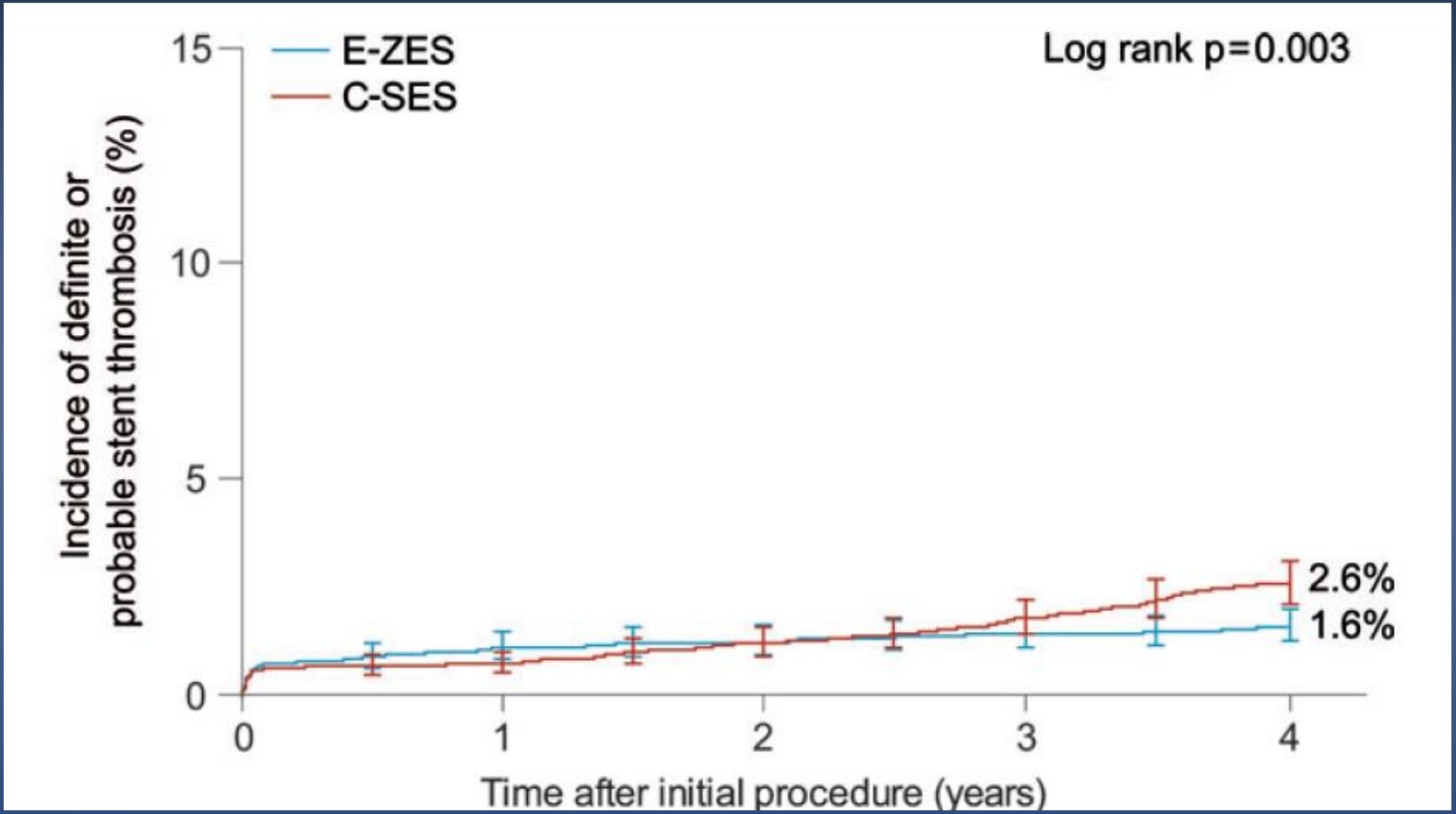
# Different Drug, Polymer and Platform and so Many Stents- Are there meaningful differences?

**Tullio Palmerini**
**University of Bologna**
**Italy**

# PROTECT trial: Endeavor vs Cypher

**8791 patients enrolled**
**Superiority design**
**Expected event rate 2.6% with Cypher**
**RRR= 40%**



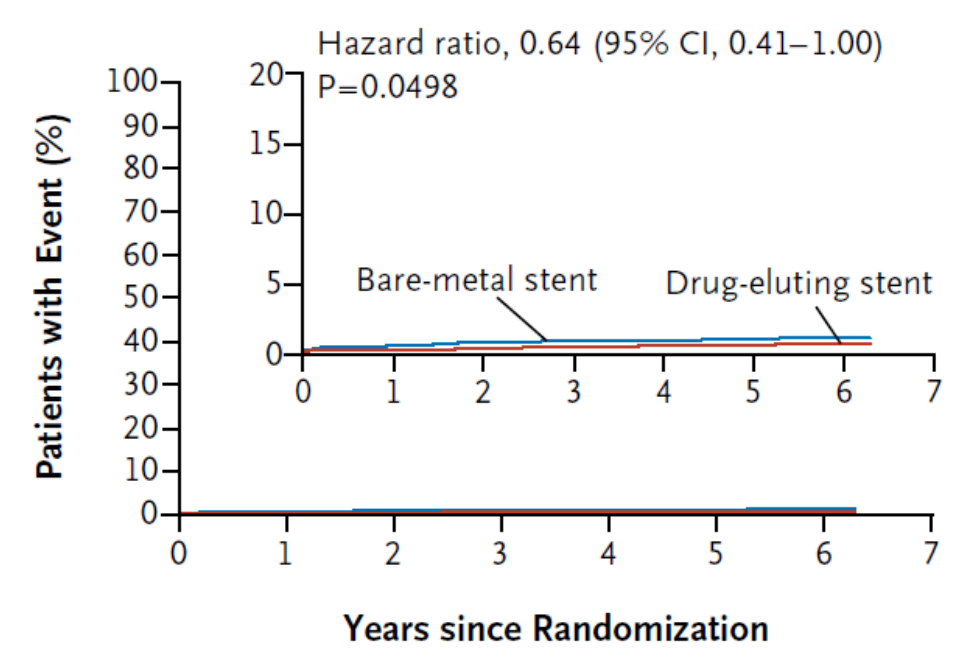

*Wiyns ey al; EHJ 2014*

# Endeavor vs Cypher

| Trial | N Pz | Comparators | Design | Fup | ST |
|---|---|---|---|---|---|
| NAPLES | 226 | ZES vs SES vs PES | Single center, non inferiority | 2 y | 4.0% vs 1.3% |
| Endeavor III | 436 | ZES vs SES | Multicenter, non inferiority | 5 y | 0.7% vs 0.9% |
| Komer | 611 | ZES vs SES vs PES | Multicenter, non inferiority | 2 y | 2% vs 2% |
| ISAR TEST II | 674 | ZES vs SES | Multicenter, non inferiority | 2 y | 1.2% vs 1.2% |
| SORT OUT III | 2332 | ZES vs SES | Multicenter, superiority | 5 y | 1.2% vs 2.1% |
| ZEST | 2645 | ZES vs SES vs PES | Multicenter, non inferiority | 1 y | 0.7% vs 0% |

# Drug-Eluting or Bare-Metal Stents for Coronary Artery Disease

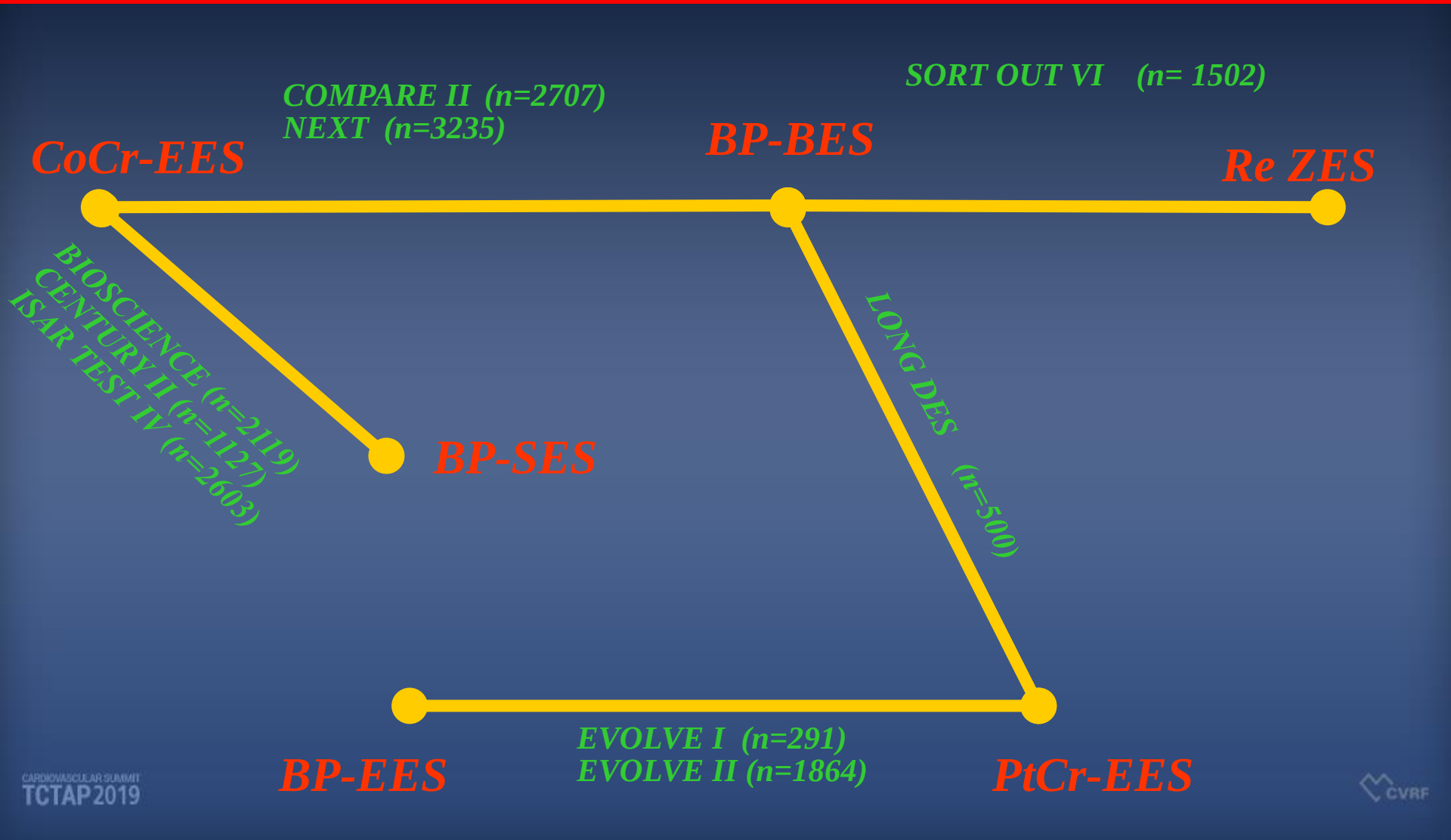
K.H. Bønaa, J. Mannsverk, R. Wiseth, L. Aaberge, Y. Myreng, O. Nygård, D.W. Nilsen, N.-E. Kløw, M. Uchto, T. Trovik, B. Bendz, S. Stavnes, R. Bjørnerheim, A.-I. Larsen, M. Slette, T. Steigen, O.J. Jakobsen, Ø. Bleie, E. Fossum, T.A. Hanssen, Ø. Dahl-Eriksen, I. Njølstad, K. Rasmussen, T. Wilsgaard, and J.E. Nordrehaug, for the NORSTENT Investigators*




**9013 patients enrolled**
**Superiority design**
**DES vs BMS**

***NEJM 2016***

# Are there meaningful differences among II generation DES?



| | Design | Study arms | Sample size | Primary endpoint | Result of primary endpoint |
|---|---|---|---|---|---|
| **BIOFLOW II** | Multicenter non inferiority | BP-CoCr-SES DP-CoCr-EES | 452 | In-stent LLL at 9 months | BP-CoCr-SES non inferiority demonstrated |
| **BIOFLOW V** | Multicenter non inferiority | BP-CoCr-SES DP-CoCr-EES | 1334 | Target lesion failure at 12 months | BP-CoCr-SES non inferiority demonstrated |
| **BIONICS** | Multicenter non inferiority | DP-Ridafo DP-RZES | 1919 | Target lesion failure at 12 months | Non inferiority demonstrated |
| **BIONIX** | Multicenter non inferiority | BP-SES DP-RZES | 2516 | Target lesion failure at 12 months | Non inferiority demonstrated |
| **BIOSCIENCE** | Multicenter non inferiority | BP-CoCr-SES DP-CoCr-EES | 2019 | Target lesion failure at 12 months | Non inferiority demonstrated |
| **CENTURI** | Multicenter non inferiority | BP-CoCr-SES DP-CoCr-EES | 1123 | Target lesion failure at 12 months | Non inferiority demonstrated |
| **EVOLVE II** | Multicenter non inferiority | BP-PtCr-EES DP-PtCr-EES | 1684 | Target lesion failure at 12 months | BP-PtCr-EES non inferiority demonstrated |
| **EVOLVE China** | Multicenter non inferiorità | BP-PtCr-EES DP-PtCr-EES | 412 | In-stent In-stent LLL | BP-PtCr-EES non inferiority demonstrated |
| **LONG-DES IV** | Multicenter non inferiorità | DP-R-ZES DP-SES | 500 | In-segment LLL 9 months | R-ZES non inferiority demonstrated |
| **LONG-DES V** | Multicenter non inferiorità | BP-BES DP-PtCr-EES | 500 | In segment LLL at 9 months | BP-BES non inferiority demonstrated |
| **MERIT V** | Multicenter non inferiorità | BP-CoCr-SES DP-CoCr-EES | 256 | In-stent LLL at 9 months | BP-CoCr-SES non inferiority demonstrated |
| **NEXT** | Multicenter non inferiority | BP-BES DP-CoCr-EES | 3235 | TLR at 1 year | BP-BES non inferiority demonstrated |
| **PLATINUM** | Multicenter non inferiorità | DP-CoCr-EES DP-PtCr-EES | 1530 | Composite of cardiac death, target vessel related MI, ischemia driven TLR | DP-PtCr-EES non inferiority demonstrated |
| **PRISON IV** | Multicenter non inferiorità | BP-CoCr-SES DP-CoCr-EES | 330 | In-stent LLL at 9 months | BP-CoCr-SES non inferiority not demonstrated |
| **SORT OUT IV** | Multicenter non inferiorità | DP-CoCr-EES DP-SES | 1527 | Composite of cardiac death, MI, stent thrombosis and TVR | DP-CoCr-EES non inferiority demonstrated |
| **TARGET II** | Multicentre non inferiority | BP-CoCr-SES DP-CoCr-EES | 1653 | Target lesion failure at 12 months | BP-CoCr-SES non inferiority demonstrated |
| **TALENT** | Multicentre RCT | BP-SES DP-CoCr-EES | 1435 | Target lesion failure at 12 months | Non inferiority achieved |

**18 RCT**
**All multicenter**
**256-3235 pts**
**TLF at 1 year**
**All non inferiority**
**NI achieved in all**

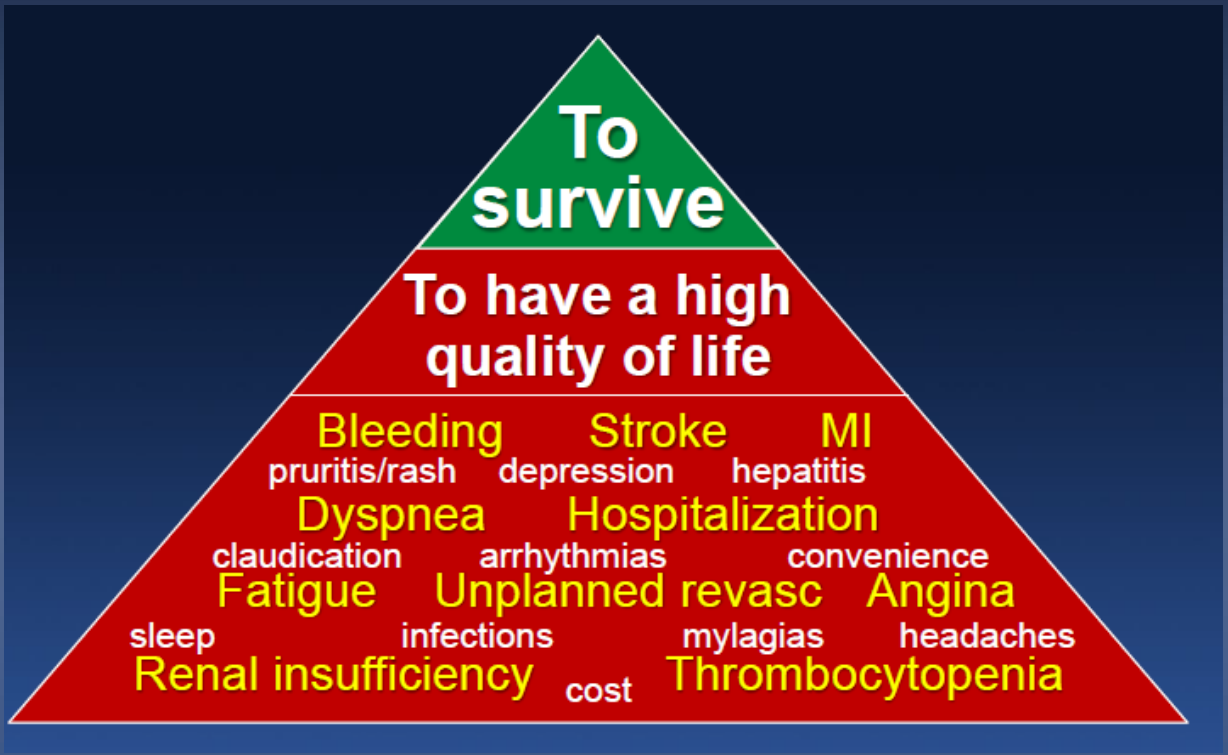
# Limitations of non inferiority trials

- Do not have power to address differences in important endpoints such as mortality or ST
- They combine heterogeneous endpoints such as death, MI, TVR
- Sometimes they have disproportional high non inferiority margin

# *Many of them were underpowered*

| | Expected | Observed | Obs/Exp | NIM |
|---|---|---|---|---|
| COMPARE II | 9.5% | 4.8% | 50% | 4% |
| NEXT | 6.9% | 4.2% | 60% | 3.4% |
| CENTURY II | 10.0% | 4.4% | 44% | 5.5% |
| SORT OUT VI | 6.5% | 5.0% | 76% | 2.5% |
| TALENT | 8.3% | 5.9% | 71% | 4% |

# *What really matters to patients?*

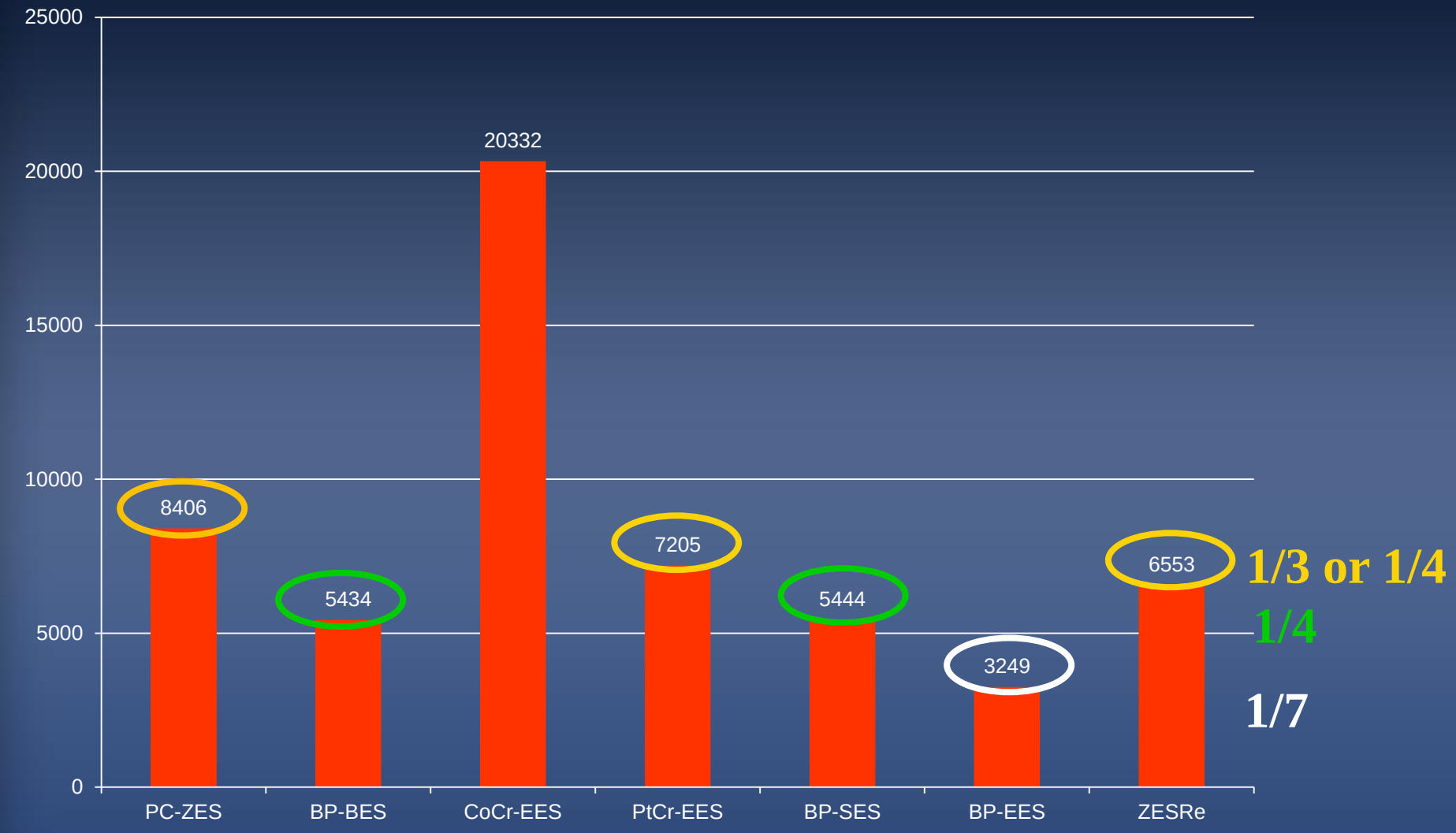


# Sample size for a superiority study on stent thrombosis

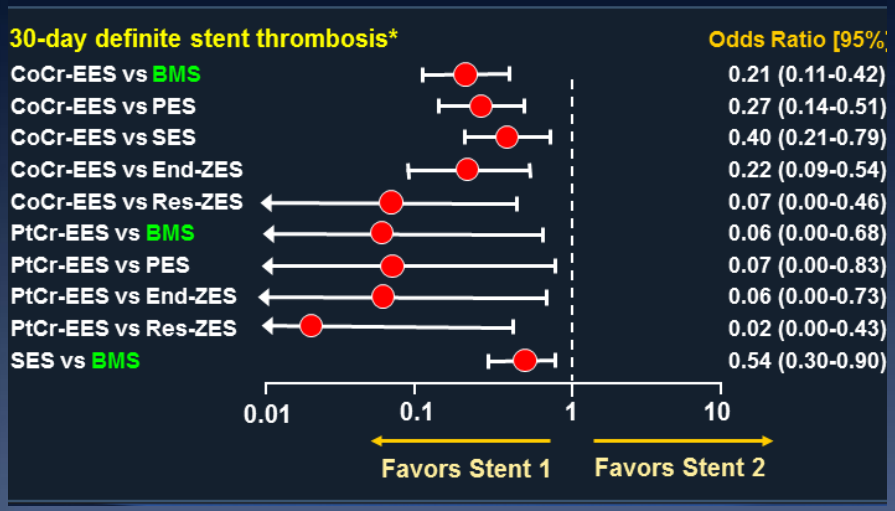
- A
- R
- a
- Power= 90%

**13,000 patients needed**

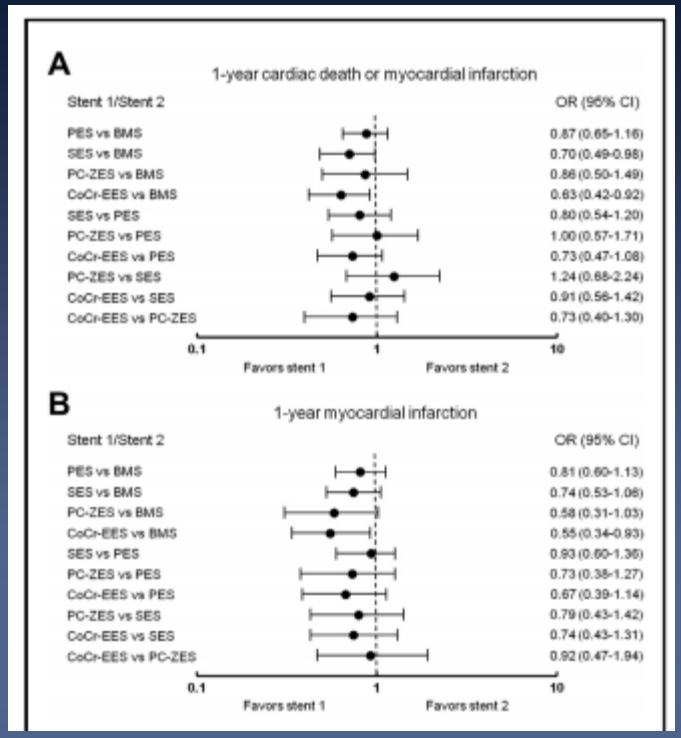
# Use of DES across RCTs



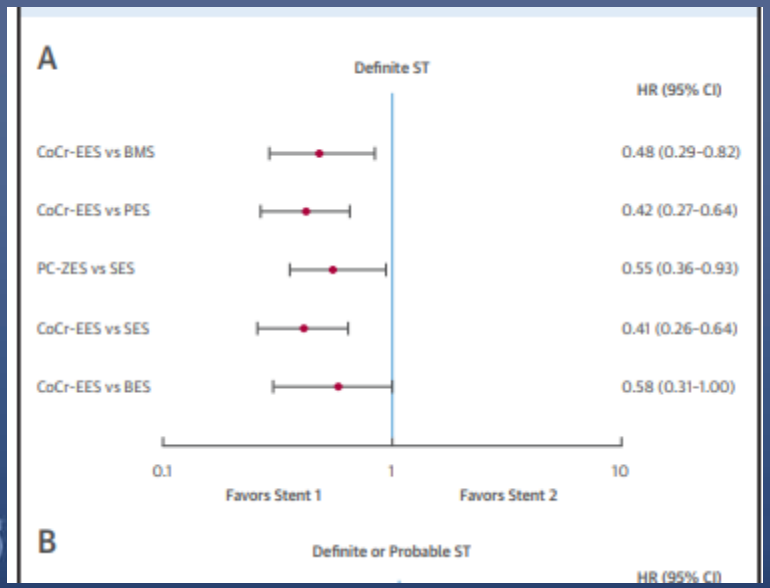
# Network meta-analyses on DES




*Palmerini et al. Lancet 2012*




*Palmerini et al. JACC 2013*



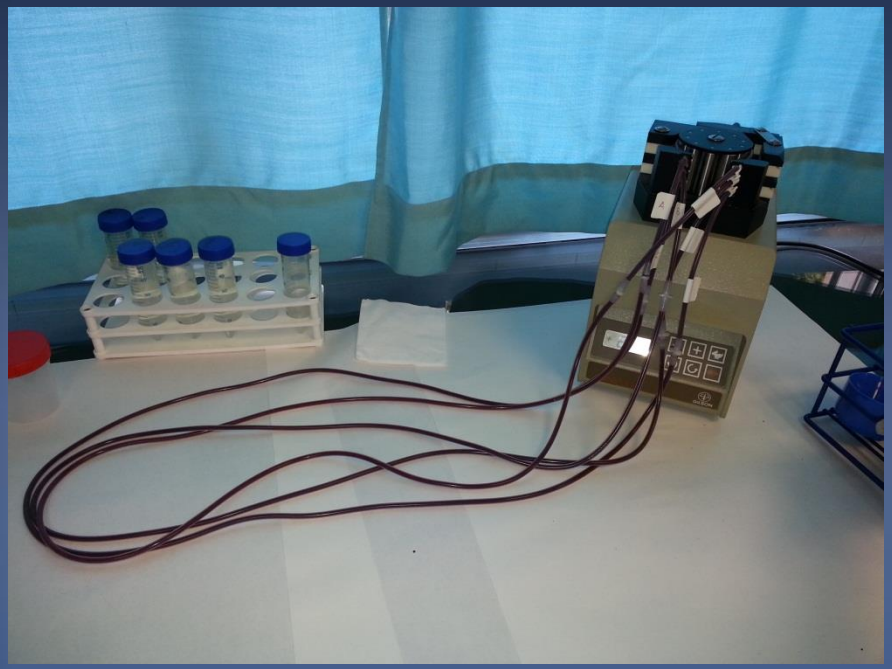

*Palmerini et al. JACC 2015*

# Stent thrombogenicity in an in vitro system of stent perfusion

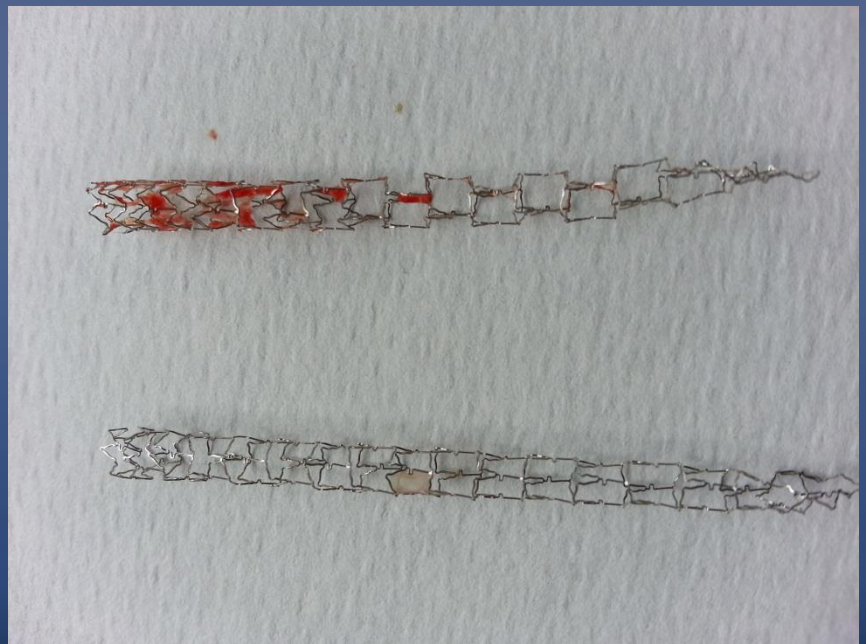
**Tullio Palmerini, Diego Della Riva, Chiara Barozzi, Luciana Tommasi, Nevio Taglieri, Mario Marengo, Gianfranco Cicoria, Carlotta Orlandi, Filippo Ferrari**

**Policlinico S.Orsola, Bologna**
**Italy**

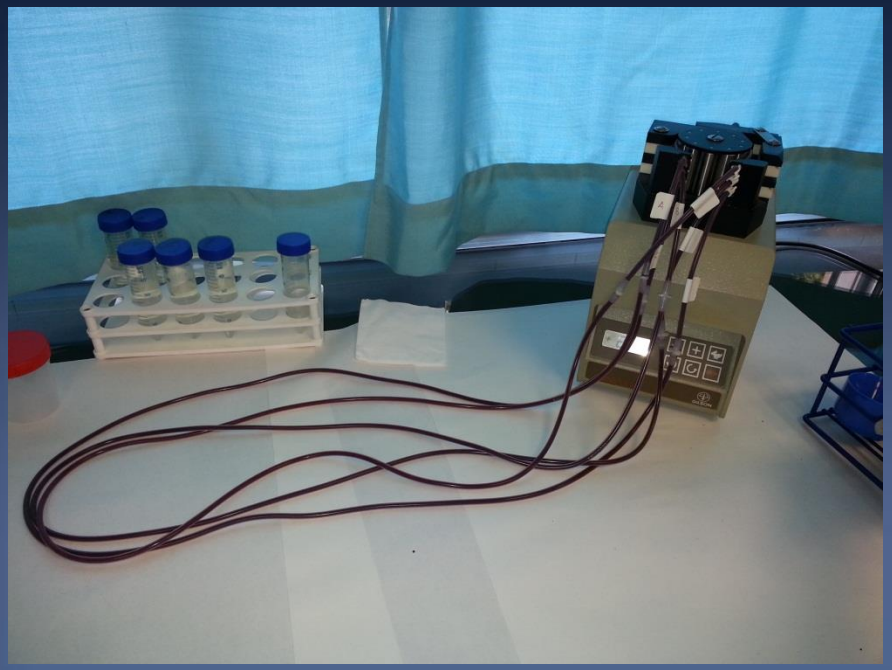
# ……Looking for a biological plausibility



*Palmerini et al, unpublished*



# Is it the drug or is it the polymer?

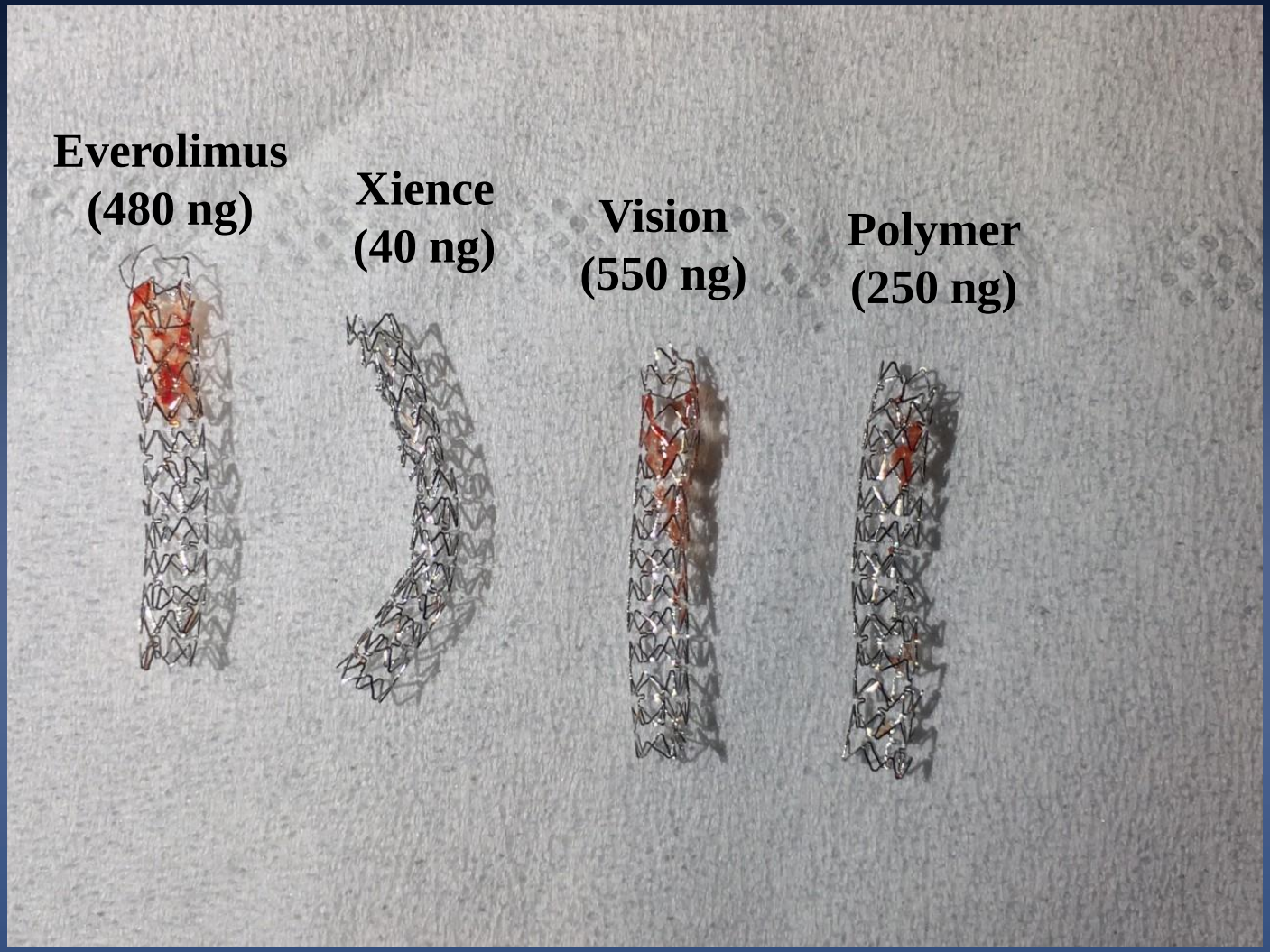


**Vision**

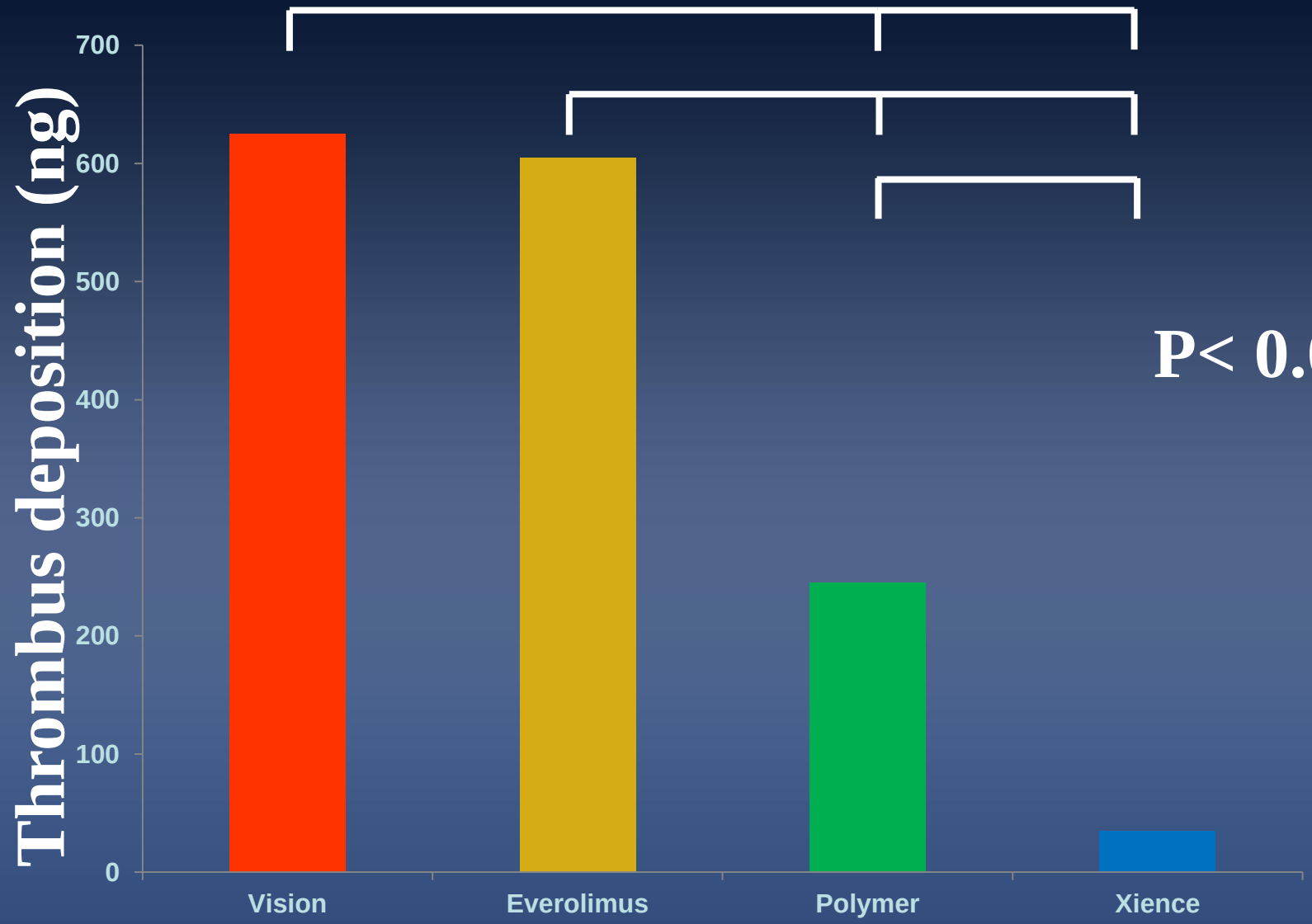
**Vision coated with fluoropolymer**

**Vision perfused with blood pre-treated with Everolimus**

**Xience**


Everolimus
(480 ng)
Xience
(40 ng)
Vision
(550 ng)
Polymer
(250 ng)

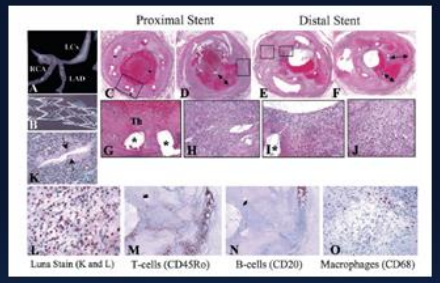
# Overall p value< 0.001



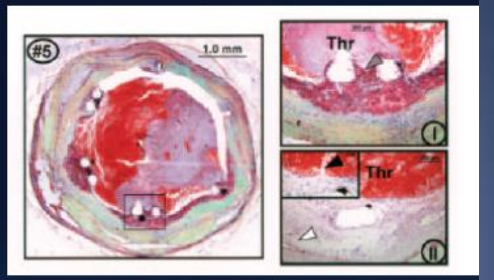

**P< 0.05**

# To bioabsorb or not to bioabsorb

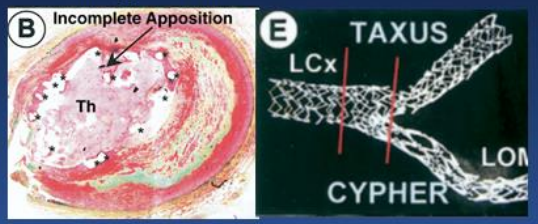
Chronic inflammation and delayed hypersensitivity



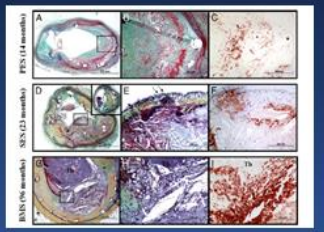

Chronic fibrin deposition and delayed healing




Late malapposition and stent fracture



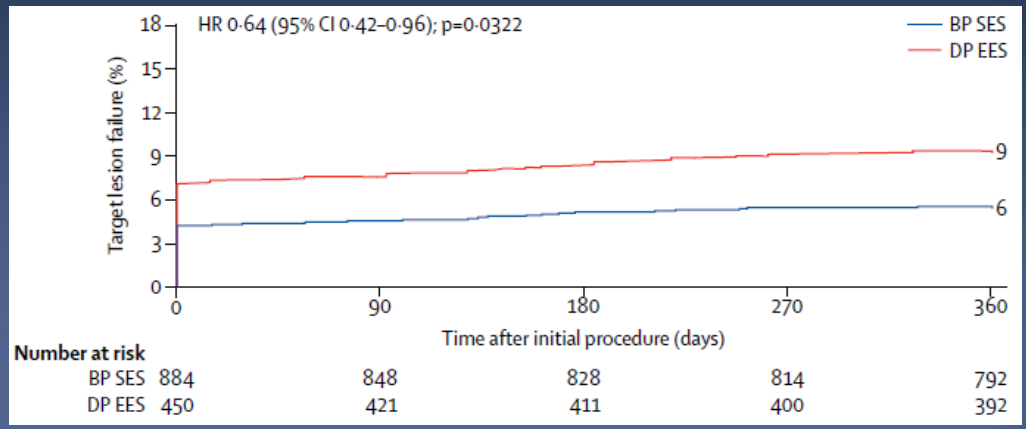

Neoaterosclerosis



# BIOFLOW V: 1-year results

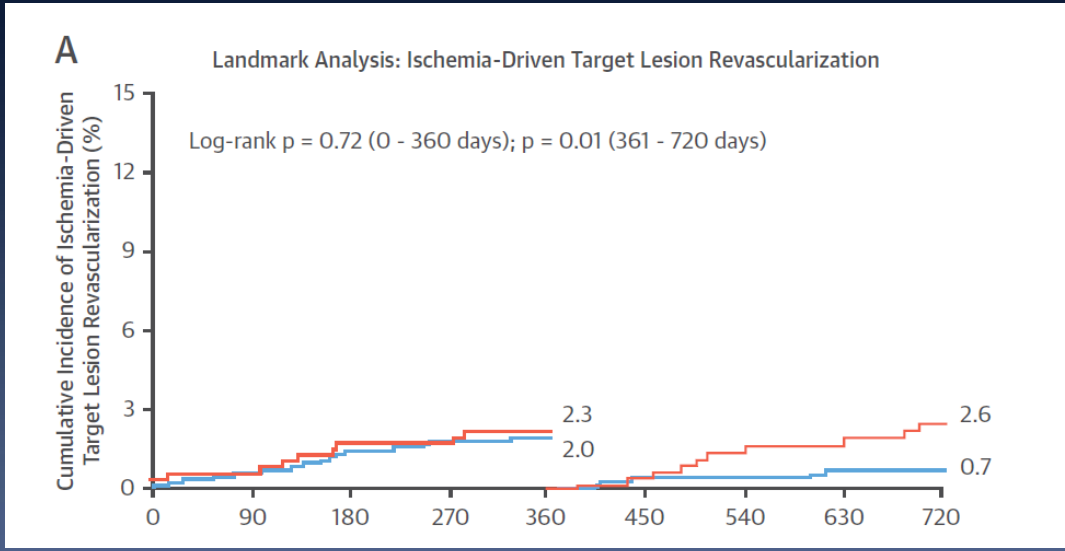
## 1334 randomized pts

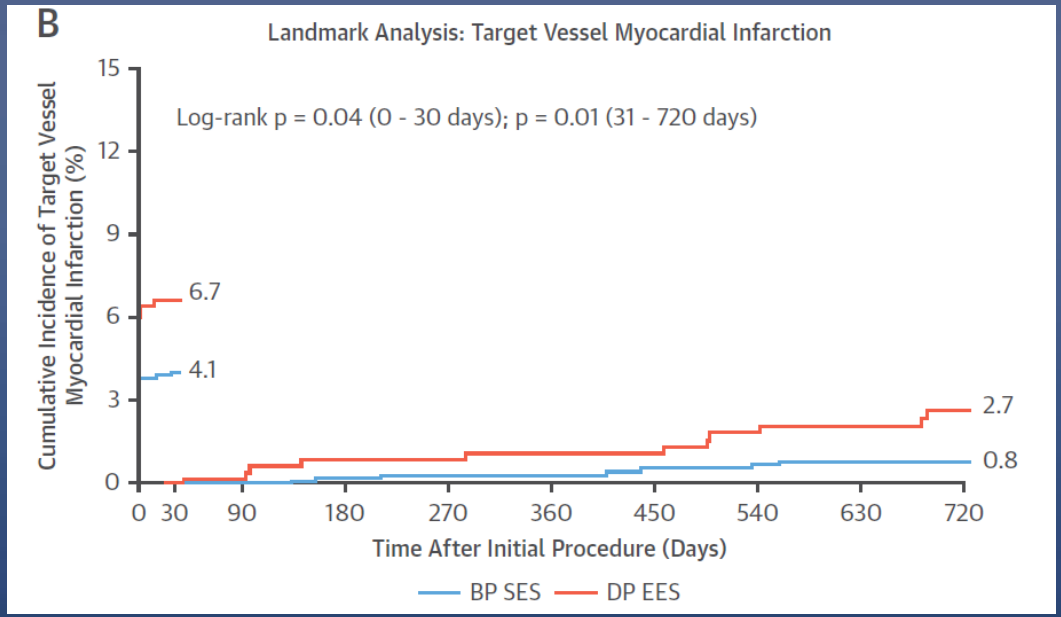
| | Bioresorbable polymer sirolimus-eluting stent | Durable polymer everolimus-eluting stent | p value |
|---|---|---|---|
| Target-lesion failure | 52/833 (6%) | 41/427 (10%) | 0·0399 |
| Cardiac death | 1/831 (<1%) | 3/425 (1%) | 0·1153 |
| Target-vessel myocardial infarction | 39/831 (5%) | 35/424 (8%) | 0·0155 |
| Clinically driven target-lesion revascularisation | 17/832 (2%) | 10/422 (2%) | 0·6856 |
| Death from any cause | 7/837 (1%) | 6/428 (1%) | 0·3823 |
| Any myocardial infarction | 41/832 (5%) | 37/425 (9%) | 0·0129 |
| Q-wave | 1/831 (<1%) | 4/422 (1%) | 0·0467 |
| Non-Q-wave | 40/831 (5%) | 34/425 (8%) | 0·0306 |
| Cardiac death or any myocardial infarction | 42/833 (5%) | 39/427 (9%) | 0·0072 |
| Major adverse cardiac events | 59/839 (7%) | 44/429 (10%) | 0·0508 |
| Target-vessel failure | 60/834 (7%) | 45/427 (11%) | 0·0521 |
| Cardiac death | 1/831 (<1%) | 3/425 (1%) | 0·1153 |
| Target-vessel myocardial infarction | 39/831 (5%) | 35/424 (8%) | 0·0155 |
| Clinically driven target-vessel revascularisation | 27/833 (3%) | 15/422 (4%) | 0·7430 |
| Stent thrombosis | 4/831 (<1%) | 5/424 (1%) | 0·175 |
| Definite or probable | 4/831 (<1%) | 3/422 (1%) | 0·694 |
| Definite | 4/831 (<1%) | 3/422 (1%) | 0·694 |
| Probable | 0/830 (0) | 0/422 (0) | .. |




*Kandzari et al; Lancet 2017*

# BIOFLOW V: 2-year results

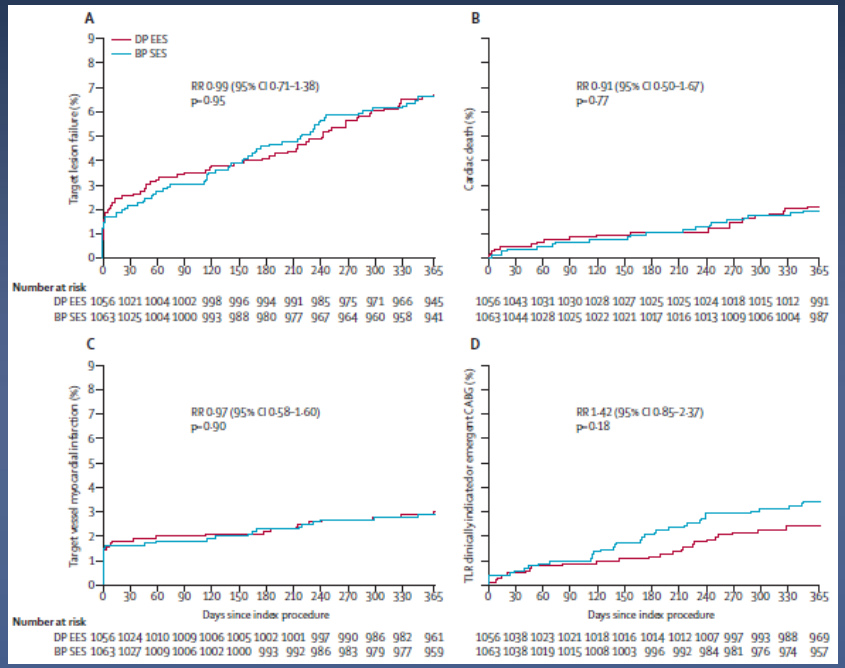



*Kandzari et al; JACC 2018*

# BIOSCIENCE: 1–year results

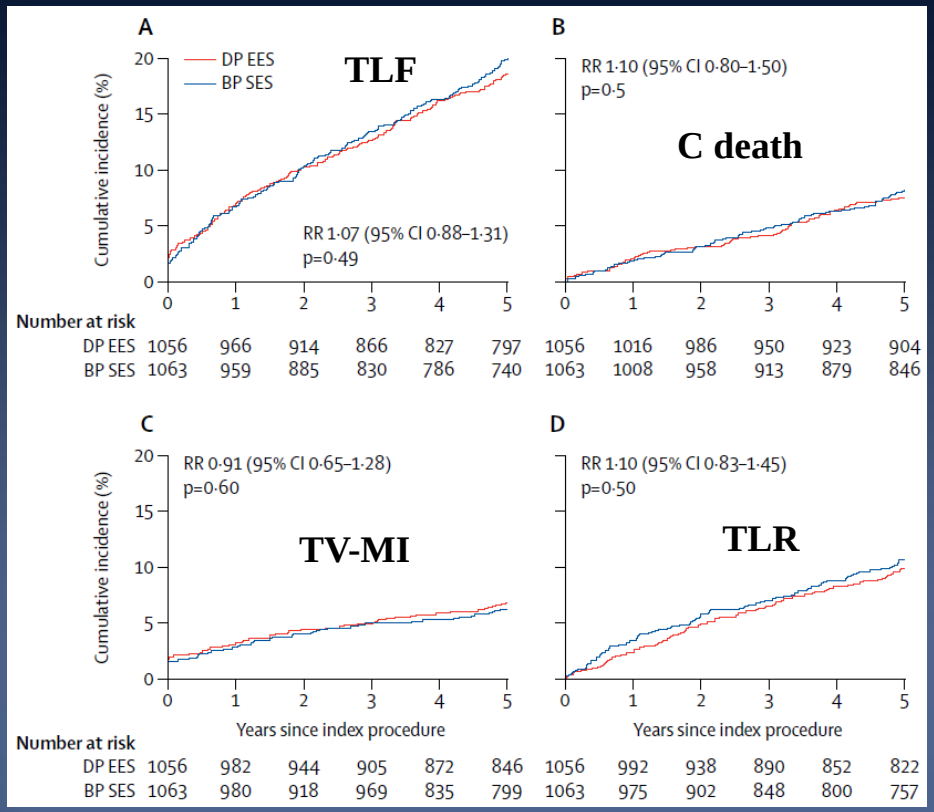
## 2119 randomized pts




| | Biodegradable polymer sirolimus-eluting stent (N=1063) | Durable polymer everolimus-eluting stent (N=1056) | Rate ratio [BP SES/DP EES] (95% CI) | p value |
|---|---|---|---|---|
| All-cause death | 34 (3·3) | 27 (2·6) | 1·27 (0·76–2·10) | 0·360 |
| Cardiac death | 20 (1·9) | 22 (2·1) | 0·91 (0·50–1·67) | 0·770 |
| MI (any) | 41 (3·9) | 45 (4·4) | 0·91 (0·60–1·39) | 0·669 |
| Q-wave | 10 (1·0) | 7 (0·7) | 1·43 (0·54–3·77) | 0·465 |
| [illegible] | 32 (3·1) | 39 (3·8) | 0·82 (0·51–1·31) | 0·404 |
| Target vessel MI | 30 (2·9) | 31 (3·0) | 0·97 (0·58–1·60) | 0·897 |
| [illegible] | 10 (1·0) | 6 (0·6) | 1·67 (0·61–4·60) | 0·316 |
| [illegible] | 20 (1·9) | 25 (2·4) | 0·80 (0·44–1·44) | 0·451 |
| Peri-procedural MI | 15 (1·4) | 20 (1·9) | 0·74 (0·38–1·46) | 0·390 |
| [illegible] | 28 (2·7) | 25 (2·4) | 1·13 (0·66–1·94) | 0·658 |
| Cardiac death or MI | 59 (5·7) | 66 (6·3) | 0·90 (0·63–1·27) | 0·537 |
| Target lesion revascularisation (any) | 41 (4·0) | 32 (3·1) | 1·30 (0·82–2·06) | 0·27 |
| Clinically-indicated TLR | 35 (3·4) | 25 (2·4) | 1·42 (0·85–2·37) | 0·18 |
| Target vessel revascularisation (any) | 53 (5·2) | 38 (3·7) | 1·41 (0·93–2·15) | 0·101 |
| Clinically-indicated TVR | 47 (4·6) | 31 (3·0) | 1·54 (0·98–2·42) | 0·061 |
| Repeat revascularisation (any) | 78 (7·6) | 59 (5·7) | 1·35 (0·96–1·89) | 0·085 |
| Target Lesion Failure* | 69 (6·7) | 70 (6·7) | 0·99 (0·71–1·38) | 0·950 |
| Target Vessel Failure† | 84 (8·1) | 81 (7·8) | 1·04 (0·77–1·42) | 0·779 |
| Death, MI, or any repeat revascularisation‡ | 123 (11·8) | 106 (10·2) | 1·17 (0·90–1·52) | 0·227 |
| Cerebrovascular event§ | 15 (1·5) | 9 (0·9) | 1·67 (0·73–3·83) | 0·217 |
| Transient ischaemic attack | 4 (0·4) | 2 (0·2) | 2·01 (0·37–10·99) | 0·411 |
| Stroke¶ | 12 (1·2) | 7 (0·7) | 1·72 (0·68–4·37) | 0·249 |
| BARC bleeding events type 2–5 | 31 (3) | 27 (2·6) | 1·15 (0·69–1·92) | 0·6 |
| Definite stent thrombosis | | | | |
| 0–30 days | 3 (0·3) | 2 (0·2) | 1·49 (0·25–8·96) | 0·66 |
| >30 days to 12 months | 6 (0·6) | 2 (0·2) | 3·03 (0·61–15·00) | 0·15 |
| 0 days to 12 months | 9 (0·9) | 4 (0·4) | 2·26 (0·70–7·33) | 0·16 |
| Probable stent thrombosis | | | | |
| 0–30 days | 16 (1·5) | 21 (2·0) | 0·76 (0·39–1·45) | 0·40 |
| >30 days to 12 months | 5 (0·5) | 10 (1·0) | 0·50 (0·17–1·47) | 0·20 |
| 0 days to 12 months | 21 (2·0) | 31 (3·0) | 0·67 (0·39–1·18) | 0·16 |

*Pilgrim et al; Lancet 2014*

# BIOSCIENCE: 5-year results




| | Biodegradable-polymer sirolimus-eluting stent (n=1063) | Durable-polymer everolimus-eluting stent (n=1056) | Rate ratio (95% CI) | p value |
|---|---|---|---|---|
| Target lesion failure* | 198 (20·2%) | 189 (18·8%) | 1·07 (0·88–1·31) | 0·487 |
| Cardiac death | 81 (8·6%) | 76 (7·5%) | 1·10 (0·80–1·50) | 0·569 |
| Target vessel MI | 62 (6·3%) | 69 (7·1%) | 0·91 (0·65–1·28) | 0·595 |
| Clinically indicated TLR | 103 (10·8%) | 97 (10·0%) | 1·10 (0·83–1·45) | 0·504 |
| All-cause mortality | 139 (14·1%) | 105 (10·3%) | 1·36 (1·06–1·75) | 0·017 |
| Any MI | 99 (10·4%) | 118 (12·3%) | 0·85 (0·65–1·11) | 0·225 |
| Q-wave | 32 (3·7%) | 24 (2·8%) | 1·37 (0·81–2·33) | 0·240 |
| Non-Q-wave | 72 (7·4%) | 97 (9·9%) | 0·75 (0·55–1·02) | 0·062 |

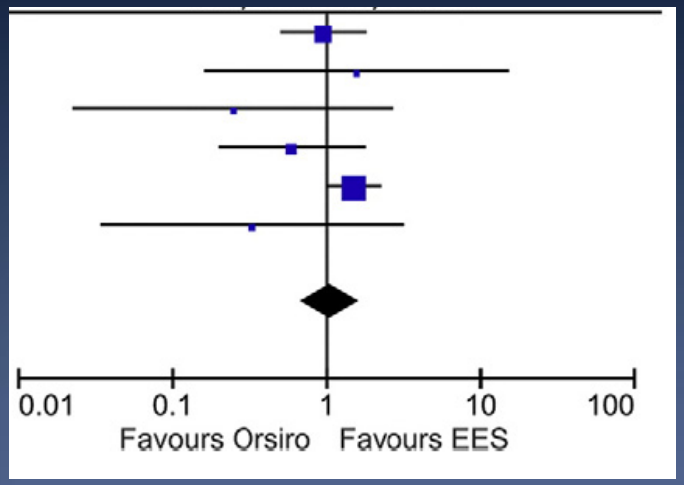


*Pilgrim et al; Lancet 2017*

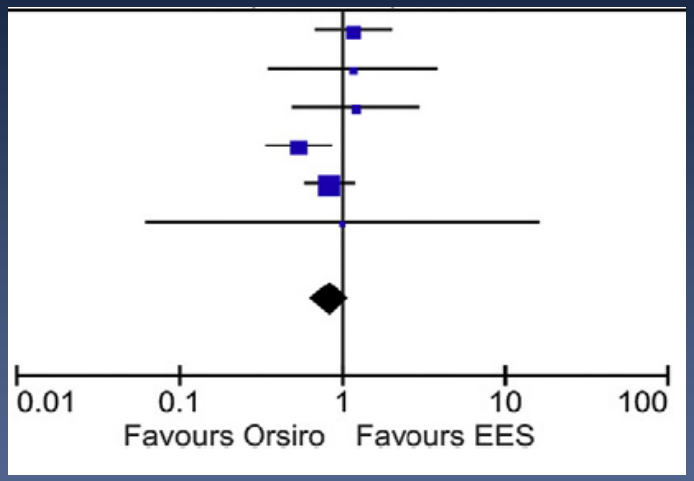
# A comparison of the ultrathin Orsiro Hybrid sirolimus-eluting stent with contemporary drug-eluting stents: A meta-analysis of randomized controlled trials☆,☆☆,★

Michael J. Lipinski, Brian J. Forrestal, Micaela Iantorno, Rebecca Torguson, Ron Waksman *

## Death

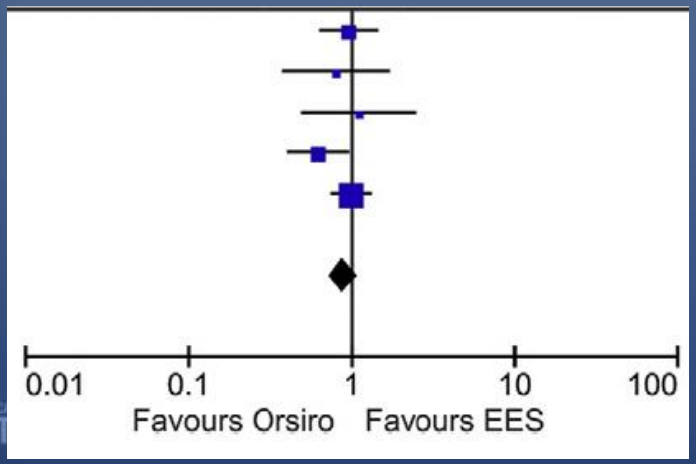



## Myocardial infarction

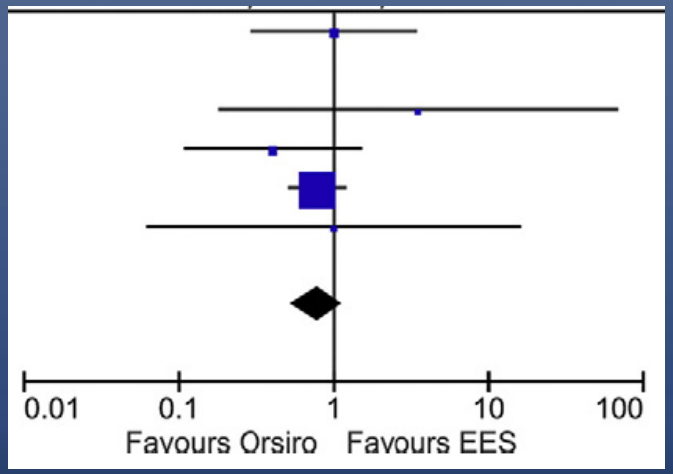



**6 RCT**
**7037 patients**

## Target Lesion Failure




## Stent thrombosis

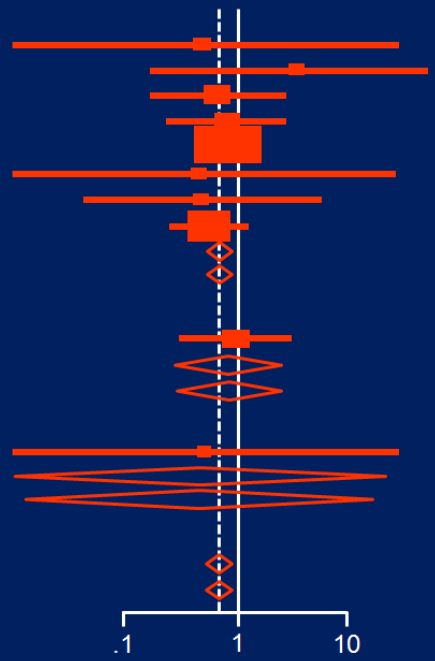


# Ultra-thin (<70 µm) vs. Thicker Strut 2nd Gen DES

10 RCTs, 11,658 pts, 3 ultra-thin strut DES:
Orsiro (60 µm), MiStent (64 µm) and BioMime (65 µm)

## 1-Year Stent Thrombosis (def/prob)

| Study | Ultra-thin Events | Ultra-thin N | 2nd Generation Events | 2nd Generation N | RR (95% CI) | % Weight (D+L) |
|---|---|---|---|---|---|---|
| **Orsiro** | | | | | | |
| BIOFLOW II | 0 | 298 | 0 | 154 | 0.52 (0.01, 26.04) | 0.78 |
| BIOFLOW IV | 3 | 354 | 0 | 176 | 3.48(0.18, 67.38) | 1.37 |
| BIOFLOW V | 4 | 884 | 3 | 450 | 0.68 (0.15, 3.03) | 5.36 |
| BIORESORT | 5 | 1169 | 6 | 1173 | 0.84 (0.26, 2.74) | 8.53 |
| BIOSCIENCE | 29 | 1063 | 35 | 1056 | 0.82 (0.50, 1.35) | 49.59 |
| ORIENT | 0 | 250 | 0 | 122 | 0.49 (0.01, 24.59) | 0.78 |
| PRISON IV | 1 | 165 | 2 | 165 | 0.50 (0.05, 5.51) | 2.08 |
| SORT OUT VII | 11 | 1261 | 20 | 1264 | 0.55 (0.26, 1.15) | 22.19 |
| D+L Subtotal (I-squared = 0.0%, *p*=0.956) | | | | | 0.74 (0.51, 1.07) | 90.69 |
| I-V Subtotal | | | | | 0.74 (0.51, 1.07) | |
| **MiStent** | | | | | | |
| DESSOLVE-III | 5 | 703 | 6 | 695 | 0.82 (0.25, 2.70) | 8.53 |
| D+L Subtotal (I-squared = NA, *p* = NA) | | | | | 0.82 (0.25, 2.70) | 8.53 |
| I-V Subtotal | | | | | 0.82 (0.25, 2.70) | |
| **BioMime** | | | | | | |
| Merit-V | 0 | 170 | 0 | 86 | 0.51 (0.01, 25.49) | 1.79 |
| D+L Subtotal (I-squared = NA, *p* = NA) | | | | | 0.51 (0.01, 25.49) | 1.79 |
| I-V Subtotal | | | | | 0.51 (0.01, 25.49) | |
| **All Stents** | | | | | | |
| D+L Subtotal ($I^2$ = 0.0%, *p* = 0.99) | | | | | **0.74 (0.53, 1.05)** | 100.00 |
| I-V Subtotal | | | | | **0.74 (0.53, 1.05)** | |



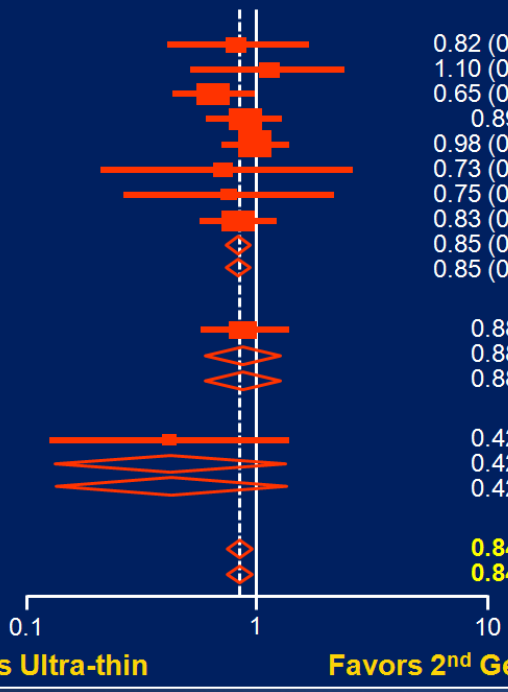

*Bangalore et al; Circ 2018*

# Ultra-thin (<70 µm) vs. Thicker Strut 2nd Gen DES

10 RCTs, 11,658 pts, 3 ultra-thin strut DES:
Orsiro (60 µm), MiStent (64 µm) and BioMime (65 µm)

## 1-Year Target Lesion Failure

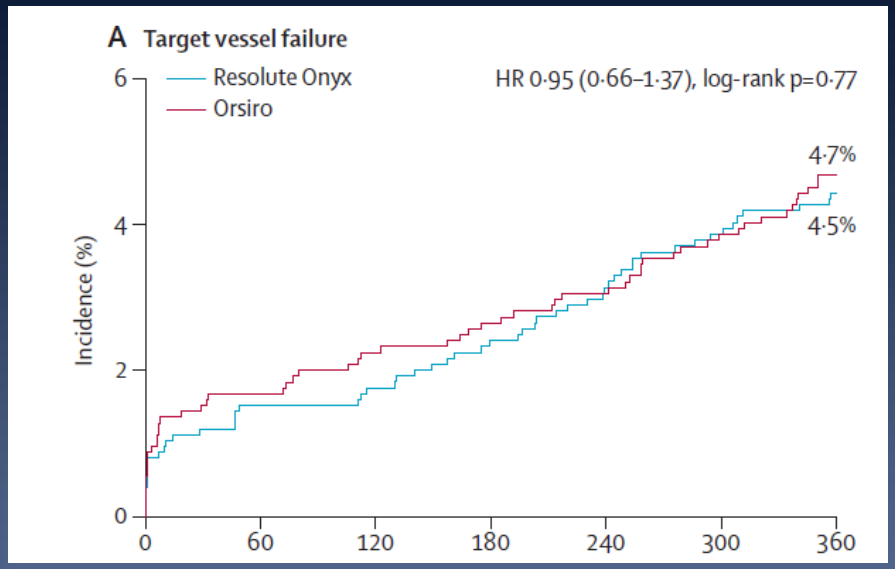
| Study | Ultra-thin Events | Ultra-thin N | 2nd Generation Events | 2nd Generation N | RR (95% CI) | % Weight (D+L) |
|---|---|---|---|---|---|---|
| **Orsiro** | | | | | | |
| BIOFLOW II | 19 | 298 | 12 | 154 | 0.82 (0.40, 1.69) | 4.83 |
| BIOFLOW IV | 20 | 354 | 9 | 176 | 1.10 (0.50, 2.43) | 4.08 |
| BIOFLOW V | 52 | 884 | 41 | 450 | 0.65 (0.43, 0.97) | 15.07 |
| BIORESORT | 47 | 1169 | 53 | 1173 | 0.89 (0.60, 1.32) | 16.37 |
| BIOSCIENCE | 69 | 1063 | 70 | 1056 | 0.98 (0.70, 1.37) | 22.84 |
| ORIENT | 6 | 250 | 4 | 122 | 0.73 (0.21, 2.59) | 1.58 |
| PRISON IV | 6 | 165 | 8 | 165 | 0.75 (0.26, 2.16) | 2.25 |
| SORT OUT VII | 48 | 1261 | 58 | 1264 | 0.83 (0.57, 1.22) | 17.26 |
| D+L Subtotal (I-squared = 0.0%, *p*=0.881) | | | | | 0.85 (0.71, 1.01) | 84.29 |
| I-V Subtotal | | | | | 0.85 (0.71, 1.01) | |
| **MiStent** | | | | | | |
| DESSOLVE-III | 40 | 703 | 45 | 695 | 0.88 (0.57, 1.35) | 13.92 |
| D+L Subtotal (I-squared = NA, *p* = NA) | | | | | 0.88 (0.57, 1.35) | 13.92 |
| I-V Subtotal | | | | | 0.88 (0.57, 1.35) | |
| **BioMime** | | | | | | |
| Merit-V | 5 | 170 | 6 | 86 | 0.42 (0.13, 1.38) | 1.79 |
| D+L Subtotal (I-squared = NA, p = NA) | | | | | 0.42 (0.13, 1.38) | 1.79 |
| I-V Subtotal | | | | | 0.42 (0.13, 1.38) | |
| **All Stents** | | | | | | |
| D+L Subtotal ($I^2$ = 0.0%, *p* = 0.88) | | | | | **0.84 (0.72, 0.99)** | 100.00 |
| I-V Subtotal | | | | | **0.84 (0.72, 0.99)** | |

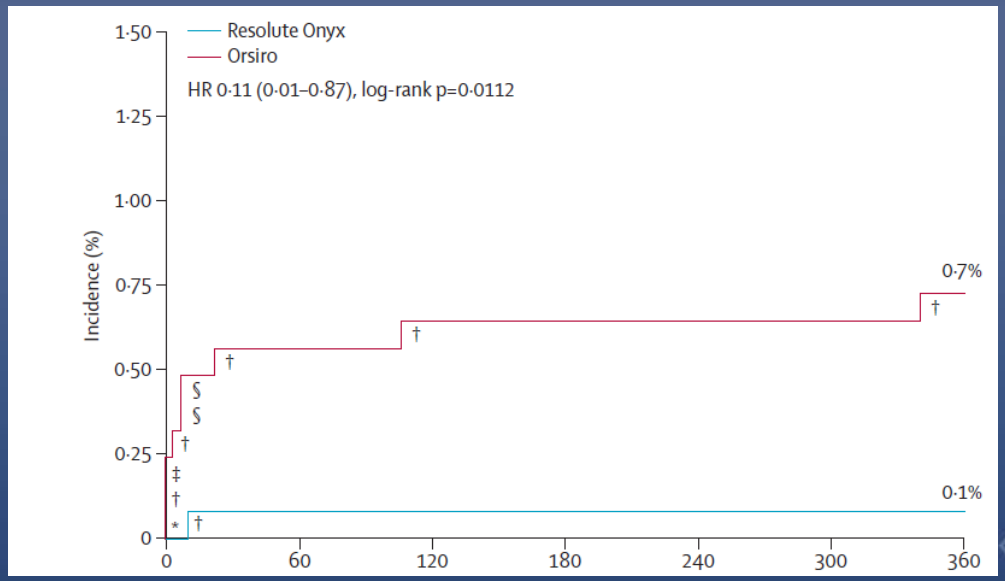



Driven by less TV-MI with no differences in CD or ID-TLR

*Bangalore et al; Circ 2018*

# BIONIX trial: ORSIRO vs Resolute




*Von Birgelen et al; Lancet 2018*

# Conclusion I

- All studies comparing different second generation DES each other had a non-inferiority design, and therefore it is not possible to tease out significant differences in low-occurrency endpoints such as stent thrombosis or MI.

- The Xience stent is the device which has received the most extensive investigation ever, with randomized trials and meta-analyses reporting improved safety and efficacy compared to BMS and first generation DES.

# Conclusion II

- Thinner strut DES have shown promising results with the potential of further improving the outcome of patients undergoing stent implantation, but further investigation is needed to confirm this hypothesis.