Erasmus MC

Joint Commission International

Ultimaster Clinical evidence

Hazem Khamis,MD,FACC
October 6 University
Egypt

Why DES are not perfect?

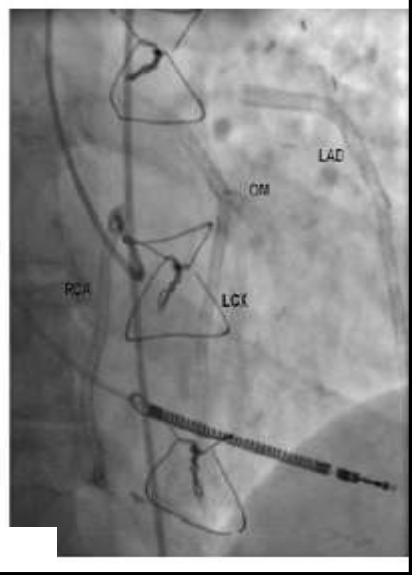
- Require long term DAPT 12 months
- Late restenosis
- Late Thrombosis up to 7 years
- Chronic inflammation with neo-atherosclerosis
- STEMI associated with high rate of stent thrombosis
- Stent Fractures and neoatherosclerosis
- Do not work well for diabetic population
- Inferior to surgery for Syntax score > 22

[redacted]

IMAGES IN CARDIOLOGY

A Heart With 67 Stents

Rami N. Khouzam, MD, Rajvir Dahiya, MD, Richard Schwartz, MD
Mineola, New York



Key Elements of Stent for Complex Cases

Polymer & Drug

Platform

Delivery System

What is the purpose of a DES polymer?

- The polymer's role is to provide a mechanically stable matrix for the drug and modulate drug release into the vessel wall
- Polymer remaining after drug release has no function
  - All polymer coatings have the potential to be damaged. Durable polymers are permanent.

Boston Scientific data on file.

The impact of DES: addressing unmet needs

First coronary angioplasty

1977

CHALLENGES:
- Elastic recoil (vascular damage)
- Restenosis

First BMS

1986

SUCCESSES:
- Addressed elastic recoil
- Restenosis reduced, but still clinically relevant
- Animal studies indicated endothelization at 28 days

CHALLENGES:
- Local coronary thrombosis

First-generation DES

2001

SUCCESSES:
- Reduced restenosis
- Reduced reintervention

CHALLENGES:
- Late stent thrombosis
- Animal studies indicated incomplete vessel healing by 180 days

DES development: e.g. Xience

2014

More biocompatible but still using a permanent, circumferential polymer

Ultimaster

A true second-generation stent: DES with abluminal bioresorbable polymer; matches biological response

BMS, bare-metal stent; DES, drug-eluting stent.

Windecker S et al. Eur Heart J 2014;35:2541–619; Tsimikas S. J Am Coll Cardiol 2006;47:2112–5; Newsome LT et al. APSF Newsletter 2007, http://www.apsf.org/newsletters/html/2007/winter/12_protocol.htm. Accessed August 2015; http://www.biosensors.com/intl/sites/default/files/pdfs/newsroom/des_history_review_6.7.11.pdf. Accessed August 2015.

Comprehensive clinical evidence resulted in recognition of Ultimaster in recent ESC/EACTS guidelines

CE-approved new-generation DES recommended for clinical use based on randomized trials with a primary clinical endpoint (in alphabetical order)

DES	Stent platform	Polymer coating	Drug
Based on durable polymer coatings			
Promus element	Platinum-chrome	PBMA and PVDF-HFP	Everolimus
Resolute	Cobalt-chrome	PBMA, PHPMA, PVP, and PVA	Zotarolimus
Xience	Cobalt-chrome	PBMA and PVDF-HFP	Everolimus
Based on biodegradable polymer coatings			
Biomatrix	Stainless steel	PDLLA	Biolimus A9
Nobori	Stainless steel	PDLLA	Biolimus A9
Yukon Choice PC	Stainless steel	PDLLA	Sirolimus
Orsiro	Cobalt-chrome	PLLA	Sirolimus
Ultimaster	Cobalt-chrome	PDLLA and PCL	Sirolimus

EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology.

Adapted from: Windecker S et al. Eur Heart J 2014;35:2541–619; Saito S et al. Eur Heart J 2014;35:2021–31.

A 1-month DAPT regimen with Ultimaster has been CE-mark approved

Patients should be maintained on clinically adequate post-procedural antiplatelet therapy (aspirin, thienopyridine, or other appropriate antiplatelet agents) according to the current guidelines.

In case of need, dual antiplatelet therapy can be discontinued earlier, but not before one month.

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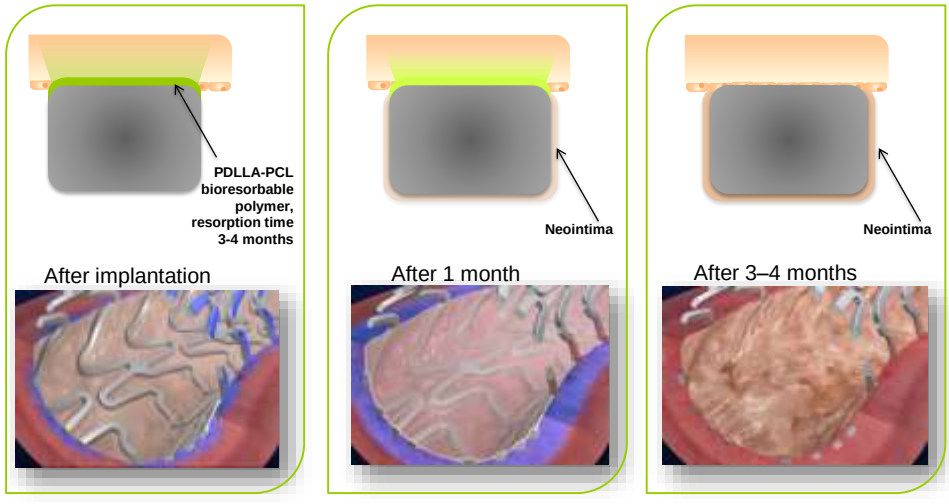
DAPT, dual antiplatelet therapy.
Ultimaster instructions for use. 2014-10. 9

Ultimaster
Drug Eluting Stent

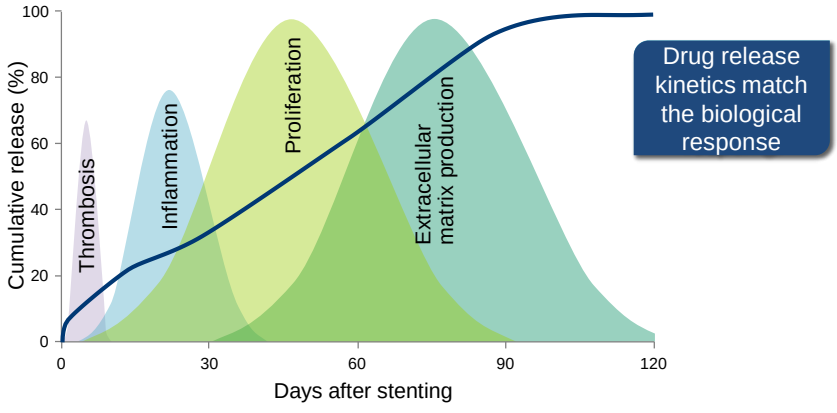
Ultimaster: designed with performance and safety in mind

Bioresorbable polymer: short-term polymer exposure promotes vascular repair



Data on file at Terumo Corporation (Report NewDES-10-3001). 11

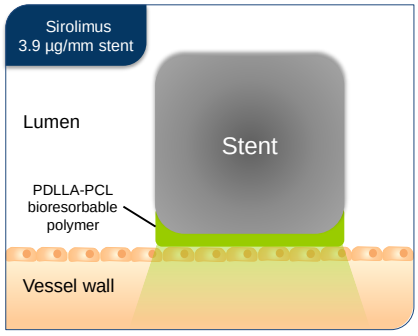
Drug release kinetics mirror the biological response to the PCI procedure



Polymer resorption time is also 3–4 months

PCI, percutaneous coronary intervention.
Data on file at Terumo Corporation (Report NewDES-10-3001 and NewDES-12-3005). 12

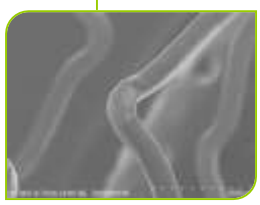
Abluminal coating: targeted drug delivery for faster stent coverage



- Allows a reduced drug dose
  - Half the amount required vs circumferential coating to deliver the same amount of drug to target tissue
- Luminal side of the stent free from drug and polymer
  - Enhances endothelial coverage

PDLLA-PCL, poly(D,L-lactide-co-caprolactone) copolymer. 13

Abluminal gradient coating: Reduces risk of polymer cracking and delamination



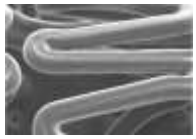
No drug polymer coating on parts of the stent that experience the **most physical stress**

Prevents the damage that can occur with other stent coatings:

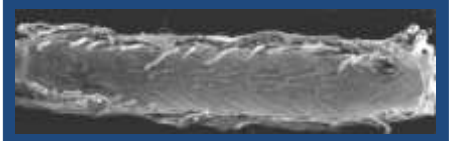
Saito N et al. Medical Devices:Evidence and Research 2016:9 33-43 14

Demonstrates evidence of rapid vascular repair

Circumferential coating



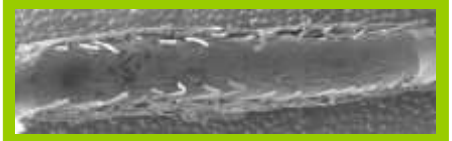
Rabbit iliac artery at 2 weeks



Endothelial coverage **73**%

Ultimaster abluminal gradient coating

Rabbit iliac artery at 2 weeks



Endothelial coverage **97**%

Both coatings were applied to the Kaname BMS platform.
Saito N et al. Medical Devices:Evidence and Research 2016:9 33-43

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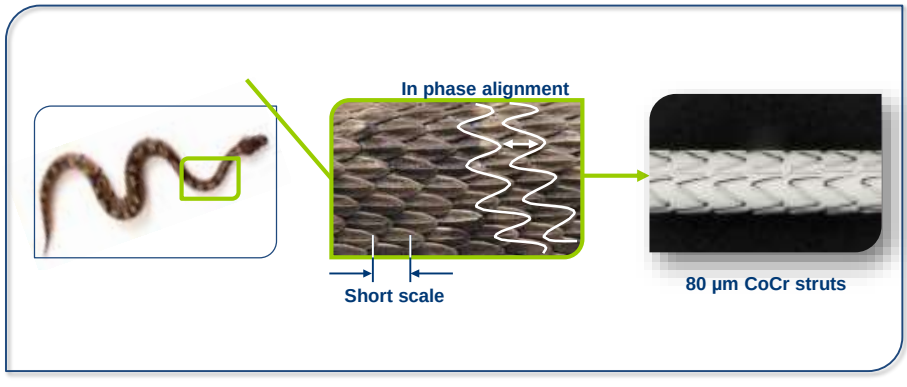
Bioinspired, vessel-friendly stent design

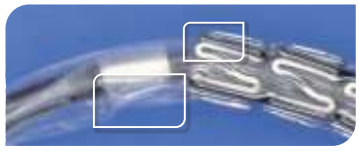


Data on file at Terumo Corporation (Doc nr. Des08-T).

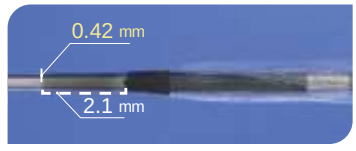
16

Ultimate stent deliverability, so physicians can focus on their patients, not their tools

Smooth balloon–stent transition essential for clinical practice



Low entry profile for outstanding trackability



Optimal stent flexibility for ultimate stent crossability

Famous Terumo hydrophilic coating

Data on file at Terumo Corporation (Doc nr. Des08-T); www.terumo-europe.com. Accessed August 2015.

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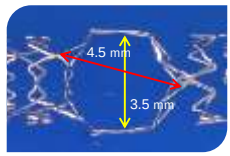
Designed to facilitate treatment of the most challenging lesions

Facilitates bifurcation treatment

- Excellent side-branch access
- Uniform scaffolding
- Radial strength
- Allows overexpansion
- Polymer integrity

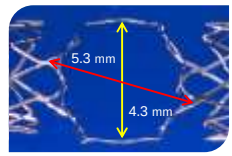
Open-cell, 2-link design for excellent side-branch access

Φ2.25–3.0 mm



NC balloon catheter
Φ4.0 mm, NP
Area: 9.62 mm²

Φ3.5–4.0 mm



NC balloon catheter
Φ5.0 mm, NP
Area: 14.5 mm²

Test method: expand a cell with a balloon at nominal pressure. Φ, diameter.
Tests performed by and data on file at Terumo Corporation (Doc nr. SideBr03-T).

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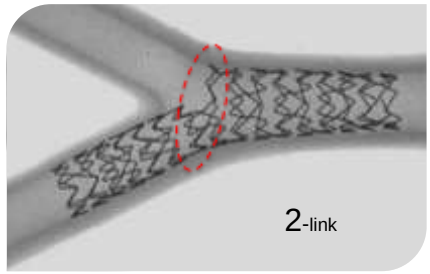
Designed to facilitate treatment of the most challenging lesions

Facilitates bifurcation treatment

- Excellent side-branch access
- Uniform scaffolding
- Radial strength
- Allows overexpansion
- Polymer integrity

Uniform scaffolding for optimal coverage of bifurcation anatomy



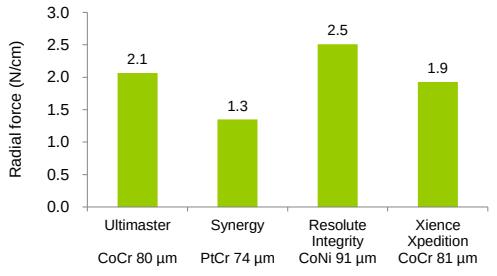
Tests performed by and data on file at Terumo Corporation (Doc nr. SideBr03-T). 19

Designed to facilitate treatment of the most challenging lesions

Facilitates bifurcation treatment

- Excellent side-branch access
- Uniform scaffolding
- Radial strength
- Allows overexpansion
- Polymer integrity

Bench-tests highlight the high radial force achieved with Ultimaster



All stents: Φ3.0 mm

Tests performed by and data on file at Terumo Corporation (Doc nr. RadStr04-T). 20

Designed to facilitate treatment of the most challenging lesions

Facilitates bifurcation treatment

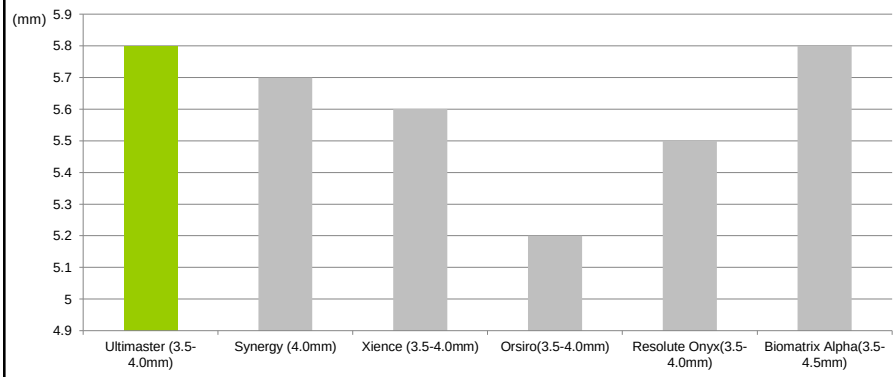
- Excellent side-branch access
- Uniform scaffolding
- Radial strength
- Allows overexpansion
- Polymer integrity

Over-expansion does not compromise structure and function of the stent

Tests performed by and data on file at Terumo Corporation (Doc nr. OverXp05-T). 21

Expansion capacity up to 5.8 mm

Result of independently initiated study



Samples of different stent sizes/models were deployed in vitro at nominal pressure (NP). Subsequently, over-expansion results for each design was tested with successive post-dilations using, used first a 5.0 × 12 non-compliant balloon followed by a 6.0 × 15 mm semi-compliant balloon with a pressure of 14ATMfor largest designs..

Jaryl Ng at al. International Journal of Cardiology 221 (2016) 171-179

Designed to facilitate treatment of the most challenging lesions

Facilitates bifurcation treatment

- Excellent side-branch access
- Uniform scaffolding
- Radial strength
- Allows overexpansion
- Polymer integrity

Gradient coating ensures polymer integrity for reduced risk of delamination, even when overexpanded

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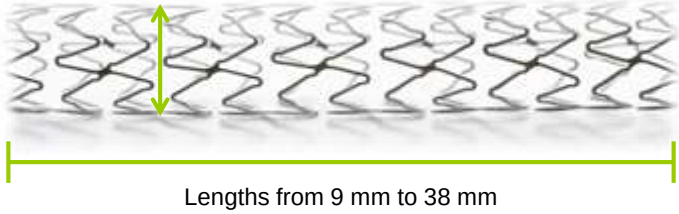
Saito N et al. Medical Devices:Evidence and Research 2016:9 33-43 23

Flexibility to manage a large spectrum of lesion sizes

Diameters from 2.25 mm to 4.00 mm



Lengths from 9 mm to 38 mm

[redacted]

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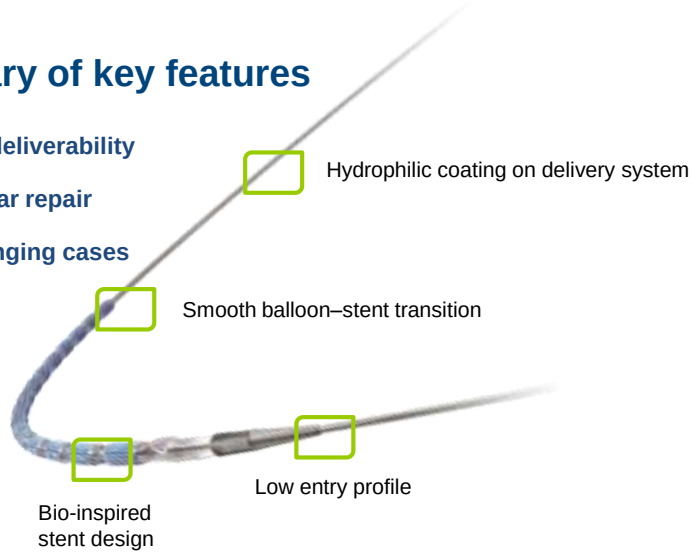
http://www.terumo-europe.com/en-emea/interventional-cardiology/stents/drug-eluting-stent/ultimaster%C2%AE-drug-eluting-stent. Accessed August 2015. 24

Summary of key features

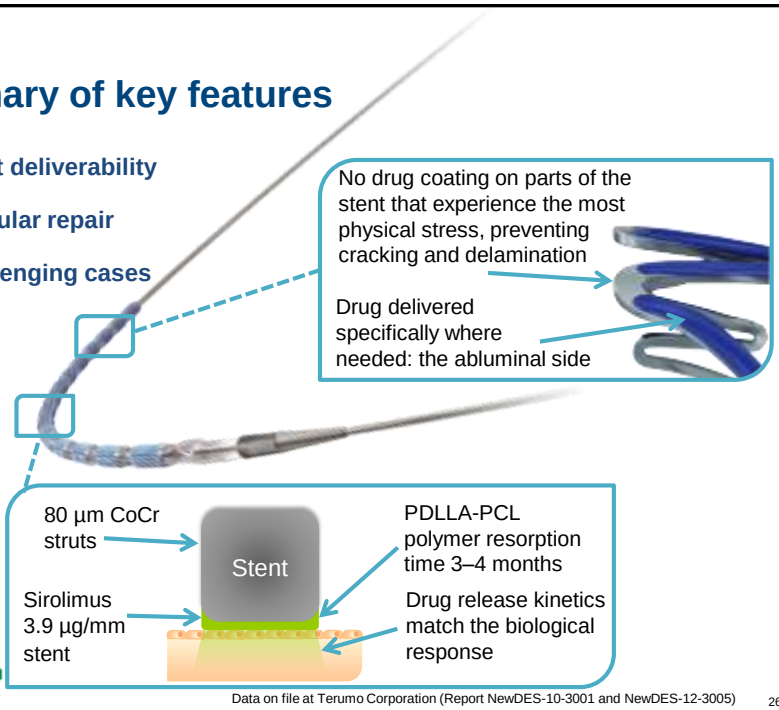
- [x] Stent deliverability
- [ ] Vascular repair
- [ ] Challenging cases



Data on file at Terumo Corporation (Doc nr. Des08-T).

Summary of key features

- [x] Stent deliverability
- [x] Vascular repair
- [ ] Challenging cases



Data on file at Terumo Corporation (Report NewDES-10-3001 and NewDES-12-3005)

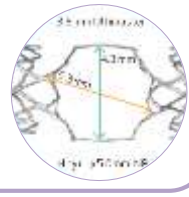
Saito N et al. Medical Devices:Evidence and Research 2016:9 33-43

Summary of key features

- Stent deliverability
- Vascular repair
- Challenging cases

Bifurcation

- 2-link design for excellent side-branch access
- Gradient coating for polymer integrity
- Allows overexpansion



A solution for any lesion

Diameters from 2.25 mm to 4.00 mm

Lengths from 9 mm to 38 mm

TERUMO INTERVENTIONAL SYSTEMS

Data on file at Terumo Corporation (Doc nr. Des08-T).

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Summary of key features

Vascular repair

- PDLLA-PCL bioresorbable polymer, resorption time 3–4 months
- Drug delivered specifically where needed: the abluminal side
- No drug coating on parts of the stent that experience the most physical stress, preventing cracking and delamination
- Sirolimus 3.9 µg/mm stent
- Drug release kinetics match the biological response
- 80 µm CoCr struts

Challenging cases

- Facilitates bifurcation treatment
  - 2-link design for excellent side-branch access
  - Gradient coating for polymer integrity
  - Allows overexpansion
- A solution for any lesion size

Stent deliverability

- Hydrophilic coating on delivery system
- Smooth balloon–stent transition
- Bio-inspired stent design
- Low entry profile

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TERUMO INTERVENTIONAL SYSTEMS

Ultimaster
Drug Eluting Stent

Ultimaster: a comprehensive clinical programme

Ultimaster clinical programme

More than 20 000 pts will be included worldwide

	TCD-10023PK	CENTURY	CENTURY II	MASTER	DISCOVERY 1TO3	CENTURY J SV	e-Ultimaster
Number of patients	22	105	1123	500	60	70	20 000
Design	Single arm, pharmaco-kinetics	Single arm, first-in-man study	Randomized 1:1 vs Xience	Randomized 3:1 vs BMS in patients with STEMI	Single arm, patients with multivessel disease	Single arm, patients requiring 2.25 diameter stents	Single arm, all-comers, real-world use; investigation of reduced DAPT regimens on clinical outcomes
Primary outcomes	Sirolimus concentration in peripheral blood samples 28 days after Ultimaster implantation	Late loss at 6 months	Freedom from TLF at 9 months	Safety at 1 month, efficacy at 6 months, safety and efficacy at 12 months	OFDI strut coverage at 3 months	TLF at 9 months	TLF at 1 year
Stage	Published	Published, follow-up ongoing	Published, follow-up ongoing	Ongoing	Ongoing	Ongoing	Enrolling

[redacted]

TERUMO

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Assessment of 'safety' refers to the side-effect profile and clinical events experienced (e.g. stroke, MI, unplanned revascularization, etc.).

CENTURY

First-in-man angiographic and OCT assessment: the CENTURY study

Objectives

- To investigate the 6-month angiographic and long-term clinical outcomes for Ultimaster
  - Effect on arterial vessel wall assessed with sophisticated imaging techniques: IVUS and OCT
  - Acute and long term safety and efficacy evaluated by numerous predefined endpoints
- To compare the results for Ultimaster with data from a historical BMS cohort

IVUS, intravascular ultrasound; OCT, optical coherence tomography.
Barbato E et al. EuroIntervention 2015;11:541–8.

CENTURY

CENTURY: summary

- Ultimaster was superior to the BMS with respect to in-stent late loss: achieving a 95% late loss reduction
- OFDI data support the efficacy and safety profile of Ultimaster:
  - Thin and homogeneous layer of neointima covered stent struts 6 months after implantation
  - Average strut coverage rate of 96.2%
- Rate of adverse events remained low with Ultimaster up to 4 years after implantation, with no late or very late stent thrombosis

Barbato E. Presented at EuroPCR 2015, abstract OP047;
Barbato E et al. EuroIntervention 2015;11:541–8.
Belesin B. Presented at EuroPCR 2016.

CENTURY II: objective

- To confirm the safety and efficacy profile previously demonstrated for Ultimaster
- To compare the outcomes achieved with Ultimaster vs Xience
  - Powered to evaluate non-inferiority for clinical outcomes
- To build on the understanding from the CENTURY study, by studying Ultimaster vs a contemporary comparator group

Saito S et al. Eur Heart J 2014;35:2021–31.

CENTURY II: summary

- The primary clinical endpoint (freedom from TLF at 9 months) was met; showing non-inferiority of Ultimaster to Xience in a population with broad inclusion criteria
- Ischaemia-driven TLR (clinical restenosis) occurred infrequently, with similar rates in both study groups
- Good long-term safety was demonstrated with both study stents, with no significant difference in 3-year rate of cardiac death, MI, and ST
- Ultimaster's bioresorbable abluminal polymer coating, and excellent deliverability, build on the legacy of previous Terumo DES for tangible clinical benefits

Iniguez R. Presented at EuroPCR 2015, abstract OP071; Merkely B. Presented at EuroPCR 2015, abstract OP135; Valdés M. Presented at EuroPCR 2015, abstract OP043; Lesiak M. Presented at EuroPCR 2015, abstract OP016; Fabbiocchi F et al. Presented at EuroPCR 2015, abstract POS155; Wöhrle J et al. Presented at EuroPCR 2015, abstract OP066; Orvin K et al. Catheterization cardiovascular interventions. DOI: 10.1002/ccd.26150.

MASTER

Investigating Ultimaster in patients with STEMI: the MASTER study

Objectives:

- Contribute to collection of clinical data on primary PCI with DES in patients with STEMI
- Generate evidence on the use of a DES with a bioresorbable polymer in this setting
- Establish superiority of Ultimaster vs BMS in patients with STEMI

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Stankovic G. Presented at EuroPCR 2015; Data on file at Terumo Corporation. 35

MASTER

MASTER: summary

- The MASTER study provides insights into a STEMI population representative of daily clinical practice
- **All primary endpoints were met (Safety at 1 month, Efficacy at 6 months, Safety & efficacy at 1 year)**
- Ultimaster achieved superior efficacy and favourable mid-term safety vs a BMS platform
- DES with bioresorbable abluminal gradient polymer coating on thin struts are a valuable treatment option for STEMI patients

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Stankovic G. Presented at EuroPCR 2015.
Valdes-Chavarri M. Presented at EuroPCR2016 36

DISCOVERY 1TO3

Endothelial coverage in patients with MVD undergoing PCI: DISCOVERY 1TO3

Objectives:

- Assess Ultimaster endothelial coverage at 1, 2, and 3 months by OFDI in patients with multivessel disease scheduled for staged PCI
- Provide insights into the target vessel itself, with OFDI after implantation of Ultimaster
- Investigate the possibility for shorter DAPT with Ultimaster

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Smits P. Presented at EuroPCR 2015.
Chevalier B. Presented at EuroPCR 2016. 37

DISCOVERY 1TO3

DISCOVERY 1TO3: summary

- DISCOVERY 1TO3 study reached primary endpoint with up to 86% strut coverage as early as 1 month despite the high complexity of patients/lesions
- 1 –year clinical outcomes confirmed safety and efficacy of Ultimaster stent in this complex multivessel diseased and treated patient group, with no cardiac death and only one acute ST
- The unique sequential OFDI analysis at 1, 2 and 3 months of treated lesions demonstrated that strut coverage of the thin strut, abluminally coated bioresorbable polymer Ultimaster stent occurs mainly within the first month with minor increase, although significant, between 1 and 3 months
- This study improves our insight on the endothelial embedding of metallic DES and can act as a guide to shorter DAPT strategies

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Smits P. Presented at EuroPCR 2015.
Chevalier B. Presented at EuroPCR 2016. 72

CENTURY J SV

Ultimaster in small vessels disease: the CENTURY SV study

Objectives:

- Confirm the efficacy and safety of Ultimaster for IHD induced by stenosis in small coronary arteries

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Saito S. Presented at EuroPCR 2016. 39

CENTURY J SV

CENTURY JSV: summary

- CENTURY JSV study reached its primary endpoint; superiority to POBA.
- Low TLF and TVF rates were shown, considering the complexity of the lesions and patients.
- No stent thromboses nor bleeding events were reported.
- Ultimaster® 2.25mmφ stent was found to be safe and effective for small coronary arteries from both clinical and angiographic outcomes

TERUMO INTERVENTIONAL SYSTEMS

Saito S. Presented at EuroPCR 2016. 73

Assessment of 'safety' refers to the side-effect profile and clinical events experienced (e.g. ST, bleeding, etc.).

Ultimaster in practice: the e-Ultimaster registry

Objectives:

- Further explore shortening DAPT with Ultimaster
- Identify geographic patterns of care
- Add evidence to unresolved treatment options
- Enhance worldwide scientific networking

Ultimaster is also being studied in investigator initiated trials

MASTER DAPT:

- Investigating abbreviated versus prolonged DAPT following stenting in patients at high bleeding risk
- First Global DAPT trial, 34 countries, 150 sites worldwide
- Enrolment will start in February 2017

Hybrid revascularization trial:

- A prospective, randomized, open-label trial of conventional CABG versus hybrid revascularization enrolling patients with MVD
- Will assess angiographic occlusion of venous bypass grafts or stent occlusion in the revascularized segment at 1 year
- Currently enrolling

Ultimaster clinical programme: key findings

More than 20 000 pts will be included worldwide

TCD-10023PK	• Sirolimus concentration in peripheral blood was very low
CENTURY	• Ultimaster demonstrated a favourable efficacy and safety profile in a first-in-man study
CENTURY II	• Ultimaster was non-inferior to Xience for key safety and efficacy outcomes
MASTER	• Ultimaster achieved superior efficacy and favourable short-term safety vs a BMS platform in a patient population that resembled clinical practice
DISCOVERY 1TO3	• Ultimaster achieved a high degree of stent coverage as early as 1 month after implantation
CENTURY J SV	• Ultimaster *is being investigated* in patients who require stenting in small vessels
e-Ultimaster	• Use of Ultimaster in clinical practice *is being investigated* in patients who are truly representative of those receiving a stent in the clinic

TERUMO INTERVENTIONAL SYSTEMS

Barbato E et al. EuroIntervention 2015;11:541–8; Saito S et al. Eur Heart J 2014;35:2021–31; Stojkovic S et al. Fundam Clin Pharmacol 2015;29:95–105; Barbato E. Presented at EuroPCR 2015, abstract OP047; Stankovic G. Presented at EuroPCR 2015; Smits P. Presented at EuroPCR 2015; Data on file at Terumo Corporation.

Ultimaster: in summary

Designed to:

- Master the most complex clinical cases and anatomy
- Support fast vascular repair
- Allow physicians to focus on their patients, not their tools

Supported by large and comprehensive clinical programme:

- Proven efficacy and safety profile against the industry standard, and across a broad range of patient populations
- Further clinical trial programme will provide real-world evidence, assessing over 20 000 patients from a broad range of countries
- Dedicated to exploring areas of unmet need and complex disease

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Thank You