/1330)
Prior MI	15.8% (264/1669)	16.4% (227/1382)
Prior CABG	12.1% (205/1693)	8.0% (112/1392)
ACS	34.7% (588/1693)	34.1% (475/1392)
NSTEMI	7.1% (120/1693)	17.6% (245/1392)
Unstable Angina	28.7% (486/1693)	16.5% (230/1392)
PARIS Score (Median, IQR)	6.0 (4.0, 8.0) (1693)	6.0 (4.0, 8.0) (1392)
PRECISE-DAPT Score (Median, IQR)	25.0 (19.0, 32.0) (1606)	27.0 (20.0, 34.0) (1295)

Procedural Characteristics

Xience short DAPT

"Clear" Patients

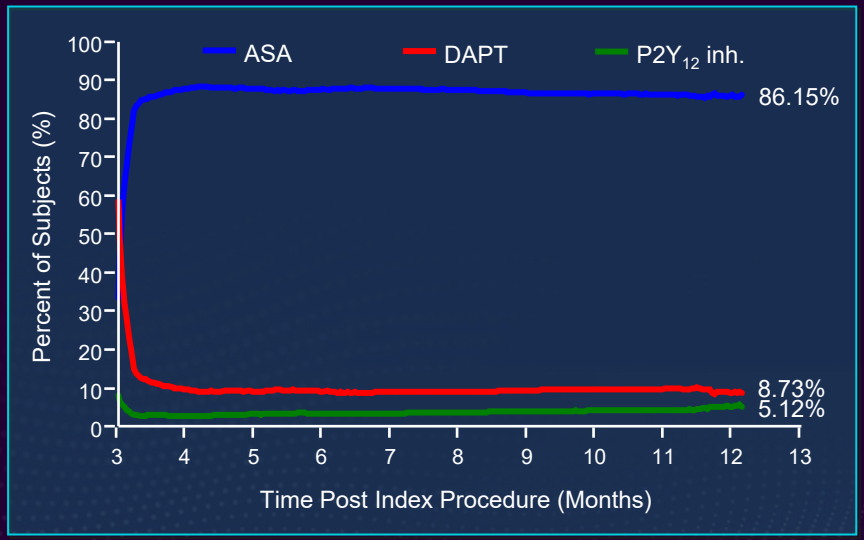
Variable	XIENCE 90 (N = 1693)	XIENCE 28 (N = 1392)
Multivessel Disease	46.0% (779/1693)	41.2% (573/1392)
Radial Access	52.2% (883/1693)	70.8% (986/1392)
B2/C Lesion	33.8% (573/1693)	35.8% (498/1392)
Bifurcation	7.6% (129/1693)	11.6% (161/1392)
Total Stent Length, mm (Mean ± SD)	25.5 ± 13.8 (1693)	27.2 ± 14.4 (1389)
	N = 2078 Lesions	N = 1700 Lesions
Target Lesion Location		
LAD	43.2% (898/2078)	45.9% (781/1700)
LCX	24.7% (513/2078)	24.1% (409/1700)
RCA	32.0% (665/2078)	29.9% (509/1700)
Pre-procedure RVD, mm (Mean ± SD)	2.99 ± 0.49 (2078)	2.99 ± 0.50 (1700)
Pre-procedure DS, % (Mean ± SD)	83.7 ± 10.3 (2078)	82.47 ± 10.80 (1699)
Target Lesion Length, mm (Mean ± SD)	16.0 ± 7.1 (2078)	18.01 ± 8.43 (1700)

Antiplatelet Usage

Primary Analysis Population

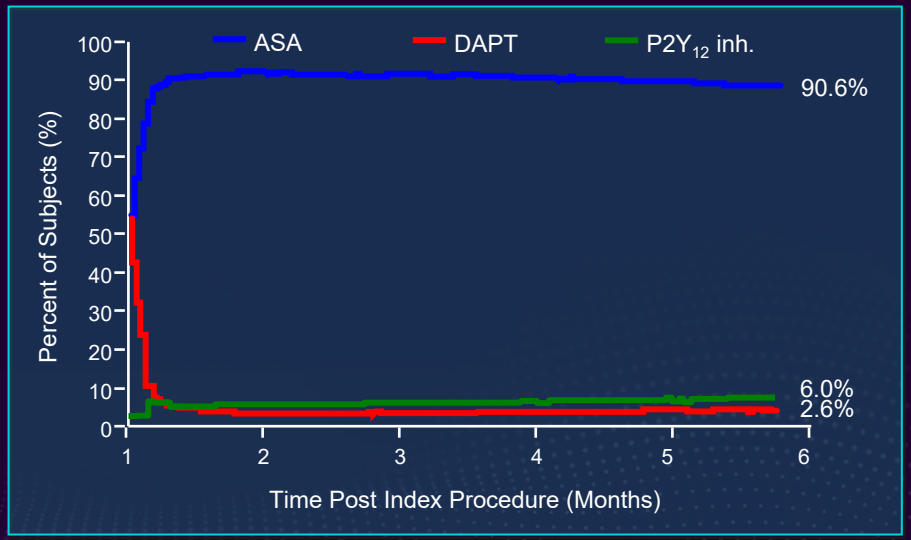
XIENCE 90

Between 3 and 12 Months



XIENCE 28

Between 1 and 6 Months



Note: Patients with adverse events during follow-up are included in the curves

ASA: includes subjects on ASA only or ASA + OAC
DAPT: includes subjects on DAPT only or DAPT + OAC
$P2Y_{12}$ inh.: includes subjects on $P2Y_{12}$ inh. and/or OAC

Study Endpoints

Xience short DAPT

Primary endpoint

- All-cause death or all MI (non-inferiority)
  - *XIENCE 90 vs control*
  - *XIENCE 28 vs control*

Key secondary endpoints

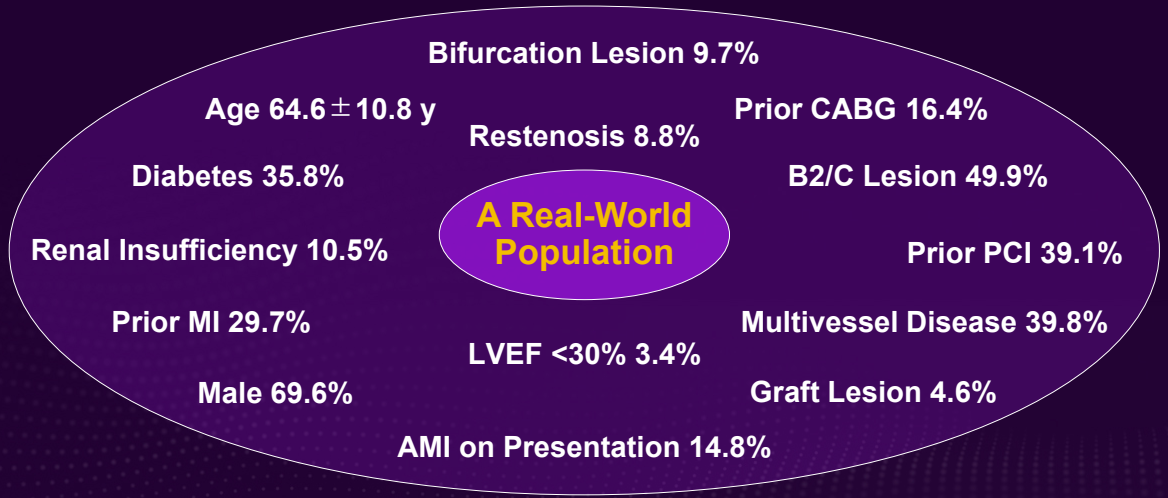
- BARC 2-5 bleeding (superiority)
  - *XIENCE 90 vs control*
  - *XIENCE 28 vs control*
- Definite/probable ST (performance goal) – *XIENCE 90 only*

XIENCE V USA: Historical Control

Xience short DAPT

A prospective, multicenter, post-approval study to evaluate the safety and effectiveness of the XIENCE stent in real-world settings between 2008-2011

8,061 patients from 192 sites in the US



DAPT Usage in XV USA

30-day Visit	94.2%
180-day Visit	90.5%
1-Year Visit	85.6%

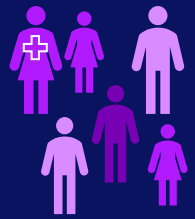
Naidu S.N. et al., J Am Coll Cardiol Intv 2012;5:626 –35

Propensity Score Stratification: XIENCE 90

Xience short DAPT

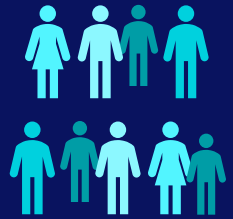
POPULATIONS

XIENCE 90 (3-mo DAPT)



Investigational Arm

XIENCE V USA (12-mo DAPT)

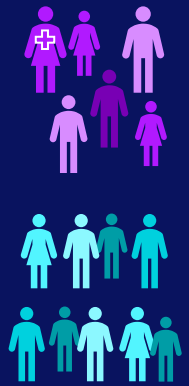


Historical Control

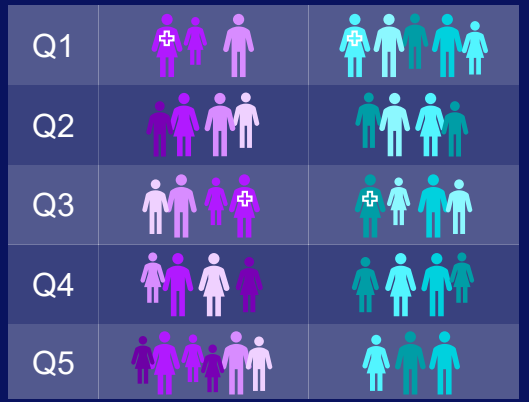
SINGLE-ARM STUDIES

PROPENSITY STRATIFICATION

Patients sorted by propensity score using baseline characteristics



Stratification in 5 quintiles



GROUPING BY PROPENSITY SCORE

Propensity Score Stratification: XIENCE 28

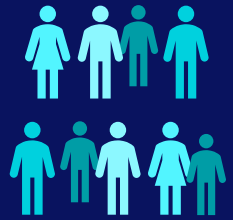
Xience short DAPT

POPULATIONS

XIENCE 28 (1-mo DAPT)

Investigational Arm

XIENCE V USA (6-mo DAPT)

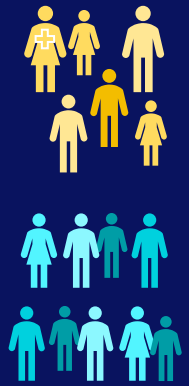


Historical Control

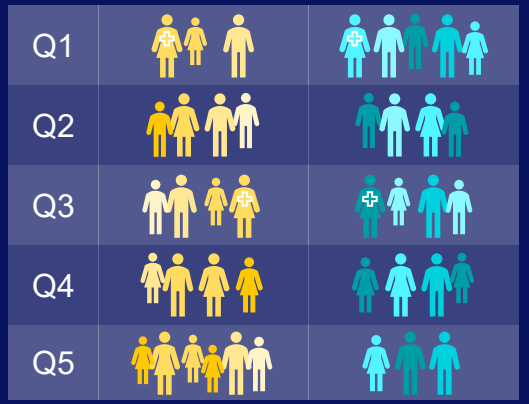
SINGLE-ARM STUDIES

PROPENSITY STRATIFICATION

Patients sorted by propensity score using baseline characteristics



Stratification in 5 quintiles



GROUPING BY PROPENSITY SCORE

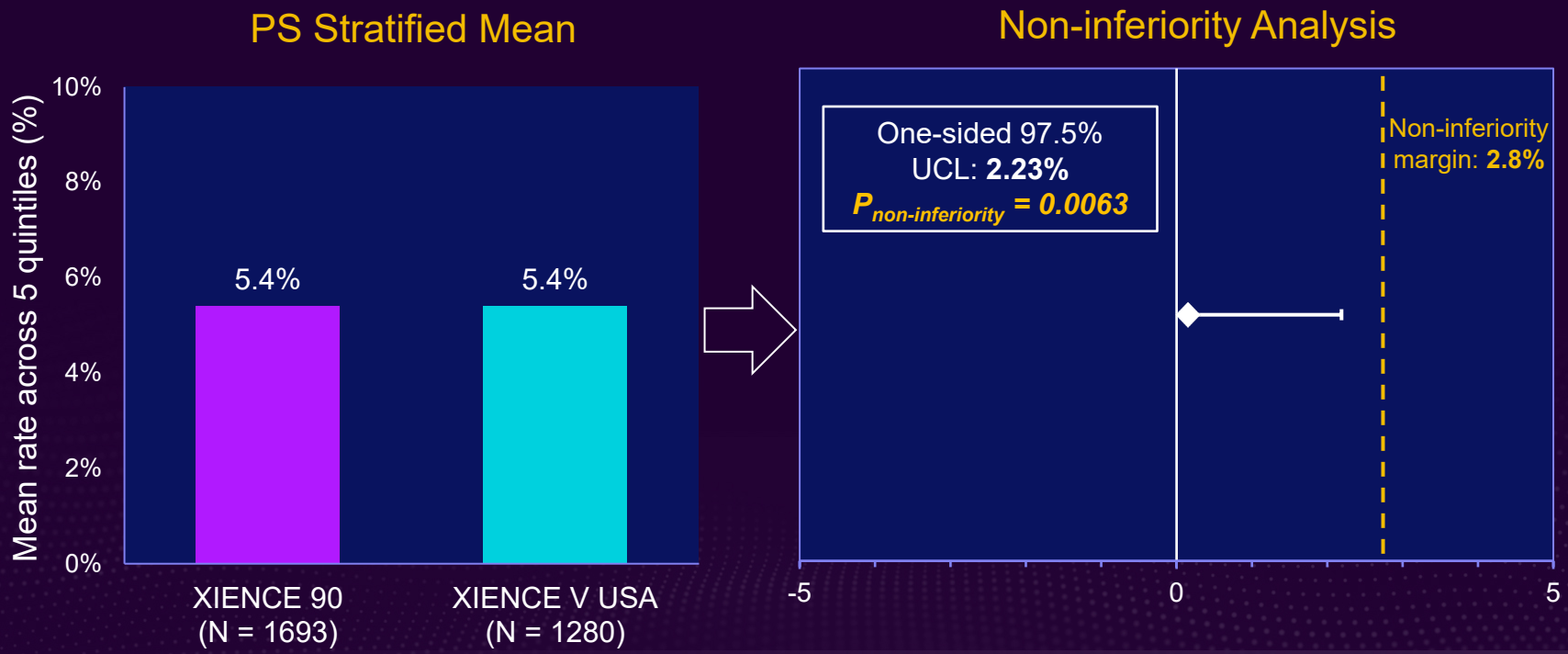
Sample Size and Power Calculations

Primary Endpoint: All Death or MI

	XIENCE 90	XIENCE 28
Control group	3-month clear HBR patients from XIENCE V USA	1-month clear HBR patients from XIENCE V USA
Primary hypothesis	Non-inferiority for all death or MI • Margin (Δ) = 2.8%	Non-inferiority for all death or MI • Margin (Δ) = 2.5%
Expected rate	6.1% between 3 and 12 months	4.3% between 1 and 6 months
Statistical model	Propensity stratification	Propensity stratification
Test significance level (α)	0.025 (1-sided)	0.025 (1-sided)
Attrition rate	15%	10%
Power (1-β)	87%	90%
Sample size (N patients)	2000	1600

XIENCE 90: All Death or MI

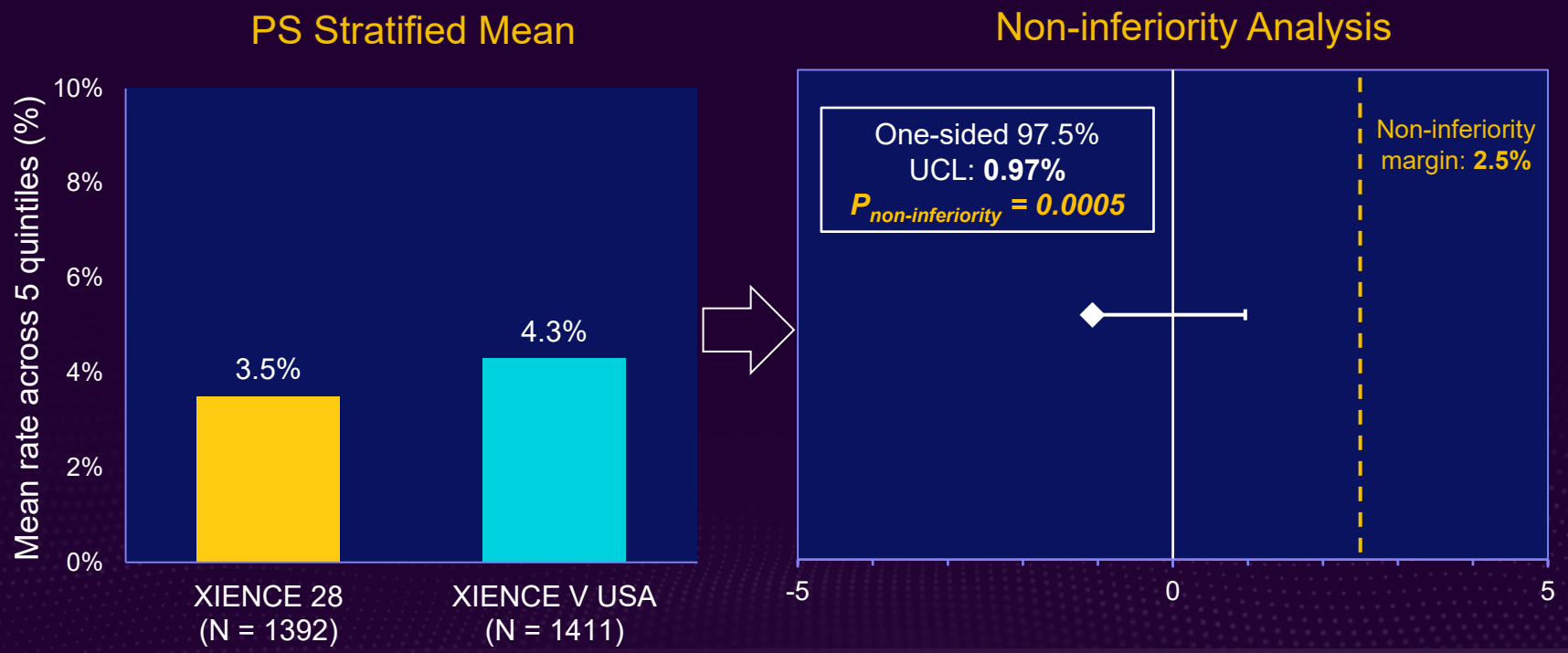
Between 3 and 12 Months



Non-inferiority tested with the stratified Farrington-Manning method

XIENCE 28: All Death or MI

Between 1 and 6 Months



Non-inferiority tested with the stratified Farrington-Manning method

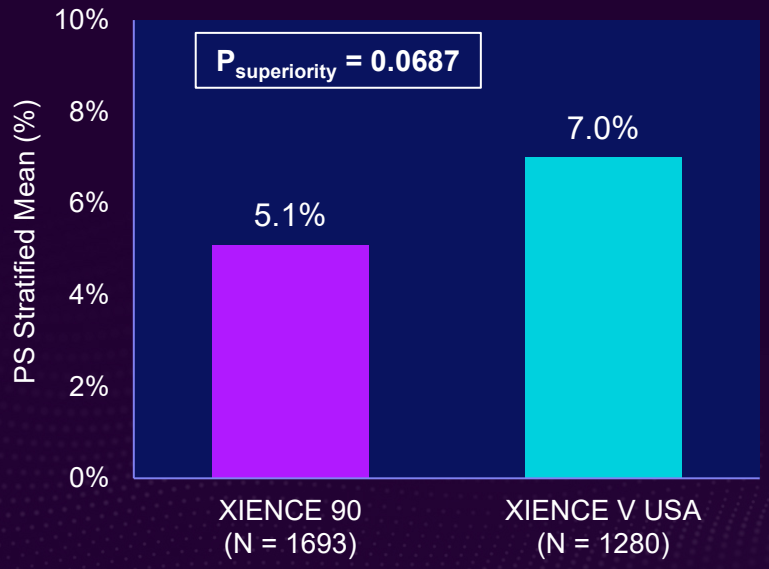
BARC 2-5 Bleeding

Xience short DAPT

Powered Secondary Endpoint

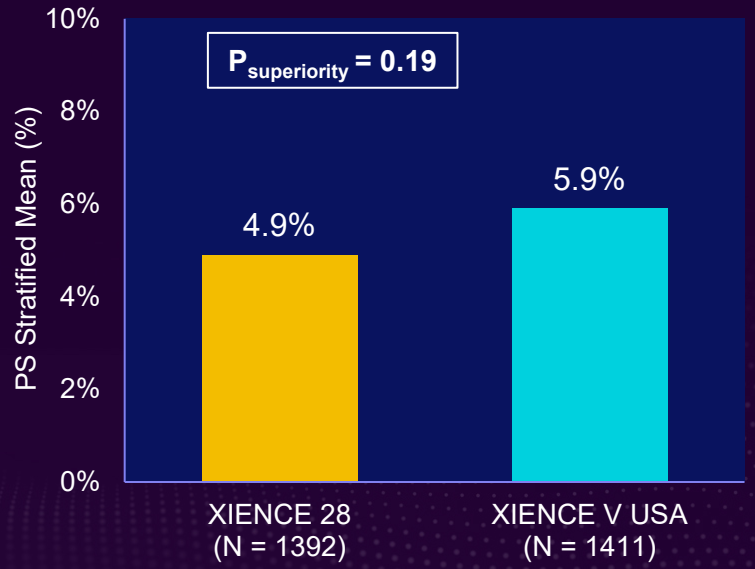
XIENCE 90

Between 3 and 12 Months



XIENCE 28

Between 1 and 6 Months



Note: XIENCE V USA protocol did not mandate collection of BARC 2 bleeding events

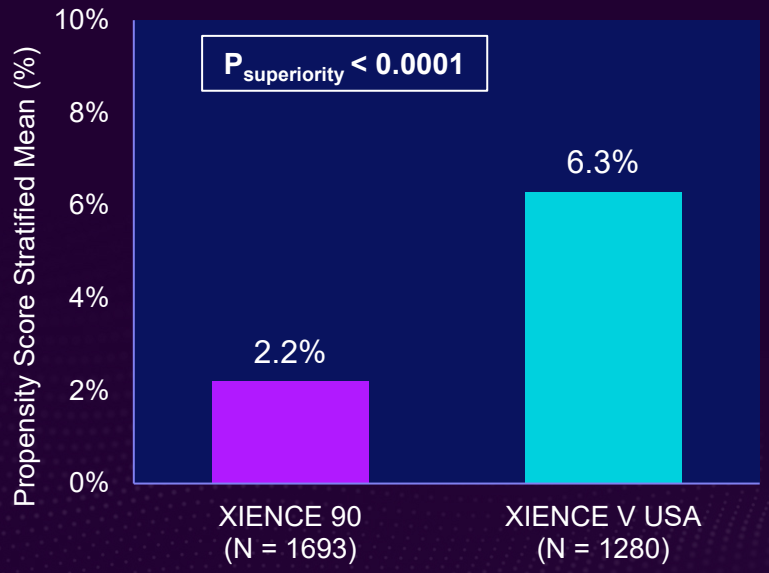
An assumed ~50% reduction in BARC 2-5 bleeding provided XIENCE 90 with 95% power and XIENCE 28 with 90% power
Superiority tested with the stratified Farrington-Manning method using a one-sided significance level of 0.025

BARC 3-5 Bleeding

Xience short DAPT

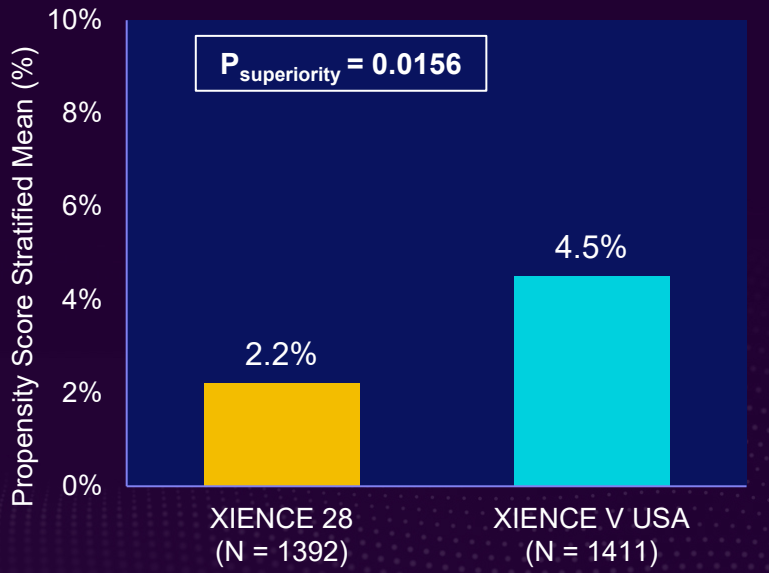
XIENCE 90

Between 3 and 12 Months



XIENCE 28

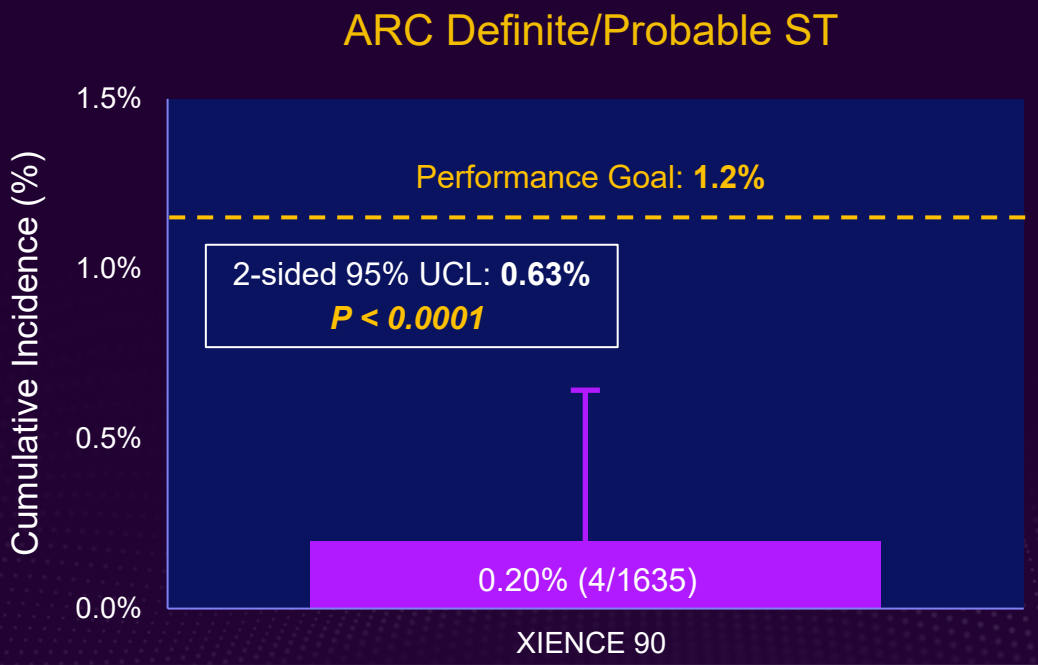
Between 1 and 6 Months



The PS stratified analysis for BARC 3-5 bleeding was *not* pre-specified

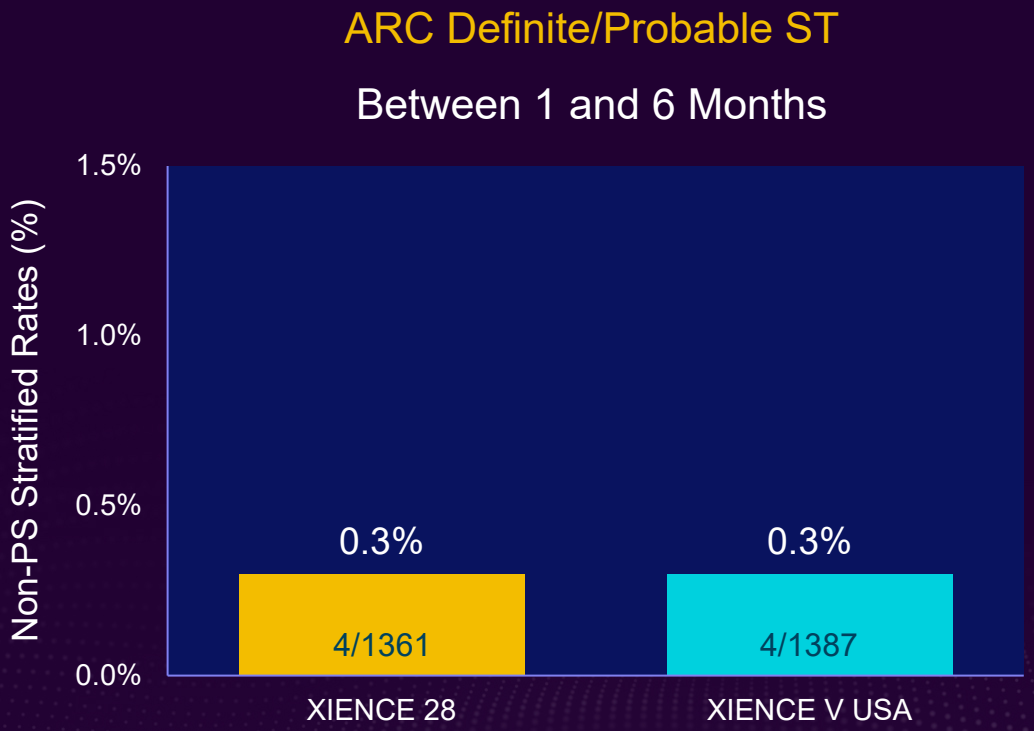
XIENCE 90: Stent Thrombosis

Powered Secondary Endpoint (3-12 Months)



An assumed 0.5% rate of definite/probable ST provided XIENCE 90 with 85% power (Exact test)

XIENCE 28: Stent Thrombosis



Definite/probable ST was *not* a powered secondary endpoint in XIENCE 28

Limitations

- The XIENCE 90 and XIENCE 28 studies present limitations inherent to the non-randomized design, despite statistical compensation using a propensity-adjusted analysis
- Findings may not be generalizable to patients who do not meet the XIENCE Short DAPT Program inclusion and exclusion criteria
- The observed treatment effect applies only to patients “free” from adverse events and adherent to the DAPT regimen in the first 1 or 3 months post-PCI
- Given that XIENCE V USA was performed approximately one decade before the XIENCE Short DAPT Program, confounders related to changes in clinical practice cannot be excluded

Conclusions

Among HBR patients undergoing PCI with the XIENCE stent, a short DAPT regimen of 1 or 3 months compared with standard DAPT up to 12 months resulted in:

- non-inferior ischemic outcomes
- similar rates of clinically relevant (BARC 2-5) bleeding, with a significant reduction in major (BARC 3-5) bleeding
- very low incidence of stent thrombosis

XIENCE 90

Kansas Heart Hospital
(Cardiovascular Research Institute of Kansas)
PI: Aziz Maksoud
RC: Lindsey Steele

Huntsville Hospital
(Heart Center Research LLC)
PI: Joshua Krasnow
RC: Karen Hensley

Lenox Hill Hospital (Northwell)
PI: Michael Kim
RC: Meriton Ruhani
Yihenew Abetu
Ian Dalangin

Baylor Heart & Vascular Hospital
PI: James Choi
RC: Angela Roy

Via Christi Regional Medical
(Cardiovascular Research Institute of Kansas)
PI: Baseem Chehab
RC: Lindsey Steele

Scottsdale Healthcare
(HonorHealth)

XIENCE 28 USA

Royal Jubilee Hospital
PI: Dr. Simon Robinson
RC: Noreen Lounsbury

Redmond Regional Medical Center
PI: Dr. Hector Picon
RC: Kathy Jones

Heart Center Research, LLC
PI: Dr. Henry Chen
RC: Karen Hensley

Anmed Health
PI: Dr. Brent McLaurin
RC: Charlesa Davis

Baylor Scott & White Heart and Vascular Hospital
PI: Dr. James Choi
RC: Angela Roy

Cardiovascular Research Institute of Kansas
PI: Dr. Aziz Maksoud
RC: Lindsey Steele

XIENCE 28 Global

Segeberger Kliniken GmbH
PI: Dr. Ralph Toelg
RC: Friederike Geyer

Az.Osp. Universitaria di Ferrara
PI: Dr. Gianluca Campo
RC: Veronica Lodolini

Elisabeth-Krankenhaus Essen GmbH
PI: Dr. Thomas Schmitz
RC: Melanie Steffen

Centro Cardiologico Monzino
PI: Dr. Daniela Trabattoni

Herzzentrum Leipzig GmbH
PI: Dr. Holger Thiele
RC: Eva Kirchhof

Universitatsmedizin Berlin
Campus Benjamin Franklin (CBF)
PI: Dr. Ulf Landmesser
RC: Julia Leibiger

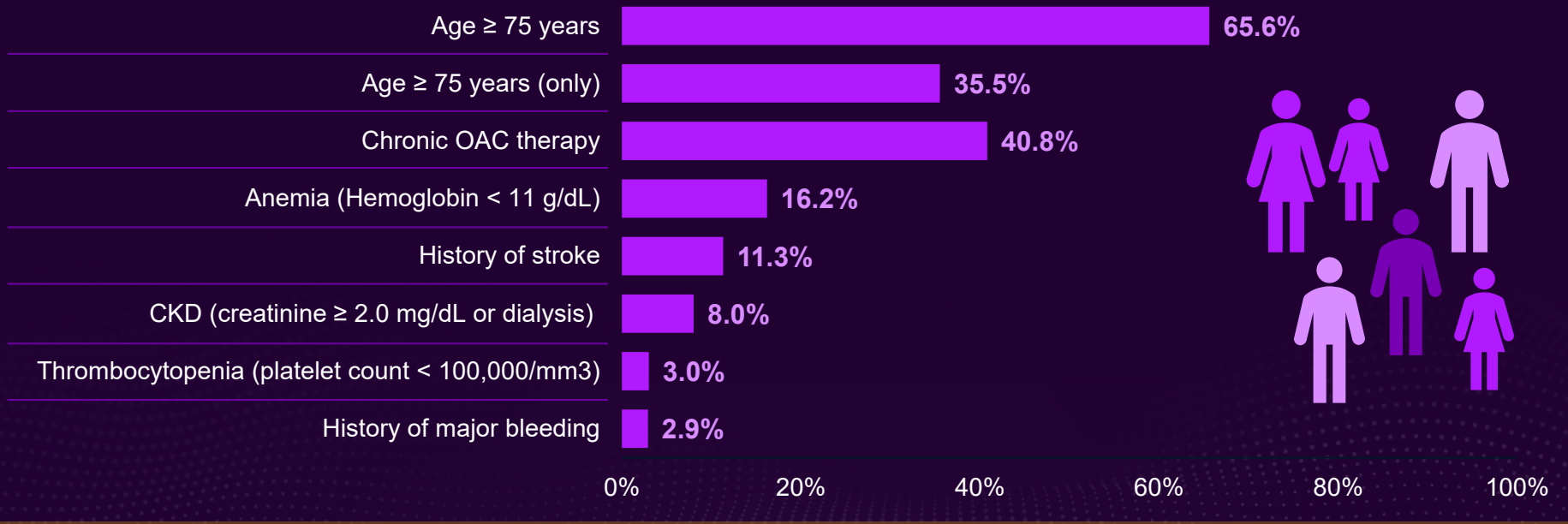
Universitats-Herzzentrum Freiburg
Bad Krozingen

Back-up slides

HBR Criteria Distribution in XIENCE 90

Xience short DAPT

All Registered Patients

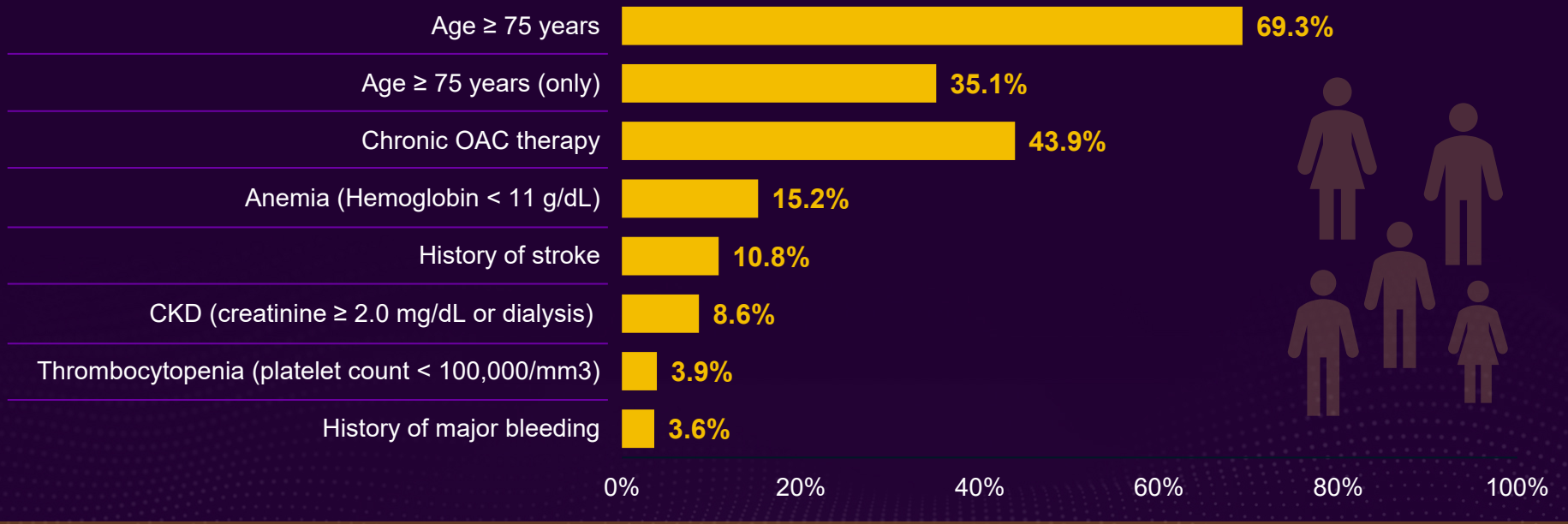


AVERAGE NUMBER OF CRITERIA MET: *1.5 ± 0.7*

HBR Criteria Distribution in XIENCE 28

Xience short DAPT

All Registered Patients



AVERAGE NUMBER OF CRITERIA MET: *1.6 ± 0.8*

Sample Size and Power Calculations

Key Secondary Endpoint: BARC 2-5 Bleeding

	XIENCE 90	XIENCE 28
Control group	3-month clear HBR patients from XIENCE V USA	1-month clear HBR patients from XIENCE V USA
Hypothesis	Superiority for BARC 2-5 bleeding	Superiority for BARC 2-5 bleeding
Expected rate control	6.0% between 3 and 12 months	4.6% between 1 and at 6 months
Expected rate test	3.0% between 3 and 12 months	2.3% between 1 and 6 months
Statistical model	Propensity stratification	Propensity stratification
Test significance level (α)	0.025 (1-sided)	0.025 (1-sided)
Attrition rate	15%	10%
Power (1-β)	95%	90%

Sample Size and Power Calculations

Key Secondary Endpoint: Definite/Probable ST

	XIENCE 90
Performance goal	1.2%
Statistical model	Exact test
Test significance level (α)	0.05 (2-sided)
Attrition rate	15%
Power (1-β)	85%
Sample size (N patients)	2000

BARC 3-5 Bleeding Rates in HBR Trials

Xience short DAPT