

PLANNED COMBINED SAFETY
ANALYSIS FOR STENTS
UTILIZING BIOLIMUS A9[®]
AND BIODEGRADABLE
POLYMER

Laura Mauri, M.D., M.Sc.

Chief Scientific Officer

Harvard Clinical Research Institute

Stent Thrombosis: the question

- Events are rare
- Predictors are poorly defined
- Results cannot be generalized from one drug-polymer combination to another

Stent Thrombosis: the question

- Current regulatory evaluation of new molecular entities requires 2000 patient exposure based on the following assumptions
 - Expected ST rate $\sim 1\%$ for bare metal stents
 - Power to detect doubling in rate of ST for a new stent
- There may be an interest in increasing the power to detect adverse events that occur infrequently and late through studies with
 - Larger total exposure (patient-years)

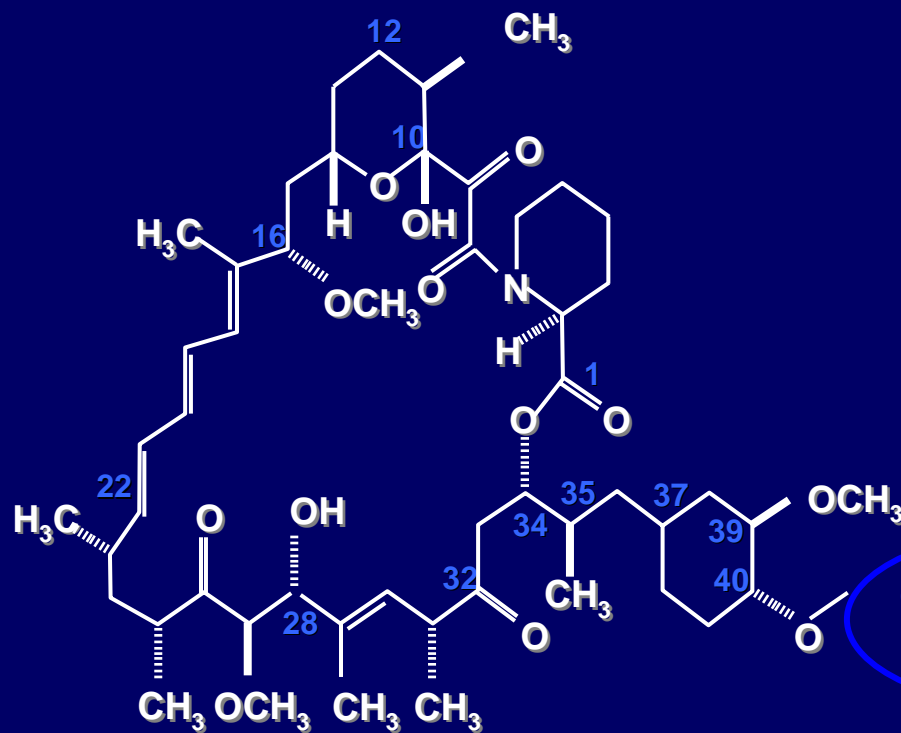
Stent Thrombosis: The question

- Where different stent platforms use the same drug-polymer combination, combining data may improve the power to detect rare adverse events
 - anticipated and unanticipated

Biolimus A9 Stent Programs

- Biolimus A9 and the biodegradable polymer is under investigation in several stent platforms:
 - Biosensors, Devax, Terumo, and Xtent
- Each stent platform has a series of trials designed to demonstrate safety and effectiveness to support approvals
- The trials vary according to stent type and target patient population

Biolimus A9 and Biodegradable Polymer



ethoxy ethyl
modification

Sirolimus
Everolimus
Zotarolimus
Biolimus A9

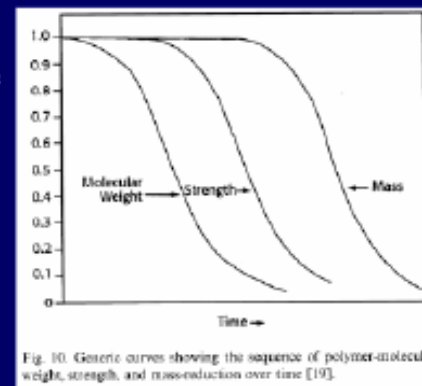
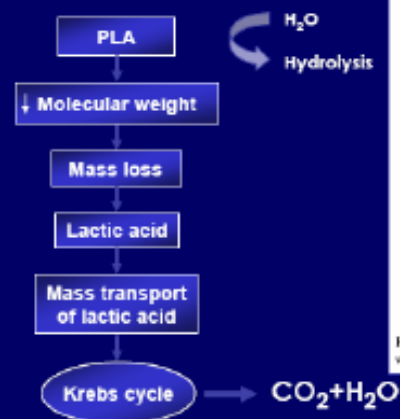
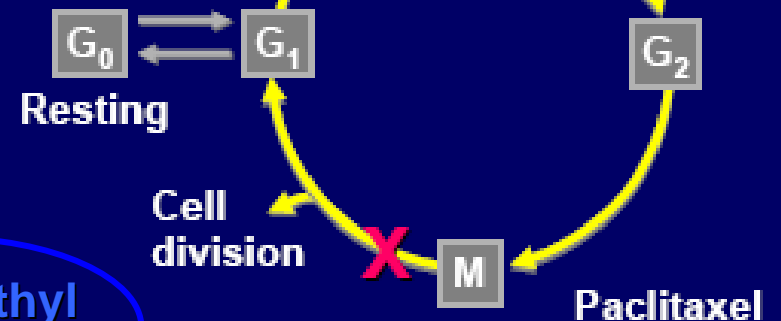


Fig. 10. Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [19].

Biolimus A9 and Biodegradable Polymer Four DES Platforms

Company	Stent Platform (s) Primer Coating	Drug / Polymer	Delivery System
BIOSENSORS	BioMatrix® DES 316L Stainless Steel Parylene C	Biolimus A9: PLA 1:1 15.6 µg / mm Abluminal	TIGER Delivery System Rapid Exchange
DEVAX	Axxess™ Plus Nitinol (SE) Parylene N/C	Biolimus A9: PLA 1:1 22 µg / mm Abluminal	Covered Sheath Rapid Exchange
TERUMO	Nobori Stent 316L Stainless Steel Parylene C	Biolimus A9: PLA 1:1 15.6 µg / mm Abluminal	Nobori Delivery System Rapid Exchange
XTENT	Custom NX™ DES Cobalt Chrome Parylene C	Biolimus A9: PLA 1:1 16.7 µg / mm Abluminal	Sheath Protected Adjustable Balloon Lengths

Biolimus A9 Clinical Evaluations

Phase I Drug Safety Studies

Clinical Trial	Study Design	N	Follow-Up	Platform
Phase 1 Single Ascending Dose	Randomized, double blind, placebo control	28	30 days	Biolimus A9 [®]
Phase 1 Multiple Ascending Dose	Randomized, double blind, placebo control	19	30 days	Biolimus A9 [®]

DES Platform PK Studies

Biosensors STEALTH PK	Single Arm Registry	27	12 mos	BioMatrix [®]
Terumo NOBORI PK	Single Arm Registry	20	12mos	Nobori [™]

Specific pre-clinical evaluations &
Independent PK studies for each platform
(n=94 pts)

DES Platform Clinical Evaluations

DES Platform FIM and Feasibility Studies				
Clinical Trial	Study Design	N	Follow-Up	Platform
Biosensors STEALTH FIM	RCT vs. Bare Metal S-Stent	120	1 -5 years	BioMatrix®
Devax AXXESS PLUS	Prospective Registry	139	1 year	AXXESS
Devax AXXENT	Prospective Registry	33	1-5 years	AXXENT
Xtent CUSTOM I	Prospective registry	30	1-5 years	Custom NX
Xtent CUSTOM II	Prospective registry	100	1-5 years	Custom NX
Xtent CUSTOM III	Prospective Registry	90	1-5 years	Custom NX

**FIM and Feasibility Safety Studies
(n=472 pts)**

Not available for sale in the United States

DES Platform Clinical Evaluations

Pivotal Studies				
Company /Clinical Trial	Study Design / Sample Size	N	Follow-Up	Platform
Biosensors STEALTH II	Randomized, Single Blind, DES Control (Taxus)	1, 600	1-5 years	BioMatrix®
Biosensors LEADERS	Randomized, Single Blind, DES Control (Cypher Select)	1,700	1-5 years	BioMatrix®
Devax DIVERGE	Prospective Registry	700	1-5 years	Axxess
Terumo NOBORI 1 1st Ph	Randomized, Single Blind DES Control (Taxus Express)	120	1-5 years	Nobori™
Terumo NOBORI 1 2nd Ph	Randomized, Single Blind DES Control (Taxus Liberte)	240	1-5 years	Nobori™
Terumo NOBORI CORE	Prospective Registry (Cypher historical control)	100	1-2 years	Nobori™
Xtent CUSTOM IV & V	Pivotal RCTs	3000	1-5 years	Custom NX

**Pivotal studies supporting approval for intended use
(n ≈ 5,500pts)**

Each trial program intended to stand alone.

DES Platform Clinical Evaluations

Registries and Post Market Studies

Biosensors BEACON	Single Arm Registry	292	1-5 years	BioMatrix®
Biosensors Continuous ACCESS	Single Arm Registry	>1000	1-5 years	BioMatrix®
Devax Continuous AXXESS	Single Arm Registry	1000	1-5 years	AXXESS
Terumo NOBORI 2	Single Arm Registry	1600	1-5 years	Nobori™
Xtent CUSTOM Registry	Single Arm Registry	> 4000	1-5 years	Custom NX

Additional Registries and Post Market Studies
(n≈7,500 pts)

Combined Safety Analysis for Biolimus A9 Stents

- Biolimus A9 and the biodegradable polymer are the common thread for all these studies
- Combining data across these trials might increase power to detect rare adverse events

Combined Safety Analysis for Biolimus A9 Stents

Objectives

Secondary safety analysis to combine data from individual studies to yield a more precise estimate of safety of the use of Biolimus A9 and the biodegradable polymer

- Exploratory analysis of safety not intended to replace requirements for each individual stent platform
- Comparison of independent effects due to drug-polymer combination vs. patient and trial level covariates

Combined Safety Analysis for Biolimus A9 Stents

Methods

- Pooling or exchangeability not possible because of differences in platforms and patients
- Minimum requirements to combine data:
 - Common definitions
 - Common methods of data acquisition and adjudication
 - Presence of common controls (bare metal, DES)
 - Adjustment for confounders at patient and trial level

Combined Safety Analysis for Biolimus A9 Stents

Methods

- Mega-analysis of data from the randomized trials and registries of stenting of *de novo* coronary artery stenoses to estimate the safety of each device and compare the Biolimus stents to the control stents
 - Hierarchical regression model (using survival methods to account for varying follow-up duration)
 - Adjustment for confounders on a patient and trial level

Combined Safety Analysis for Biolimus A9 Stents

Methods

- A hierarchical survival analysis will be used to link the predictor variables to the expected value of the (binary-valued) safety outcomes for each patient in each trial.
- Either frequentist or Bayesian methods could be applied.

Combined Safety Analysis for Biolimus A9 Stents

Adjustment for Confounders Patient level

- Total stent length
- Reference vessel diameter (RVD)
- Multivessel treatment
- Diabetes
- Ejection Fraction
- Number of diseased vessels
- Acute coronary syndrome presentation

Combined Safety Analysis for Biolimus A9 Stents

Adjustment for Confounders

Trial Level

- U.S. versus outside U.S. trials
- Presence of blinding of patients and evaluators to treatment assignment
- Stent platform
- Bifurcation lesion treatment
- Left main coronary artery treatment
- Interactions between platform and the drug-polymer combination would be considered.

Combined Safety Analysis for Biolimus A9 Stents

Registry versus RCT

- Propensity score methods to match registry patients to the randomized patients
- Registry group patients for whom there are no randomized patients with similar characteristics would be excluded to increase robustness to model misspecification
- Sensitivity analysis to exclude all registry patients

Combined Safety Analysis for Biolimus A9 Stents: Anticipated Results

Anticipated results include estimates and confidence intervals for event rates (stent thrombosis) for

- Biolimus stents
- Biolimus platforms
- Patient subsets
- And in comparison to bare metal and drug-eluting controls

Combined Safety Analysis for Biolimus A9 Stents: Conclusions

- A pre-specified combined safety analysis could be performed at varying time points with varying durations of follow-up and yield greater precision regarding safety
- This analysis could also identify predictors of stent thrombosis with greater certainty
- If a consistent effect is attributable to this drug-polymer combination across platforms, a combined mega-analysis would increase the power to detect this effect