Relevant Clinical Trial Designs: Balancing Regulatory and Medical Evidence Needs

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Potential Conflicts of Interest

- **Strategic and Scientific Advisory Boards:**
  Medtronic Vascular, Boston Scientific,
  Abbott Vascular

Desirable Technical Qualities in a DES

- Easy to deliver, pushable and trackable
- Low profile but visible
- Flexible in a crimped state
- Flexible and conformable in an expanded state
- Complete or near-complete apposition
- Good scaffolding and excellent radial strength
- Minimal vessel and intimal injury
- Thromboresistant materials
- Rapid re-endothelialization
- Functional endothelial layer (NO producing)
- Reliable and consistent inhibition of NIH
- Minimal or no long term inflammation
- No persistent responses or long term safety concerns
- Available in the widest range of sizes and lengths
- Competitively priced and on consignment

The Ideal DES

- Remarkable ease of use
- Unparalleled efficacy
  - Suppression of neointimal hyperplasia
- Impeccable safety
  - No adverse effects on vessel function or flow dynamics
  - No risk of LST or VLST
  - No need for more than short term DAPT

Generational Changes in Stent Specs

	Elemental Composition by Weight %			
	316L (Stainless Steel)	**Platinum Chromium Alloy**	**L605 (Cobalt Chromium Alloy)**	**MP35N (Cobalt Chromium Alloy)**
Iron	64	37	3.0 max	1.0 max
Platinum	-	33	-	-
Cobalt	-	-	52	34
Chromium	18	18	20	20
Nickel	14	9	10	35
Tungsten	-	-	15	-
Molybdenum	2.6	2.6	-	9.75
Manganese	2.0 max	0.05 max	1.5	0.15 max
Titanium	-	-	-	1.0 max

Stent Strut Thickness

Cypher™	Express®	Liberté®	Driver™	Vision™	Element™
0.0055" Stainless Steel	0.0052" Stainless Steel	0.0038" Stainless Steel	0.0036" MP35N	0.0032" L605	0.0032" Platinum Chromium

Thinner Stent Struts, Less Polymer Coating, Lower Drug Load

Stent	Strut Thickness	Polymer Thickness	Drug Load	Shape
Cypher	140 μm	12.6 μm	~10 ug/mm	Wedge
Taxus Express	132 μm	16 μm	1 ug/mm2	Wedge
Taxus Liberte	97 μm	16 μm	1 ug/mm2	Wedge
Biomatrix	137 μm		15.6 μg/mm	
Endeavor	91 μm	5.3 μm	10 ug/mm	Oval
Xience V	81 μm	7.8 μm	~6 ug/mm	Square
CardioMind	67 μm	8 μm	6.3 ug/mm	Oval

Many DES to Choose From

cypher

TAXUS

Xience V

Promus™

CoStar

AXXION DES

ENDEAVOR

PICO Elite

amg

Paclitaxel-Eluting Coronary Stent

Eurocor

TAXCOR

Paclitaxel-Eluting Coronary Stent System

translumina

YUKON Choice DES

Drug Eluting Stent

JANUS

Tacrolimus eluting Carbostent™

Coroflex

Dexamet

APOLLO

Paclitaxel Eluting Coronary Stent

euca TAX

Paclitaxel Eluting Coronary Stentsystem

Endeavor Resolute Stent

NOBORI

BIOMATRIX

DRUG ELUTING CORONARY STENT SYSTEM

Uncompromised Patient Benefit

through the Combination of Safety and Efficacy

Clinical Approval of New Prostheses / Devices

- Substantial body of evidence to support both safety and clinical efficacy
  - Preclinical in vitro and in vivo, Clinical evidence
- Subject that evidence to scrutiny and assessment by “independent” regulatory agencies
  - No single global organization
  - Requirements and levels of evidence different for different agencies and geographies
  - In Australia TGA, PDC, CPCAG, HI BNG, MSAC

Gathering the Supporting Evidence
RCT / Registry Trade off

RCT's	Registries
Less complex Highly selected	More complex Real world
100% monitoring	3-20% monitoring
All events adjudicated	All *reported* events adjudicated
95% follow up	80-95% follow up

Event rates are critically dependent on detailed data collection, reporting analysis, event adjudication

Major DES RCT's: Inclusion / Exclusion Criteria

	Sirius	Taxus IV	Taxus V	EII	EIV	Spirit III
SVG Lesions	✗	✗	✗	✗	✗	✗
Bifurcations	✗	✗	✗	✗	✗	✗
Left Main	✗	✗	✗	✗	✗	✗
Vessel diam 2.25 mm	✗	✗	✗	✓	✗	✗
Long lesions ≥ 30 mm	✗	✗	✗	✗	✗	✗
Visible thrombus	✗	✗	✗	✗	✗	✗
Heavily Calcified	✗	✗	✗	✗	✗	✗
ISR	✗	✗	✗	✗	✗	✗

Major DES Registries: Inclusion Criteria

	ARRIVE I and II	E-FIVE	E-Cypher
SVG Lesions	✓	✓	✓
Bifurcations	✓	✓	✓
Left Main	✓	✓	✓
Vessel diameter ≤ 2.25	✓	✓	✓
Long lesions ≥ 30 mm	✓	✓	✓
Visible thrombus	✓	✓	✓
Heavily Calcified	✓	✓	✓
ISR	✓	✓	✓

Major DES Registries: Inclusion Criteria

	ARRIVE I and II	E-FIVE	E-Cypher
Chronic Renal Failure	✓	✓	✓
Surgery known or suspected	✓	✓	✓
Major systemic disorders	✗ ✓	✗ ✓	✗ ✓
Malignancy known or suspected	✗ ✓	✗ ✓	✗ ✓
Peptic Ulcer	✓	✓	✓
Acute MI	✓	✓	✓
Warfarin dependent	✓	✓	✓

ENDEAVOR Clinical Program

Trial Designs

	ENDEAVOR I	ENDEAVOR II	ENDEAVOR II CA	ENDEAVOR III	ENDEAVOR IV	ENDEAVOR PK
Study Type	Multi-center (n = 8), OUS Prospective Non-randomized	Multi-center (n = 72), OUS Prospective Randomized	Multi-center (n = 15), OUS Prospective Non-randomized	Multi-center (n = 29), US Prospective Randomized	Multi-center (n = 80), US Prospective Randomized	Multi-center (n = 6), US Prospective Non-randomized
# of Patients	Endeavor: 100	Total : 1197 Endeavor: 598 Driver Control: 599	Endeavor: 300	Total : 436 (3:1 randomization) Endeavor CYPHER	Total : 1548 Endeavor TAXUS	Endeavor: 43
Lesion Criteria	Single *de novo lesion in native coronary artery ≤15 mm in length and* ≥3.0 to ≤3.5 mm in diameter and coverable with one stent	Single *de novo lesion in native coronary artery* ≥14 mm and ≤27 mm in length and ≥2.25 to ≤3.5 mm in diameter and coverable with one stent	Single *de novo lesion in native coronary artery* ≥14 mm and ≤27 mm in length and ≥ 2.25 to ≤3.5 mm in diameter and coverable with one stent	Single *de novo lesion in native coronary artery* ≥14 mm and ≤27 mm in length and ≥2.5 to ≤3.5 mm in diameter and coverable with one stent	Single *de novo lesion in native coronary artery* ≤27 mm in length and ≥2.5 to ≤3.5 mm in diameter and coverable with one stent	De novo lesions in native coronary artery ≤27 mm in length and ≥2.5 to ≤3.5 mm in diameter
Anti-platelet Therapy	Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks	Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks	Aspirin indefinitely, and Ticlopidine or Clopidogrel for 12 weeks	Aspirin indefinitely, and Ticlopidine or Clopidogrel for minimum of 12 weeks	Aspirin indefinitely, and Ticlopidine or Clopidogrel for minimum of 6 months	Aspirin indefinitely, and Ticlopidine or Clopidogrel for minimum of 12 weeks
Status	60-month follow up complete.	60-month follow up complete.	48-month follow up complete.	48-month follow up complete.	24-month follow up complete.	24-month follow up complete.

ENDEAVOR II

Double-blind RCT vs Driver

PI: Jean Fajadet, Richard Kuntz and William Wijns

Single *De Novo* Native Coronary Artery Lesions
Reference Vessel Diameter 2.25 mm-3.5 mm
Lesion Length: 14-27 mm
Pre-dilatation required

Endeavor Stent
Active Arm
n = 600

N = 1,200 patients
72 sites
Europe, Asia Pacific, Israel, New Zealand and Australia

Driver Stent
Control Arm
n = 600

Clinical/MACE

30d | 6mo | 8mo | 9mo | 12mo | 2yr | 3yr | 4yr | 5yr

Angiography/IVUS

Angio = first 600 pts
IVUS = first 300 pts (plus IVUS for overlapping stents)

Primary Endpoint: TVF at 9 months
Secondary Endpoints: MACE at 30 days and 9 months, BR at 8 months
Drug Therapy: ASA and Clopidogrel ≥3 months
Zotarolimus Dose: 10 μg per mm stent length

Fajadet et al. *Circulation*. 2006;114:98-806.

ENDEAVOR II

Baseline Characteristics

	Endeavor n = 598	Driver n = 599	*P* value
Males (%)	77.2	75.3	NS
Diabetics (%)	18.2	22.2	NS
Unstable Angina (%)	33.2	33.3	NS
RVD (mm)	2.73	2.76	NS
Lesion Length (mm)	14.04	14.38	NS
B2/C Lesions (%)	78.4	79.1	NS

ENDEAVOR Clinical Program

Key Baseline Data Across Trials

Baseline Characteristics	EI n = 100	EII n = 598	EII CA n = 296	EIII n = 323	EIV N = 773	EPK N = 43
Diabetics (%)	16.0	18.2	25.8	29.7	31.2	41.9
Unstable Angina (%)	41.5	33.2	19.4	51.1	51.6	55.6
RVD (mm)	2.96	2.73	2.63	2.75	2.73	2.54
Lesion Length (mm)	10.94	14.04	16.49	14.96	13.41	15.02
B2/C lesions (%)	49.0	78.4	74.4	67.2	69.6	67.4
Angiographic F/U* (%) (#/N)	92.0 92/100	88.6 264/298	79.6 117/147	85.8 277/323	87.8 144/164	100 6/6

*12 month follow up for EI, 8 month follow up for other trials

DES vs. BMS Trials – 5-Year Data

Baseline Demographics

	ENDEAVOR II N = 598	*SIRIUS N = 533*	*TAXUS IV N = 662*
RVD (mm)	**2.73**	**2.78**	**2.75**
Lesion Length (mm)	**14.0**	**14.4**	**13.4**
Stent:Lesion Length	**1.84**	**1.40**	**1.58**
B2/C Lesions (%)	**78.4**	**58.6**	**50.8**
Diabetes Mellitus (%)	**18.2**	**25.0**	**24.4**
LAD (%)	**43**	**44**	**40**
Plavix/Ticlid LOT (m)	**3**	**3**	**6**
Inclusion 2.25 vessels*	**yes**	**no**	**no**

*2.25 stent is an investigational device in the U.S.

Results come from separate clinical trials which randomized DES to BMS. Data may differ in a head-to-head comparison.

ENDEAVOR II, Fajadet et al, Circulation. 2006;114:98-806.
Sirius Trial, Holmes et al, *Circulation.* 2004.
TAXUS IV, Stone et al, *Circulation.* 2004.

ENDEAVOR was an international trial. TAXUS IV and SIRIUS were US trials.

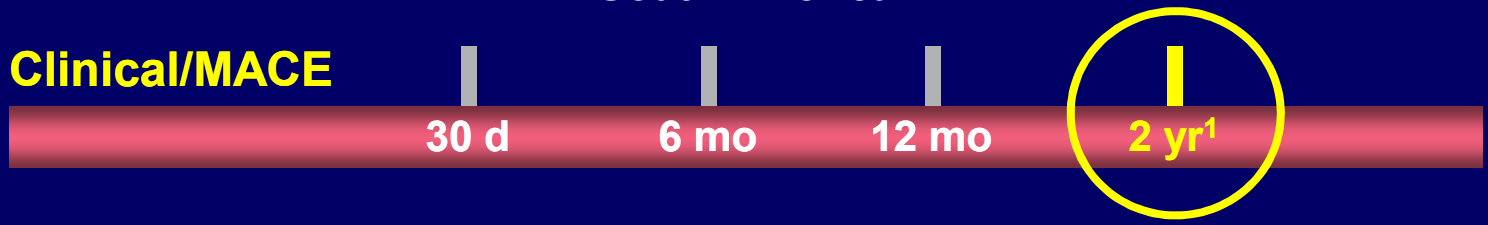
E-Five Registry Study Design

Prospective, Multicenter Registry

PI: Chaim Lotan, Ian Meredith and Martin Rothman

Single and multiple coronary artery lesions
Stent diameters: 2.25 – 4.0 mm
Stent length: 8/9 – 30 mm

N = 8,000 patients
N = 2,000 at 2 years
200 sites
Europe, Asia Pacific, Israel, New Zealand, South America



Primary endpoint: MACE at 12 months
Secondary endpoints: MACE at 30 days and 6 mo, stent thrombosis, procedure success rate; device success rate; lesion success rate
Drug therapy: ASA and clopidogrel ≥3 months
Zotarolimus dose: 10 μg per mm stent length

[1]Prespecified number of centers (27)
Rothman M. ACC 2009.

E-Five Registry

Patient Demographics

	All Patients n = 8314	*2-Yr Subset n = 2116[1]*
Male (%)	76.7	77.3
Age (years)	63.3 ± 11.1	62.1 ± 11.0
Prior MI (%)	32.2	35.3
Non Q Wave	12.2	12.8
Q Wave	21.3	23.5
Prior PCI (%)	25.3	24.1
Prior CABG (%)	7.5	6.9
Diabetes Mellitus (%)	32.7	30.1
Acute Coronary Syndrome (%)	47.8	40.7
Recent MI (< 72 hours) (%)	13.9	11.4
Unstable Angina (%)	33.9	29.3
Moderate/severe Renal Impairment[2] (%)	6.5	5.6

1. Prespecified subset.
2. Serum creatinine ≥140 µmol/L and no renal transplant.

Rothman M. ACC 2009.

Abbott Vascular XIENCE V Trials
N = ~19,000

5 year F/U	3 year F/U	3 year F/U	Enrollment Complete	Enrollment Complete	Enrolling	Enrolling	Enrollment Complete
SPIRIT FIRST	**SPIRIT II**	**SPIRIT III**	**SPIRIT IV**	**SPIRIT V**	**XIENCE V SPIRIT WOMEN**	**XIENCE V USA**	**XIENCE V India**
Safety and Performance	Clinical Support for CE Launch	U.S. and Japan Approval	U.S. Continued Access	Post CE Mark Approval International	Post CE Mark Approval International	U.S. Post Approval	India Post Approval
Europe N=60	International N=300	N=1170 U.S.: 65 sites N=1082 (1075 pts enrolled) Japan: 12 sites N=88 (88 pts enrolled)	N=3690 66 sites (3,690 pts enrolled)	N=3,000 100 sites Registry N=2,700 Diabetic study N=300	N=2,110 100 sites Registry N=1,660 (1660 pts enrolled) Randomized arm vs Cypher N=450 (284* pts enrolled)	Expanded Enrollment: N=~8000 (5060* pts enrolled)	N=1000

*As of August 2009

SPIRIT IV Study Algorithm

3690 pts enrolled at 66 U.S. sites

RVD ≥2.5 mm - ≤3.75 mm; Lesion length ≤28 mm

Max. 3 lesions with a maximum of 2 per epicardial vessel

Pre-rand: ASA ≥300 mg, clopidogrel ≥300 mg load unless on chronic Rx

Randomized 2:1 XIENCE V:TAXUS Express

Stratified by diabetes and intended number of lesions treated

Pre-dilatation mandatory

Everolimus-eluting

XIENCE V

Paclitaxel-eluting

TAXUS

Aspirin ≥80 mg QD for 5 years; clopidogrel 75mg QD for at least 12 mos (if not at high risk for bleeding)

Clinical f/u only: 1, 6, 9 months and yearly for 1-5 years

Major Exclusion Criteria

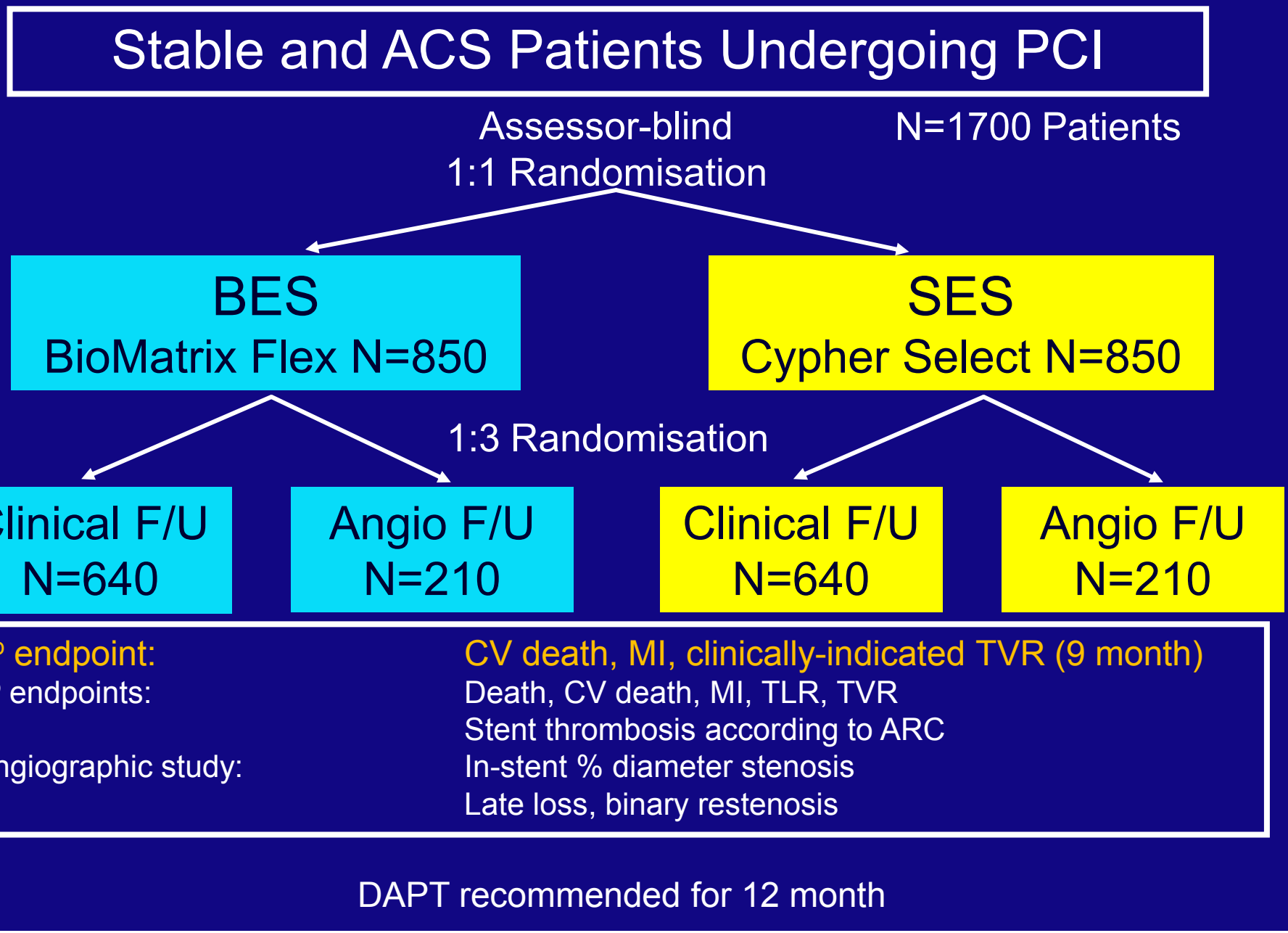
- Any target lesion or vessel meets any of the following:
  - Left main or ostial LAD/LCX
  - In or distal to a bypass graft conduit
  - Bifurcation with sidebranch diameter ≥2 mm AND ostial DS >50% OR requiring pre-dilatation
  - Total occlusion, thrombus, restenotic, excessive tortuosity, angulation or heavy calcification
- Prior coronary brachytherapy
- High probability of additional PCI within 9 mos

SPIRIT III / SPIRIT IV Differences

	SPIRIT III	SPIRIT IV
N patients	**1002**	**3690**
Max # lesions per patient	**2**	**3**
Max # vessels per patient	**2**	**3**
Max # lesions per vessel	**1**	**2**
Bifurcation lesions	**Yes if <50% ostial DS and <2.0 mm**	**Yes if <50% ostial DS or <2.0 mm**
Ostial RCA lesions	**No**	**Yes**
N pts with diabetes mellitus	**290 (29.0%)**	**1185 (32.1%)**
N pts with intended angio F/U	**564 (56.3%)**	**0**
Primary powered clinical EP	**TVF (NI)**	**TLF (NI, Sup)**

TVF = cardiac death, MI, or ischemia-driven TVR
TLF = cardiac death, target vessel MI, or ischemia-driven TLR

Trial Design



Patient Eligibility

Inclusion Criteria

Coronary artery disease

- Stable angina
- Silent ischemia
- Acute coronary syndrome including UA, NSTEMI and STEMI

At least one lesion with

- Diameter stenosis ≥ 50%
- RVD: 2.25-3.5 mm
- Number of lesions: no limitation
- Number of vessels: no limitation
- Lesion length: no limitation

Written informed consent

Exclusion Criteria

Known allergy to

- aspirin, clopidogrel, heparin, stainless steel, sirolimus, biolimus, contrast material

Planned, elective surgery within 6 months of PCI unless dual APT could be maintained

Pregnancy

Participation in another trial

Patient Demographics

	BES 857 Patients	SES 850 Patients
Age in years	65 ± 11	65 ± 11
Male gender	75%	75%
Arterial hypertension	74%	73%
Diabetes mellitus	**26%**	**23%**
- insulin-dependent	10%	9%
Hypercholesterolemia	65%	68%
Family history	40%	44%
Smoking	24%	25%
Previous MI	**32%**	**33%**
Previous PCI	**36%**	**37%**
- with drug-eluting stent	12%	14%
Previous CABG	**11%**	**13%**
Chronic stable angina	45%	44%

Patient Characteristics

	BES 857 Patients	SES 850 Patients
Acute coronary syndrome	55%	56%
- Unstable angina	22%	21%
- Non-ST-elevation MI	17%	18%
- ST-elevation MI	16%	17%
Left ventricular ejection fraction	56 ± 11%	55 ± 12%
Number of lesions per patient	1.5 ± 0.7	1.4 ± 0.7
Lesions per patient		
- 1 lesion	63%	69%
- 2 lesions	29%	22%
- 3 lesions	7%	8%
- > 4 lesions	1%	2%
De novo lesions	92%	91%
Long lesions (>20 mm)	31%	27%
Small vessels (RVD ≤2.75 mm)	68%	69%
Off label use	81%	78%

RESOLUTE All Comers:

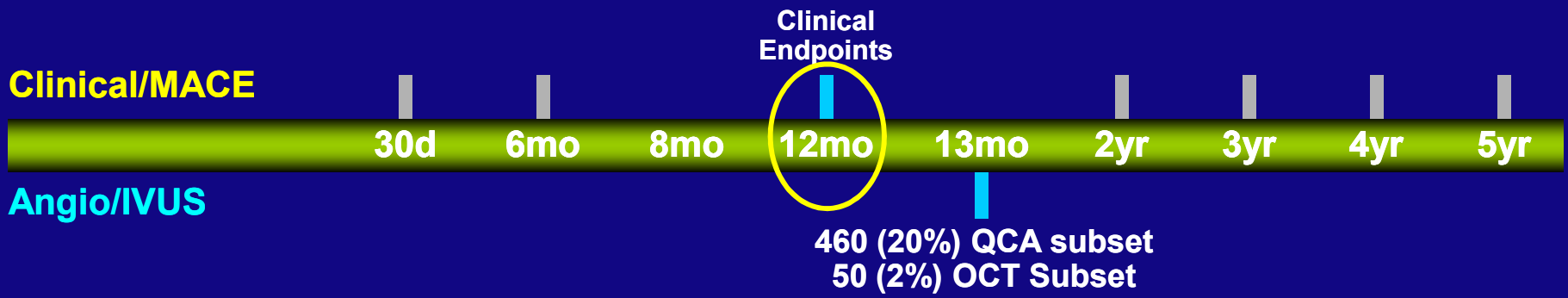
Co-PIs: Profs. Serruys, Silber, Windecker

Open –label Non-Inferiority Study
All Comers with symptomatic coronary artery disease

Resolute Stent
n ≈ 1,150

N = 2,300 patients
15 – 20 sites (100% monitored)
Western Europe

Control Xience V Stent
n ≈ 1,150



Primary Endpoint: Composite - Cardiac Death, Target Vessel MI, TLR @ 12mo
Secondary Endpoints: Composite @ 30d, 6mo, 2 – 5 yr; angiographic & optical coherence tomography (OCT) parameters @ 13 mo
Drug Therapy: ASA and clopidogrel/ticlid >6 months (per guidelines)

RESOLUTE All Comers:

What Does All-comers Mean?

- Aims for consecutive enrollment
  - *Consecutive consenting of all CAD patients eligible for PCI*
  - *Involvement of entire cath lab staff to ensure enrollment also during nights & weekends*
  - *Screening log for verification*
- Minimal exclusion criteria:
  - *Pregnancy*
  - *Intolerance to DAPT*
  - *Participation in another clinical trial*
  - *Planned surgery within 6 months*
- Expected highly complex patient population
  - *Including Acute MI patients (non-STEMI and STEMI)*
  - *No limitations on number of treated lesions, vessels or lesion length*

RESOLUTE All Comers:

Unique Study Design Attributes

- Real-world, All-comers patient population
- Limited number of sites participating
  - *High volume, referral sites*
  - *Experienced with conducting clinical trials*
  - *Committed to clinical trials with dedicated trial personnel*
- Event adjudication based on ARC definitions
  - *TLF defined as: Repeat revascularization of the target lesion, MI that may be associated with the target lesion and cardiac death*
  - *Updated standardized MI definition due to inclusion of STEMI patients*
- Angiographic Follow-up performed post Clinical F/U
  - *20% of patients randomly assigned to repeat angiography at 13 months*
  - *Powered angiographic endpoints*

Balancing Regulatory and Medical Evidence Needs

- Balance of RCT and Registries with relevant clinical endpoints understanding the limitations of both
- Tensions between the need to obtain clean unequivocal evidence (proof of concept) and need to establish real world applicability and safety
- All-comer type RCT will play an increasingly important role in meeting these needs