All Contemporary DES Comparison, Worldwide Clinical Trial Summary

> Tullio Palmerini University of Bologna Italy

Disclosure

- Speaker fee from Abbott
- Research grant from Eli Lilly

Are there meaningful differences among II generation DES?

What really matters to patients?



Sample size for a superiority study on stent thrombosis

Assuming a 1-year event rate of 13,000 patients needed

Power= 90%

Use of DES across RCTs



Comparison of a Polymer-Based Paclitaxel-Eluting Stent With a Bare Metal Stent in Patients With Complex Coronary Artery Disease A Randomized Controlled Trial





Stone et al; JAMA 2005

Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis



Tullio Palmerini, Giuseppe Biondi-Zoccai, Diego Della Riva, Christoph Stettler, Diego Sangiorgi, Fabrizio D'Ascenzo, Takeshi Kimura, Carlo Briguori, Manel Sabatè, Hyo-Soo Kim, Antoinette De Waha, Elvin Kedhi, Pieter C Smits, Christoph Kaiser, Gennaro Sardella, Antonino Marullo, Ajay J Kirtane, Martin B Leon, Gregg W Stone

Stent Thrombosis Network Meta-analysis Primary EP: ARC Definite ST (FU to 2 years)



Stent Thrombosis Network Meta-analysis Primary EP: ARC Definite ST (FU through 2 years)



Palmerini et al, Lancet 2012

Network meta-analysis: 49 RCTs and 50,844 pts





Palmerini et al. Lancet 2012;379:1393-402

What is a network meta-analysis?

NMA can be weak if it relies only on indirect evidence

Inconclusive if indirect and direct evidence go in opposte directions

trials

trials

Strong if there is consistency between direct and indirect evidence

Stent Thrombosis Network Meta-analysis Primary EP: ARC Definite ST (FU through 2 years) 49 RCTs, 50,844 pts

Consistency between direct and indirect estimates of 1-year stent thrombosis for CoCr-EES vs. BMS



Palmerini T et al. Lancet 2012

Bern Registry

Primary Endpoint ARC Definite ST @ 4 Years

EES vs. SES Hazard Ratio* = 0.41, 95% CI 0.27-0.62, P<0.0001 EES vs. PES Hazard Ratio* =0.33, 95% CI 0.23-0.48, P <0.0001



Raber JACC 2011

Pooled analysis of 5 RCTs

NORSTENT trial





Valgimigli et al BMJ 2015

Bonaa NEJM 2016

Chronic inflammation and delayed hypersensitivity



Chronic fibrin deposition and delayed healing



Permanent polymer is bad BMS are safer than DES

Late malapposition and stent fracture



Neoaterosclerosis



The Concept of Fluoropassivation Fluoropolymer coated surfaces are thromboresistant in blood-contact application



Ting-Yu Liu et al. Polym. Adv. Technol. 2005:16:413-419 Massa TM et al. J Biomed Materials Research Part A DOI 10.1002/ibm.a

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





Next step.....



Vision

Vision coated with fluoropolymer

Vision perfused with blood pre-treated with Everolimus

Xience



To bioabsorb or not to bioabsorb



Chronic inflammation and delayed hypersensitivity



Chronic fibrin deposition and delayed healing



Late malapposition and stent fracture



Neoaterosclerosis







New generation PP vs BP DES



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

Most 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%

Long-Term Safety of Drug-Eluting and Bare-Metal Stents



Evidence From a Comprehensive Network Meta-Analysis

Tullio Palmerini, MD,* Umberto Benedetto, MD,† Giuseppe Biondi-Zoccai, MD,‡ Diego Della Riva, MD,* Letizia Bacchi-Reggiani, MSTAT,* Pieter C. Smits, MD, PHD,§ Georgios J. Vlachojannis, MD, PHD,§ Lisette Okkels Jensen, MD, || Evald H. Christiansen, MD, PHD,¶ Klára Berencsi, MSTAT, || Marco Valgimigli, MD,# Carlotta Orlandi, MD,* Mario Petrou, MD,† Claudio Rapezzi, MD,* Gregg W. Stone, MD**



RCT with at least 3-year fup 51 RCTs with 52,158 patients Mean follow up 4 years

Palmerini et al; JACC 2015



Palmerini et al; JACC 2015

Stent (company)	A x x e s s (Devax Inc)	Biomatrix (Biosensors)	Elixir DESyne (Elixir Medical Corp)	Elixir Myolimus (Elixir Medical Corp)	Excel Stent (JW Medical Systems)	Firehawk (MicroPort Medical)	In fin n i u m (Sahajanad Medical Technologies)	In spiron (Scitech)	N o b o r i (Terum o)	Orsiro (Biotronik)	Supralimus (Sahajanad Medical Technologies)
Stent Platform	Nitinol	SS	Co Cr	CoCr	SS	Co Cr	SS	CoCr	SS	Co Cr	SS
Strut thickness(µm)	152	112	80	80	119	86	80	75	112	60	80
Polymer	Abluminal PLA	Abluminal PLA	Abluminal PLA	Abluminal PLA	PLA	PLA	PLLA, PLGA, PCL, PVP	PLA, PLGA	Abluminal PLA	PLLA	PLLA, PLGA, PVP
Time of polymer degradation (months)	6–9	6-9	6-9	6-9	6-9	6-9	7	6-9	6-9	7	7
Eluted drug	Biolimus A9	Biolimus A9	Novolimus	Novolimus	Sirolimus	Sirolimus	Paclitaxel	Sirolimus	Biolimus A9	Sirolimus	Sirolimus

New generation of BP-DES







Orsiro

CoCr platform with 60 µm thick struts PLLA polymer matrix Polymer degradation: 7 months Sirolimus

Ultimaster

CcCr platform with 80 µm thick struts PDLLA polymer matrix Polymer degradation time: 3-4 months Sirolimus

Synergy

PtCr platform with 74 μm thick struts PDLLA polymer matrix Polymer degradation time: 3 months Everolimus

BIOSCIENCE (Orsiro vs Xience)

CENTURY II (Ultimaster vs Xience)





EVOLVE II (Synergy vs Promus)

15



BIO-RESORT (Synergy vs Orsiro vs Res)



Conclusions I

- Although there have been several RCTs investigating safety and efficacy of different DES, there is a significant imbalance in the amount of data available for different DES, with fluorinated permanent polymer CoCr-EES being the most investigated devices ever with 31 RCTs and more than 20.000 patients receiving this stent.
- Across randomized trials, meta-analyses and observational studies CoCr-EES have been shown to reduce early and late stent thrombosis not only compared to other DES, but even BMS.

Conclusions II

- At a median follow up of 4 years, no significant advantage is apparent with BP-BES compared to second generation DP-DES. In contrast, CoCr-EES is associated with lower rates of stent thrombosis than BES.
- New BP DES have been shown to be non-inferior to second generation PP-DES, but RCTs performed so far have been underpowered to detect differences in ST or MI.