

# La Importancia de la Innovación en Medicina Cardiovascular

- Congreso CACI 2019
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- *Professor in Cardiology*
- *Tel-Aviv University*
- *Interventional Cardiologist*
- *Past Director: Cath Lab Shamir Medical Center*
- *Currently: Rabin Medical Center, Beilinson*

# Disclosures

- ICI Israel
- 

Faculty

Representative at ICI CACI

# ICI meeting 2019

December 8-10, 2019 | Tel-Aviv, Israel

[www.icimeeting.com](http://www.icimeeting.com)





# CACI - Colegio Argentino de Cardioangiólogos Intervencionistas



October 11 at 2:07 AM · 🌐

ICI - Innovations in Cardiovascular Interventions Meeting





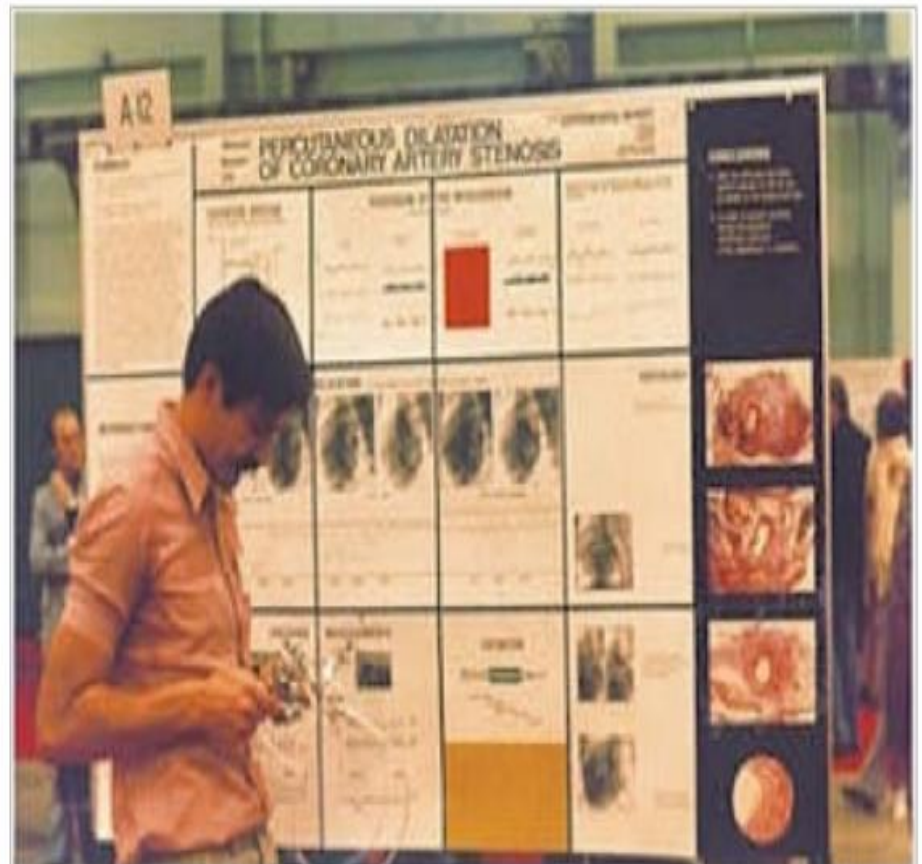
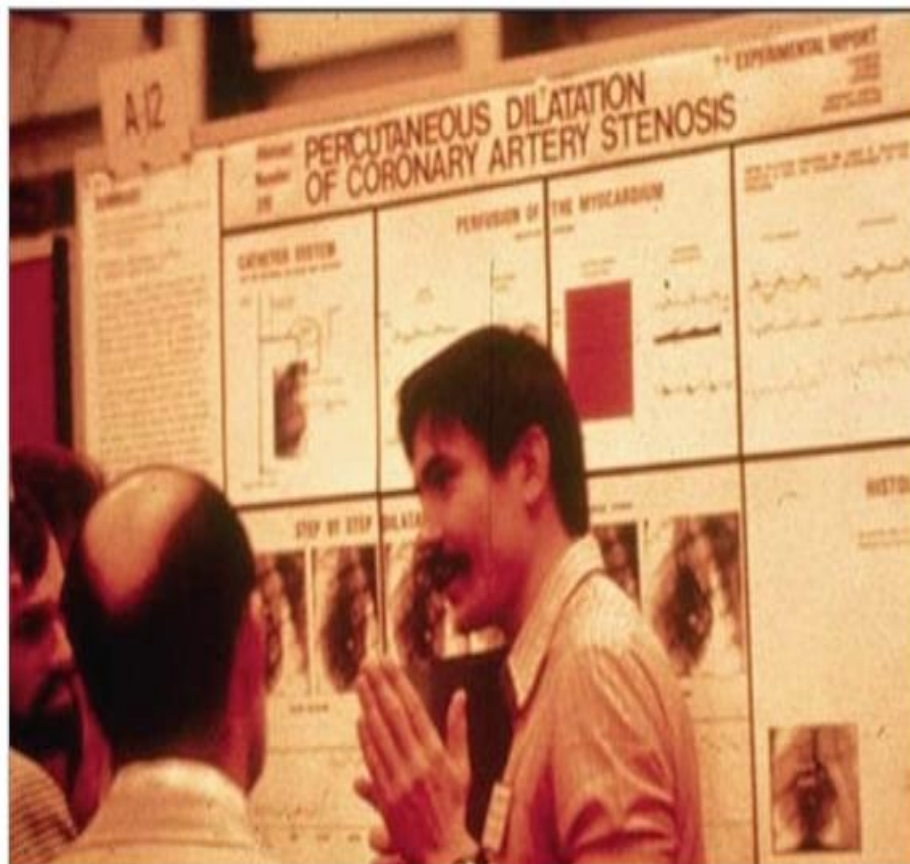


# The Medical Center Innovation Lab

- Our Goal: To Enable Solutions for Unmet Clinical Needs Within The Hospital

*AHA 1976*

*The poster that created a  
revolution!*



# FIRST PATIENT TO UNDERGO PTCA

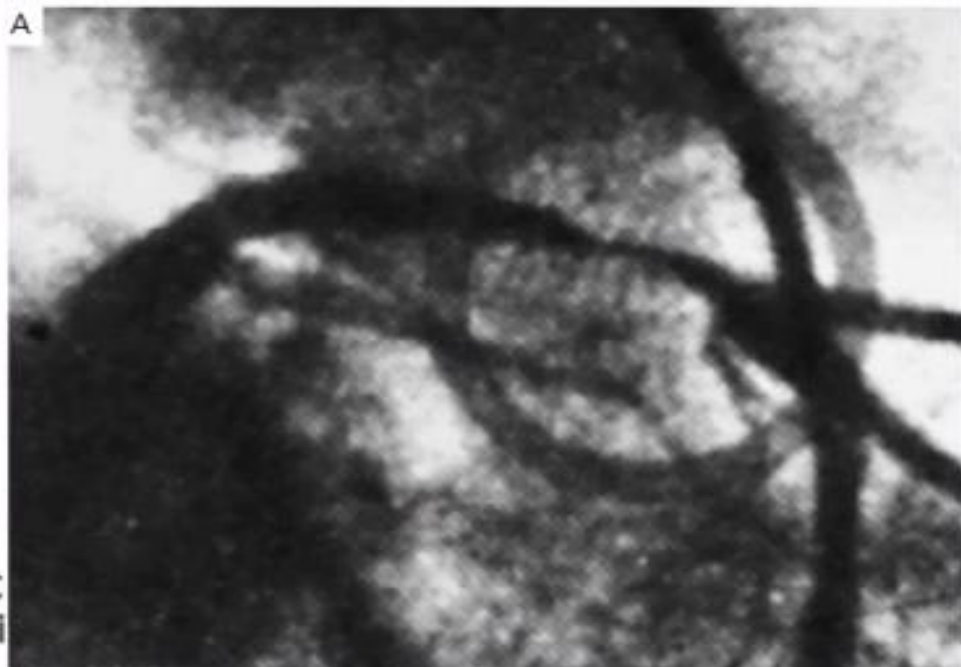
## 23 YEAR FOLLOW-UP

Meier B. *N Engl J Med* 2001;344:144

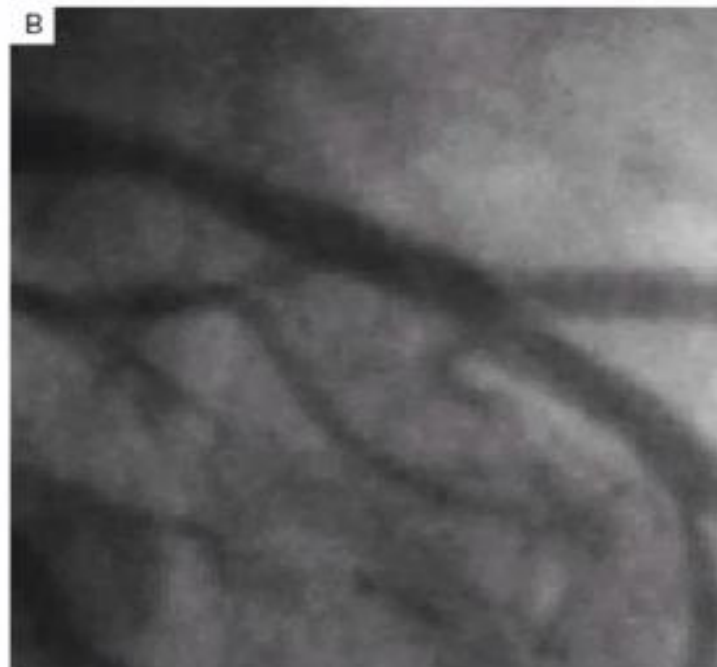
### *First Percutaneous Transluminal Coronary Angioplasty*

- 16 September 1977, Zurich, by Andreas Grüntzig
- 38 year old patient with isolated proximal LAD lesion

1977

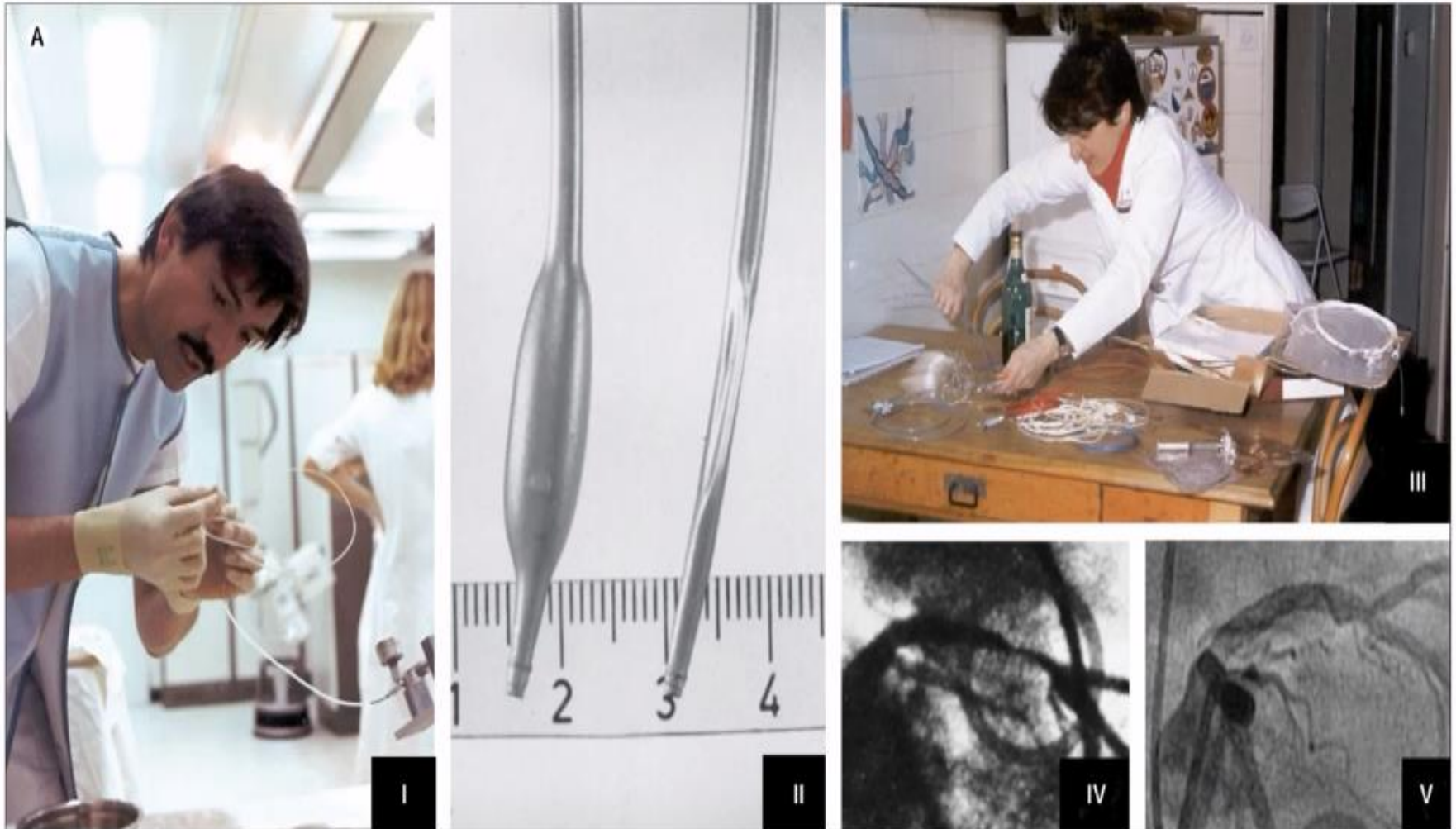


2000





# The Early Years of Discovery and Innovation





# Julio Palmaz

Doctor



Julio Palmaz is a doctor of vascular radiology at University of Texas Health Science Center at San Antonio. He studied at the National University of La Plata in Argentina, earning his medical degree in 1971. [Wikipedia](#)

**Born:** December 13, 1945 (age 73 years), [La Plata, Argentina](#)

**Nationality:** Argentine

**Known for:** Co-inventor of the Palmaz-Schatz Stent

**Education:** [University of California, Davis](#), [National University of La Plata](#)

# The Biodesign Innovation Model in CV Medicine – from Concept to Implementation

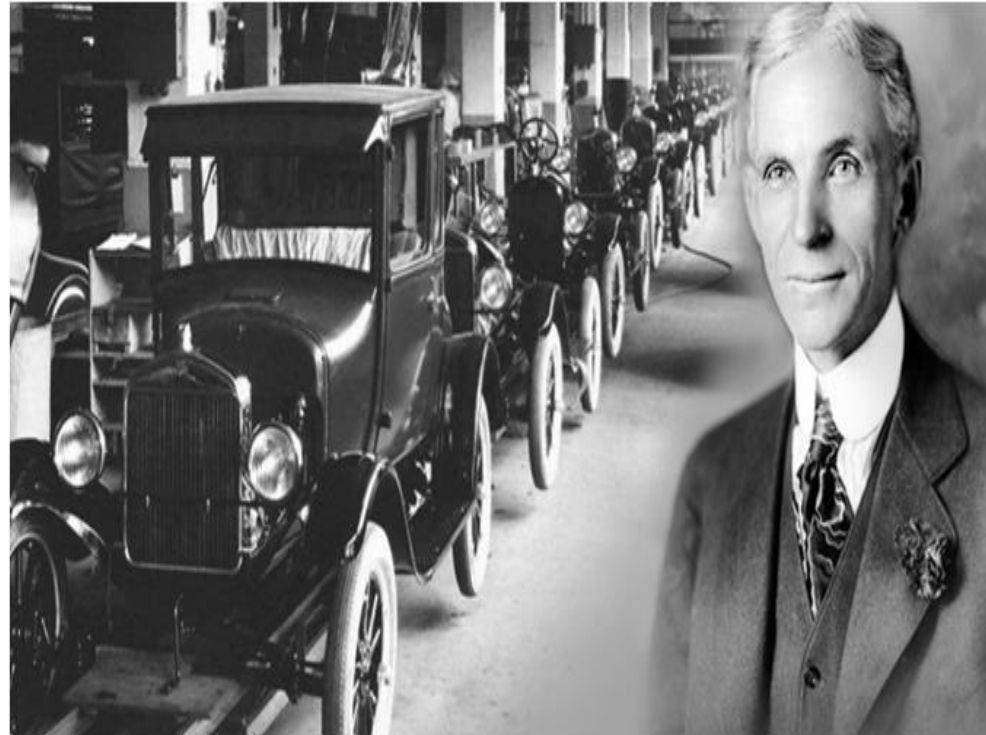
How do we innovate?

# The Moment of Epiphany





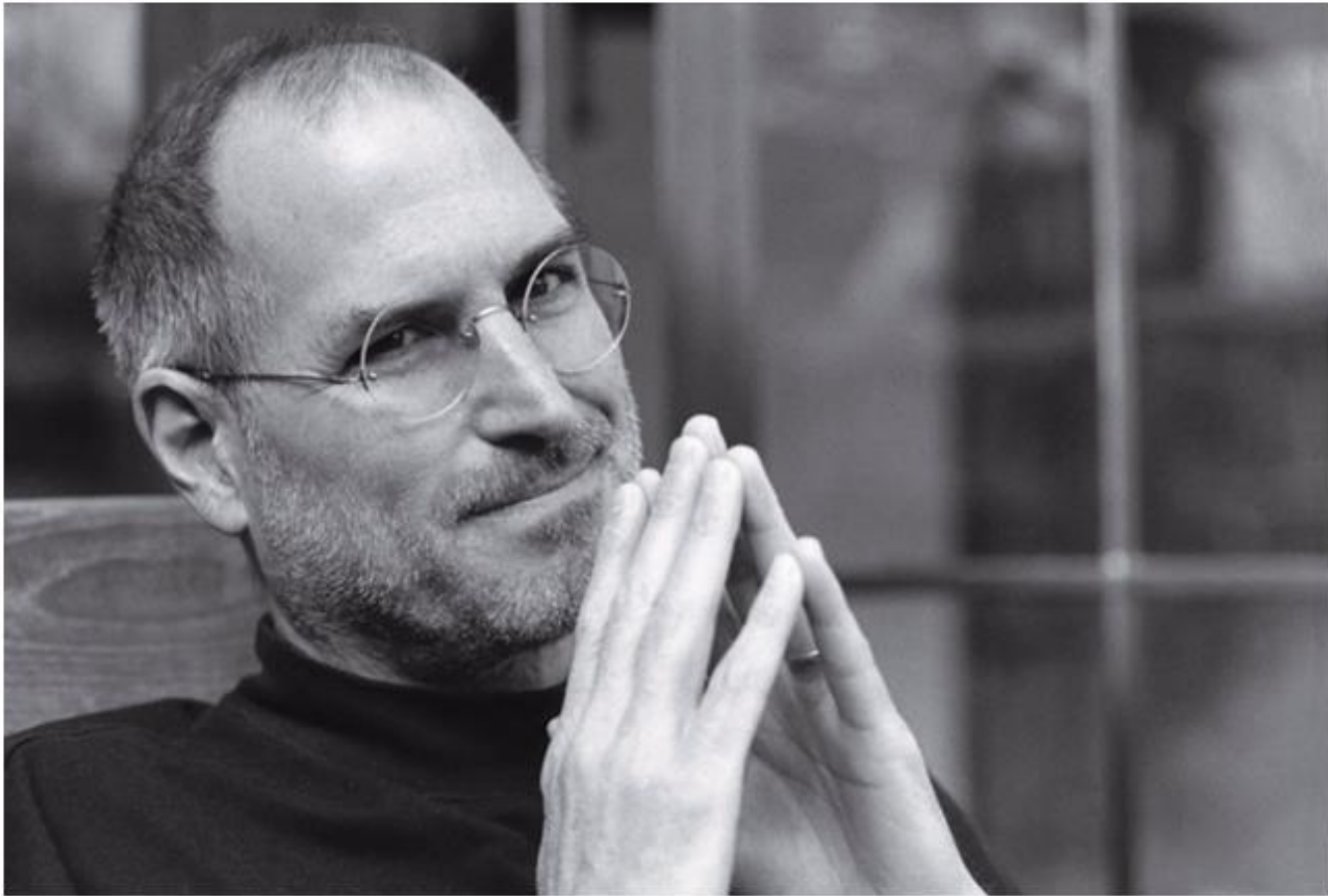
# Don't ask the customer



“If I asked customers what they wanted they'd have said faster horses.”

*Henry Ford*

# Don't ask the customer

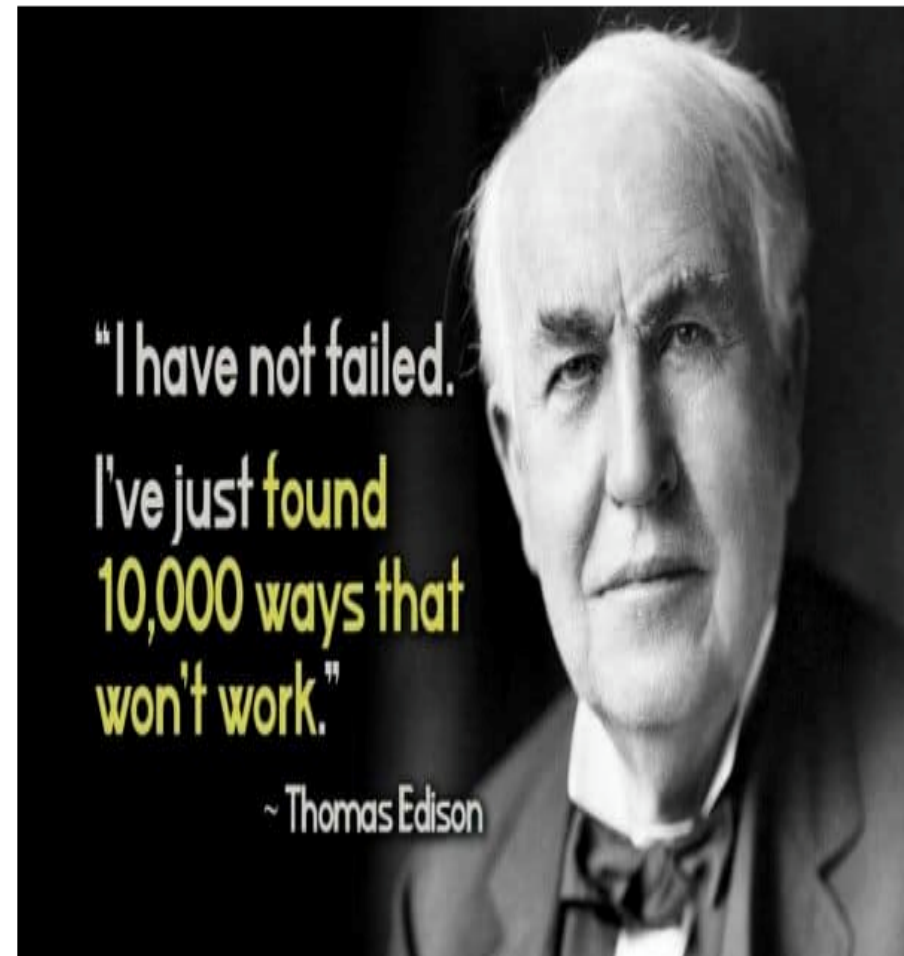


“It isn't the customer's job to know what they want.”

*Steve Jobs*

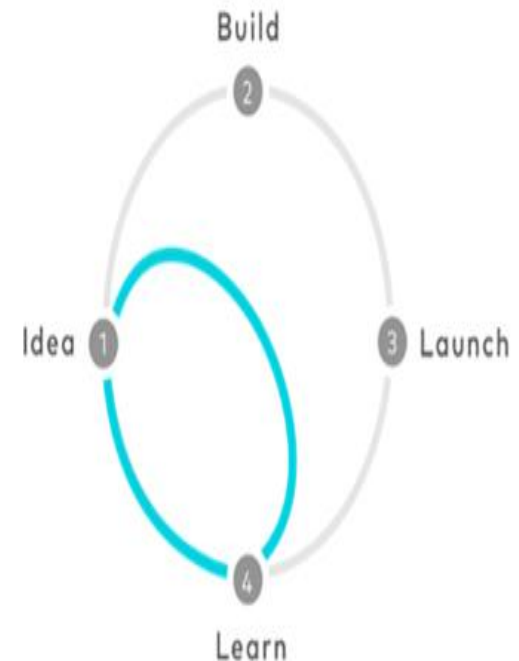
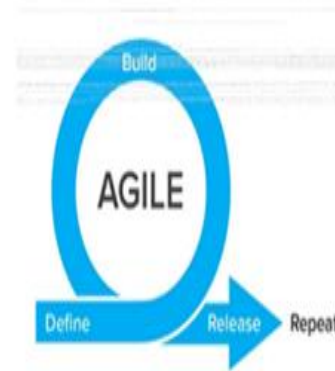
# Needs-Based Innovation

However, although talent, creativity and mostly- grit and perseverance, are necessary, a structured method to the development of innovation is possible.



# Established Methods

- Design Sprint (Google Ventures)
- The Waterfall model
- Human-Centered design (IDEO)
- Design Thinking
- Lean Startup methodology
- Agile

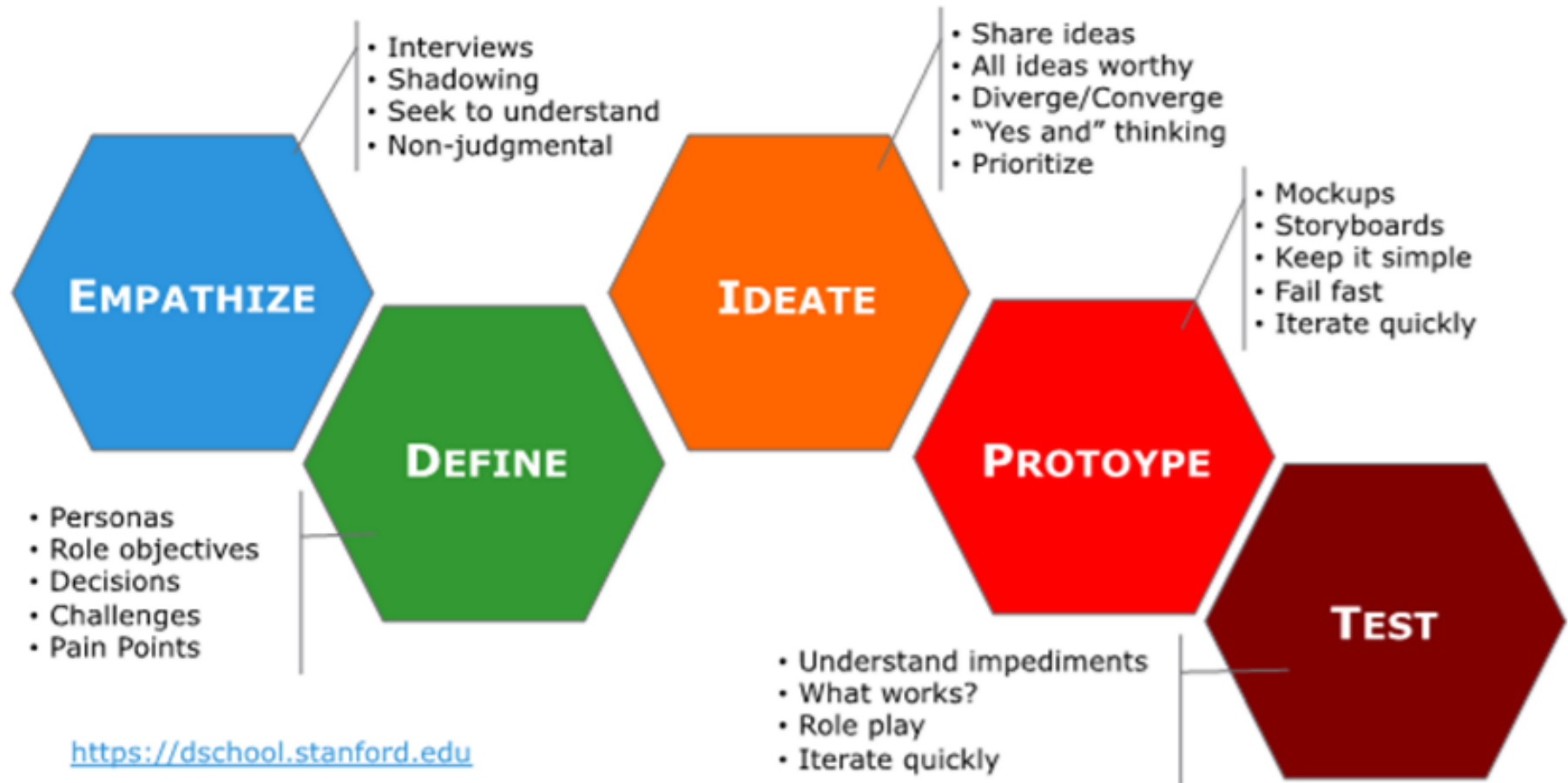


# IDEO



# Design Thinking

## Stanford d.school Design Thinking Process



# Empathy

## TASKS

What tasks are users trying to complete? What questions do they need answered?

## FEELINGS

How is the user feeling about the experience? What really matters to them?



**NAME**

## INFLUENCES

What people, things or places may influence how the user acts?

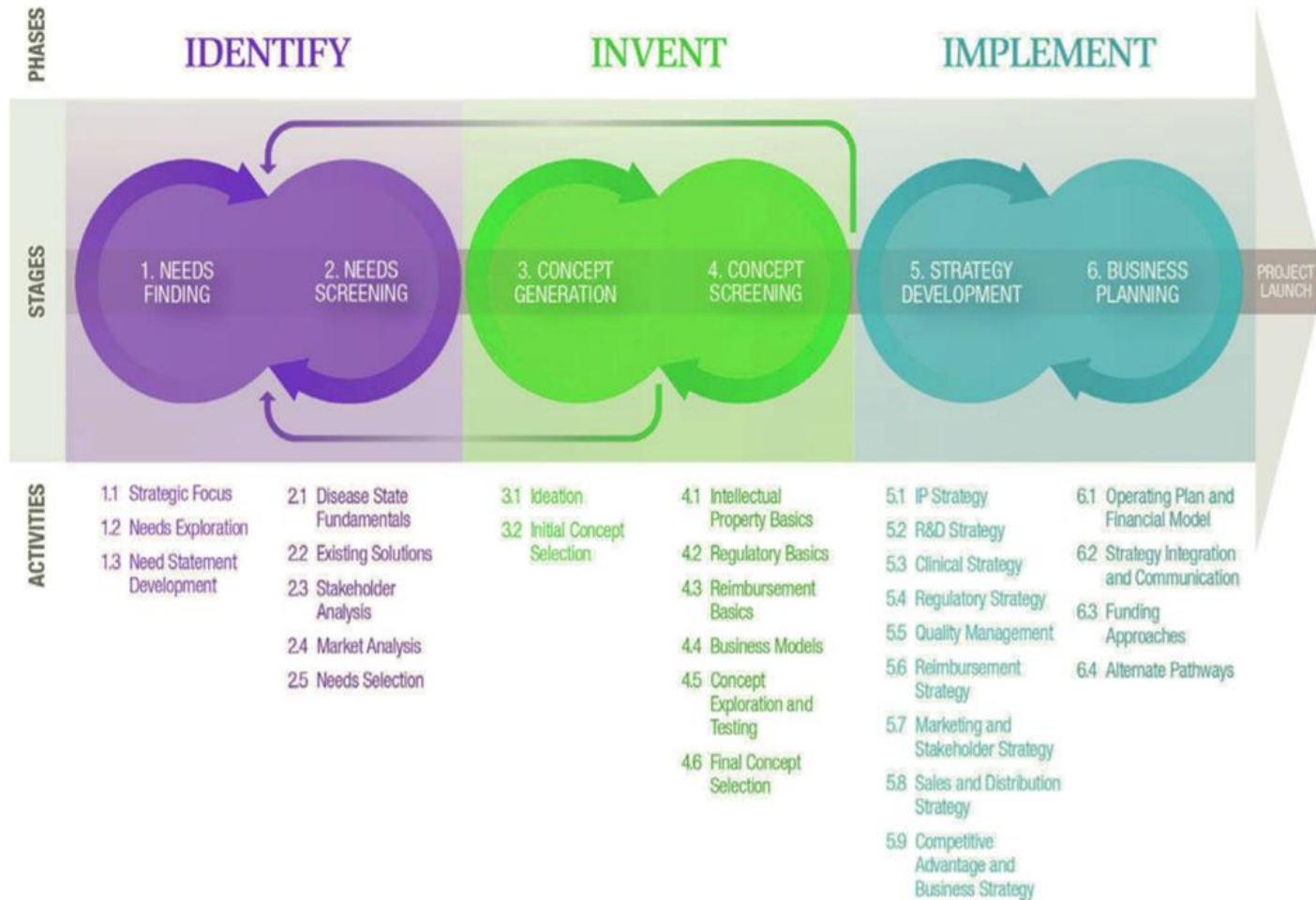
## PAIN POINTS

What pain points might the user be experiencing that they hope to overcome?

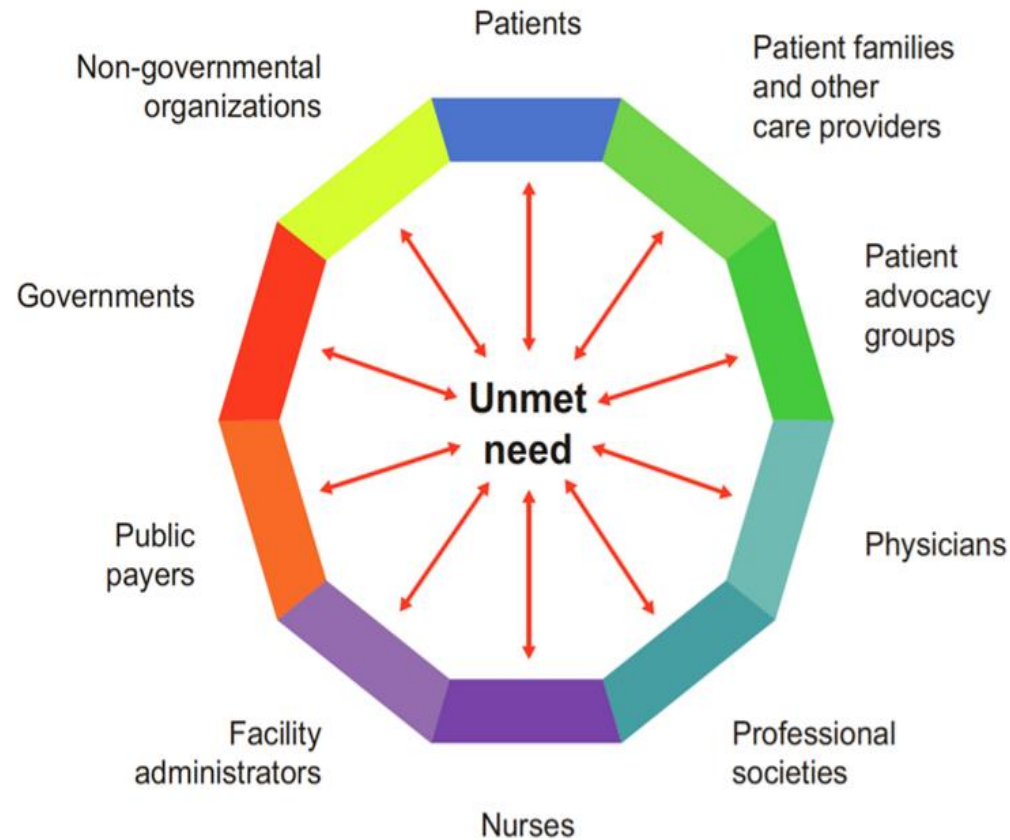
## OVERALL GOAL

What is the users ultimate goal? What are they trying to achieve?

# The Stanford Biodesign



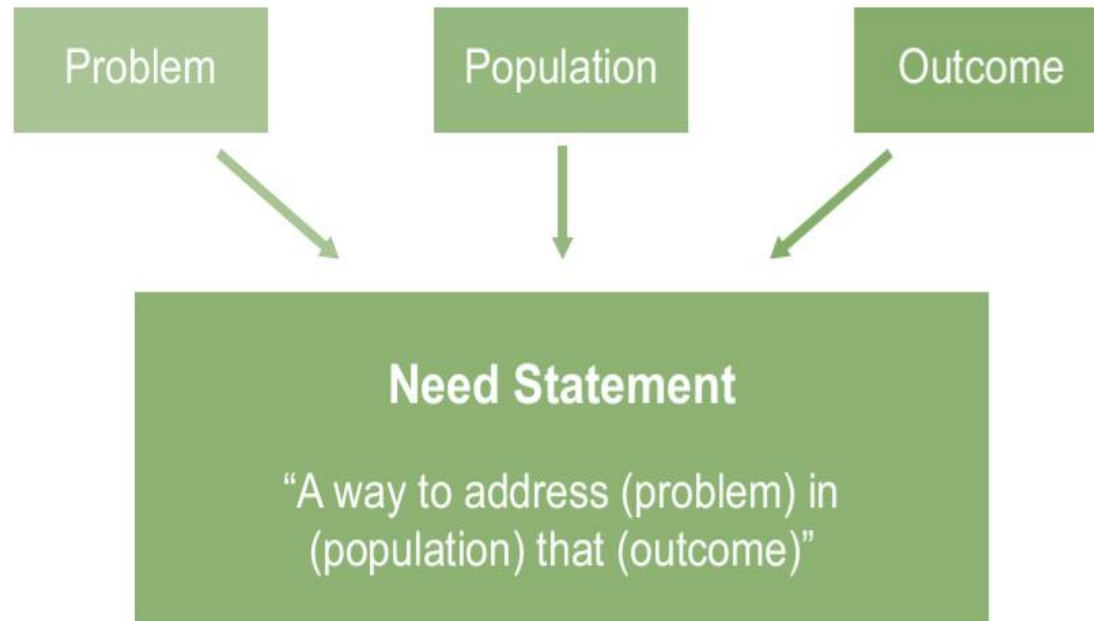
# The Stanford Biodesign



Yock et al. BIODESIGN The Process of Innovating Medical Technologies. 2nd EDITION



# Need Characterization



# Needs Criteria

A list of requirements to answer the unmet need

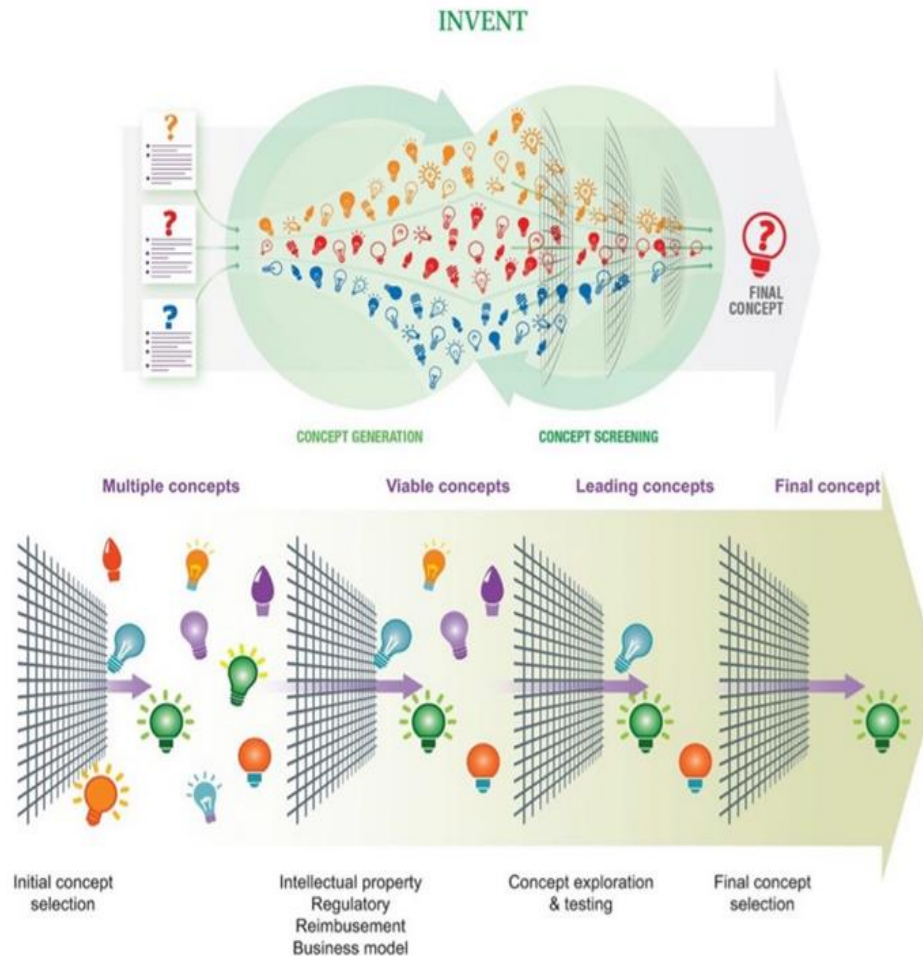
## **“Must have” criteria**

- Function
- Safety
- Regulatory

## **“Nice to have” criteria**

- Features
- Design
- Cost

# "Fail Early, Fail Often"

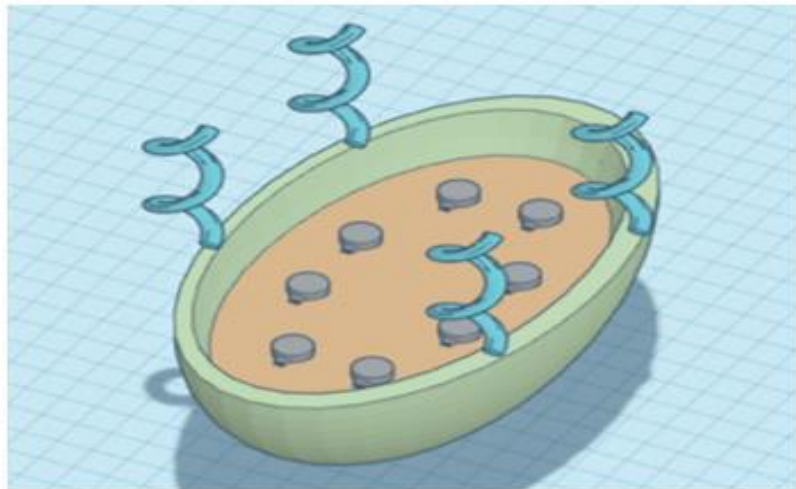
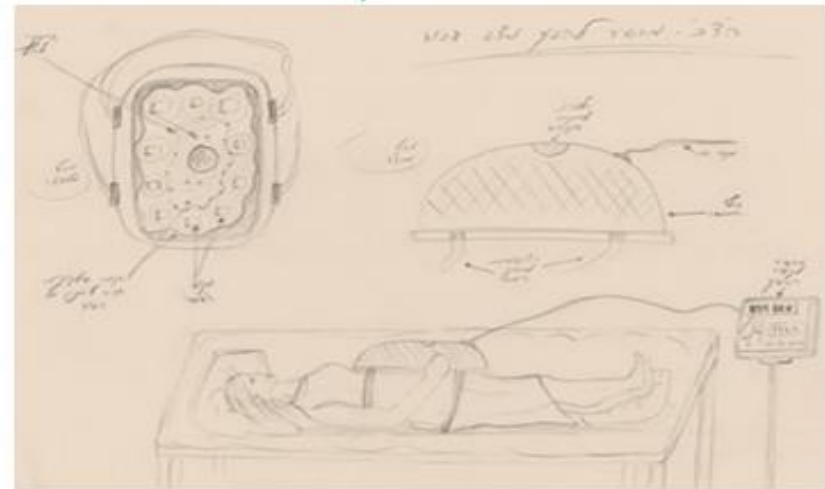
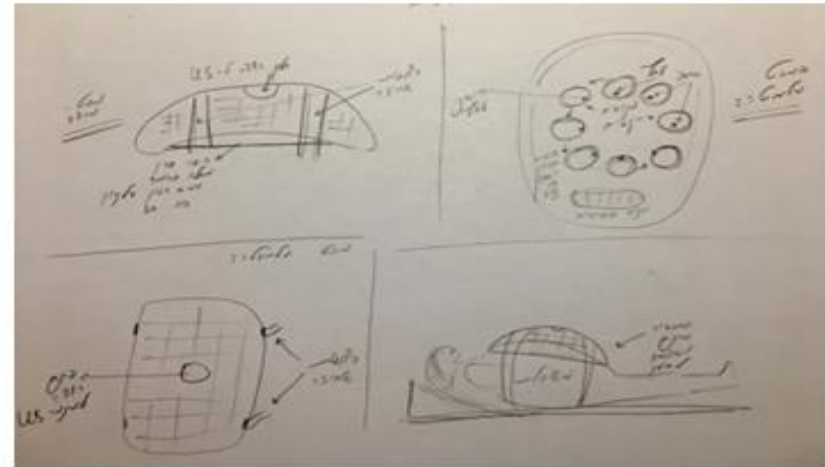
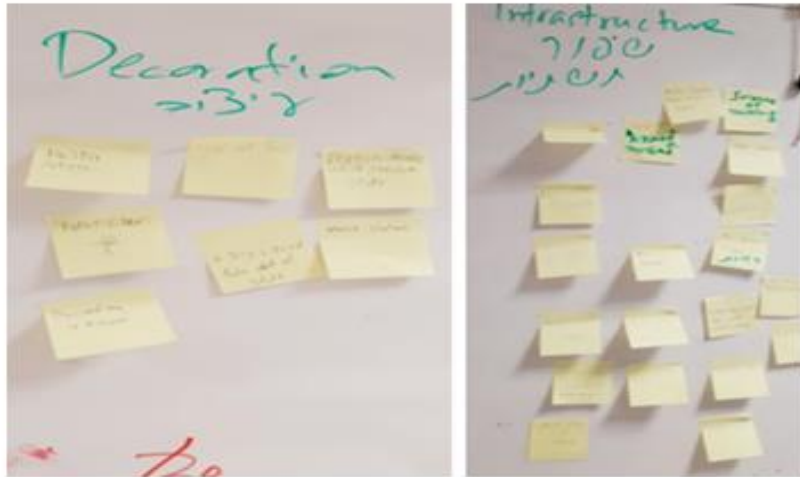


# Brainstorming for solutions

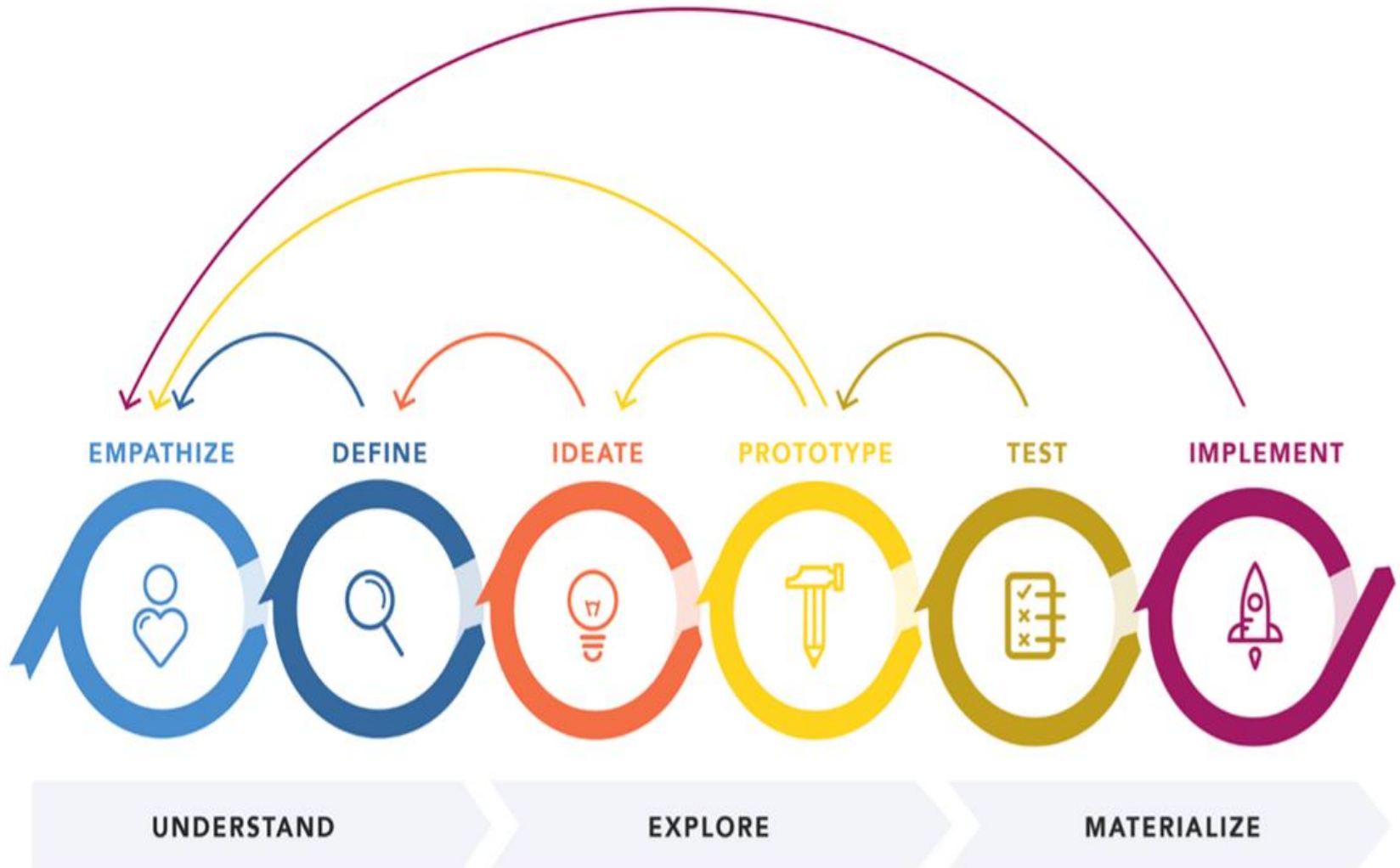




# From Ideas to Design



# Reiteration



# The RMC Innovation Lab Process







132 Needs Risen

28 After Early Filters

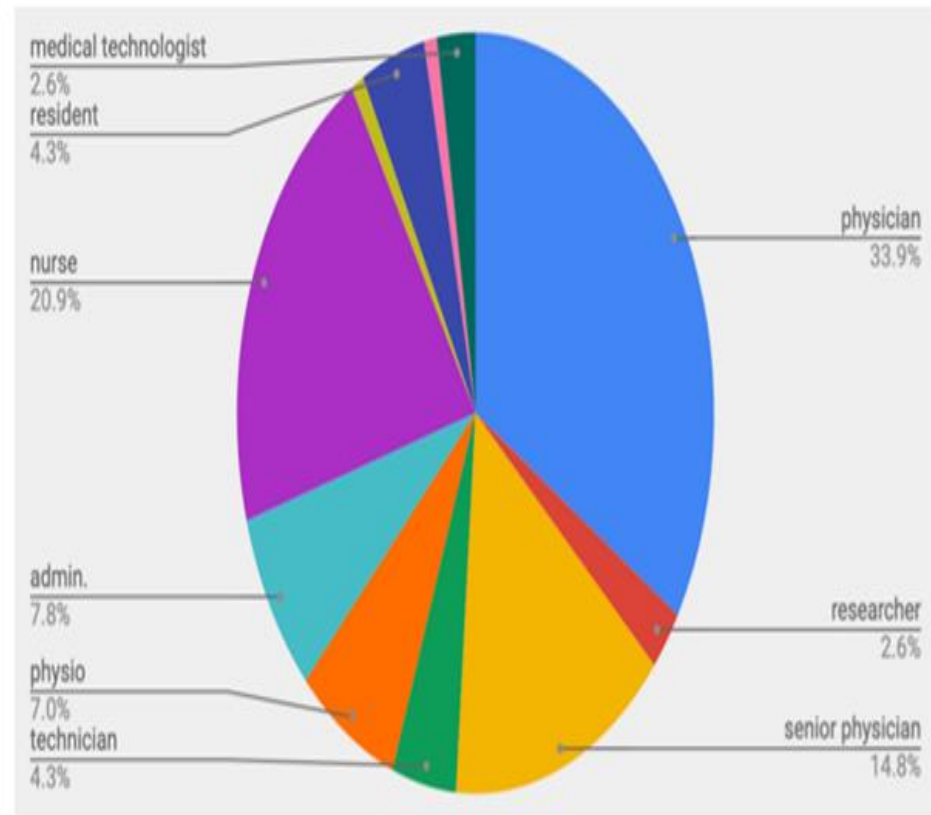
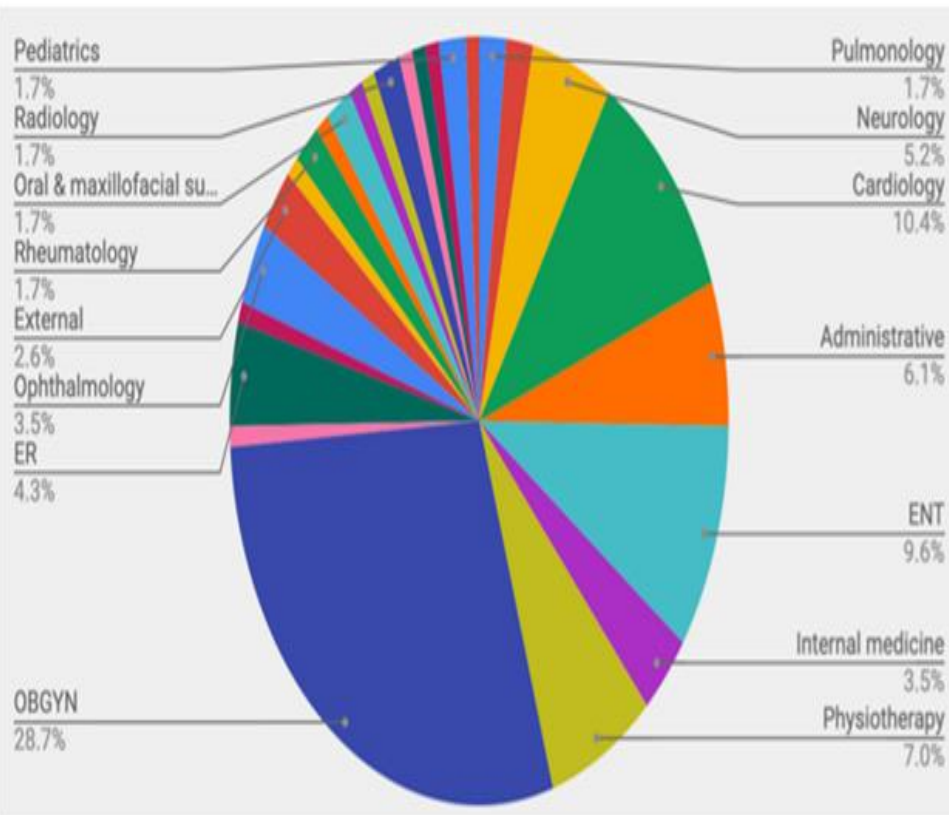
16 After "Deep Dive"

8 Ongoing Leading Projects



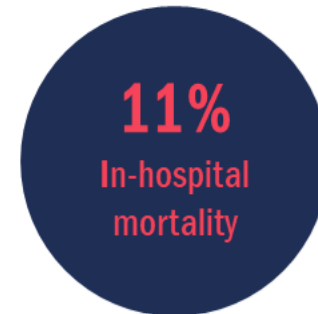
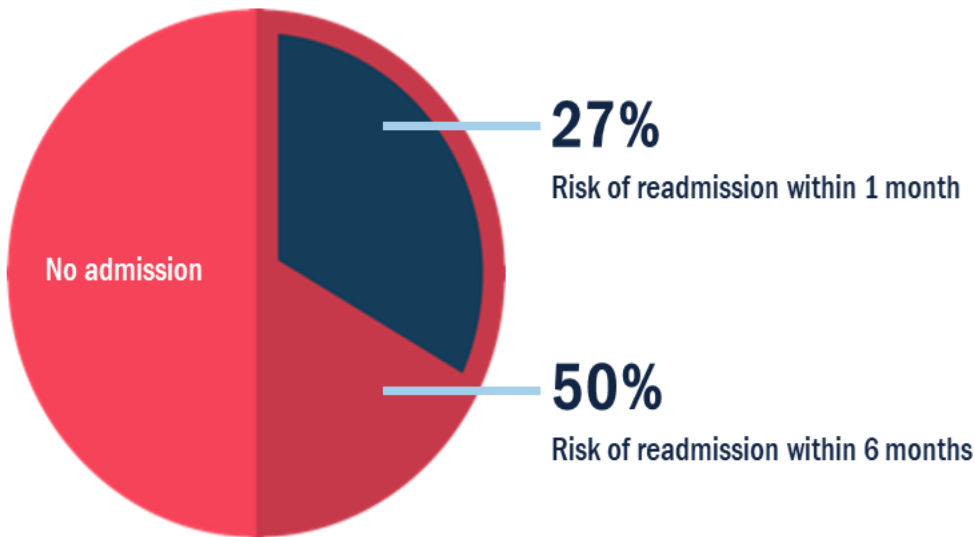


# All Sectors and Disciplines



# Heart Failure Exacerbations- a Gigantic Unmet Need

## Following an admission



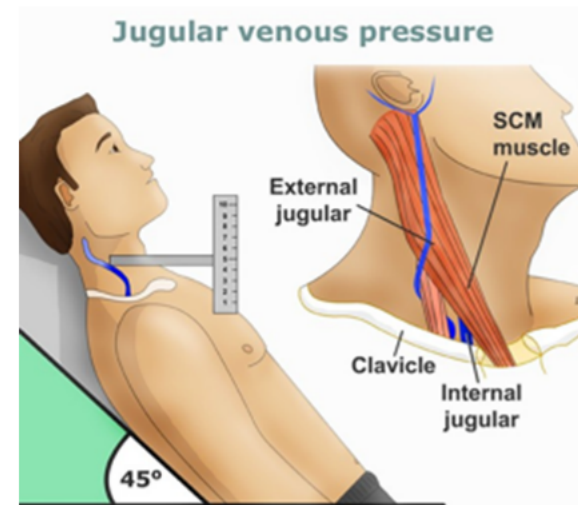
1 Circulation. 2016;133:447-54

# Can We Predict Heart Failure Exacerbations?

Non-invasive methods have thus far failed to accurately predict the development of acute HF exacerbations<sup>1,2</sup>.

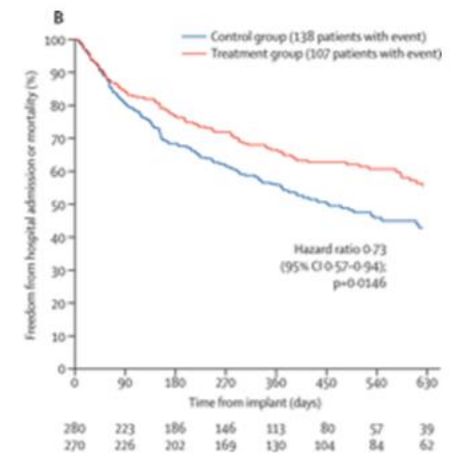
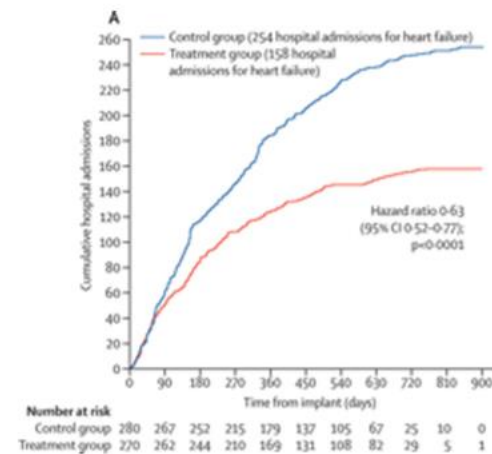
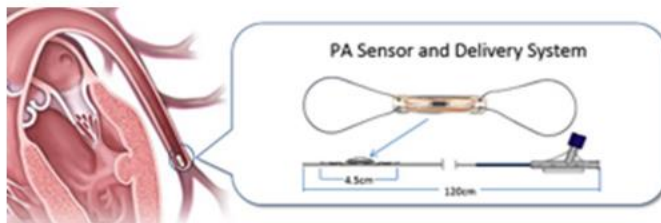
1 Eur J Heart Fail 2005; 7:953-95

2 Curr Heart Fail Rep 2009; 6:287-292.



# Invasive HF Monitoring

- Invasive pressure-guided therapy has been shown to improve outcomes.
- Thus far, only right-sided pressure sensors have shown clinical efficacy and safety.



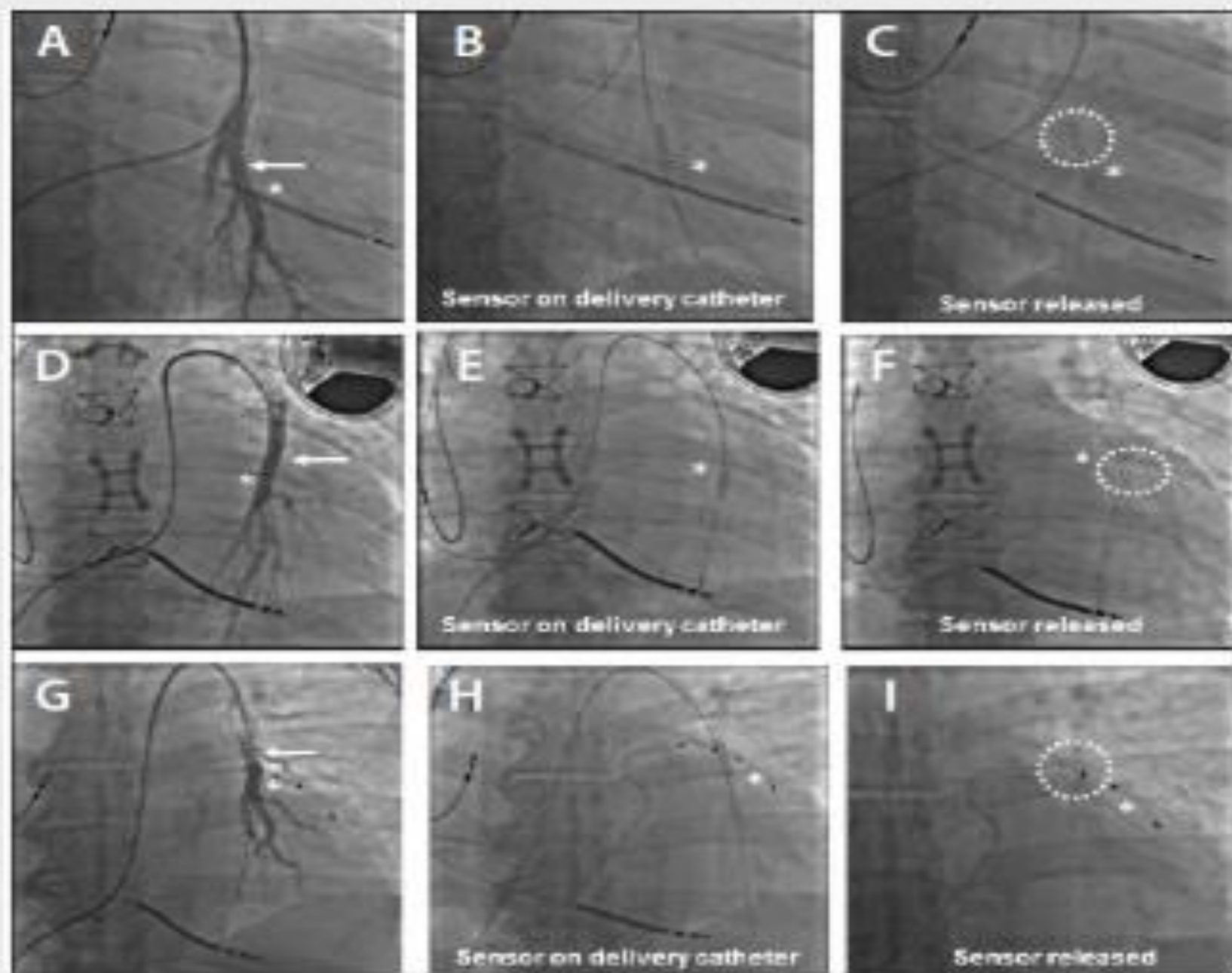
Abraham WT, et al. Lancet. 2011 Feb 19;377(9766):658-66.



**TABLE 1. PROCEDURAL STEPS FOR THE CARDIOMEMS PULMONARY ARTERY SENSOR IMPLANT**

Steps	Components	Comments
Venous access	Femoral access with an 8-F sheath, upsized to a 12-F sheath	Internal jugular access should be considered for conditions that render placement of the catheter via the femoral approach difficult
Right heart catheterization	Measurement of right atrial, right ventricular, pulmonary artery, and pulmonary capillary wedge pressures; measurement of cardiac output by Fick principle or thermodilution method	Knowledge of cardiac filling pressures and cardiac output is essential for management of patients with NYHA class III symptoms
Engagement of left pulmonary artery	Ideal sensor placement is within a branch of the left pulmonary artery	The catheter can often be steered to the left pulmonary artery; use of an angled catheter or a guidewire may be required
Identification of appropriate sensor implant site	Ideal vessel diameter is 7–11 mm	Selective angiography is required to identify an appropriate-sized pulmonary artery branch
Placement of a 0.018-inch guidewire to the distal vessel location	The system uses a 0.018-inch over-the-wire delivery system	Various 0.018-inch guidewires can be used, including Hi-Torque Steelcore (Abbott Vascular), Platinum Plus (Boston Scientific Corporation), and CardioMEMS
Sensor preparation	The over-the-wire port of the delivery catheter is flushed with heparinized saline; the sensor and distal portion of the delivery catheter are agitated in heparinized saline	–
Advancement to the desired implant location	Continuous fluoroscopy should be used to view the sensor as it traverses through the right heart and left pulmonary artery	Use of fluoroscopic guidance ensures safe passage of the sensor to the implant location
Deployment	Counter-clockwise rotation of the hub, followed by withdrawal of the tether release system	–
Calibration	A hospital unit antenna is placed under the patient's back to calibrate the system	Use of fluoroscopy can optimize antenna location
Documentation of sensor location	Cine studies should be done to document final sensor location	–
Sheath removal	Options for hemostasis include manual or suture based	Figure-of-eight suture is an effective and safe method for hemostasis

Abbreviation: NYHA, New York Heart Association.



## Medications

Drug	Class	Adjustment	Date	Dose	Frequency
Warfarin (Coumadin)	Anticoagulant	Start	04-27-2017	3 mg 0.0 Tablet	Use as Directed
Carvedilol (Coreg)	Beta-Blocker	Start	04-27-2017	25 mg 0.0 Tablet	Use as Directed
Levothyroxine (Synthroid)	Hormone Replace	Start	04-27-2017	0.125 mg 0.0 Tablet	Use as Directed
Atorvastatin (Lipitor)		Start	04-27-2017	100 mg 0.0 Tablet	Use as Directed
Bumetanide (Bumex)	Loop Diuretic	Start	04-27-2017	0.5 mg 0.0 Tablet	Use as Directed
Amlodipine (Lipitor)	Statin	Start	04-27-2017	40 mg 0.0 Tablet	Use as Directed
Aspirin	Antiplatelet	Start	04-27-2017	81 mg 0.0 Tablet	Use as Directed
Benzocaine (Lidocaine)	ACE-Inhibitor	Start	04-27-2017	10 mg 0.0 Tablet	Use as Directed

## Right Heart Cath Implant Values

### Right Heart Cath Implant Values

Please enter values obtained during PA Sensor implant procedure.

RA Mean:  mmHg

PA Mean:  mmHg

RV Systolic:  mmHg

PA Systolic:  mmHg

RV Diastolic:  mmHg

PA Diastolic:  mmHg

PCWP:  mmHg

Cardiac Output:  L/min

Figure 5. Current medications and RHC implant values are entered into a secure website.

# CardioMEMS

- Patients must lie in bed.
- No compensation for drift- repeat hemodynamic study.
- Very limited information.
- Right-sided data.
- No option for early alerts.





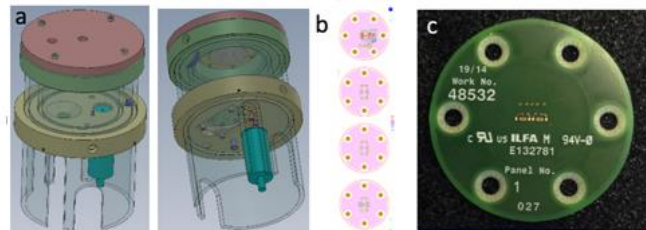
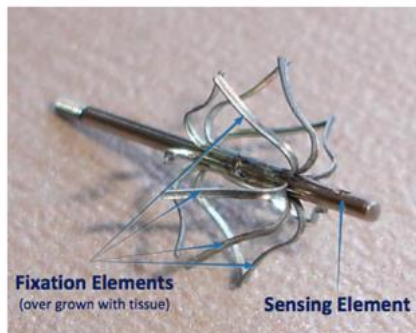
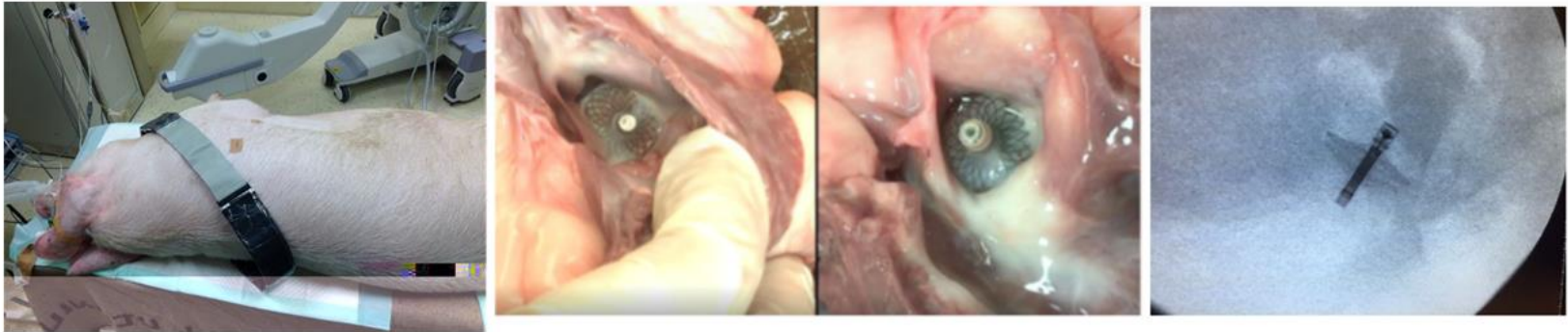
# Needs Criteria

- ✓ Wireless, ambulatory monitoring
- ✓ May be used in every position
- ✓ No calibration needed
- ✓ Left-sided hemodynamics
- ✓ Robust but concise data
- ✓ Safe
- ✓ Not more expensive than competition
- ✓ Personalized data, early alert...?



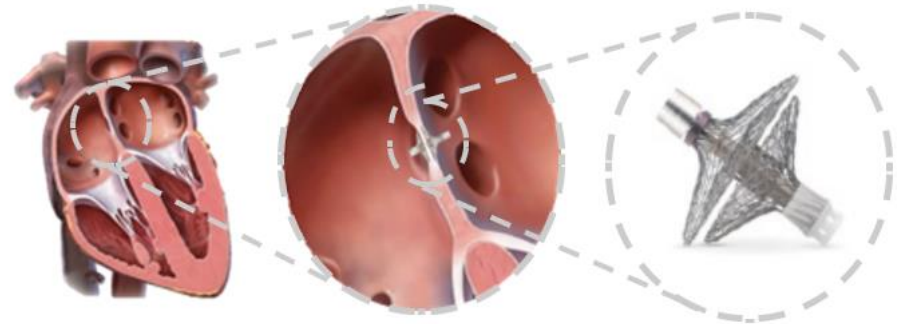


# Prototyping and Concept Selection



# The V-LAP™

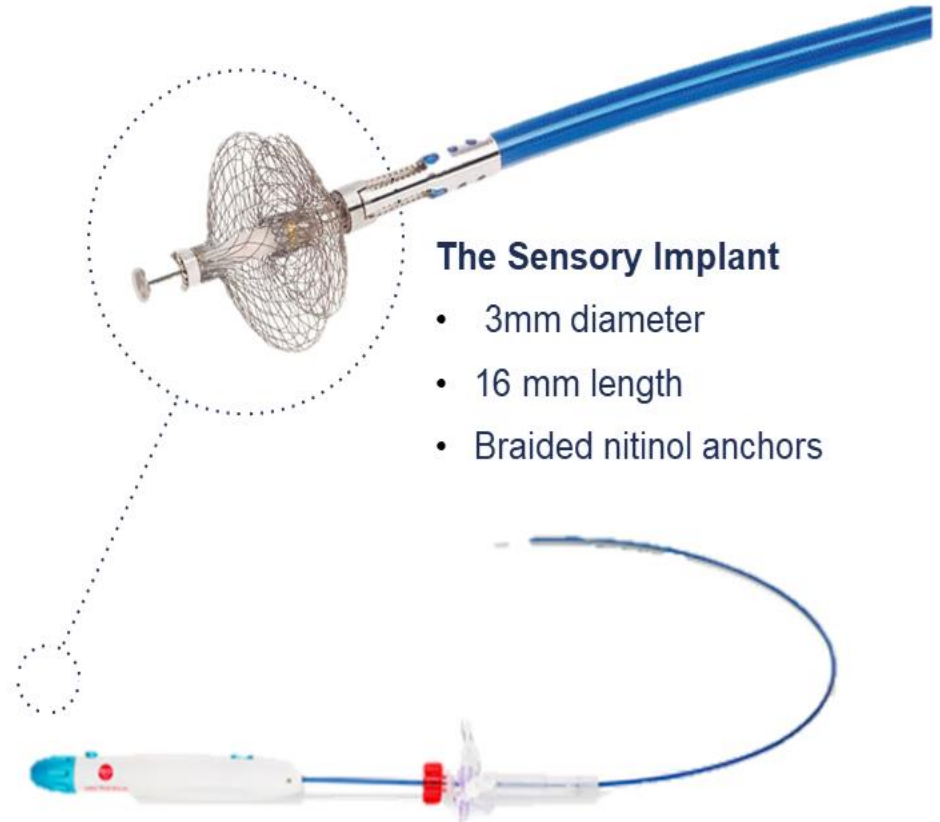
The V-LAP™ is a novel **battery-less** and **wireless** left-sided pressure monitoring system, directly assessing left-atrial pressure (LAP).





# The V-LAP™

- Implanted via a dedicated 12F transfemoral approach.
- Fully digital – ASIC chip.
- Drift compensation.
- Numerous data and early warning options!

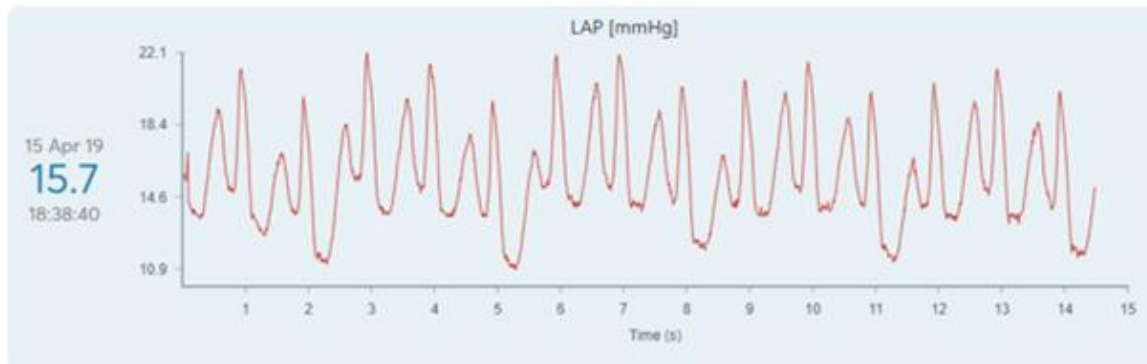


## The Sensory Implant

- 3mm diameter
- 16 mm length
- Braided nitinol anchors

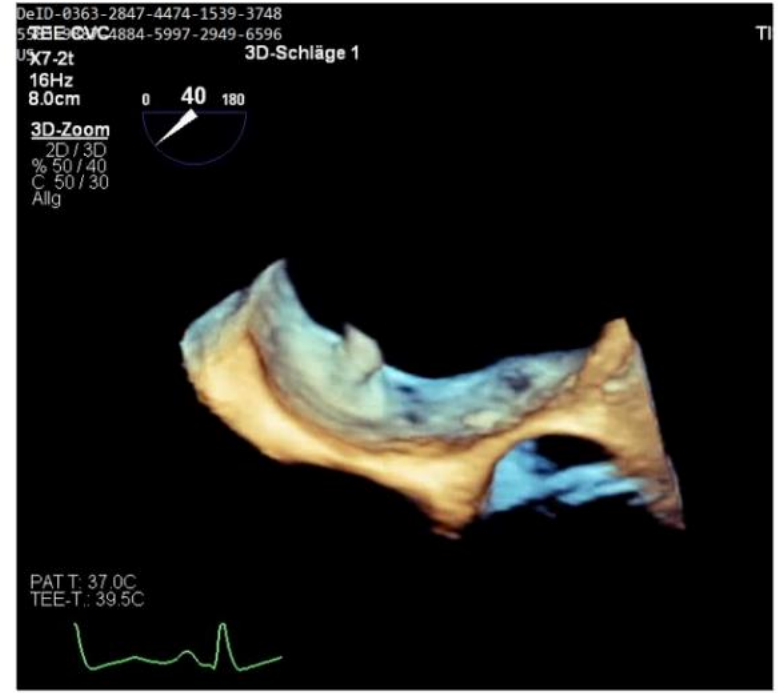
# Personal Ambulatory Hemodynamic Data

- Activation by an external unit remotely powers the implant.
- Measurements are then captured and displayed via a cloud-based system.



# VECTOR-HF Interim Results

Implanted in 8 patients thus far (Germany, Italy and the UK).



Courtesy of H. Sievert, et al. The CardioVascular Center Frankfurt, Germany

# Accurately fulfills to the need criteria

- ✓ Flexible, wireless, digital monitoring
- ✓ Robust, may be used in every position
- ✓ Direct left-sided information
- ✓ Assisted by AI- Early alert system
- ✓ Safe!
- ✓ Cost as required





# Structured Innovation in CV Medicine

- *Harness the clinical experience*
- *Needs-Based innovation method*
- *Focus on empathy and user experience*
- *Work according to objective criteria*
- *Fit with correct partners*
- *Understand that failure is a necessary part of the game...*

# Interventional Pharmacology



Eric J. Topol

TIMI  
TAMI  
GUSTO

Robert M. Califf



Eugene Braunwald

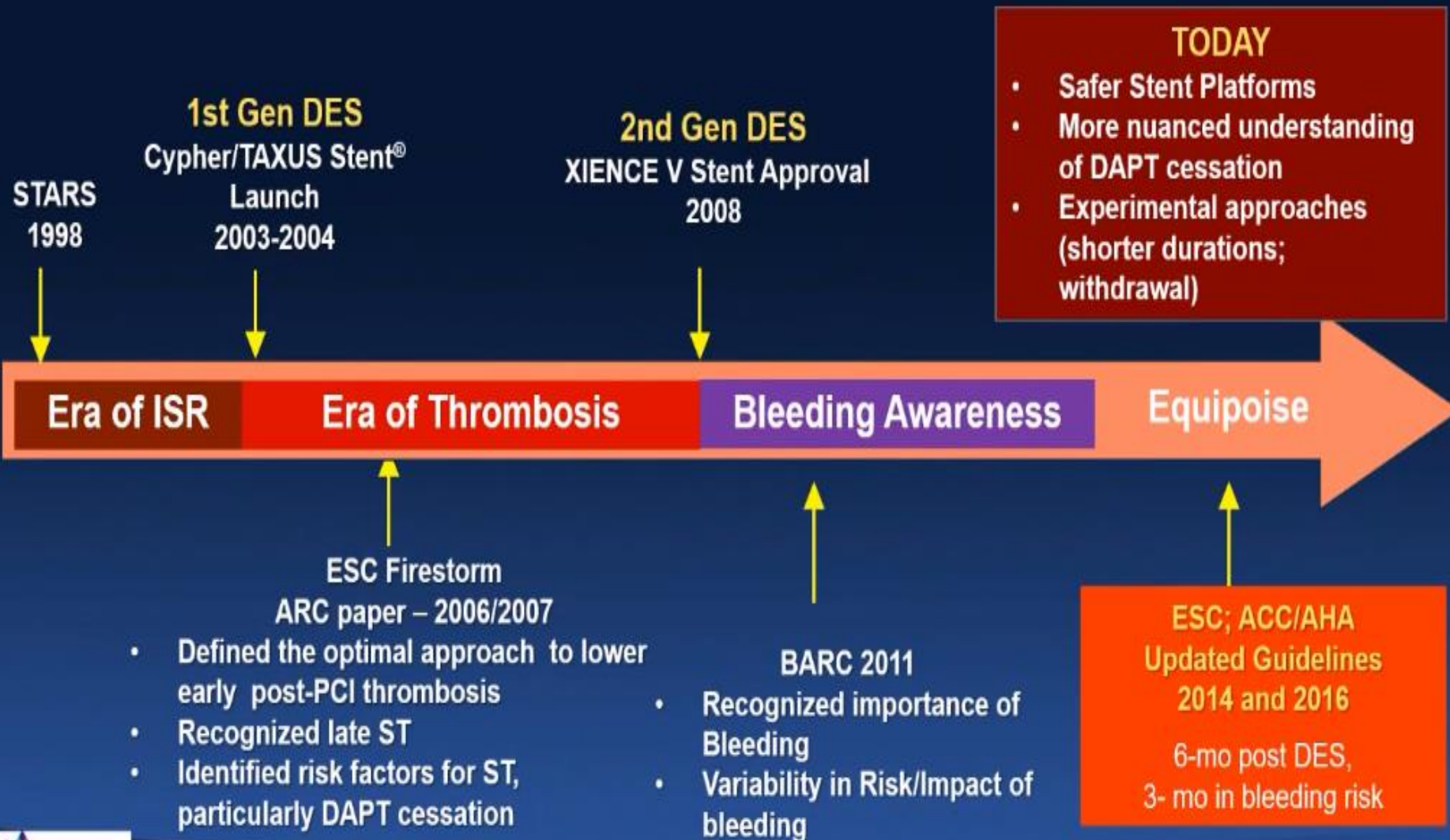


*The idea of antiplatelet therapy for reducing thrombosis following PCI was kindled about four decades ago.*





# BRIEF HISTORY OF DAPT





# Overview of Current Stent Design

Durable Polymer Coated Stent		Bioabsorbable Polymer Coated Stent				Bioabsorbable Scaffold	
------------------------------	--	------------------------------------	--	--	--	------------------------	--

Abbott/Boston

Medtronic

BIOSENSORS

Terumo

Boston

Schect

Envision Scientific

Abbott

Xience/ Promus<sup>1</sup>  
CoCr/ PtCr-EES

Resolute Onyx<sup>1</sup>  
CoNi-ZES

BioMatrix<sup>1</sup>  
316L-BES

Ultimaster<sup>1</sup>  
CoCr-SES

Synergy<sup>1</sup>  
PtCr-EES

Inspiron<sup>1</sup>  
CoCr-SES

ABLUMINUS DES  
CoCr-SES

Absorb<sup>2</sup>  
PLLA-EES



Strut thickness

81  $\mu\text{m}$

81  $\mu\text{m}$

120  $\mu\text{m}$

80  $\mu\text{m}$

74  $\mu\text{m}$

75  $\mu\text{m}$

73  $\mu\text{m}$

150  $\mu\text{m}$

Polymer coating

Circumferential  
7-8  $\mu\text{m}/\text{side}$

Circumferential  
6  $\mu\text{m}/\text{side}$

Abluminal  
10  $\mu\text{m}$

Abluminal  
20  $\mu\text{m}$

Abluminal  
15  $\mu\text{m}$

Abluminal  
4  $\mu\text{m}$

Abluminal  
< 5  $\mu\text{m}$

Circumferential  
3  $\mu\text{m}/\text{side}$



# Coronary Physiology Options

**Hyperemic**



**FFR\***

**Contrast FFR**

**$\leq 0.80$**

**$\leq 0.83$**

**Non-Hyperemic**

**Whole-Cycle**

**Diastolic / Sub-Cycle**

**Pd / Pa\***

**RFR\***

**Abbott**  
4-5 beats

**$\leq 0.91$**

**$\leq 0.89$**

**DFR**

**BSc**  
5 beats

**iFR\***

**Volcano**  
5 beats

**dPR**

**ACIST**  
5 beats

**DFR**

**Opsens**  
4 beats

**$\leq 0.89$**



Thank you!

## CROWDSOURCING



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Thank you for 10 years of customer-driven innovation.

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Just Delivered

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- Sales Cloud
- Search
- Community Cloud
- Non-Product Categories
- Industries
- IoT Cloud

**Trial Org Template - 250mb Limitation on combined Data/File storage**

Today there is a hardcoded limitation on the combined amount of File and Data storage in order to create a template trial org that contains not only Setup but also Data. Today this limit is as follows: File Storage + Data Storage LESS THAN OR

1 comment - 3 months ago

Reid Jackson

1,350 Points

Upvote Downvote

UNDER POINT THRESHOLD

"In the first 10 years of its existence, IdeaExchange received over

**1.1 MM**

votes and delivered close to

**30%**

of the product suggestions.

The latest release included

**61 ideas**

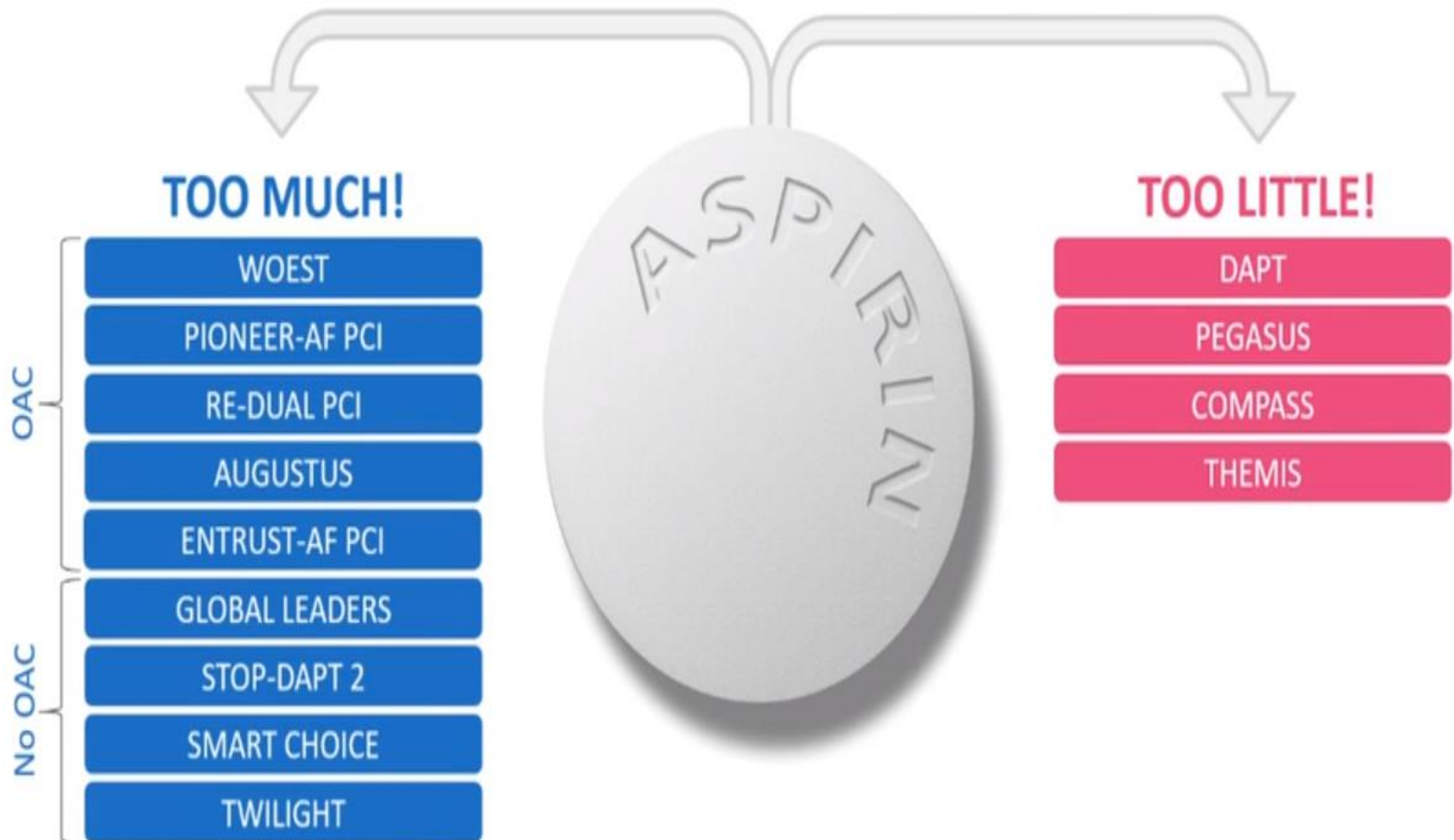
from IdeaExchange."

- Harvard Business School case study



# A 30-year story of success in antithrombotic trials

## Aspirin, *quo vadis?*



# Need for periprocedural anticoagulation

*PCI is associated with plaque rupture and subsequent activation of the coagulation system*

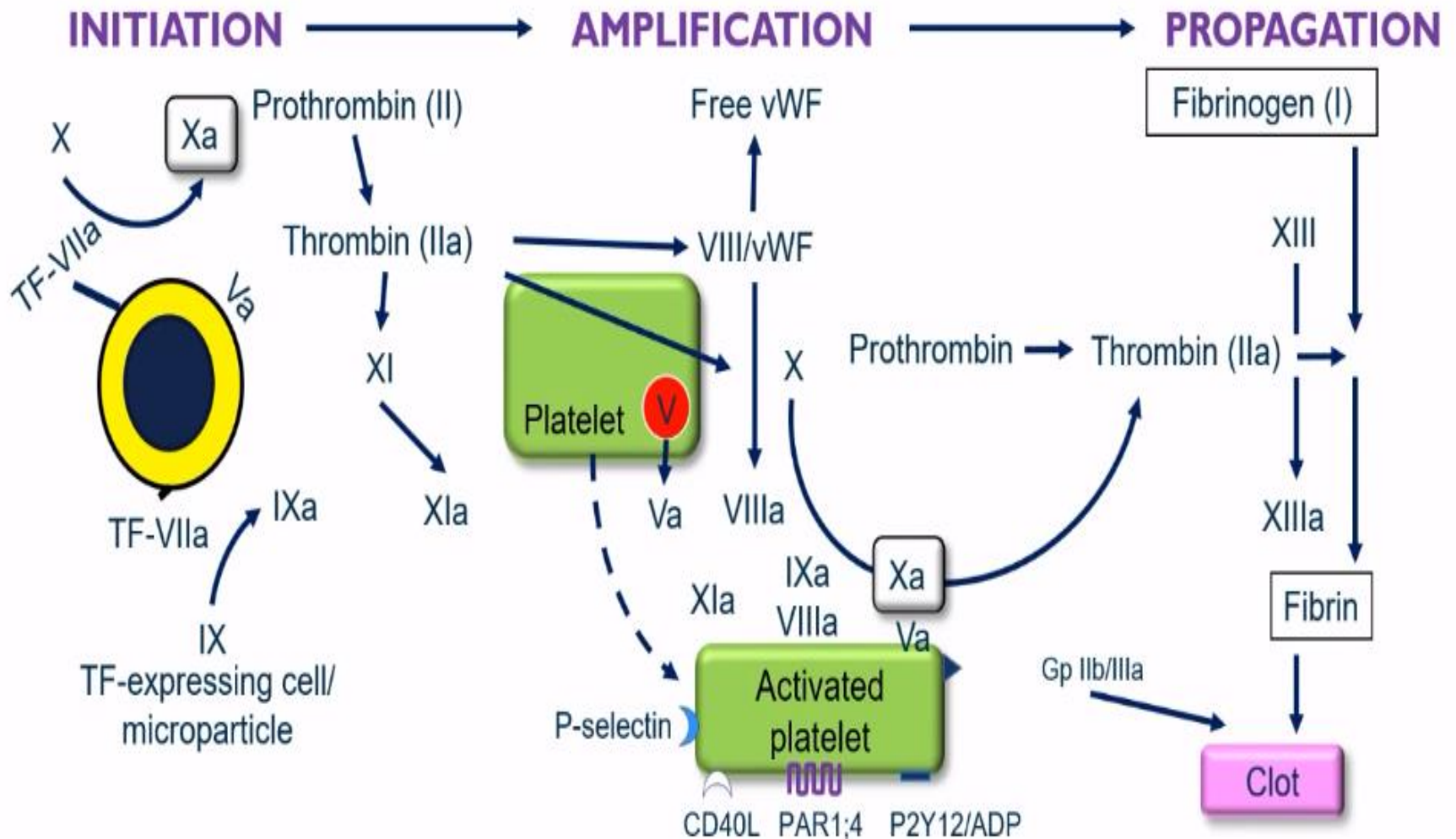


*Formation of thrombin and platelet aggregation*



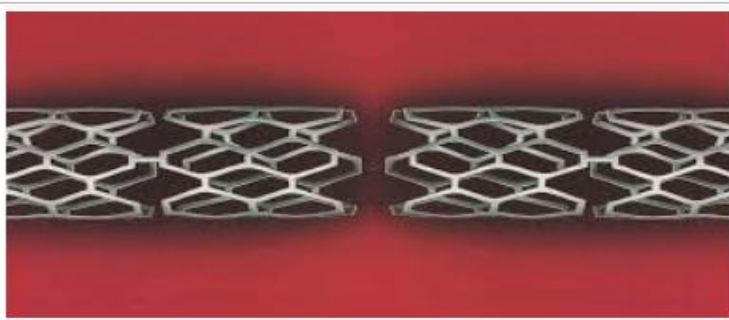
*Acute, subacute, and long-term ischemic complications*

# Thrombus Formation Involves Both Blood Coagulation and Platelet Activation

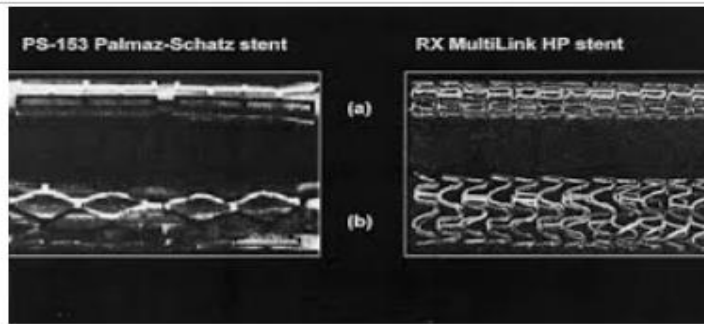


Together with





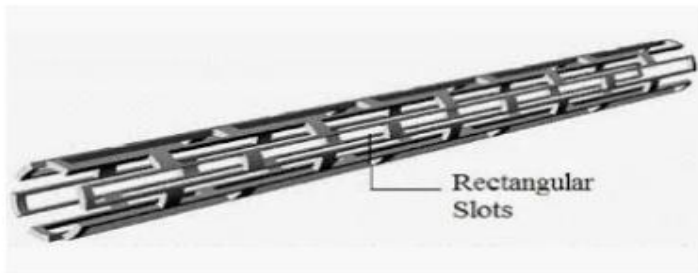
PALMAZ-SCHATZ Balloon-Expandable ...  
ourstory.jnj.com



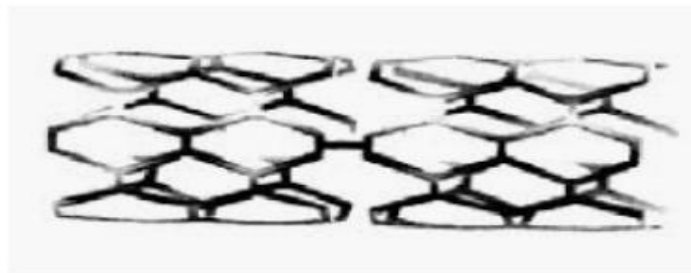
The Palmaz-Schatz® stent (left) and the ...  
researchgate.net



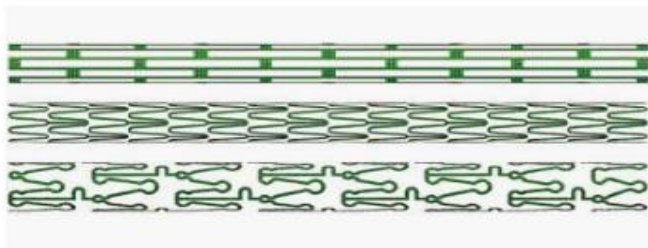
Palmaz-Schatz Crown...  
pconline.com



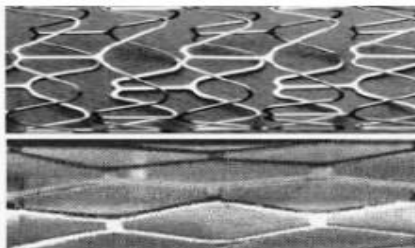
Palmaz-Schatz stent model. | Download ...  
researchgate.net



Palmaz-Schatz stent: each half ...  
researchgate.net



stents. Top: Palmaz-Schatz (PS ...  
researchgate.net



upper) Guidant/ACS Multilink™ ...  
researchgate.net

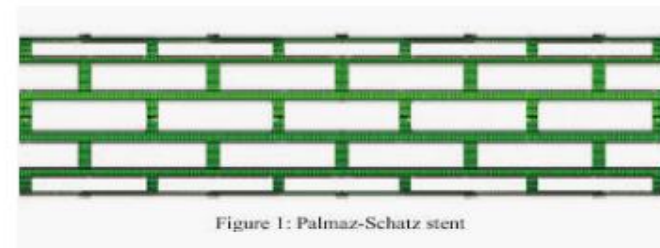
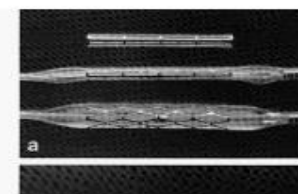
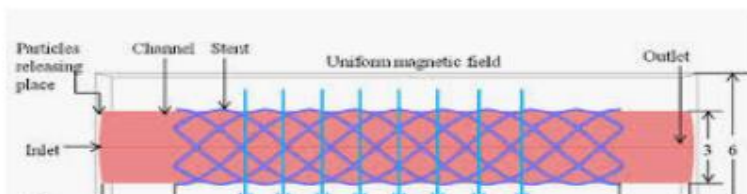


Figure 1: Palmaz-Schatz stent

Figure 1 from Finite element analysis ...  
semanticscholar.org





# Currently available antithrombotic agents

Medication	UFH	Enoxaparin	Fondaparinux	Bivalirudin
Mechanism	AT-III-mediated factor Xa and thrombin inhibitor	AT-III-mediated factor Xa and thrombin inhibitor	Indirect factor Xa inhibitor	Direct thrombin inhibitor, reversible
Factor Xa/IIa	1:1	4:1	Only Xa	Only IIa
Predictable dose response	No	Yes	Yes	Yes
Half-life	1-2 hr	5-7 hr	17-21 hr	25 min
Activates platelets	Yes	Yes	Yes	No
Incidence of HIT	0.5%	<0.1%	Negligible	Negligible
Antidote	Protamine	Protamine (partial)	None	None

# Heparin

Antithrombotic agent of choice since the inception of PCI in the late 1970s.

However, it was thought to have a number of limitations:

- × Inter- and intra-individual variations
- × Inability to bind to clot-bound thrombin
- × Occurrence of HIT
- × Complex kinetics leading to a non-linear response



Heparin

LMW  
Heparin

In the late 90's, data on LMW Heparin started accumulating and trials focusing on its use in PCI came to the fore.

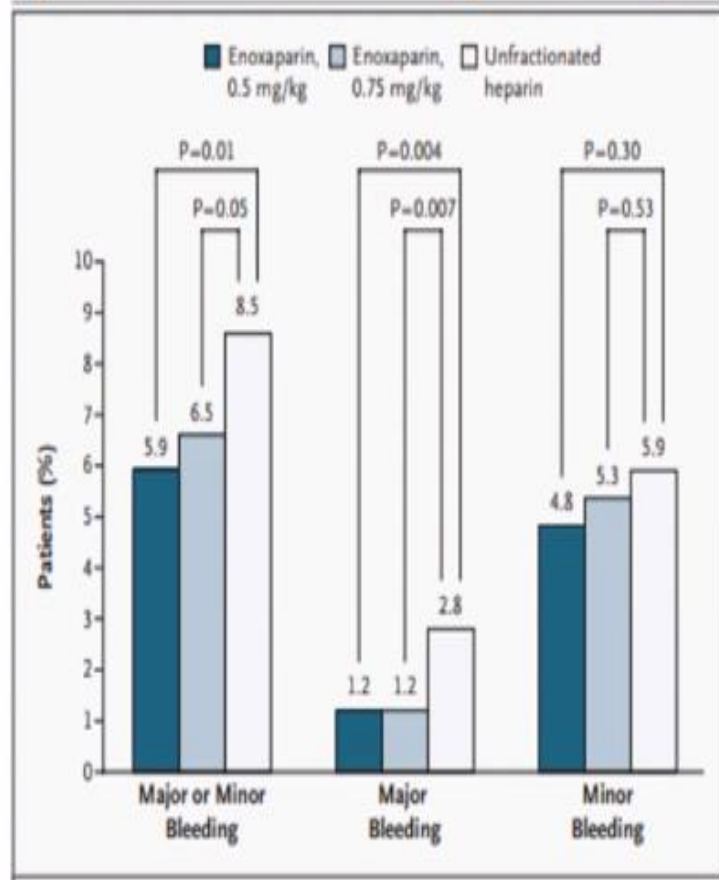
The rationale behind it was the following:

- ✓ Powerful anti-thrombotic effect
- ✓ More predictable anticoagulant effect, thereby decreasing the need for intraprocedural monitoring
- ✓ Decreased incidence of HIT
- ✓ More sustained anticoagulant effect



## STEEPLE Trial

Significant decrease in bleeding with enoxaparin



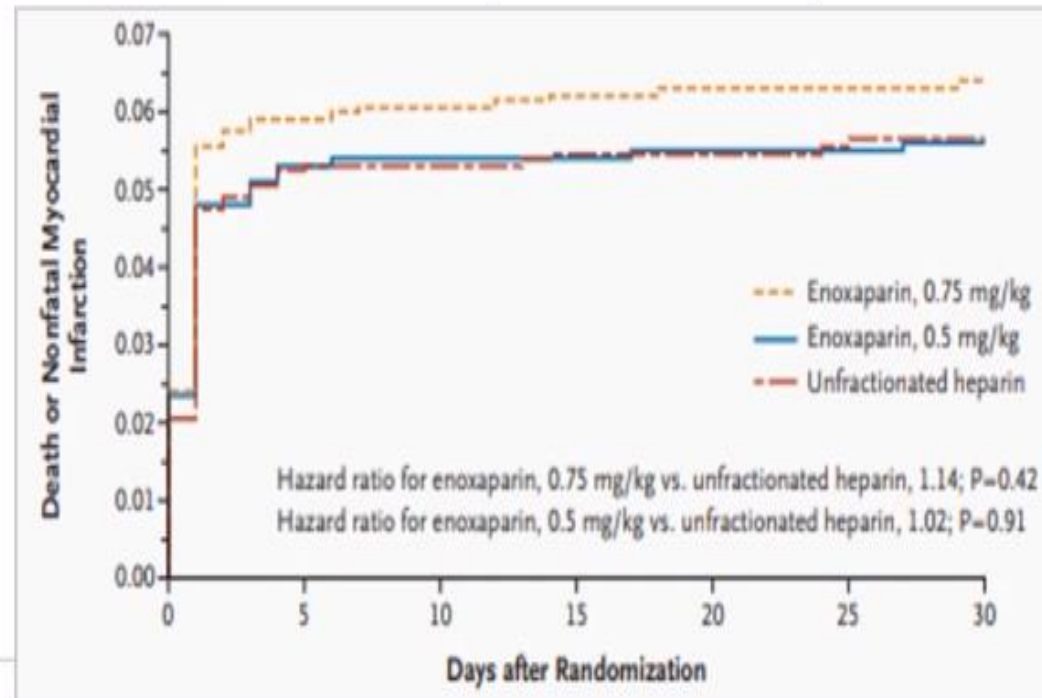
N Engl J Med 2006;355:1006-17

together with

## Enoxaparin versus Unfractionated Heparin in Elective Percutaneous Coronary Intervention

Gilles Montalescot, M.D., Ph.D., Harvey D. White, M.B., Ch.B., D.Sc., Richard Gallo, M.D., Marc Cohen, M.D., P. Gabriel Steg, M.D., Philip E.G. Aylward, M.B., Ch.B., Ph.D., Christoph Bode, M.D., Ph.D., Massimo Chiariello, M.D., Spencer B. King III, M.D., Robert A. Harrington, M.D., Walter J. Desmet, M.D., Carlos Macaya, M.D., Ph.D., and Steven R. Steinhubl, M.D., for the STEEPLE Investigators<sup>†</sup>

No difference in ischemic endpoint between enoxaparin and UFH





Heparin

Heparin

Inhibitors

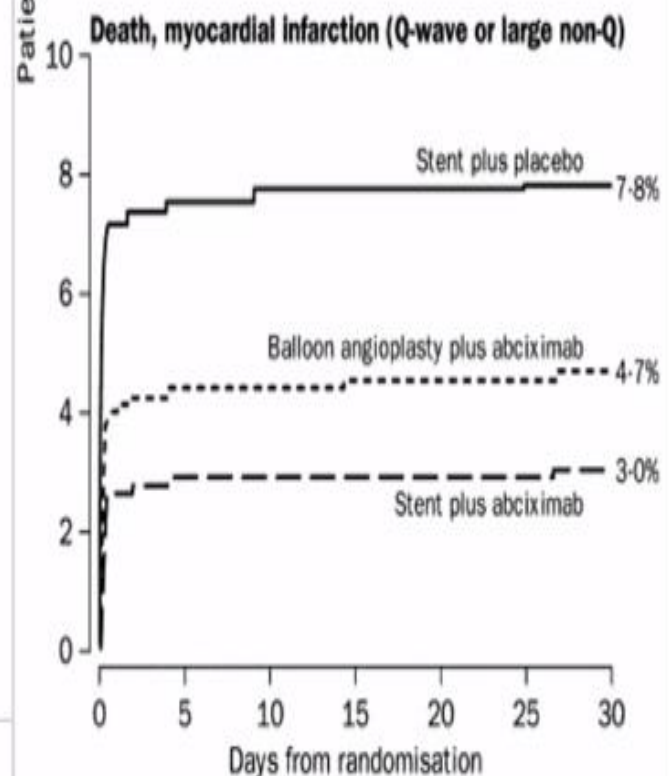
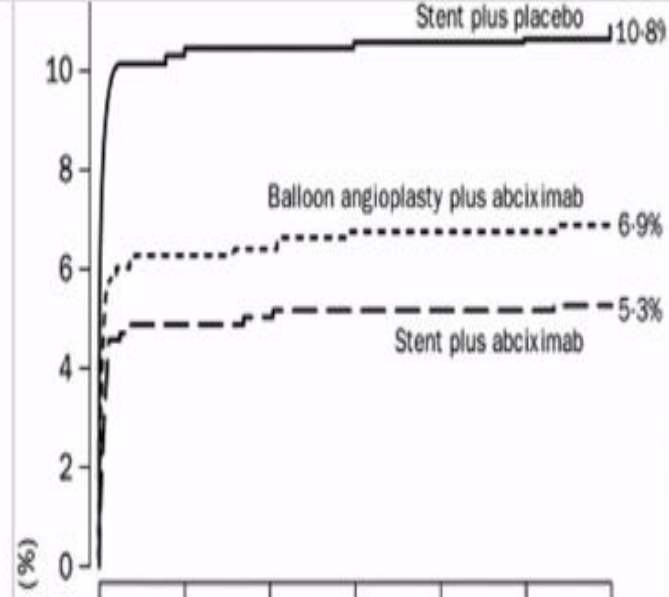
Simultaneously, trials exploring the use of GP IIb/IIIa inhibitors in PCI were being conducted.

*Because of the specificity of the GP IIb/IIIa integrin receptor for fibrinogen, it was felt that blockade of this receptor would effectively inhibit platelet aggregation and thus abolish the formation of thrombus.*

**Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade**

*EPISTENT trial,  
The Lancet, 1998*

The EPISTENT Investigators\*



Heparin

LMW  
Heparin

GP IIb/IIIa  
Inhibitors

Xa  
Inhibitors

Bivalirudin

Direct thrombin inhibitors were also considered an appealing option for PCI

**Bivalirudin and Provisional Glycoprotein IIb/IIIa Blockade Compared With Heparin and Planned Glycoprotein IIb/IIIa Blockade During Percutaneous Coronary Intervention**  
REPLACE-2 Randomized Trial

*REPLACE-2*  
*ISAR-REACT 3*

ORIGINAL ARTICLE

Bivalirudin versus Unfractionated Heparin during Percutaneous Coronary Intervention

Adnan Kastrup, M.D., Franz Josef Neumann, M.D., Julinda Mehlli, M.D., Robert A. Byrne, M.B., M.R.C.P.I., Rainsuke Iijima, M.D., Heinz Joachim Bötner, M.D., Ahmed A. Khatib, M.D., Stefanie Schulz, M.D., James C. Blankenship, M.D., Jürgen Pache, M.D., Jan Minners, M.D., Melchior Seyfarth, M.D., et al., for the ISAR-REACT 3 Trial Investigators\*

*Bivalirudin is non-inferior to Heparin plus planned Gp IIb/IIIa blockade for ischemic end points and is associated with less bleeding.*

**DEATH, MI, URGENT REVASC, OR MAJOR BLEEDING**

Favors  
Bivalirudin

Favors  
Heparin Plus Gp  
IIb/IIIa Inhibitor



*In patients with stable and unstable angina who underwent PCI, bivalirudin did not provide a net clinical benefit as compared with UFH, but it did significantly reduce major bleeding.*



Heparin

LMW  
Heparin

GP IIb/IIIa  
Inhibitors

Xa  
Inhibitors

Bivalirudin

...however subsequent data suggested that while there was no difference in ischemic benefit, even the decrease in bleeding was due to unbalanced Gp IIb/IIIa inhibitor use!

**Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial**

*MATRIX*

*VALIDATE-SWEDEHEART*

Marco Valgimigli, Enrico Frigoli, Sergio L. Stefano Garducci, Paolo Rubartelli, Carlo Marco Nazzaro, Alessandro Lupi, Bernardo Gennaro Sardella, Nicoletta de Cesare, *et al.*  
on behalf of the MATRIX Investigators

ORIGINAL ARTICLE

## Bivalirudin versus Heparin Monotherapy in Myocardial Infarction

David Erlinge, M.D., Ph.D., Elmir Omerovic, M.D., Ph.D., Ole Fröbert, M.D., Ph.D., Rikard Linder, M.D., Ph.D., Mikael Danielewicz, M.D., Mehmet Hamid, M.D., Eva Swahn, M.D., Ph.D., Loghman Henareh, M.D., Ph.D., Henrik Wagner, M.D., Ph.D., Peter Hårdhammar, M.D., Ivar Sjögren, M.D., Jason Stewart, M.D., *et al.*

GP IIb/IIIa  
Inhibitors

Xa  
Inhibitors

Bivalirudin

LMW  
Heparin

Heparin

## 2018 ESC/EACTS Guidelines on myocardial revascularization

### DOWNGRADES

Class I Bivalirudin for PCI in NSTEMI-ACS Class IIb

Class IIa Bivalirudin for PCI in STEMI Class IIb

### Peri-interventional therapy

Anticoagulation is recommended for all patients in addition to antiplatelet therapy during PCI.<sup>703,726</sup>

I

A

Routine use of UFH is recommended.

I

C

Routine use of enoxaparin should be considered.<sup>737</sup>

IIa

B

Routine use of bivalirudin may be considered.<sup>708,710,728,744–746</sup>

IIb

A

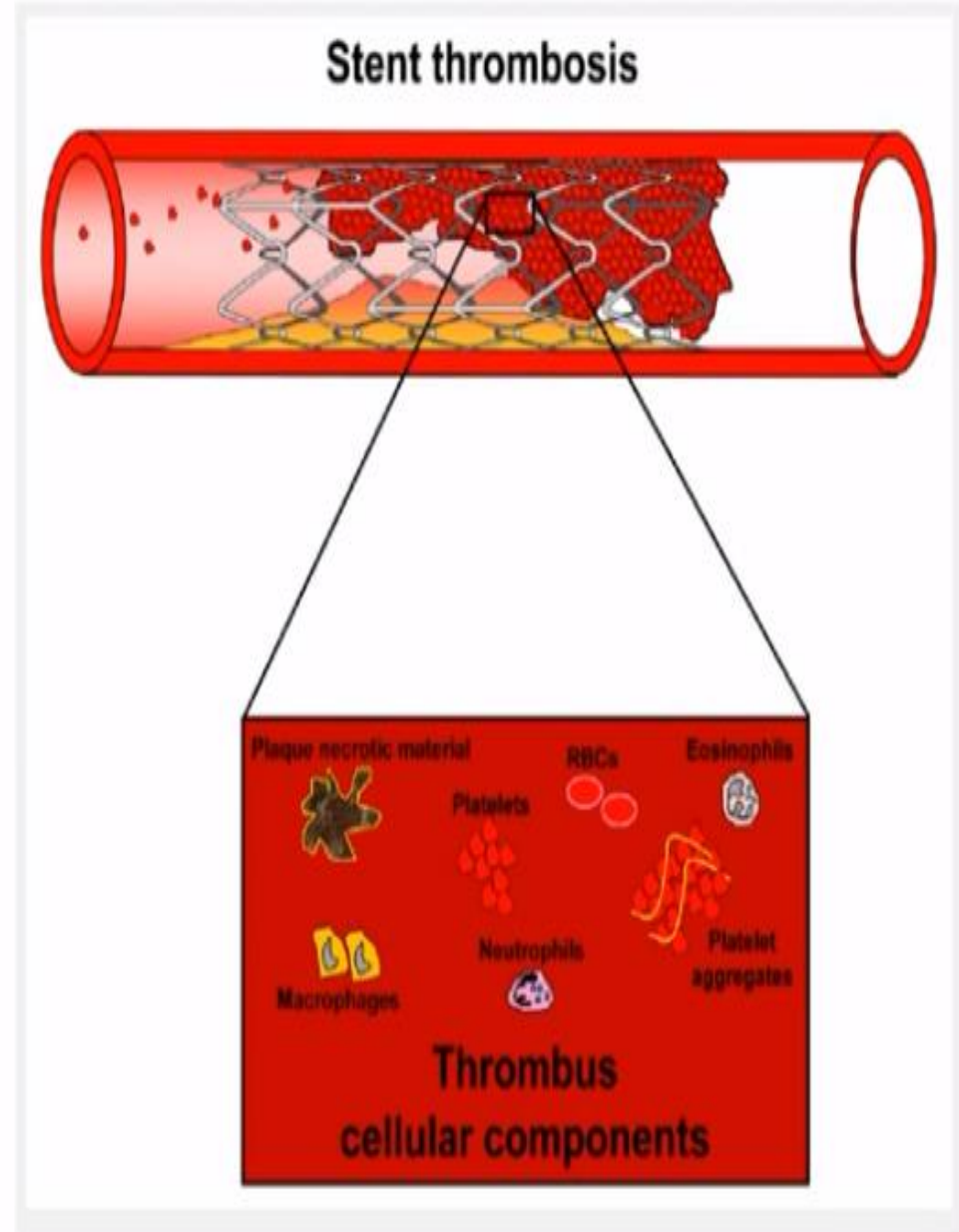
*Back to the future!*



# Moving on to the antiplatelet agents now...

*Platelets play a key role in stent failure.*

*For this reason, antiplatelet therapy is the cornerstone of antithrombotic therapy after PCI.*

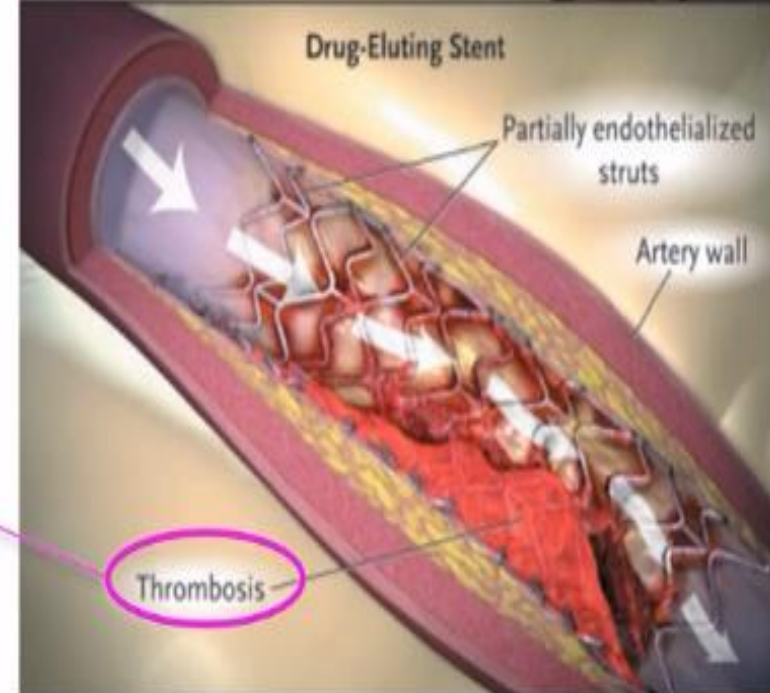
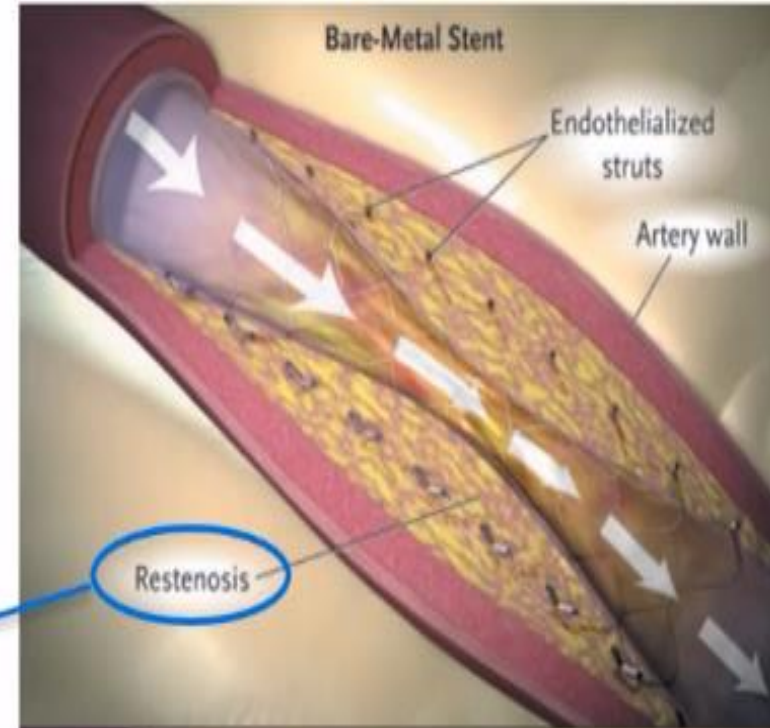


# Why DAPT after Stenting?

## Restenosis vs. Thrombosis

Smooth Muscular Cell Proliferation

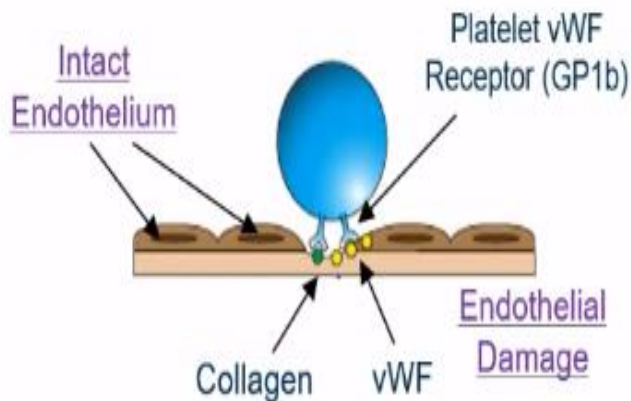
Platelet and Coagulation Pathways Activation



# Currently available antiplatelet agents

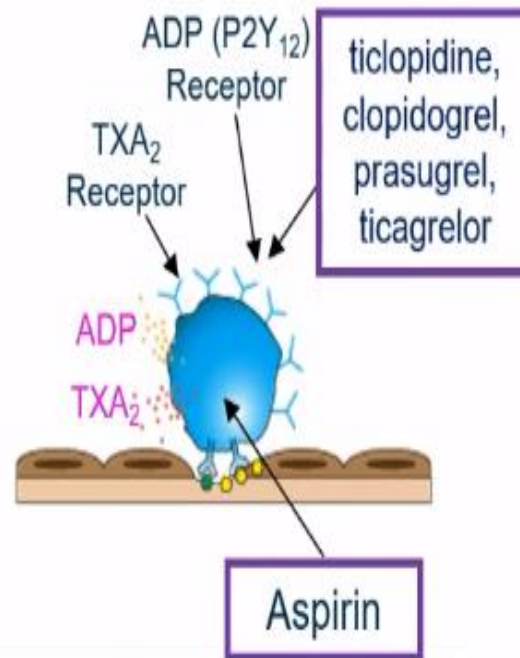
## Platelet-Mediated Thrombosis Targets

### ADHESION



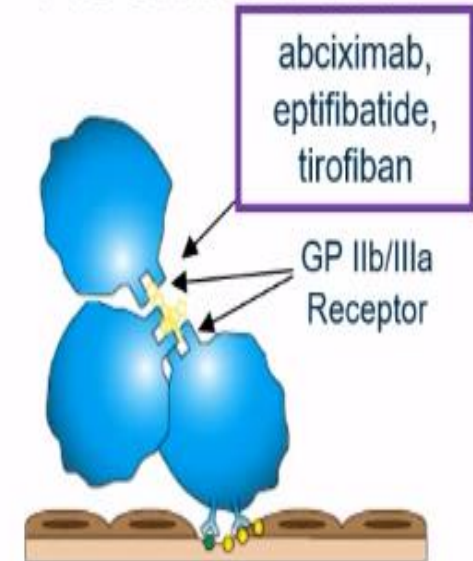
**No currently approved antiplatelet agents specifically target Adhesion**

### ACTIVATION



**Most approved antiplatelet agents affect different aspects of platelet Activation**

### AGGREGATION



**GP IIb/IIIa inhibitors inhibit the "final common pathway," Aggregation**

GP = glycoprotein; vWF = von Willebrand factor; ADP = adenosine diphosphate; TX = thromboxane.



- *In 1977, when Dr. Andreas Grüntzig was treating his first patient, he was of course confronted with the basic question of treatment for vascular injury.*
- *He subsequently decided on Aspirin, which was to be stopped after the critical period for restenosis.*





# Pharmacotherapy to support elective PCI

In the early "POBA" days :

5000 U unfractionated heparin

± aspirin



Bare metal stents Era I

Aspirin, heparin, dextran, dipyridamole

Warfarin x 1 month



Bare metal stents Era II

Aspirin, heparin, ticlopidine



Antonio Colombo

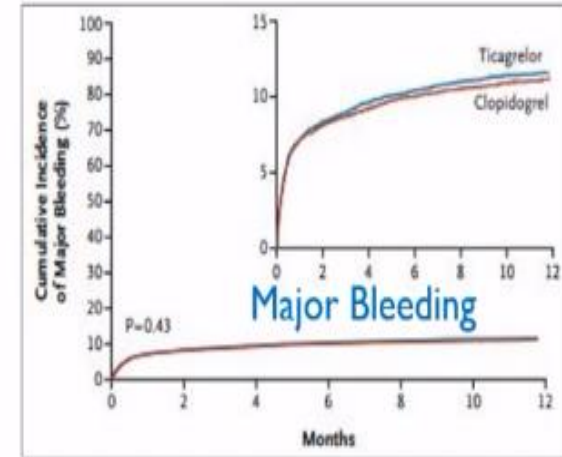
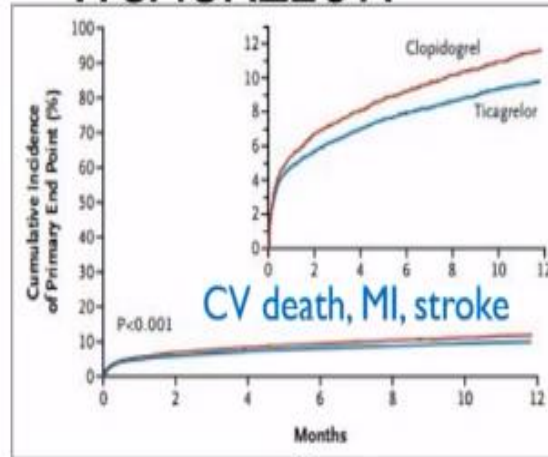


Marie-Claude Morice



# Rise of the P2Y<sub>12</sub> Inhibitors

## TICAGRELOR



FANTASTIC

CLASSICS  
PCI-CURE

TRITON TIMI 38  
PLATO

1998

2000 2001

2007

2009

Together with

ESC Congress Paris 2019 World Congress of Cardiology

N Engl J Med 2009; 361:1045-1057

# ISAR-REACT 5:

## Ticagrelor vs. Prasugrel in Acute Coronary Syndromes

S. Schüpke, F.-J. Neumann, M. Menichelli, K. Mayer, I. Bernlochner, J. Wöhrle, G. Richardt, C. Liebetrau, B. Witzenbichler, D. Antoniucci, I. Akin, L. Bott-Flügel, M. Fischer, U. Landmesser, H. A. Katus, D. Sibbing, M. Seyfarth, M. Janisch, D. Boncompagni, R. Hiltz, W. Rottbauer, R. Okrojek, H. Möllmann, W. Hochholzer, A. Migliorini, S. Cassese, P. Mollo, E. Xhepa, S. Kufner, A. Strehle, S. Leggewie, A. Allali, G. Ndrepepa, H. Schühlen, D. J. Angiolillo, C. W. Hamm, A. Hapfelmeier, R. Tölg, D. Trenk, H. Schunkert, K.-L. Laugwitz, A. Kastrati,  
for the ISAR-REACT 5 Investigators

Together with

# Study Schedule



DZHK  
DEUTSCHES ZENTRUM FÜR  
HERZ-KREISLAUF-FORSCHUNG E.V.

TUM

Technische Universität München



## STEMI

### Randomization

**Ticagrelor**  
180 mg loading

**Prasugrel**  
60 mg loading

### Angiography + PCI

**Ticagrelor**  
90 mg 1-0-1

**Prasugrel**  
10 mg 1-0-0\*

## Unstable Angina, NSTEMI

### Randomization

**Ticagrelor**  
180 mg loading

*Prasugrel<sup>#</sup>*  
*60 mg loading*

### Angiography

**Prasugrel**  
60 mg loading

### PCI

**Ticagrelor**  
90 mg 1-0-1

**Prasugrel**  
10 mg 1-0-0\*



# Primary End point

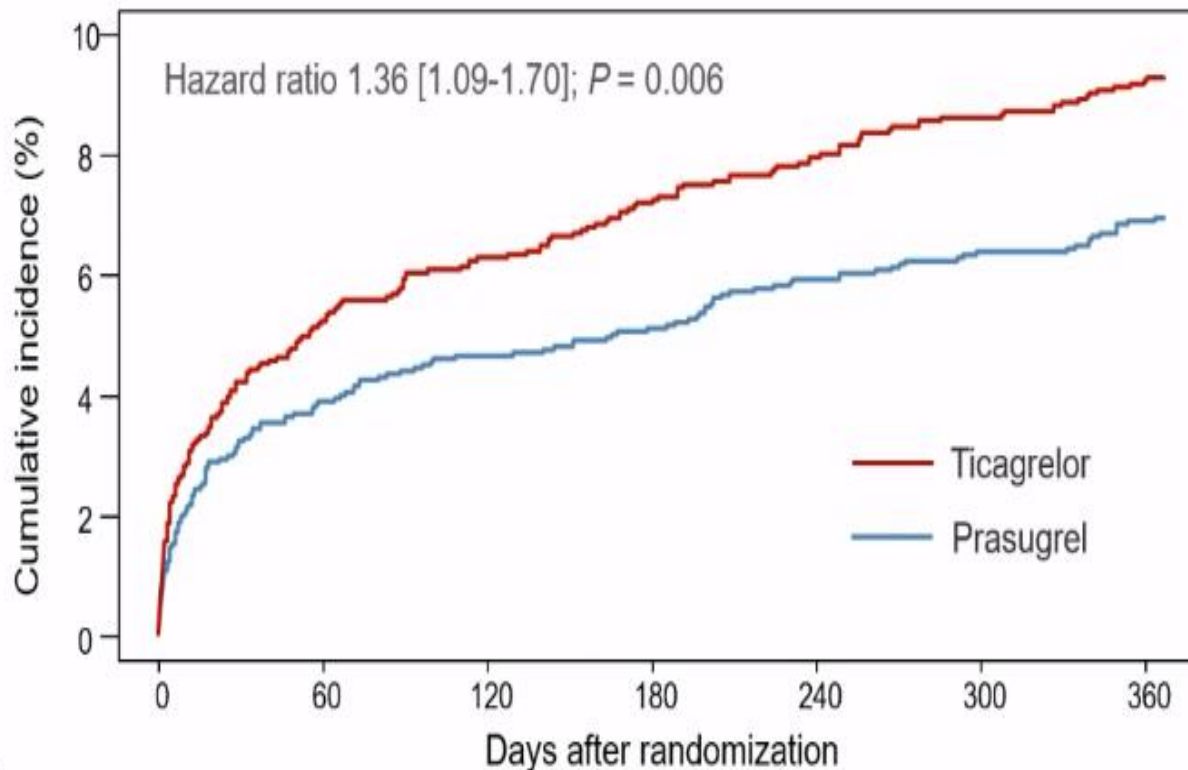
(Composite of Death, MI or Stroke)



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Technische Universität München



## Patients at Risk

Ticagrelor	2012	1879	1857	1836	1816	1801	1788
Prasugrel	2006	1892	1877	1863	1839	1829	1819

# BARC 3-5 Bleeding

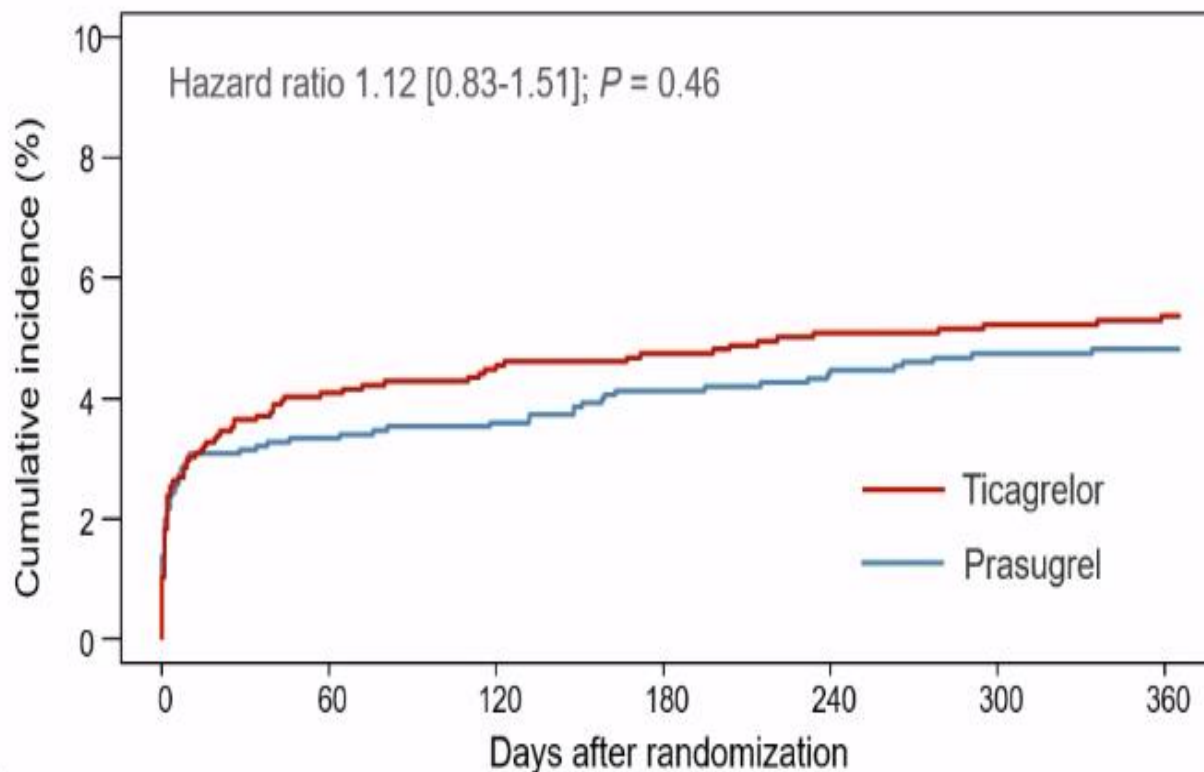
(Safety End point)



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HERZ-KREISLAUF-FORSCHUNG E.V.



Technische Universität München



## Patients at Risk

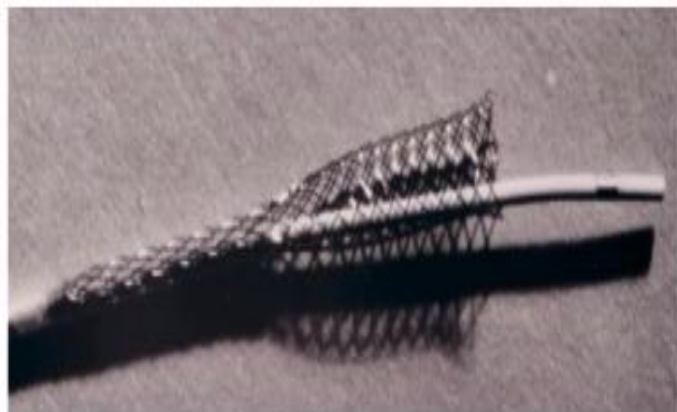
Ticagrelor	1989	1442	1400	1360	1320	1301	1280
Prasugrel	1773	1466	1428	1399	1359	1333	1320

# Evolution of DAPT Duration



1995

Advent of BMS  
**4 weeks of DAPT**



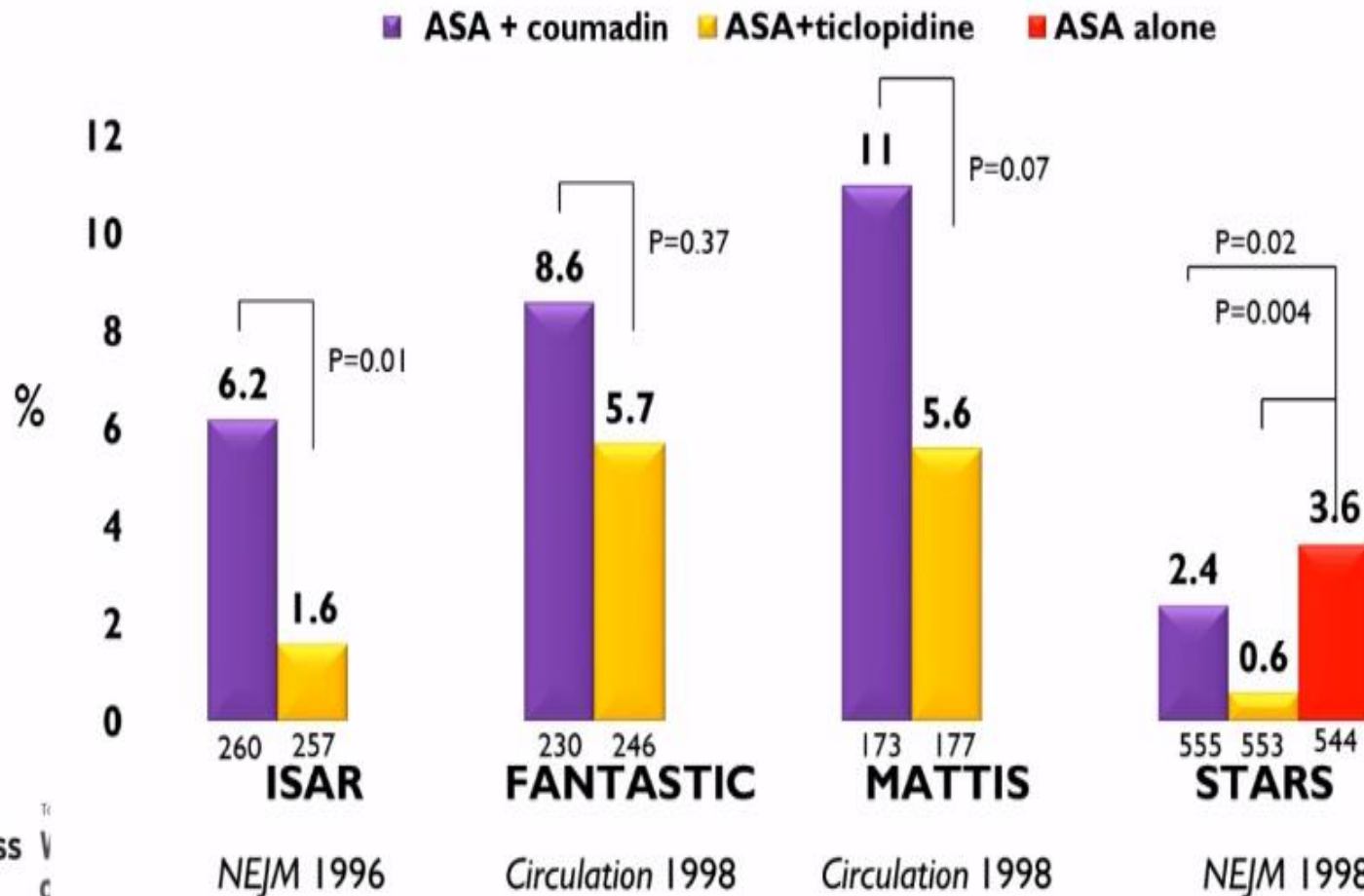
*Initial enthusiasm of angioplasty was significantly limited by vessel closure due to recoil, dissections and restenosis thus leading to development of stents.*

*With the advent of BMS, there was an improvement in long-term lumen patency and clinical outcomes.*

*However, the use of DAPT was still necessary to reduce the rates of early stent thrombosis in BMS.*

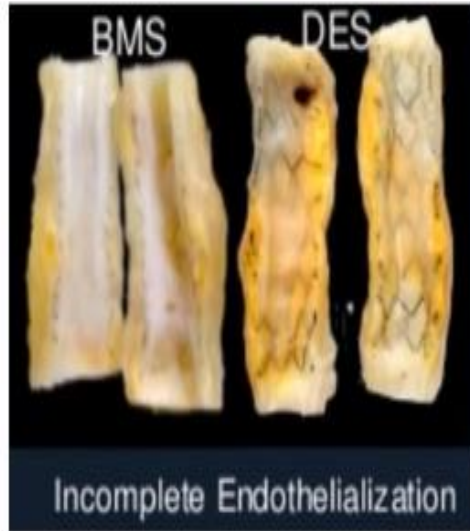
# Evidence for DAPT After Stent Implantation

## Death, MI, or Revascularization at 30 Days





# Evolution of DAPT Duration



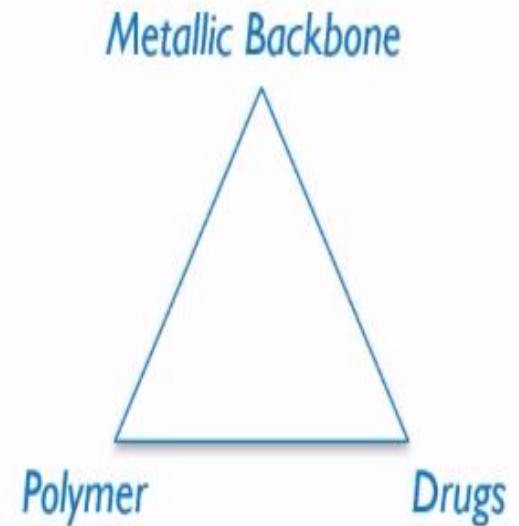
1995

Advent of BMS  
4 weeks of DAPT



Early 2000s

Introduction of 1<sup>st</sup> Generation DES  
**3-6 months of DAPT**



Drug eluting stents (DES) were clearly superior to BMS in reducing restenosis and rates of repeat revascularization.

Thus, DAPT was reserved for 3–6 months for the use of first generation DES to prevent ST and to ensure endothelialization.

# Introduction of Drug Eluting Stents

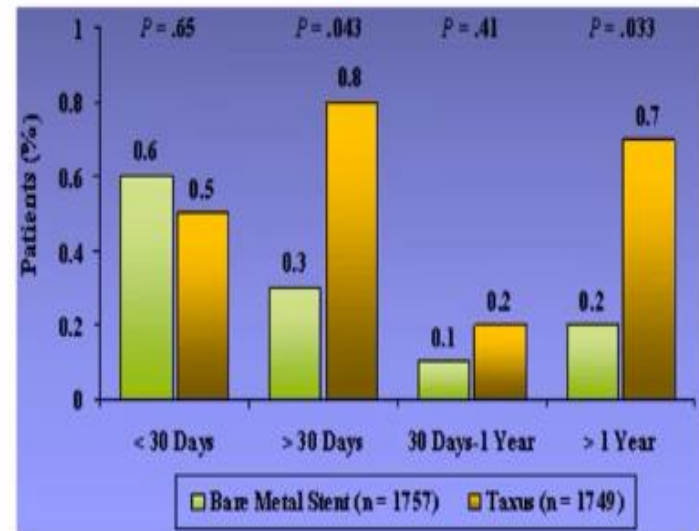
- ✓ True 'Disruptive Technology'
- ✓ Paclitaxel or Sirolimus-Eluting platforms
- ✓ Marked reductions in restenosis/revascularization - the Achilles of BMS
- ✓ Randomized data suggested no safety signal with 3-6 month DAPT duration

# The Firestorm on DES (ESC conference 2006)

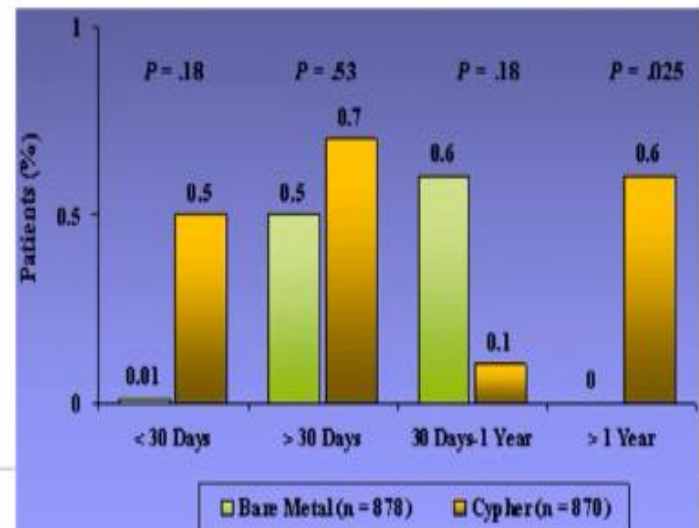


Edoardo Camenzind

TAXUS Vs. BMS



CYPHER Vs. BMS





# The Firestorm on DES (ESC conference 2006)



Edoardo Camenzind

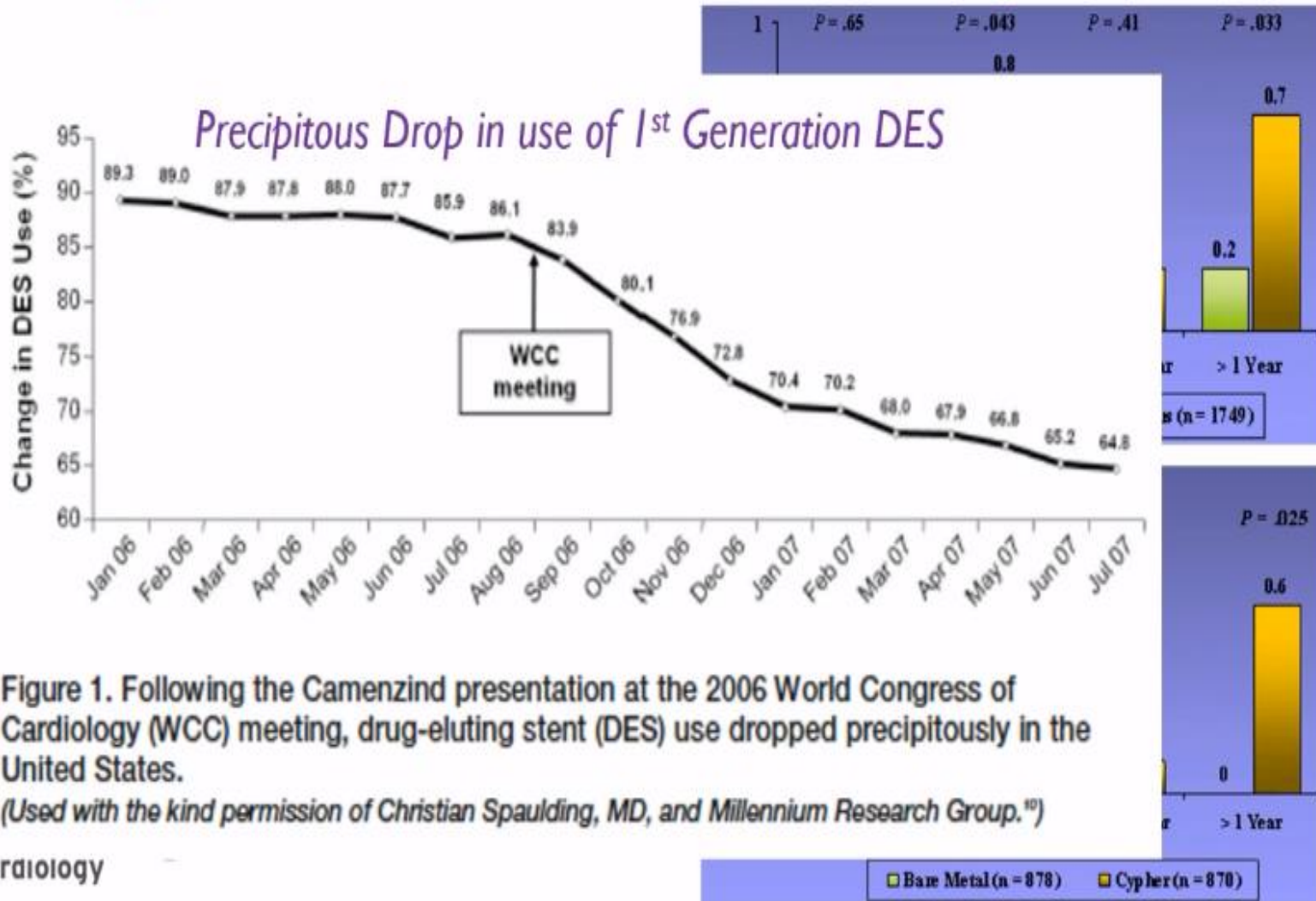


Figure 1. Following the Camenzind presentation at the 2006 World Congress of Cardiology (WCC) meeting, drug-eluting stent (DES) use dropped precipitously in the United States.

(Used with the kind permission of Christian Spaulding, MD, and Millennium Research Group.<sup>10</sup>)



# First concerns about late safety of 1<sup>st</sup> generation DES

Cardiologists Question the Risks in Using Drug-Coated Stents,  
*New York Times 2006*

## Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

*Eugène P McFadden, Eugenio Stabile, Evelyn Regar, Edouard Cheneau, Andrew T L Ong, Timothy Kinnaird, William O Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pichard, Lowell F Satler, Ron Waksman, Patrick W Serruys*

Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concern has arisen about the potential for late stent thromboses related to delayed endothelialisation of the stent struts. We report four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paclitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.

# Evolution of DAPT Duration



1995

Advent of BMS  
4 weeks of DAPT



Early 2000s

Introduction of 1<sup>st</sup> Generation DES  
3-6 months of DAPT



2006-2007

12-month DAPT for 1<sup>st</sup> Gen DES



Late 2000s

**Entry of the 2<sup>nd</sup> Generation DES**

With ubiquitous use of 2<sup>nd</sup> generation DES and lower rates of stent thrombosis, there was increasing support for shorter duration of DAPT.

This coincided with an increased awareness regarding the impact of bleeding on outcomes.

Concerns about bleeding

- Bivalirudin trials and CRF group
- Duke group

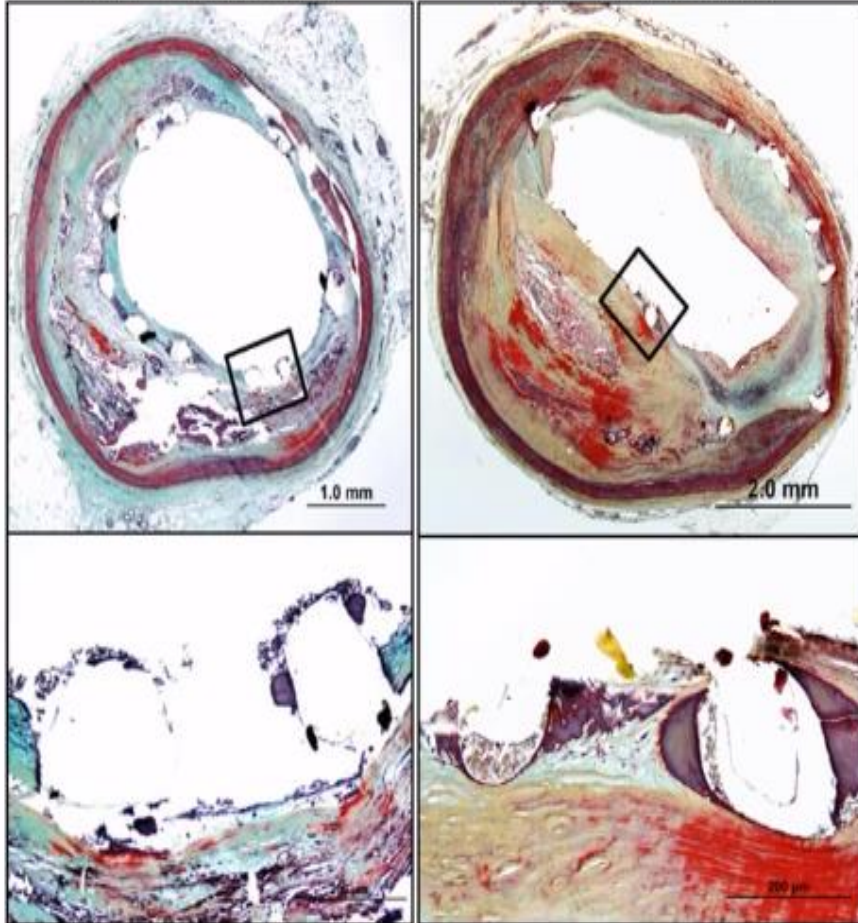


# First- versus Second-Generation DES and Risk for Stent Thrombosis...Where is the difference?

1<sup>st</sup> generation DES

SES 13 months

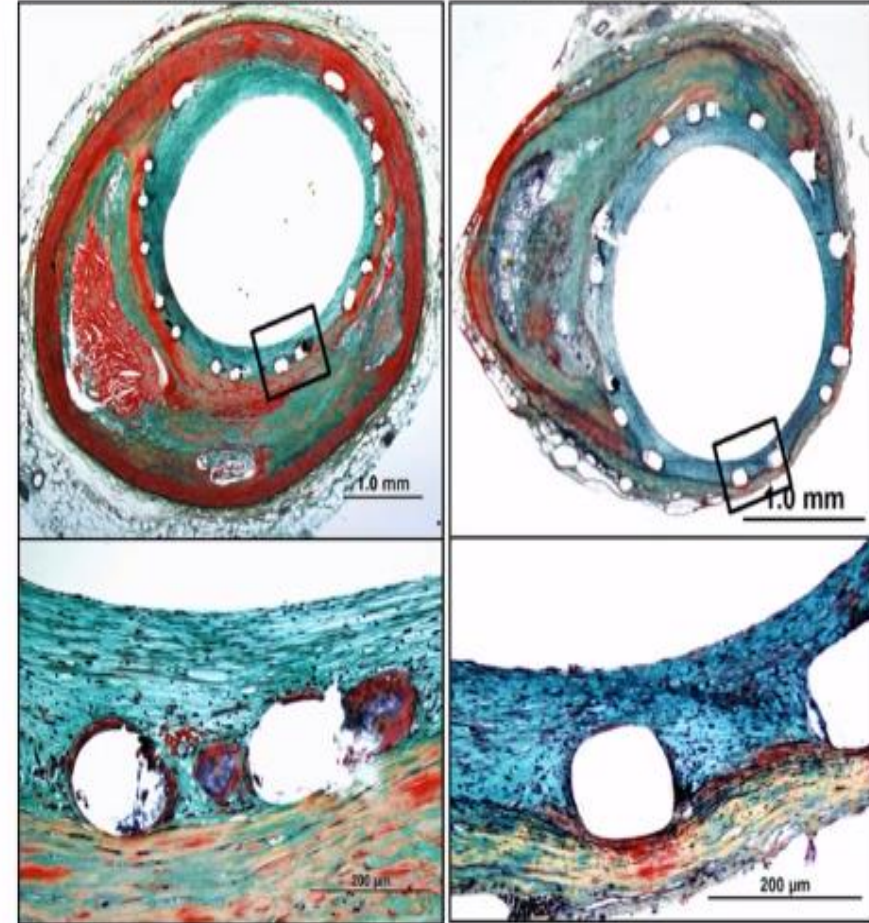
PES 11 months



2<sup>nd</sup> generation DES

ZES 3 months

EES 6 months



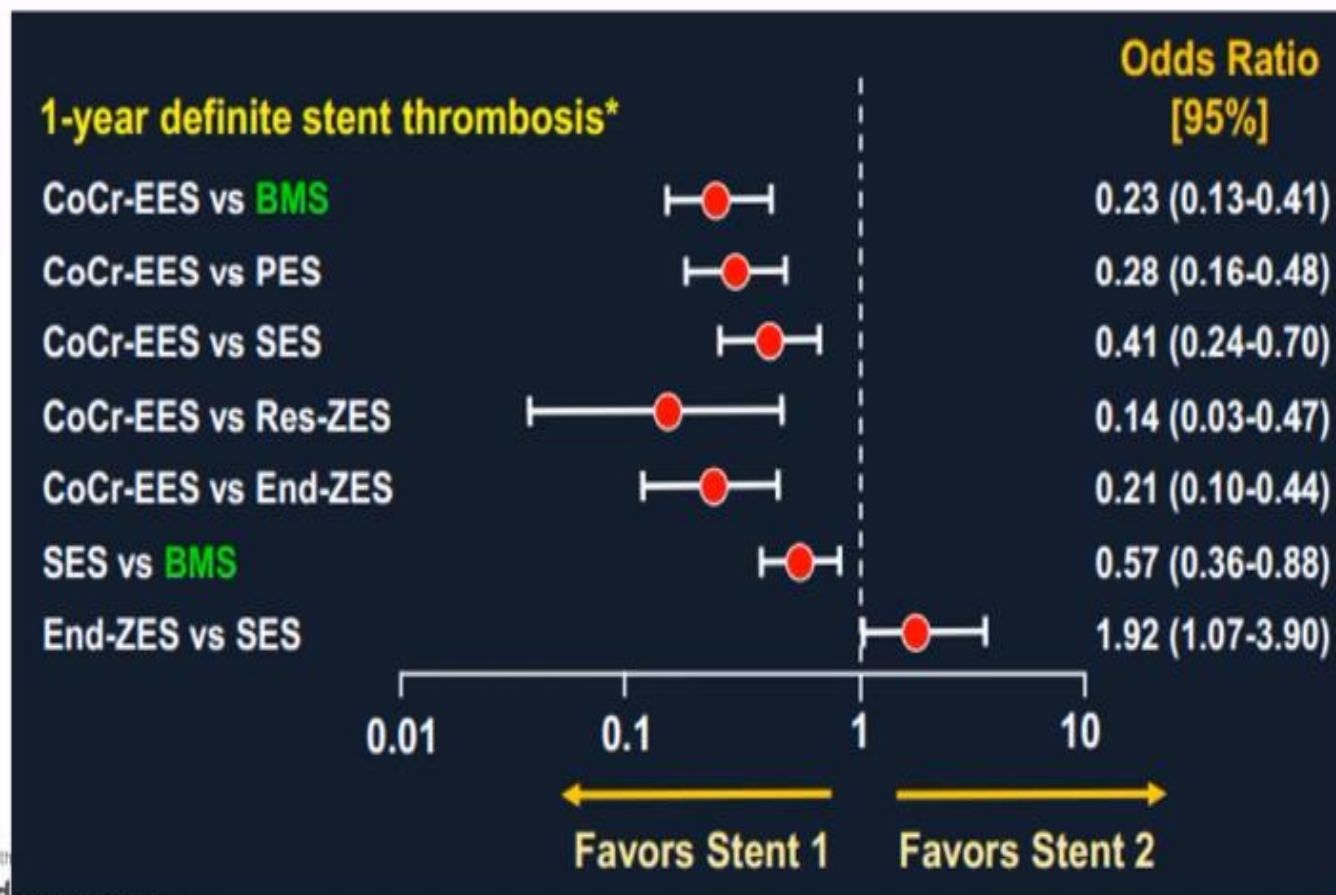
Representative Images of 1<sup>st</sup> generation vs. 2<sup>nd</sup> DES in Human Coronary Arteries

# Stent thrombosis: has the firestorm been extinguished?

## THE LANCET

Volume 379, Issue 9824, 14–20 April 2012, Pages 1368–1369

### Second-Generation DES are safer!

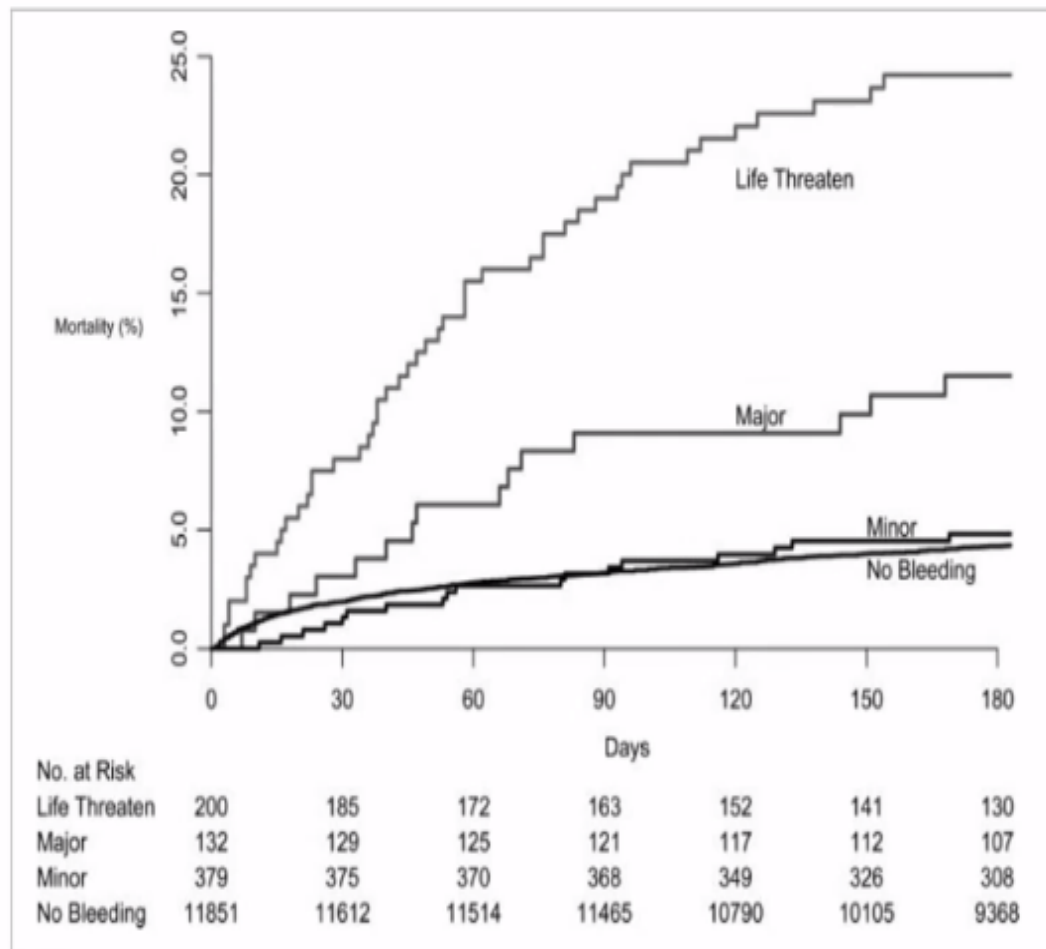


Together with



# Adverse Impact of Bleeding on Prognosis in Patients With Acute Coronary Syndromes

John W. Eikelboom, MBBS, MSc; Shamir R. Mehta, MD, MSc; Sonia S. Anand, MD, PhD;  
Changchun Xie, PhD; Keith A.A. Fox, MBChB; Salim Yusuf, MBBS, DPhil



**First Alarm  
(2006): Bleeding  
is Bad!**

Together with

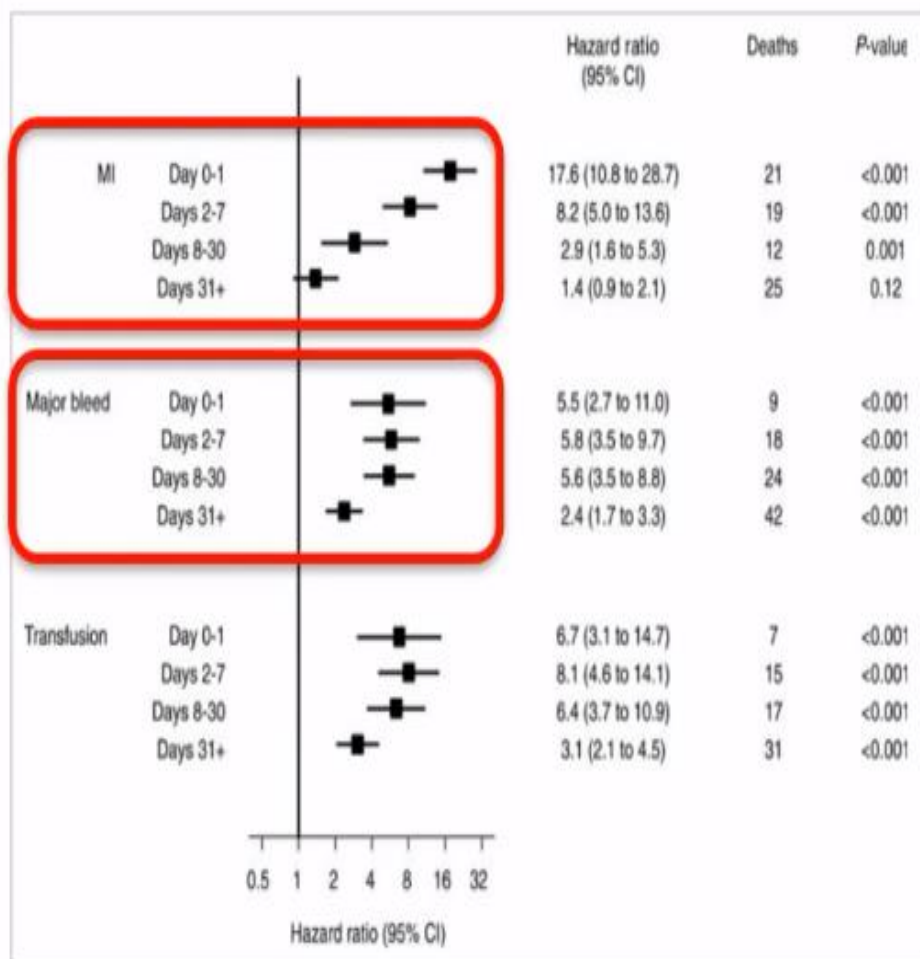
ESC Congress Paris 2019 World Congress of Cardiology

Circulation. 2006;114:774-782.

## Associations of major bleeding and myocardial infarction with the incidence and timing of mortality in patients presenting with non-ST-elevation acute coronary syndromes: a risk model from the ACUTY trial

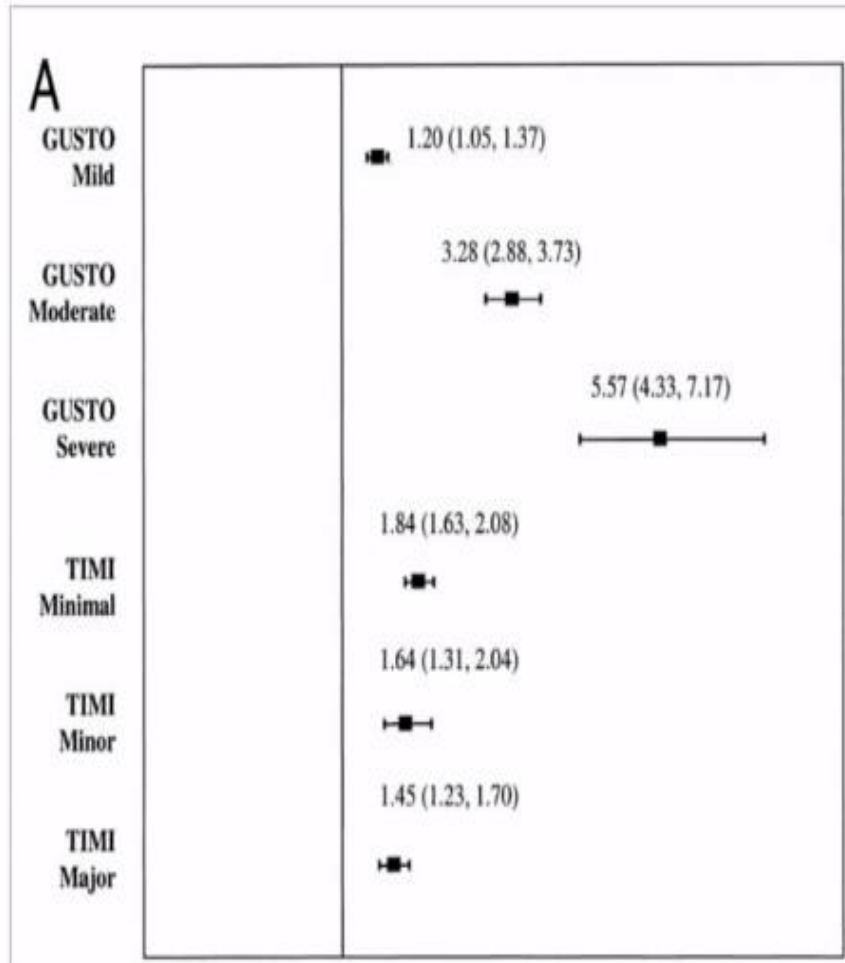
*Major bleeds and MI have similar overall strength of association with mortality in the first year after ACS.*

*MI is correlated with a dramatic increase in short-term risk, whereas major bleeding correlates with a more prolonged mortality risk.*



# Lack of Uniform definitions

*Impact of GUSTO and TIMI bleedings on mortality*



- Association of GUSTO bleeding with mortality persisted after multivariable adjustment while the risk with TIMI bleeding did not.
- This suggests that bleeding assessed with clinical criteria is more important than that assessed by laboratory criteria in terms of outcomes.

Together with



# Introduction and Validation of the BARC Criteria

**Circulation**  
JOURNAL OF THE AMERICAN HEART ASSOCIATION



## Standardized Bleeding Definitions for Cardiovascular Clinical Trials: A Consensus Report From the Bleeding Academic Research Consortium

Roxana Mehran, Sunil V. Rao, Deepak L. Bhatt, C. Michael Gibson, Adriano Caixeta, John Eikelboom, Sanjay Kaul, Stephen D. Wiviott, Venu Menon, Eugenia Nikolsky, Victor Serebruany, Marco Valgimigli, Pascal Vranckx, David Taggart, Joseph F. Sabik, Donald E. Cutlip, Mitchell W. Krucoff, E. Magnus Ohman, Philippe Gabriel Steg and Harvey White

**Importance of Bleeding as an End Point**  
 Hemorrhagic complications occur with a frequency of 1% to 10% during treatment for ACS and after PCI.<sup>18-20</sup> This wide

Predictor	Bleeding rates N (%)	Unadjusted HRs for death at 2 years			Adjusted <sup>b</sup> HRs for death at 2 years		
		No. of deaths	Hazard ratio (95% CI)	P-value	No. of deaths	Hazard ratio (95% CI)	P-value
<b>BARC</b>							
Type 2	76 (3.8)	3	1.028 (0.326-3.237)	0.963	3	0.590 (0.145-2.406)	0.462
Type 3 (or 5)	67 (3.3) <sup>a</sup>	23	12.69 (8.010-19.890)	<0.0001	23	7.586 (4.662-12.346)	<0.0001
Type 3	39 (1.9) <sup>a</sup>	9	7.597 (3.850-14.99)	<0.0001	9	4.184 (2.065-8.477)	<0.0001
Type 3B	14 (0.7) <sup>a</sup>	5	11.665 (4.76-28.586)	<0.0001	5	6.421 (2.306-17.884)	<0.0001
Type 3C	14 (0.7) <sup>a</sup>	9	45.35 (22.958-89.582)	<0.0001	9	40.54 (19.68-83.508)	<0.0001
Type 2, 3 (or 5)	143 (7.1) <sup>a</sup>	26	5.502 (3.588-8.437)	<0.0001	26	3.766 (2.374-5.975)	<0.0001

**Strong association with 2-year mortality**



# Evolution of DAPT Duration



2010s  
Finding the "sweet spot"



1995

Advent of BMS  
4 weeks of DAPT



Early 2000s

Introduction of 1<sup>st</sup> Generation DES  
3-6 months of DAPT



2006-2007

12 months of DAPT for 1<sup>st</sup> Gen DES



Late 2000s

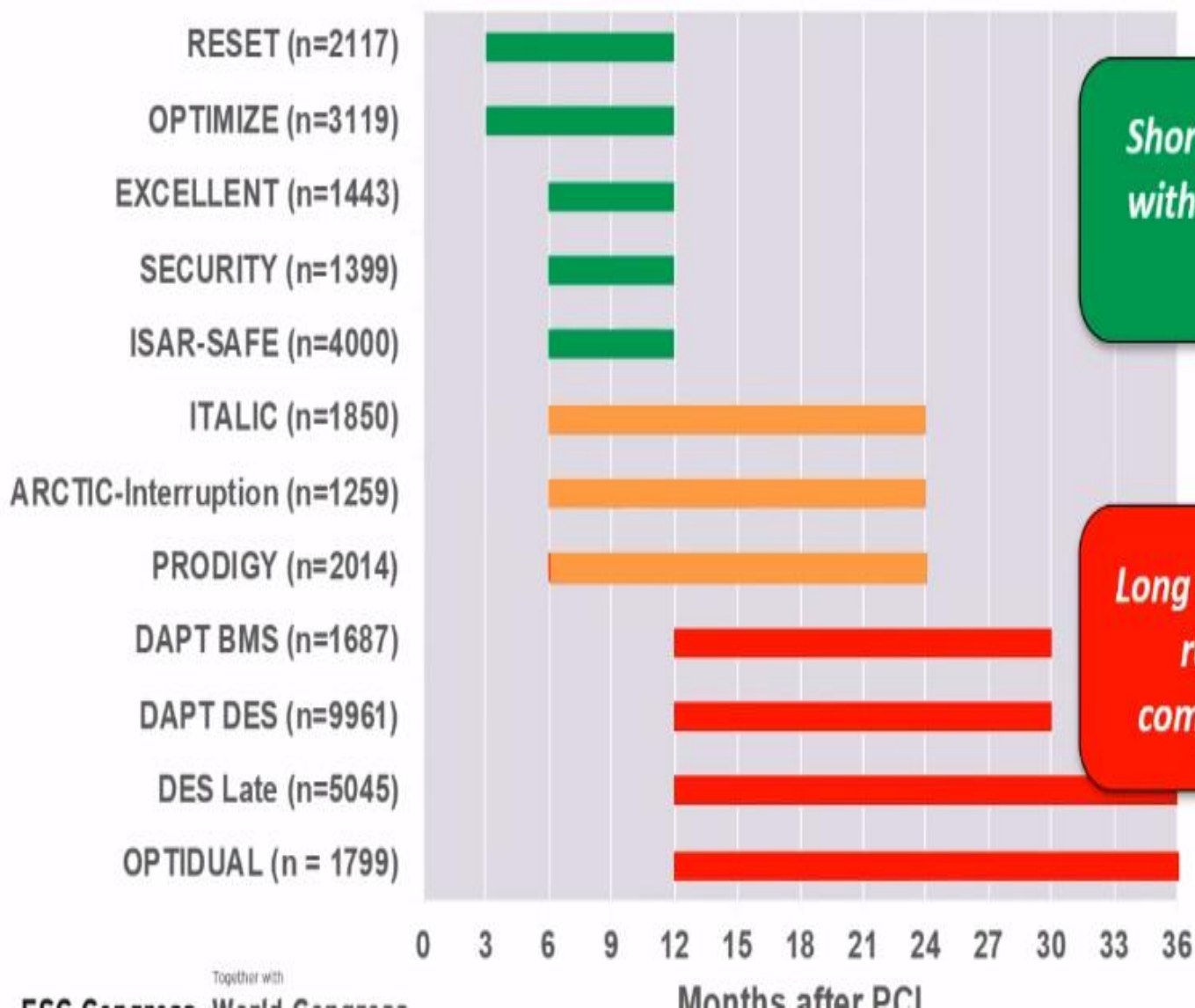
Entry of the 2<sup>nd</sup> Generation DES

Short DAPT Trials

Long DAPT Trials

# Contemporary Trials of DAPT Duration after Stenting

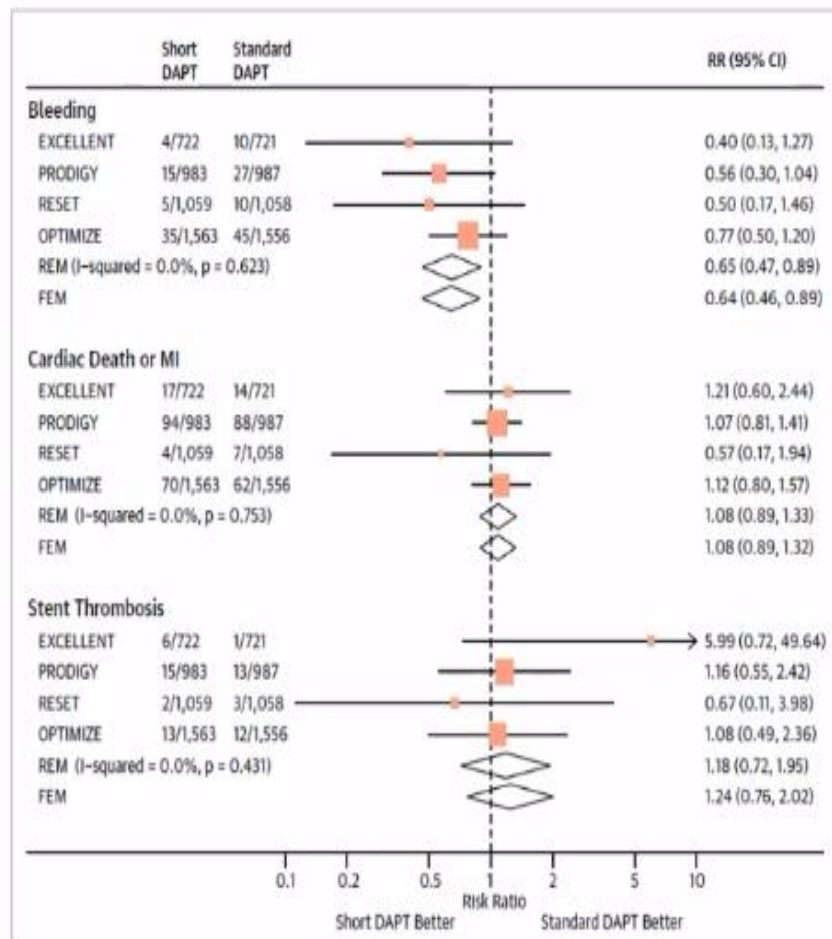
Timing of aspirin only vs. DAPT



*Short DAPT (<12 months) safer with similar efficacy compared to standard DAPT?*

*Long DAPT (>12 months) further reduces ischemic events compared to standard DAPT?*

# What is the *Minimum* Duration of DAPT after PCI?



Stefanini et al, JACC 2014

No advantage of prolonging DAPT beyond 6 months in reducing thrombotic risk with contemporary DES



The NEW ENGLAND  
JOURNAL of MEDICINE

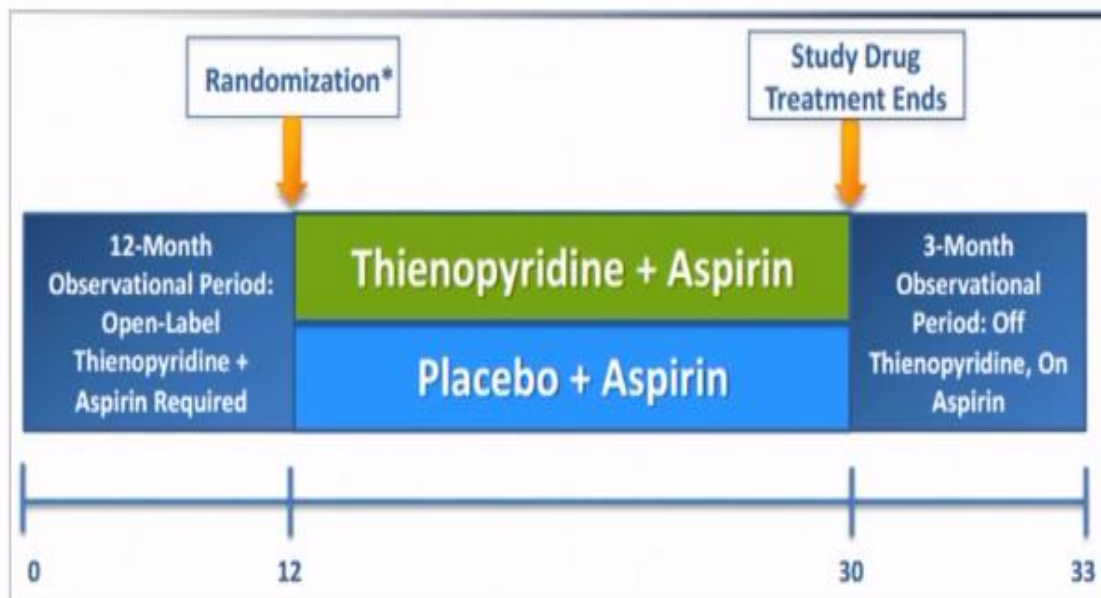
ESTABLISHED IN 1812

DECEMBER 4, 2014

VOL. 371 NO. 25

Twelve or 30 Months of Dual Antiplatelet Therapy  
after Drug-Eluting Stents

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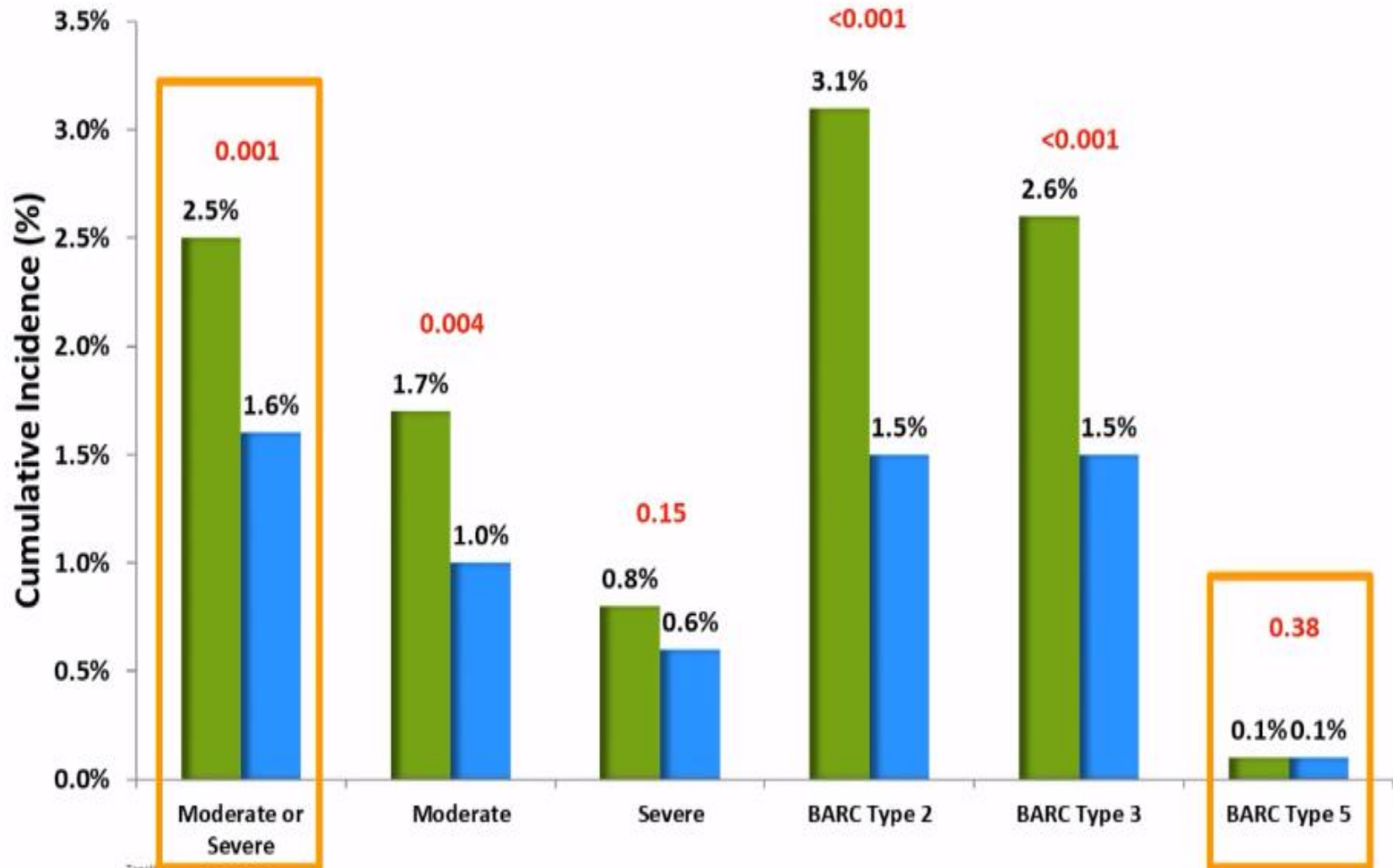


*Is there a benefit in extending DAPT beyond one year?*



# DAPT Results – Primary Safety Endpoint

Moderate or Severe Bleeding: 12-30 Months



*... despite the large amount of data, no conclusive answer on optimal DAPT duration was evident!*



Therefore, an individualized approach based on ischemic vs. bleeding risk assessment was the need of the hour

# Development of tools for decision-making

## Risk Prediction Models

Coronary Thrombosis and Major Bleeding After PCI With Drug-Eluting Stents  
Risk Scores From PARIS

**PARIS score**  
Baber U, et al.  
JACC 2016

Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention

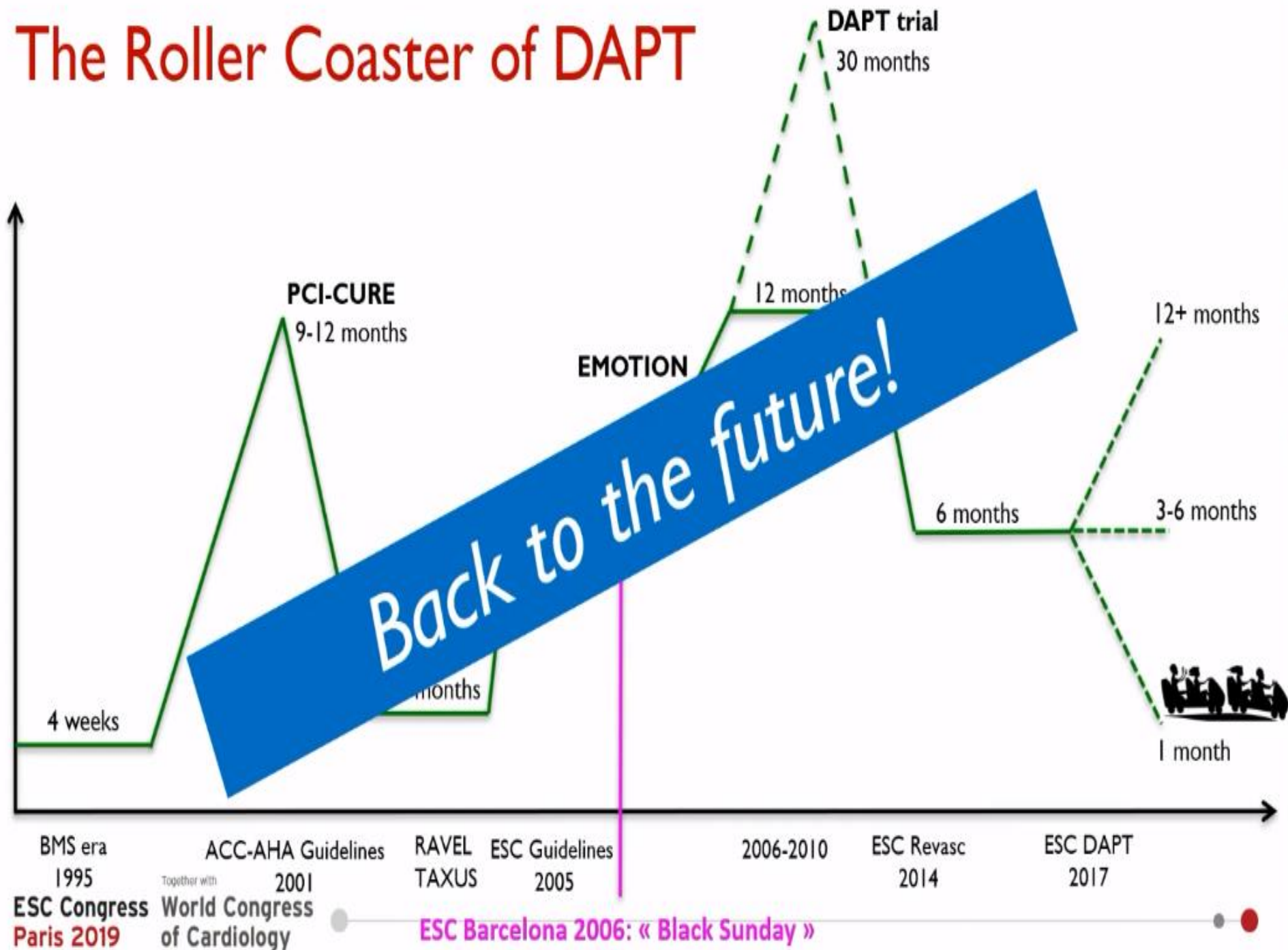
**DAPT score**  
Yeh RW, et al.  
JAMA 2016

Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials

**PRECISE-DAPT**  
Costa F, et al.  
Lancet 2017



# The Roller Coaster of DAPT







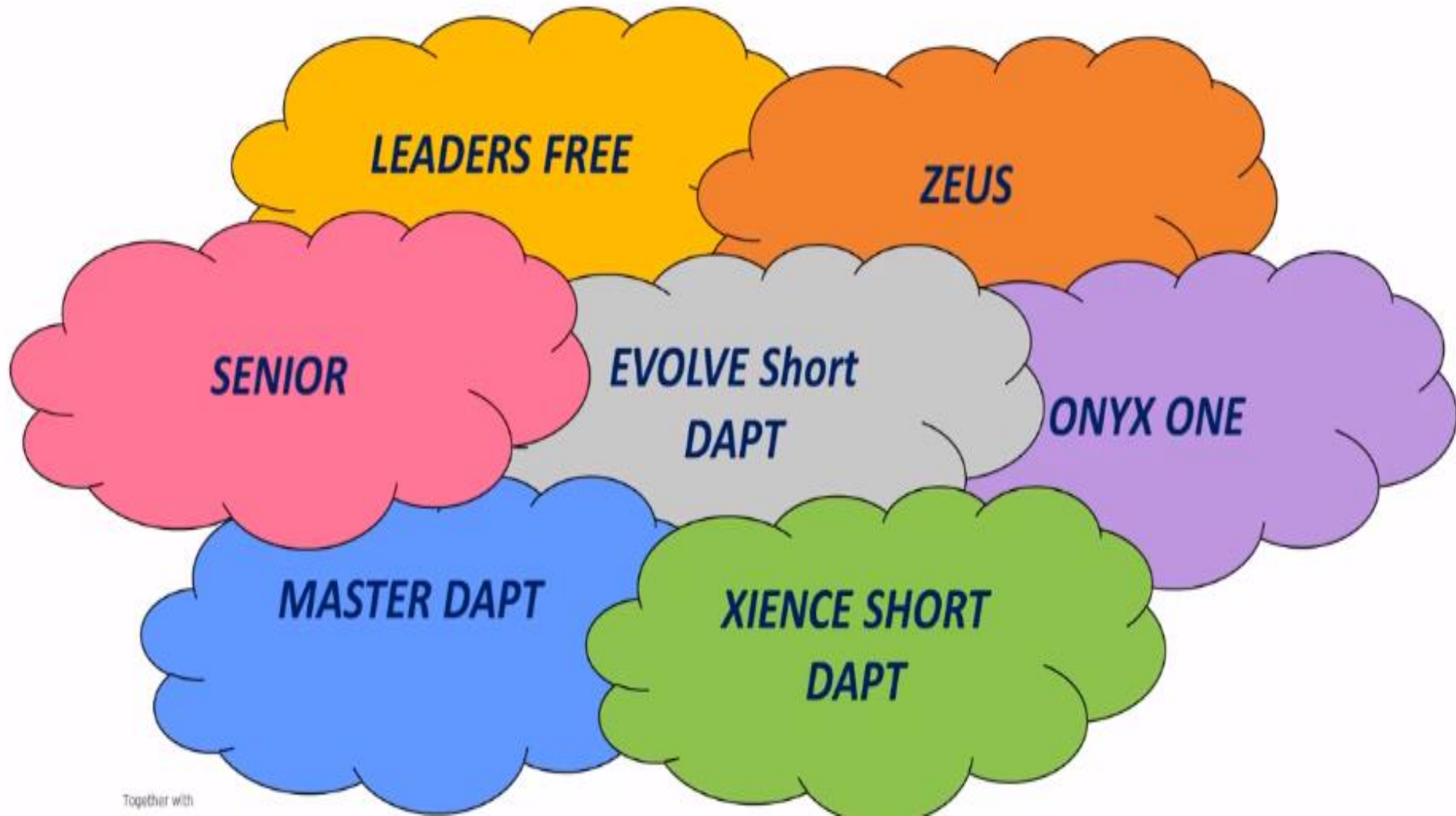
Reduction of ischemic events...



...only at cost of increased bleeding rates.

# Future Outlook

*Multiple Trials evaluating High Bleeding Risk Patients...*



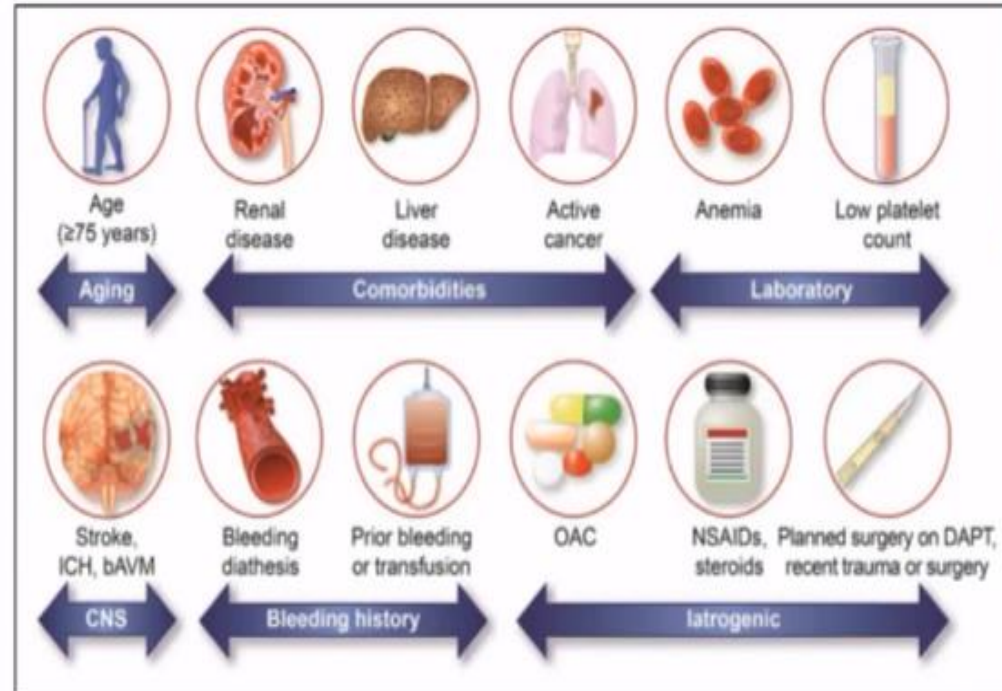


- 31 experts from Europe, USA, Japan and South Korea
- Two meetings in 2018: Washington (US) April 13-14 and Paris (FR) October 19-20
- Compliant with the ARC Charter, organized by CERC (Massy, FR)
- Non-profit initiative, sponsored by 22 pharma and device companies

# ARC for High Bleeding Risk

*Presented at EuroPCR 2019!*

- A consensus definition of patients at HBR was developed based on review of available evidence.
- Represents the first pragmatic approach to a consistent HBR definition in clinical trials evaluating the safety and effectiveness of devices and drug regimens for patients undergoing PCI.



Patients are considered to be at HBR if at least 1 major or 2 minor criteria are met



Recently, there has been more recognition for trials that withdraw rather than add to current treatments

## Do Current Clinical Trials Meet Society's Needs?

A Critical Review of Recent Evidence

Stuart J. Pocock, PhD,\* Bernard J. Gersh, MB, ChB, DPhil.†

*"...we need clinical trials that can investigate the withdrawal of certain established medications to see whether such withdrawal induces patient benefit, harm, or no difference compared with continued medication."*

- Stuart Pocock, PhD & Bernard Gersh, MB, ChB, DPhil

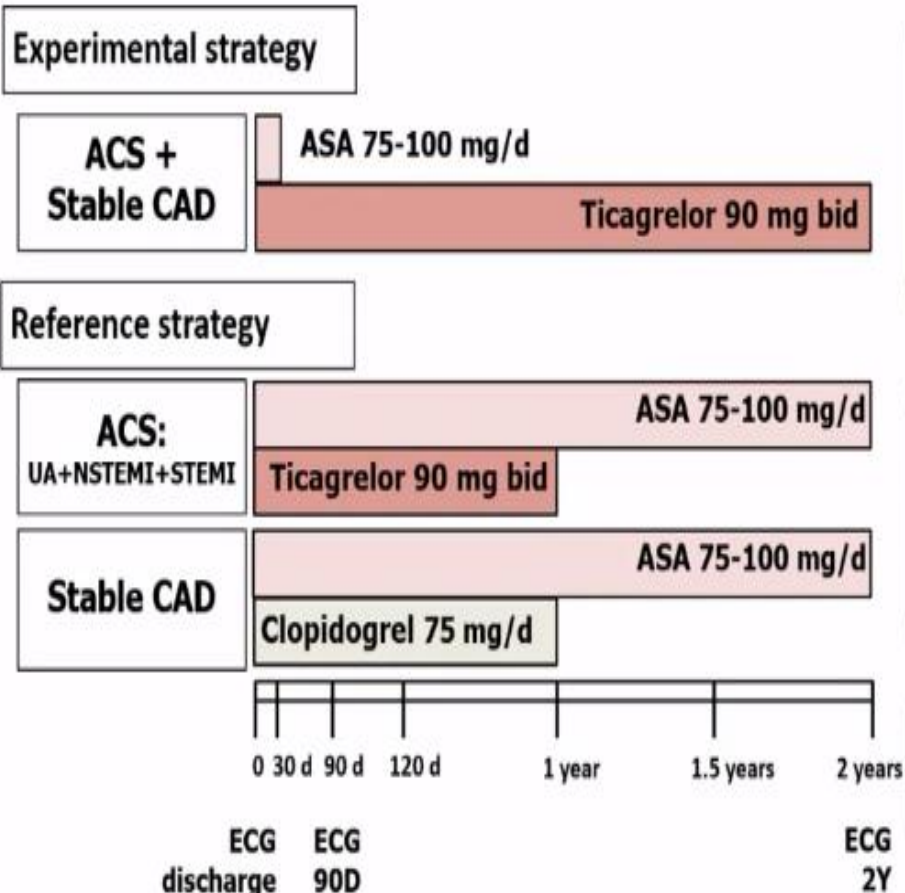
*Can we safely withdraw aspirin, when novel, more potent P2Y<sub>12</sub> inhibitors are used?*



# GLOBAL LEADERS

Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial

*Pascal Vranckx\*, Marco Valgimigli\*, Peter Juni\*, Christian Hamm, Philippe Gabriel Steg, Dik Heg, Gerrit Anne van Es, Eugene P McFadden, Yoshinobu Onuma, Cokky van Meijeren, Ply Chichareon, Edouard Benit, Helge Möllmann, Luc Janssens, Maurizio Ferrario, Aris Moschovitis, Aleksander Zunakowski, Marcello Dominici, Robert Jan Van Geuns, Kurt Huber, Ton Slagboom, Patrick W Serruys, Stephan Windecker, on behalf of the GLOBAL LEADERS Investigators*



**"All-comers" PCI population**  
**N = 15,991**  
 1:1 Randomisation, open-label design, 130 centers worldwide

- Any type of lesions: Left main, SVG, CTO bifurcation, ISR, etc.
- Unrestricted use of DES (number, length)

Bivalirudin-supported  
 BioMatrix DES by default

**Primary endpoint:** Composite of all-cause mortality or non-fatal new Q-wave MI up to 2 years post randomization


**Safety endpoint:** Investigator-reported BARC 3 or 5 bleeding up to 2 years



# GLOBAL LEADERS - A Missed Opportunity?

Primary and secondary outcomes  
at 24 months (Intention to treat)

	Experimental group	Reference group	Risk Ratio (95% CI)	p-value
Number of pts.	N=7980	N=7988		
All-cause mortality or new Q-wave MI	<b>3.81</b> % (304)	<b>4.37</b> % (349)	<b>0.87</b> (0.75-1.01)	<b>0.073</b>
All-cause mortality	<b>2.81</b> % (224)	<b>3.17</b> % (253)	<b>0.88</b> (0.74-1.06)	0.18
New Q-wave MI	<b>1.04</b> % (83)	<b>1.29</b> % (103)	<b>0.80</b> (0.60-1.07)	0.14
BARC 3 or 5 Bleeding	<b>2.04</b> %	<b>2.12</b> %	<b>0.97</b> (0.78-1.20)	0.77
BARC 5 Bleeding	<b>0.28</b> %	<b>0.30</b> %	<b>0.92</b> (0.52-1.64)	0.78
BARC 3 Bleeding	<b>1.88</b> %	<b>1.99</b> %	<b>0.95</b> (0.76-1.18)	0.63

 Ticagrelor monotherapy in ACS and SA

 ASA monotherapy in ACS and SA

## Limitations

- Linked to a single stent platform
- Lack of centralized adjudication; investigator-reported events
- Comparator arm has multiple embedded comparisons



# TWILIGHT



## **Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: Rationale and design of the TWILIGHT study**

### **Primary Objective:**

To determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months in reducing clinically relevant bleeding (BARC 2, 3 or 5) among high-risk patients who have undergone successful PCI

### **Secondary Objective:**

To determine the impact of antiplatelet monotherapy with ticagrelor alone versus DAPT with ticagrelor plus aspirin for 12 months on major ischemic adverse events (all-cause death, non-fatal MI or stroke) among high-risk patients who have undergone successful PCI

# TWILIGHT - Trial Schema



Enrollment Period

Randomization Period

Observational Period

High-Risk PCI  
Patients (n=9000)

N = 8200

Ticagrelor + Aspirin

Standard of Care

Ticagrelor + Placebo

Standard of Care

3 months

Short course DAPT

12 months

Monotherapy with potent platelet inhibitor provides  
ischemic protection while reducing ASA related bleeding

3 months

Standard therapy at  
physician's discretion

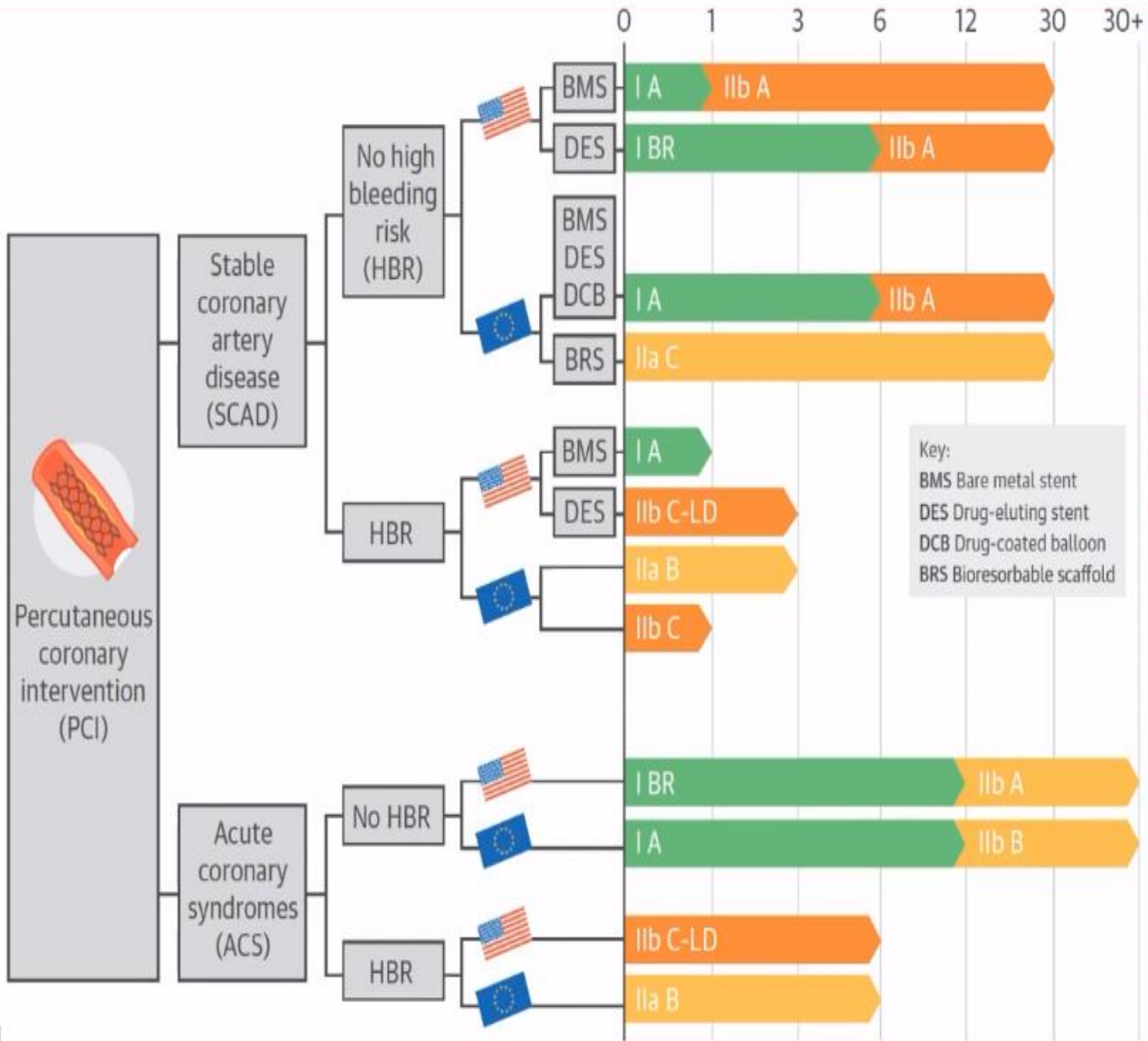
TIME 0 M

3 M

15 M

18 M

# ACC/AHA vs. ESC GUIDELINES ON DAPT DURATION IN PCI PATIENTS





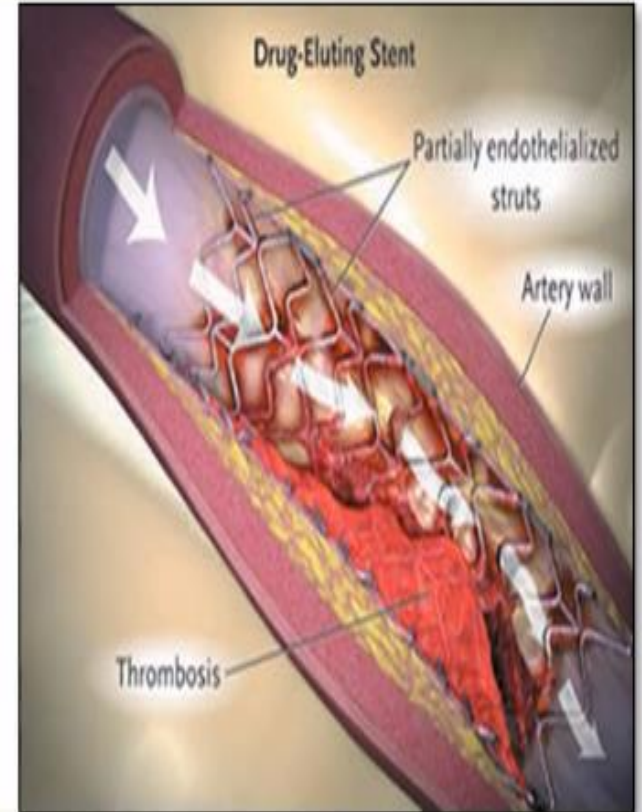
# ATRIAL FIB. + PCI STENT

**STROKE**



**OAC > DAPT**  
*for Stroke prevention*

**STENT THROMBOSIS**



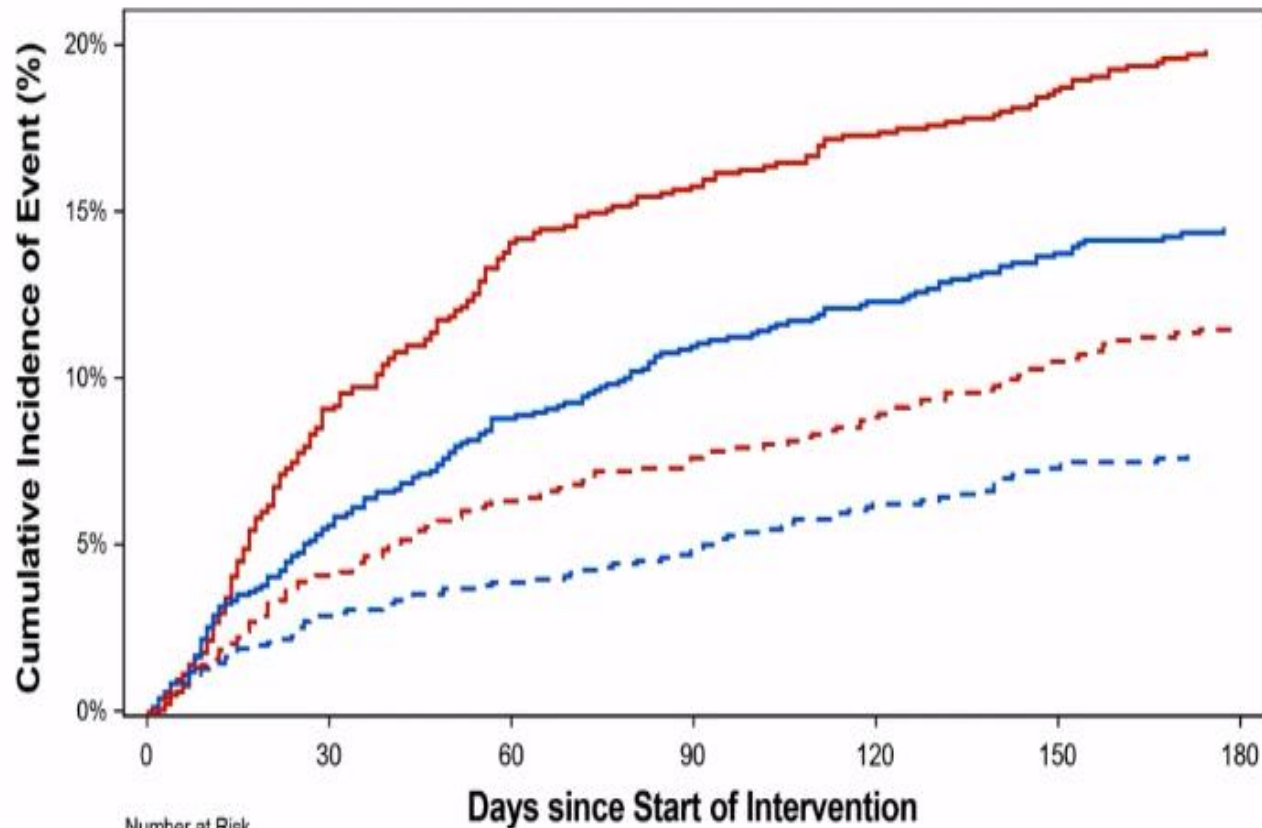
**DAPT > OAC**  
*for Stent Thrombosis prevention*

**TRIPLE THERAPY**

**BLEEDING**



# AUGUSTUS Major / CRNM Bleeding



VKA + Aspirin (18.7%)

Apixaban + Aspirin (13.8%)

VKA + Placebo (10.9%)

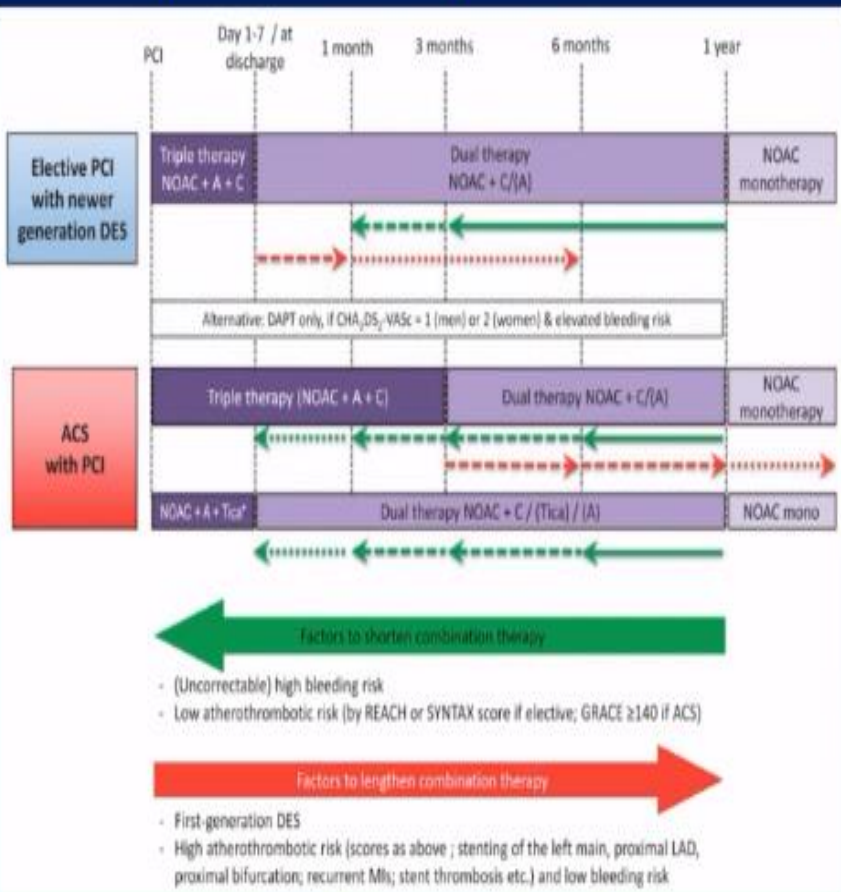
Apixaban + Placebo (7.3%)

**Apixaban + Placebo  
vs. VKA + Aspirin:  
11.4% absolute risk  
reduction (NNT=9)**

	Number at Risk						
	0	30	60	90	120	150	180
Apixaban and Aspirin	1145	1038	975	937	903	880	485
Apixaban and Placebo	1143	1075	1044	1007	975	947	538
VKA and Aspirin	1123	962	881	838	800	776	467
VKA and Placebo	1126	1007	947	917	883	851	528

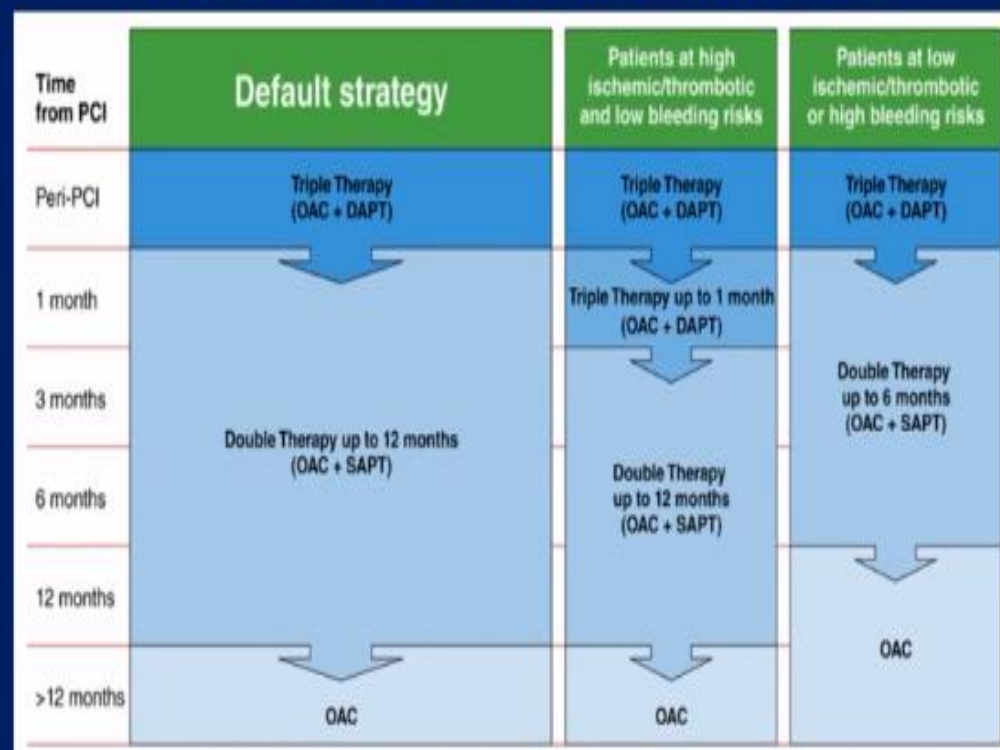
# GUIDE ON USE OF NOACs IN PCI AND AFIB

## European Heart Rhythm Association



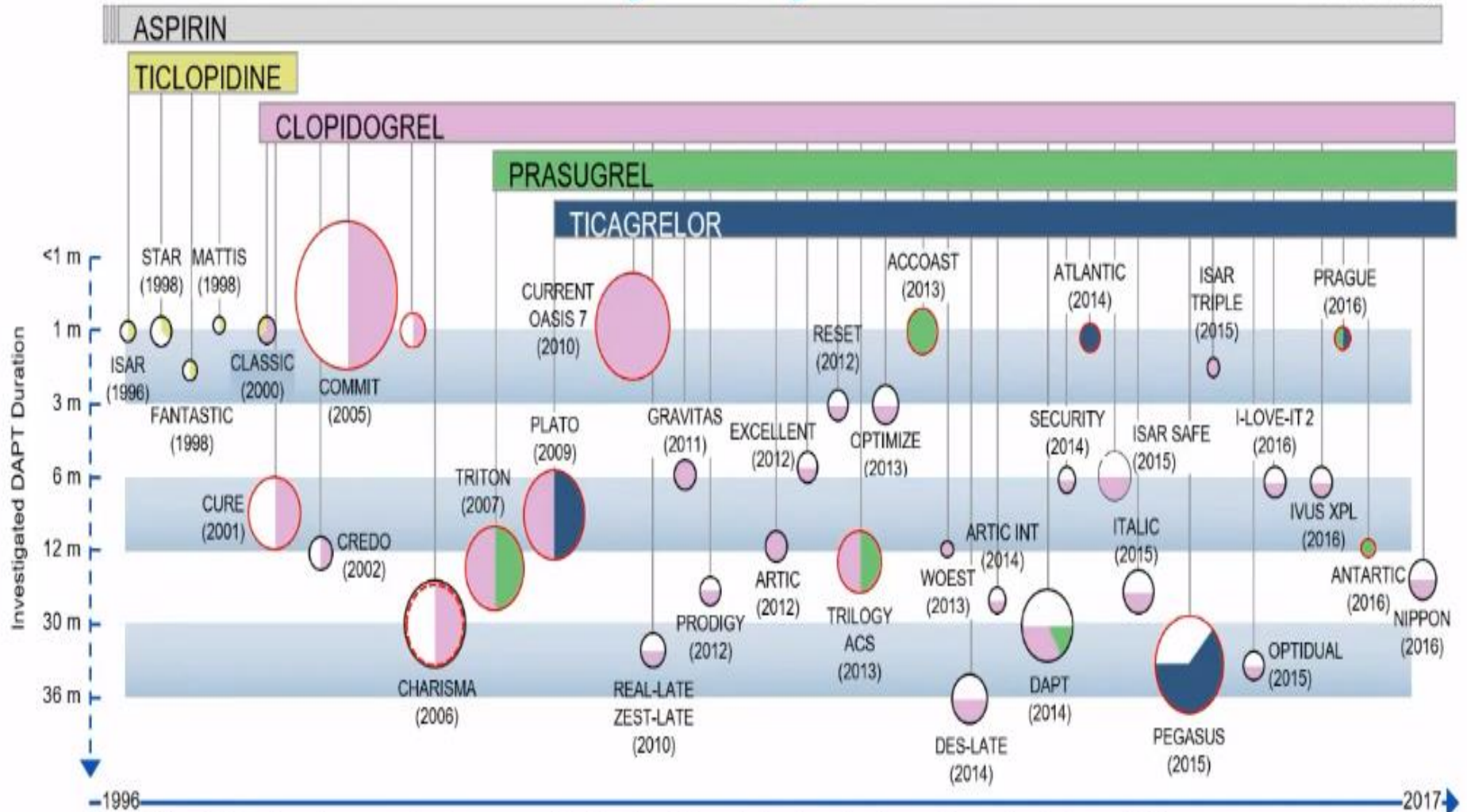
Steffel J, Eur Heart J, 2018

## North American consensus statement



Angiolillo D, Circulation, 2018

# History of Dual Antiplatelet Therapy (DAPT) in Patients with Coronary Artery Disease



Size of the circles denotes sample size

Perimeter of the circles denotes type of investigated population



- Mixed clinical presentation at the time of stent implantation

-- DAPT initiated in patients with prior myocardia infarction

- Acute coronary syndrome at presentation

- DAPT for primary prevention



# Optimal revascularization: towards a SYNTAX II strategy 2.0

