Heart Diseases and Stent Technology in Brazil: Panoramas, Outlooks, Challenges. How much interdisciplinary is all that?

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Outline

1. Panorama and outlooks on heart diseases in Brazil

2. Stent history, interventional cardiology and knowledge exchange

3. Research issues: our possible contributions

4. Final remarks

1. Panorama and outlooks on heart diseases in Brazil

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Facts & Figures

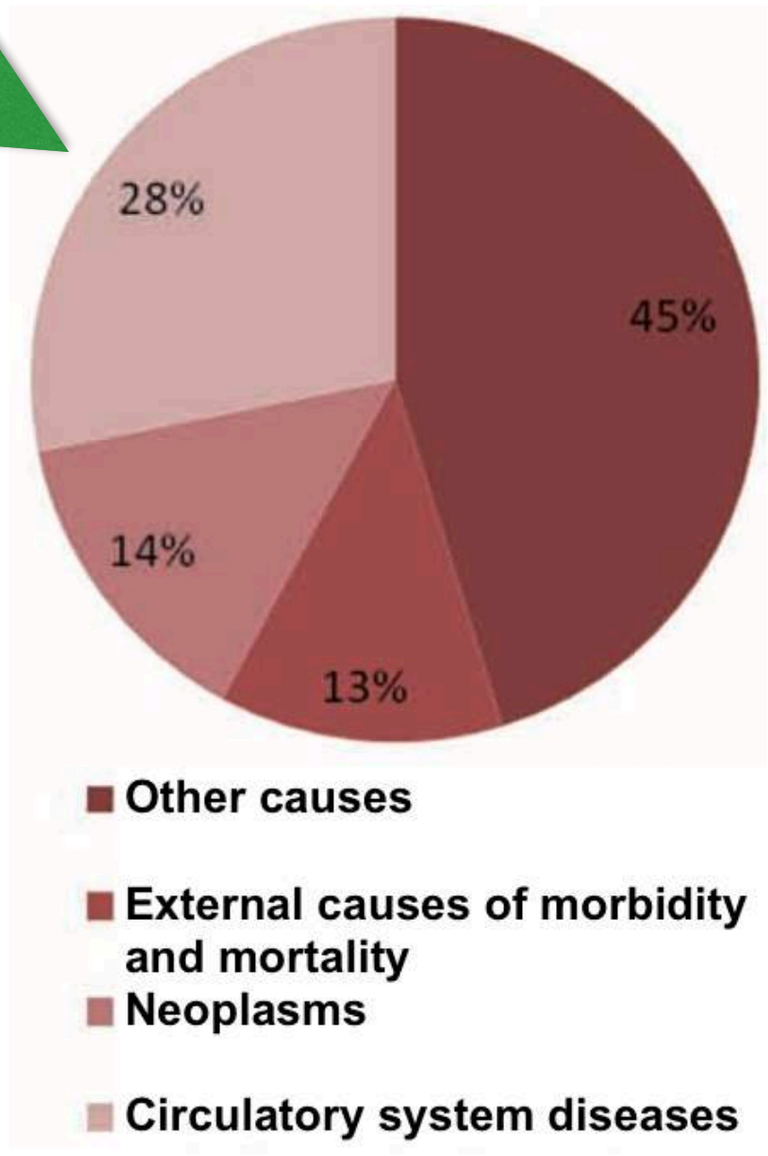
- CAD[1], AMI[2] are the main causes of obits in South America, especially in Brazil

- 3rd major cause of SUS hospitalizations in 2009

- highest hospitalization cost: R$1,9 bi = 19% of total

- direct + indirect costs of ACS[3] ≈ R$ 3,8 bi in 2011

28% of deaths by CVD[4] as a whole (1996-2011)



Polanczyk & Ribeiro. *Heart*, 95(11):870–876, 2009
Teich & Araujo. Rev Bras Cardiol 24.2 (2011): 85-94

[1]CAD: coronary artery disease
[2]AMI: acute myocardial infarction
[3]ACS: acute coronary syndrome
[4]CVD: cardiovascular diseases

- 2000-2005: 154,406 angioplasty procedures registered (CENIC[1]/SBHCI[2])

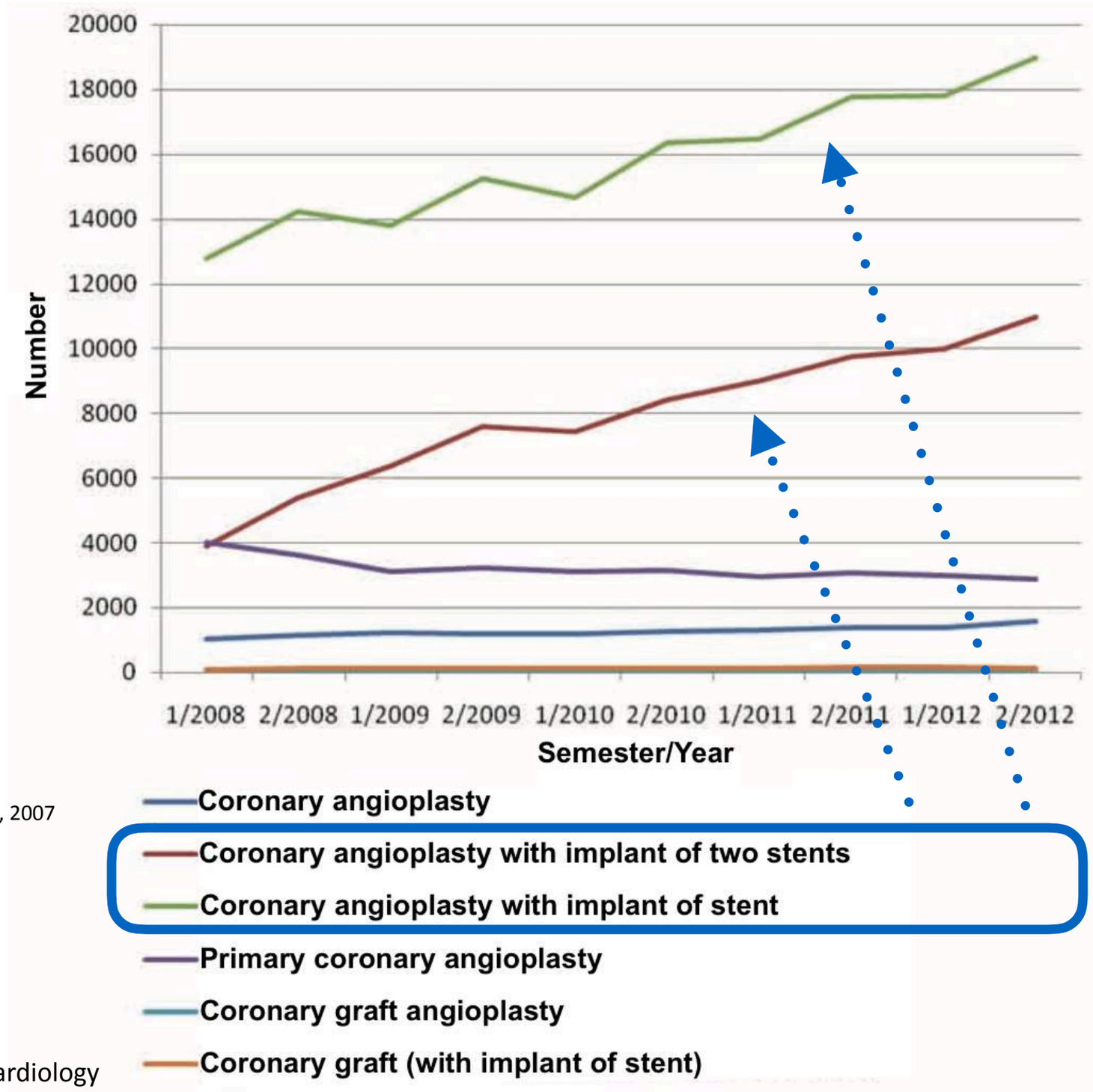
- DES used in 10,426 percutaneous coronary interventions

- 2008-2012: 543,937 stent-based angioplasties => **increase of 352%** rel. 2000-2005!

Cardoso et al. *Arq. Bras. Card.*, 89(6):356–61, 2007

Adapted from BRATS, Ano VII(22), 2013.

Number of hospitalizations for angioplasty funded by SUS (2008-2012)



[1] CENIC: National Centre of Cardiovascular Interventions

[2] SBHCI Brazilian Society of Hemodynamics and Interventional Cardiology

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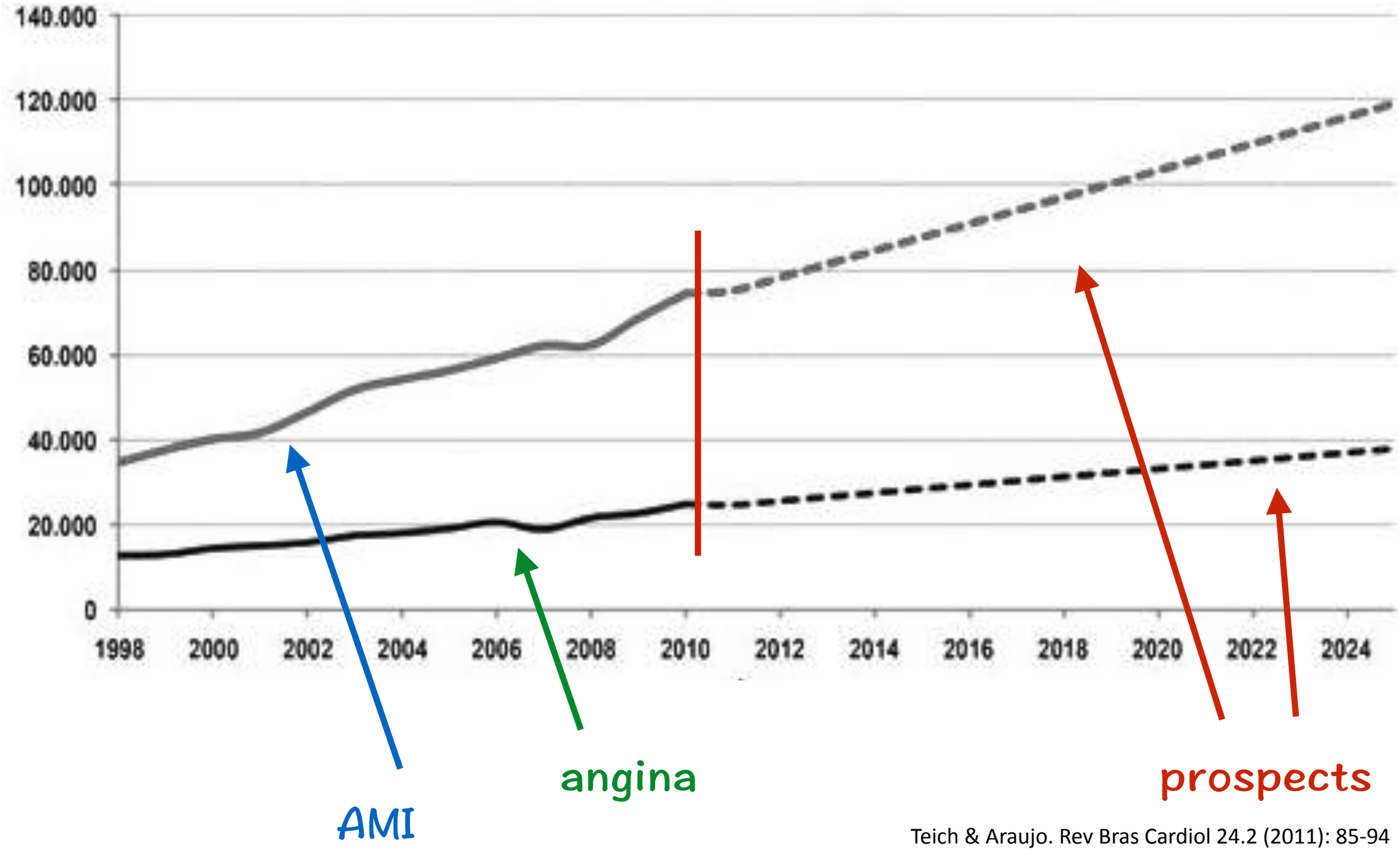
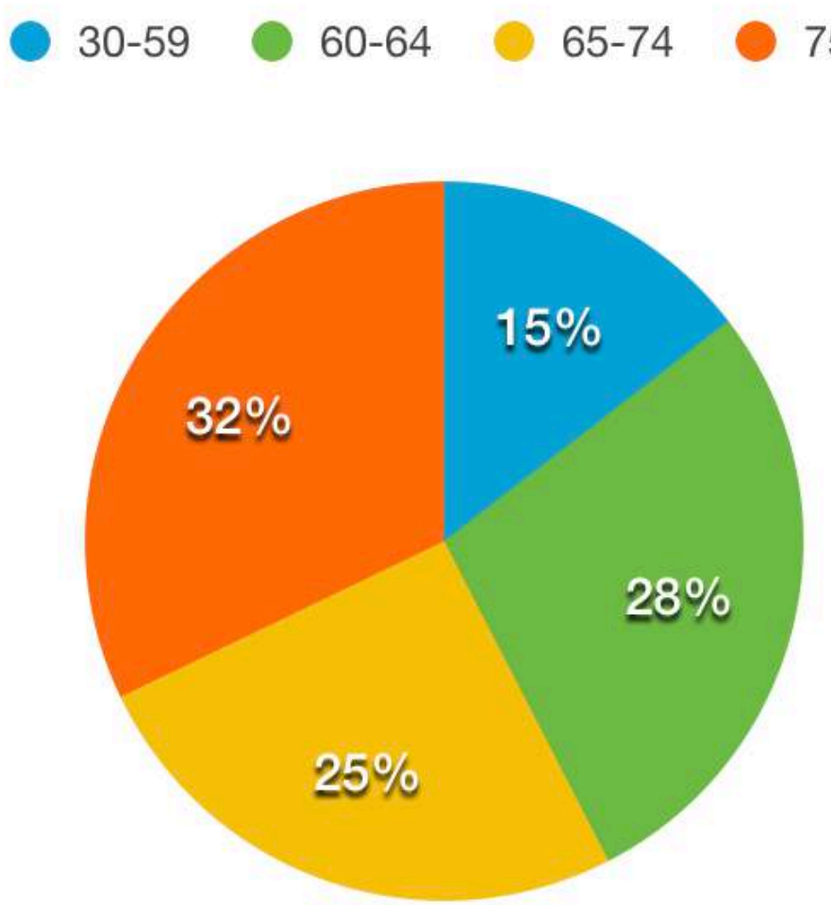
Number of hospitalizations registered in SUS + prospects (AMI, angina) x year



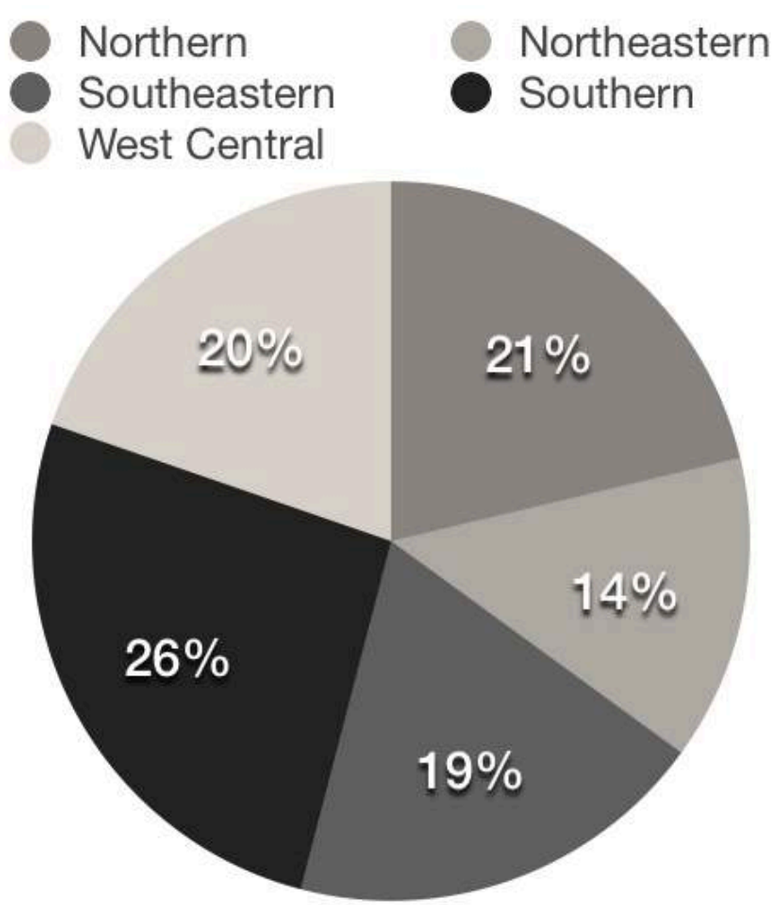
Teich & Araujo. Rev Bras Cardiol 24.2 (2011): 85-94

Some 2013's figures

Percentage values of people fitted with a stent or submitted to angioplasty by age group



Ditto by Brazil's regions



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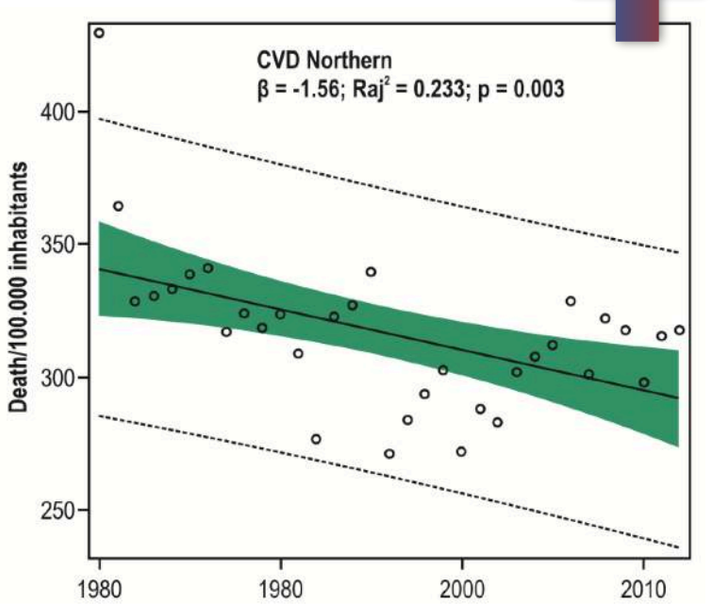
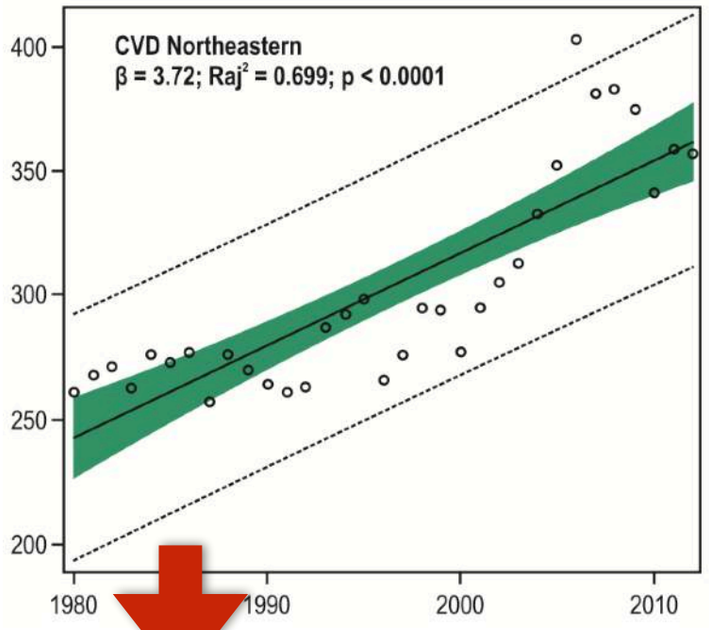
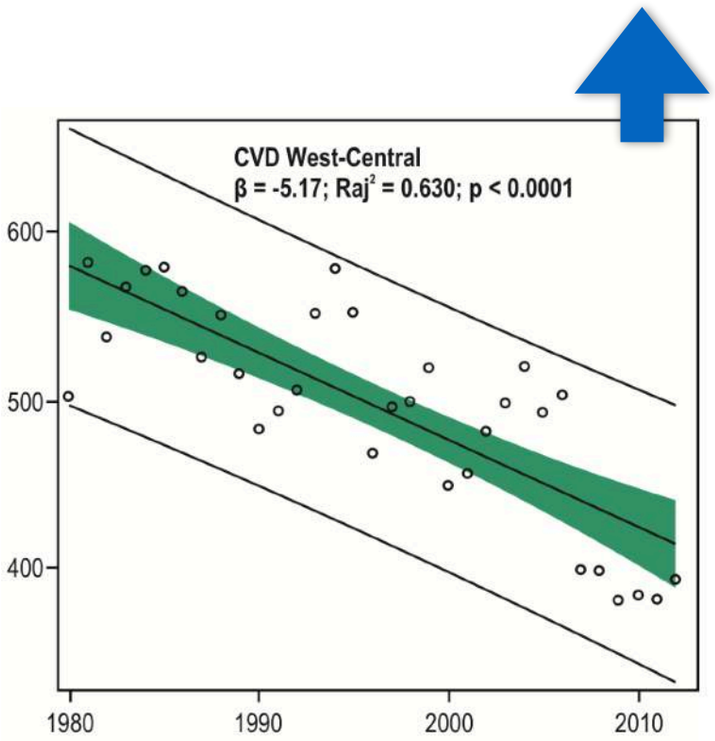
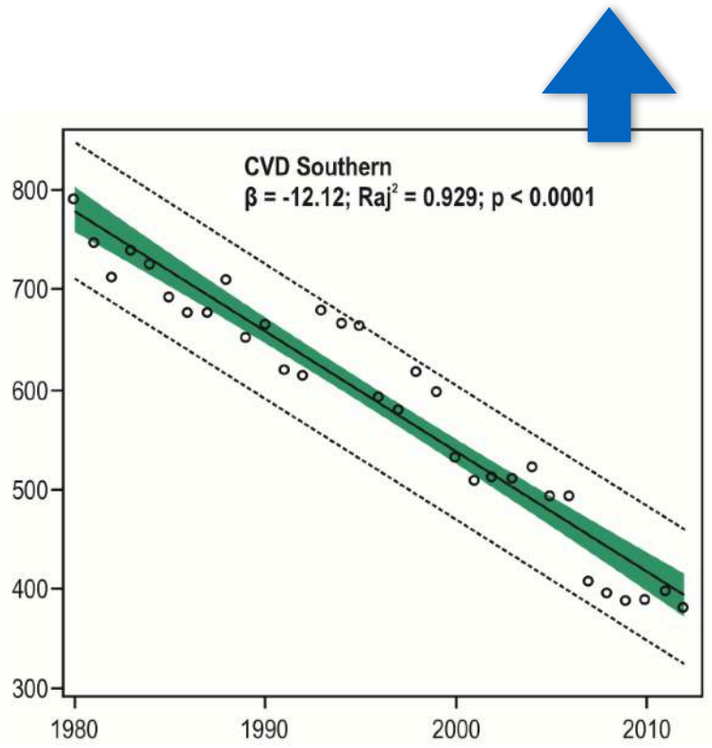
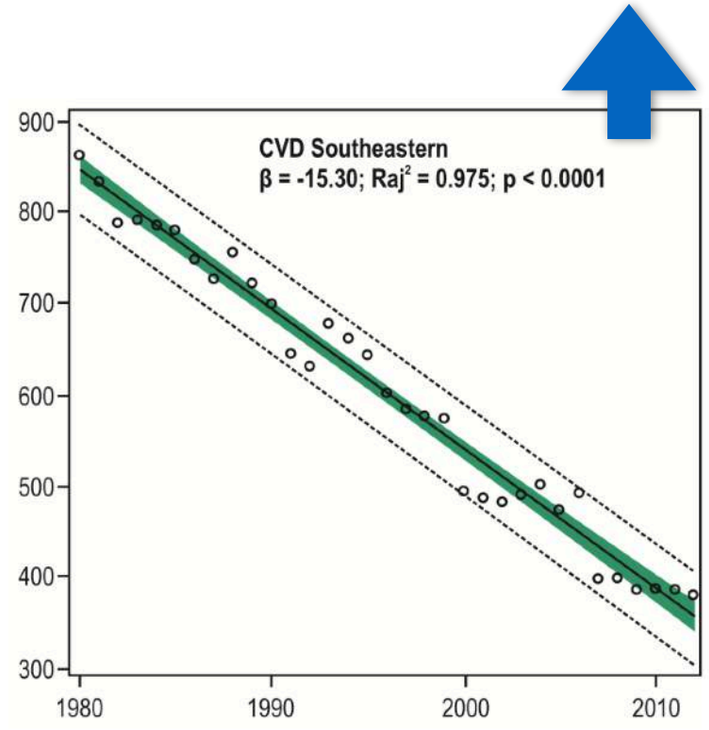
CVD mortality trends (2008-2012) (individuals ≥ 30) by region





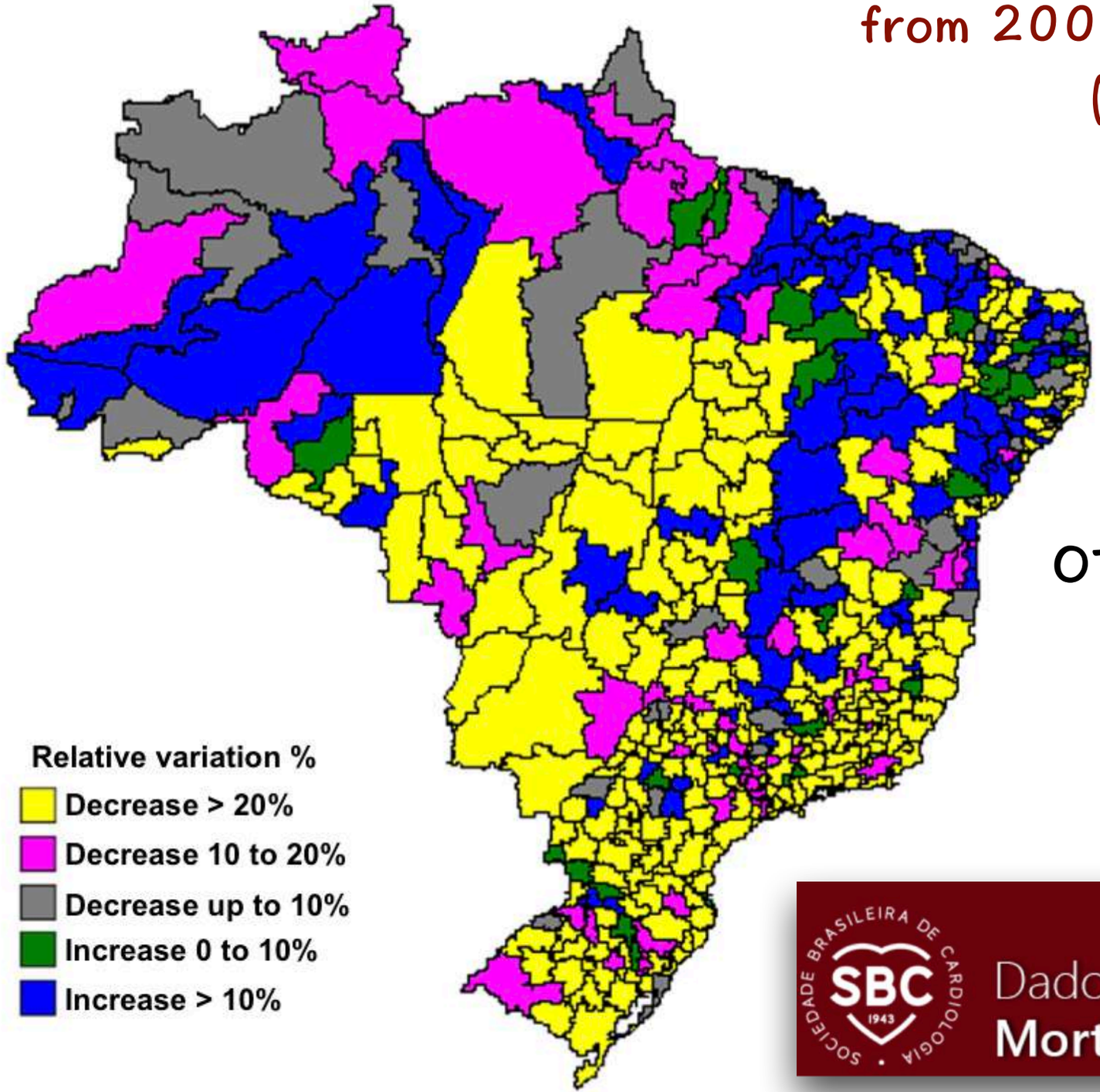






Mansur & Favarato. Arq. Bras. Card., 107(2):137–146, 2016

Relative variation in CVD mortality for men from 2003 to 2012 per federation unit (source: http://goo.gl/YsFdkm)



other geocharts here

Dados e Estatísticas de Mortalidade Cardiovascular

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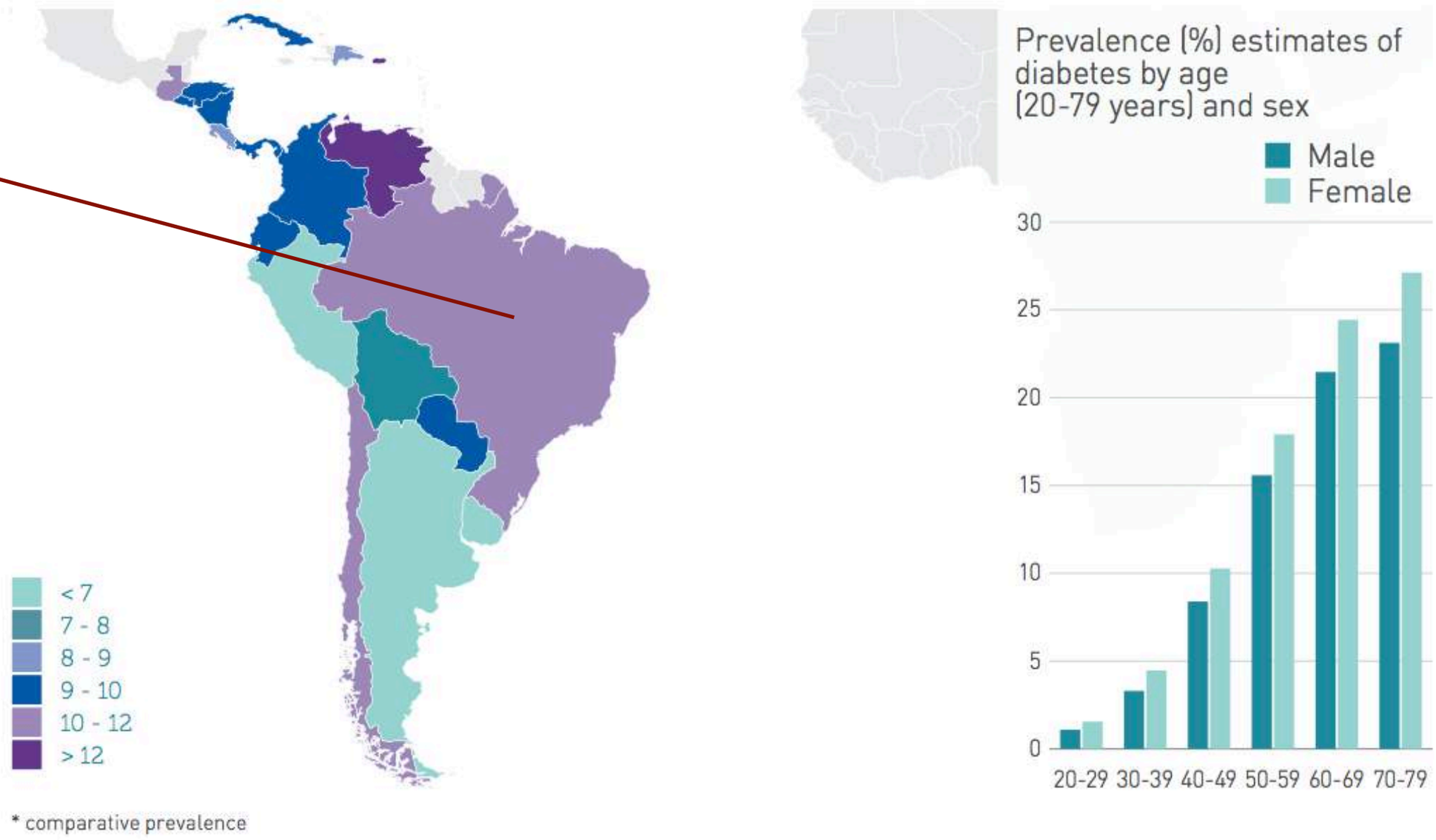
Some 2015's figures

Brazil

- highest number of diabetic people (ave. 14.3 million)
- 68,5% diabetic children aged < 15 (type 1)
- 130,700 obits (people aged < 60)
- US$ 28 bi spent to combat DM

Diabetes mellitus map (South America)

Source: IDF Diabetes Atlas 2015



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Remark on data sources

- DATASUS: main data source about health status in the country;

- Lastly fed after the National Health Survey 2013

- NHS managed by MS & IBGE and planned to occur each 5 years;

- NHS 2013 results published in 4 volumes:

Volume I Dec 2014	Volume II Jun 2015
Volume III Aug 2015	Volume IV Jun 2016

Balance of NHS 2013 results: Malta &Szwarcwald.
Sao Paulo Med. Journal. 133(4):286–289, 2015.

Source: Health Portal. Available on: http://goo.gl/YLqNie

2. Stent history, interventional cardiology and knowledge exchange

Why "stent"??

http://circinterventions.ahajournals.org/content/4/2/206.full

- Word acceptable origin: derives from the name of an English dentist.

- Famous for improving and modifying the denture base of the gutta-percha*, creating the **Stent's compound**

  * a natural latex produced from tropical trees native to Southeast Asia

Charles Thomas Stent
(1807-1885)

Logo stamp of
Stent's Compound

When stenting?

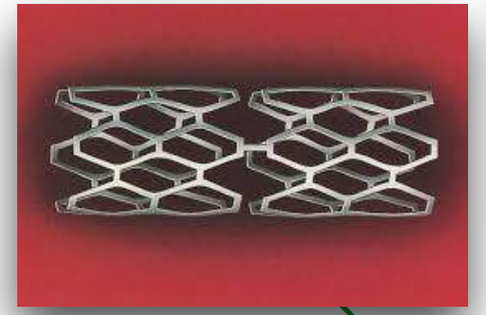
- atherosclerosis (buildup of fats, cholesterol, and calcium in the arteries)
- angina or persistent chest pain
- chronic shortness of breath
- history of heart attacks
- arteries are too narrowed or weakened blood vessels
- severe disease in multiple vessels
- history of diabetes

extreme situations

(Brief) stent timeline

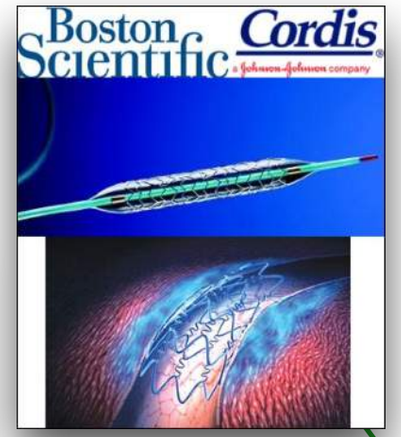
1977

1st balloon angioplasty
in humans
Andreas Gruentzig



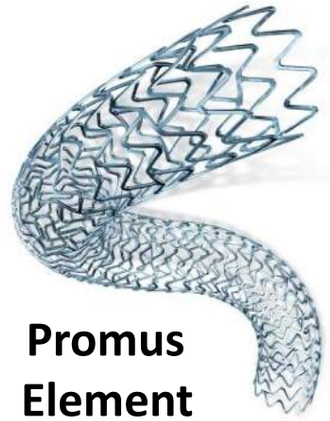
1994

Palmaz-Schatz
BMS (USA only)
30% restenosis



2003

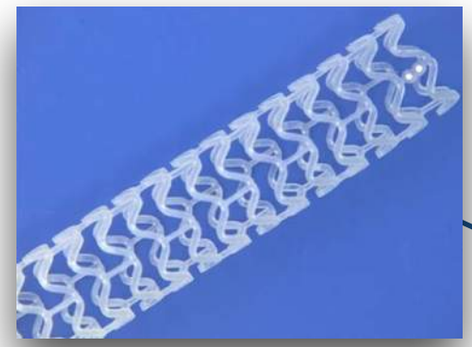
1st generation
DES
(Cypher-Cordis)
< 5% restenosis
durable polymer



Promus
Element

2009

2nd generation
DES
thinner;
more flexible



Abbot Absorb GT1
Approval: July 2016 (USA)

2013

3rd generation
DES
biodegradable
polymer
(2% restenosis)

2016

4th generation?
polymer-free

Ernst, Eur. Med. J. Interv. Cardiol. 1 (2014): 100-6

Interventional cardiology in Brazil

- well-organized scientific bodies
- long-term and dedicated studies
- good research base

SOCIEDADE BRASILEIRA DE HEMODINÂMICA E CARDIOLOGIA INTERVENCIONISTA

Arquivos Brasileiros de CARDIOLOGIA

Incorporation of DES into SUS: CONITEC 111, 2014 Portaria MS 26/2014

Incorporation Rate	DES utilisation percentage (%)	Number of patients
Year 1	10.00	1,095.54
Year 2	12.50	1,369.425
Year 3	12.50	1,369.425
Year 4	15.00	1,643.31
Year 5	50.00	5,477.70
Total	***100.00***	***10,955.40***

Annual average number of first implants 2,191.08

Source: Report 111, Page 36, Figure 12

Period	Budget impact	
	inflation rate neglected	inflation rate considered
Year 1	R$5,054,963.98	-
Year 2	R$12,163,924.74	R$12,392,836.52
Year 3	R$19,291,027.64	R$19,950,629.44
Year 4	R$27,843,551.12	R$29,328,303.14
Year 5	R$56,351,962.72	R$61,559,545.85

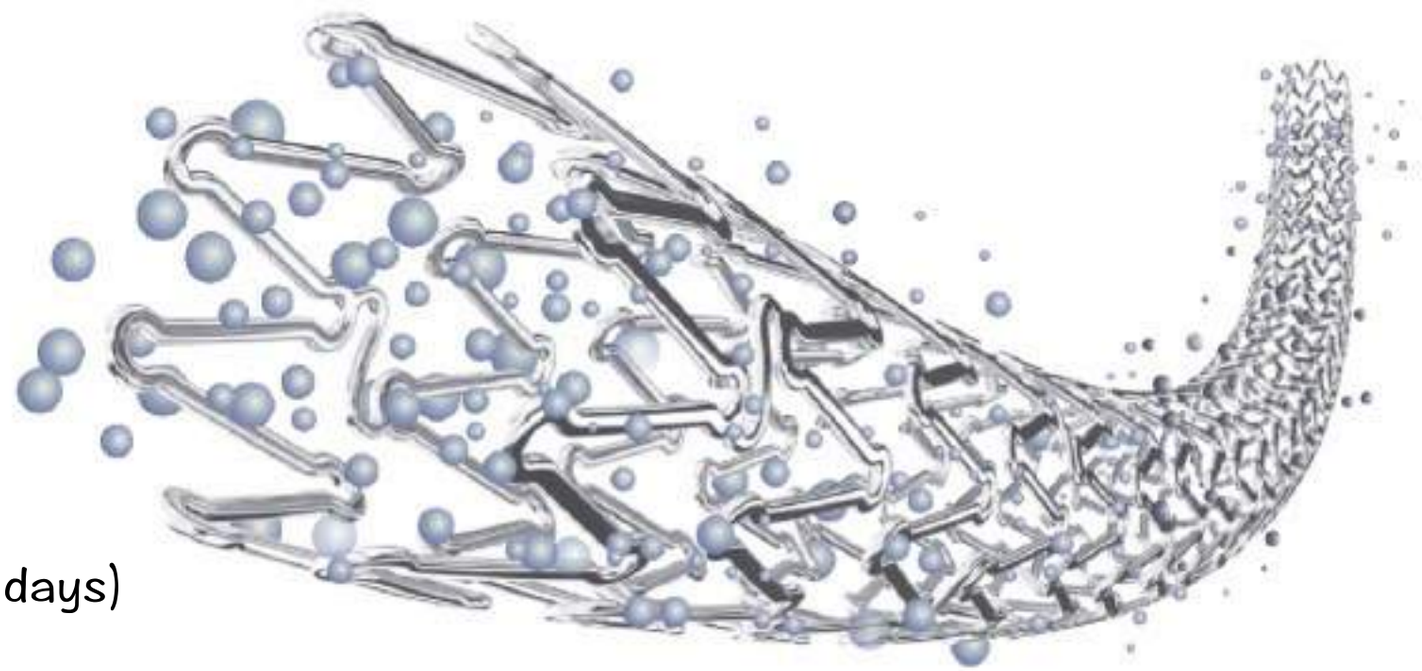
Source: Report 111, Page 37, Table 5

Scitech Inspiron: 1st DES made in Brazil under international standards

why not to be proud?

Main characteristics:

- Abluminal Coating
- Biodegradable polymer
- Sirolimus Elution (pt. rapamicina)
- Moderate drug release profile
  (60% in 10 days and the remainder in 45 days)
- In 6 to 9 months the polymer is completely degraded
- Cobalt-Chromium Platform
- High Flexibility
- Great side branch access
- Thinner Links (80 µm)



Source: http://www.scitechmed.com/products/interventional-cardiology/inspiron/

Groundbreaking moments

- 1st stent implantation **of the world** (1987)
- 1st bioabsorbable DES implantation **of Brazil** (Feb 2015)

  Both performed at HCOR/São Paulo by Dr. José Eduardo Sousa

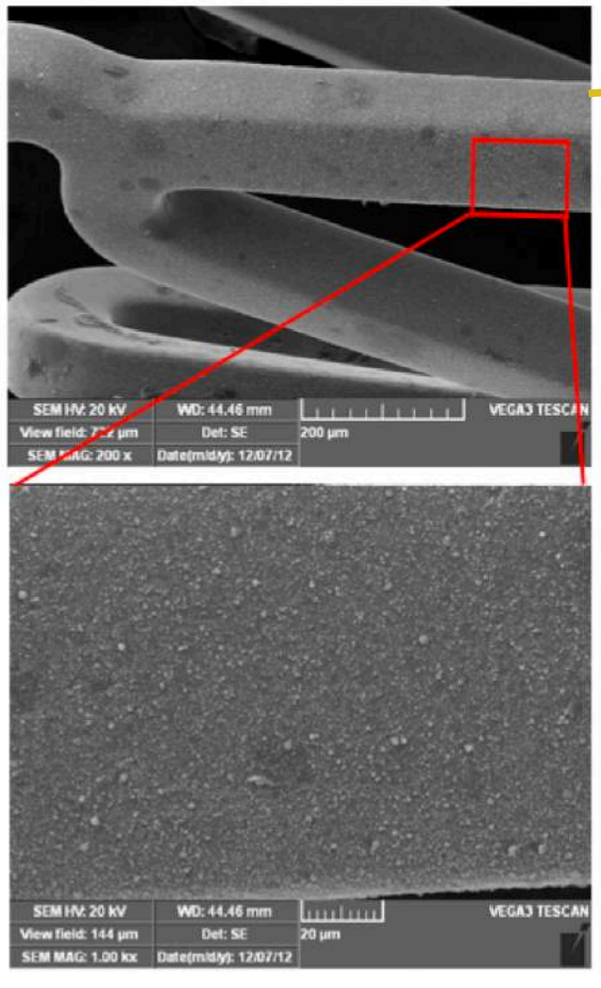
Till here, almost 30 years have gone and many hearts, fortunately, maintain beating!

Drug-eluting stent animation

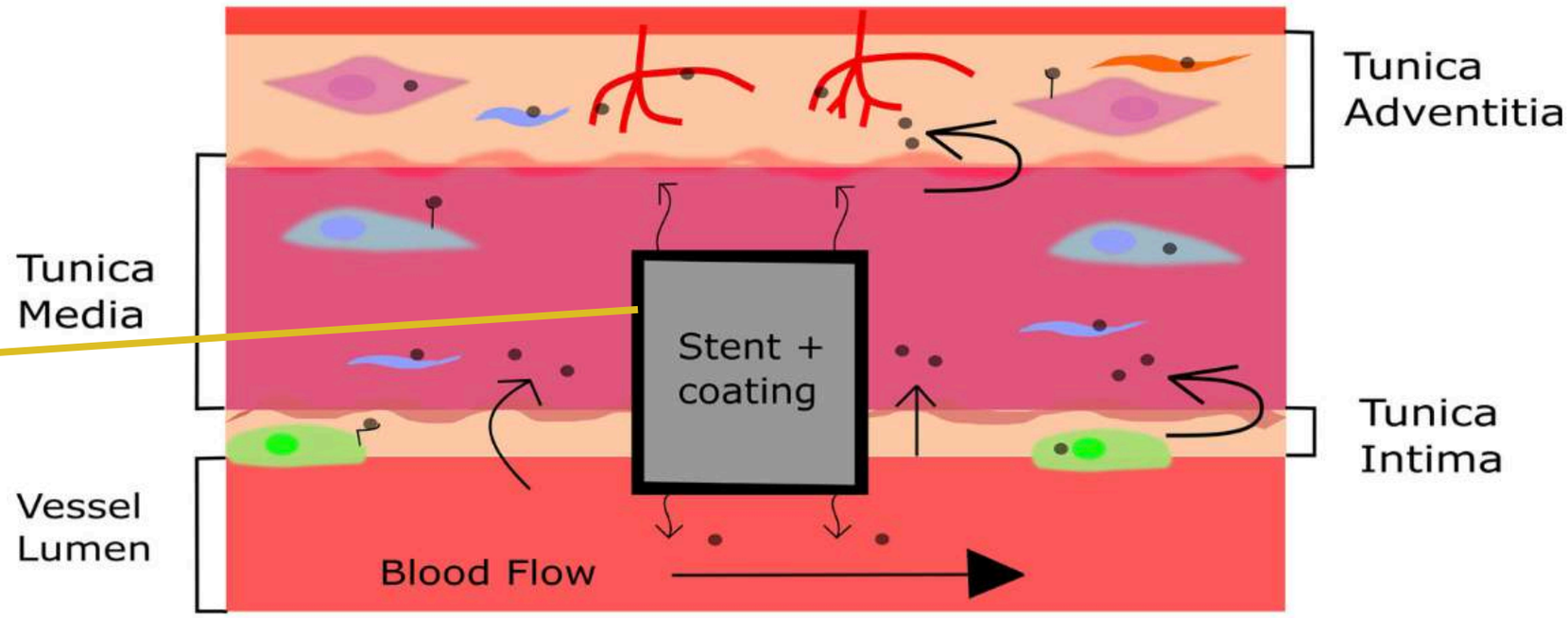
From Medtronic®

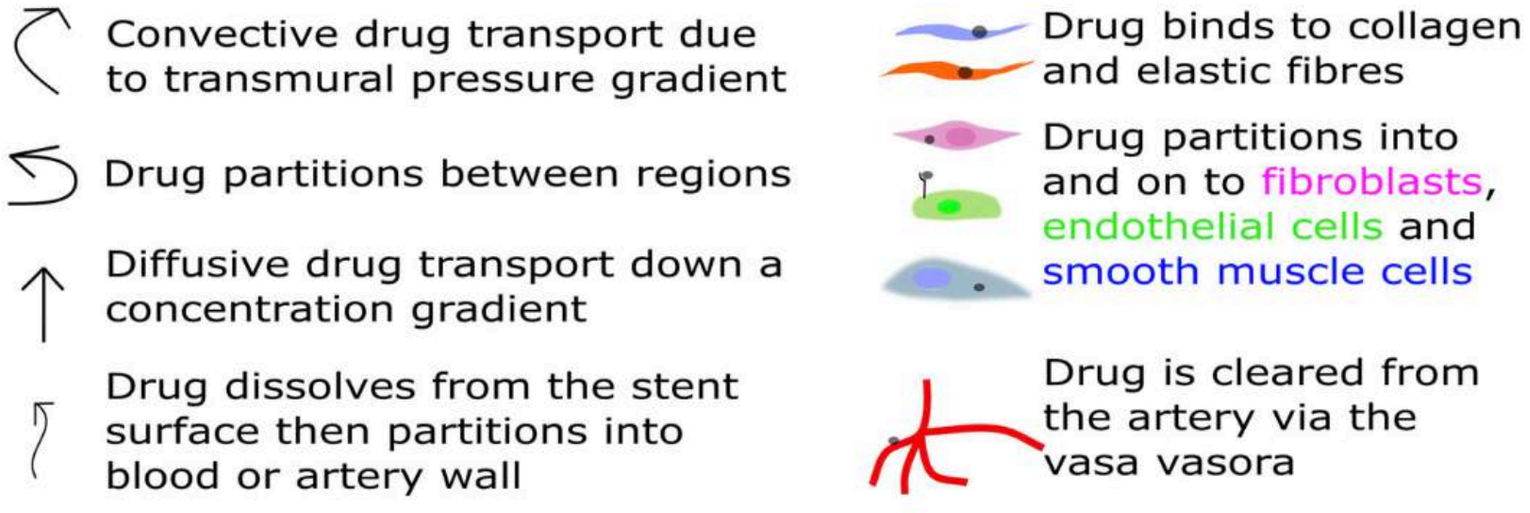
Drug elution complexity

- drug binding
- controlled release
- tissue uptake
- atherosclerosis impact
- anisotropy effects
- in vitro models
- in vivo models (rabbits, pigs)



Hu et al. ACS Appl. Mater. Interfaces, (7) 11695−11712, 2015





McKittrick et al. Annals of Biomed. Engg. 44(2), 477–487, 2016

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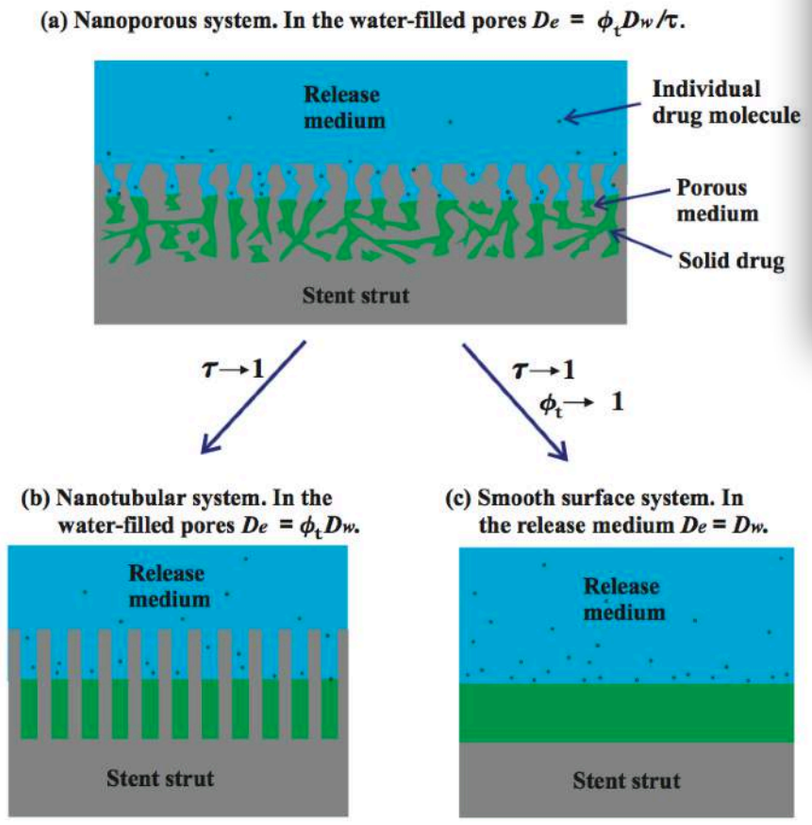
1st generalized model of drug elution for polymer-free DES

McGinty et al, *Acta biomaterialia* 18 (2015): 213-225.



$$\frac{\partial c_w}{\partial t} = D_w \frac{\partial^2 c_w}{\partial x^2}, \quad 0 < x < \infty, t > 0,$$

$$\frac{\partial c_p}{\partial t} = D_a \frac{\partial^2 c_p}{\partial x^2}, \quad c_b = \phi k_a c_p/(\phi_s k_d), \quad s(t) < x < 0, t > 0,$$

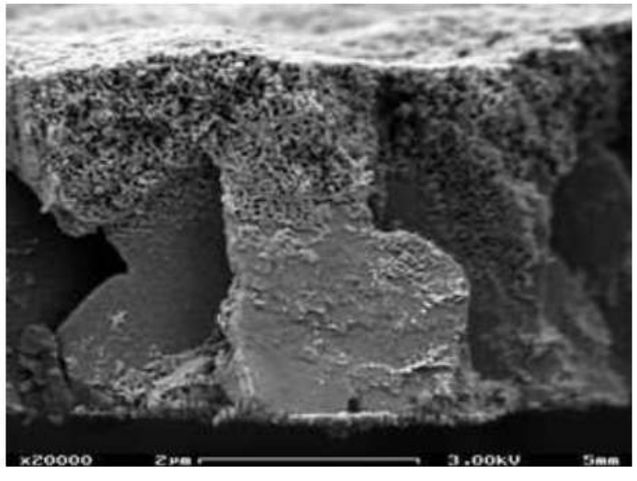
$$c_p = c_w, \quad -D_e \frac{\partial c_p}{\partial x} = -D_w \frac{\partial c_w}{\partial x} \quad \text{on } x = 0, t > 0,$$

$$c_p = c_s, \quad -D_a \frac{\partial c_p}{\partial x} = \frac{ds}{dt}(c_s - c_0) \quad \text{on } x = s(t), t > 0,$$

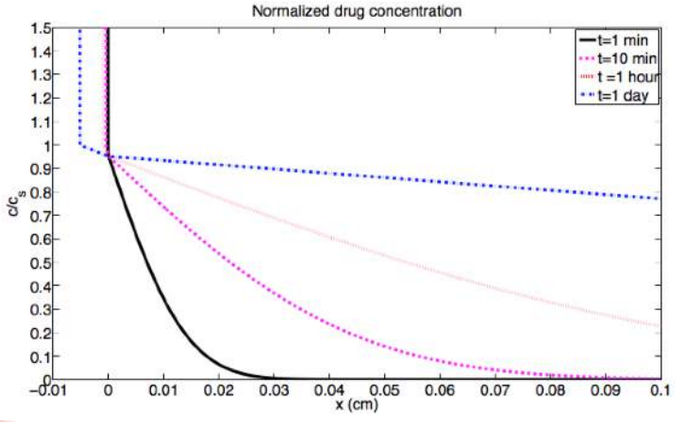
$$c_w \to 0 \quad \text{as } x \to +\infty, t > 0, \quad c_w = 0 \quad \text{at } t = 0, x > 0,$$

$$c_p = c_0 \quad \text{at } t = 0, -L_d < x < 0, \quad s(t = 0) = 0.$$

diffusion equations with a moving front (Stefan condition)



- macroporous
- microporous
- nanotubular
- smooth surface



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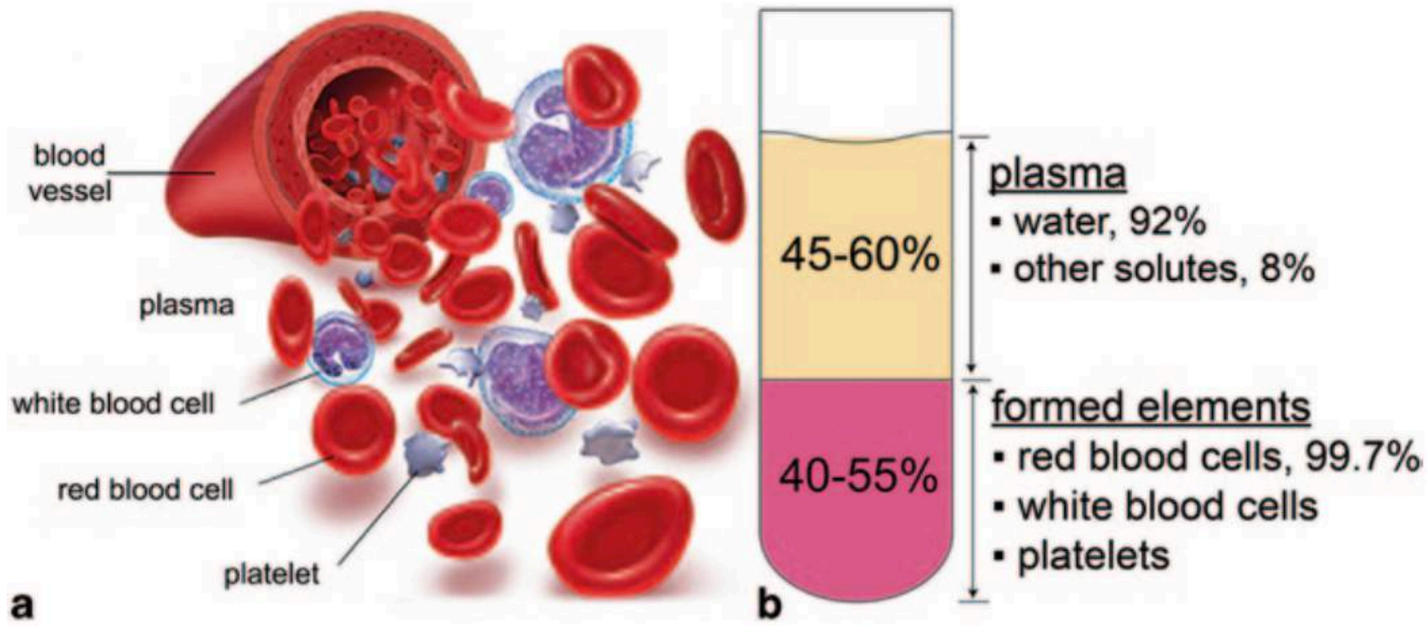
3. Research issues: our possible contributions

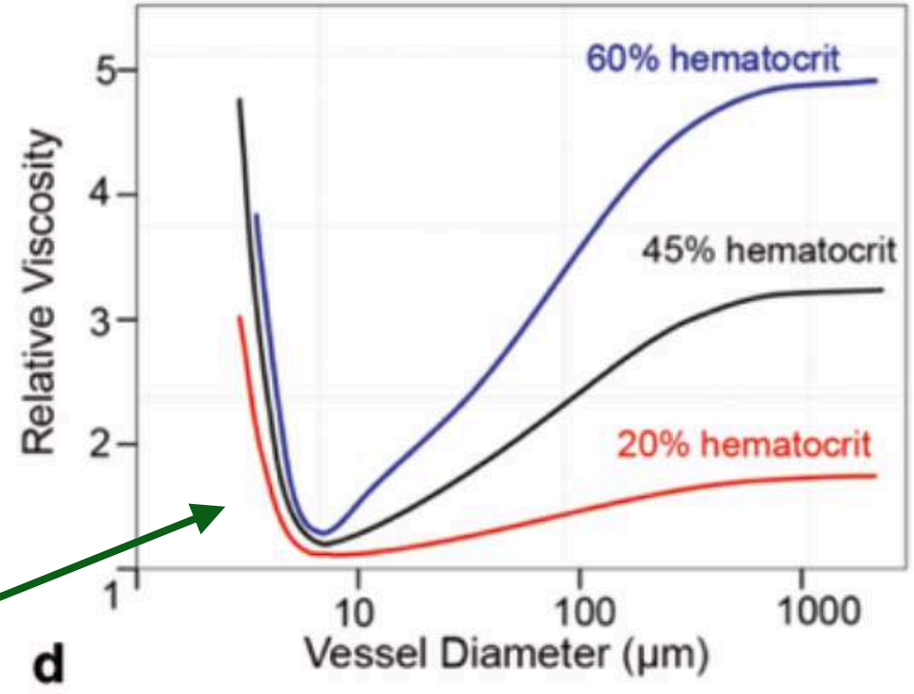
Frontline: Hemodynamics

- blood properties
- how it flows
- density; viscosity;
- heterogeneity



- large vessel ø ≈ Newtonian
- small vessel ø (1mm -> 7 µm)
  => non-Newtonian

$$\mu = k \exp(T_0/T)\gamma^{n-1}$$



"Fahraeus-Lindqvist effect"

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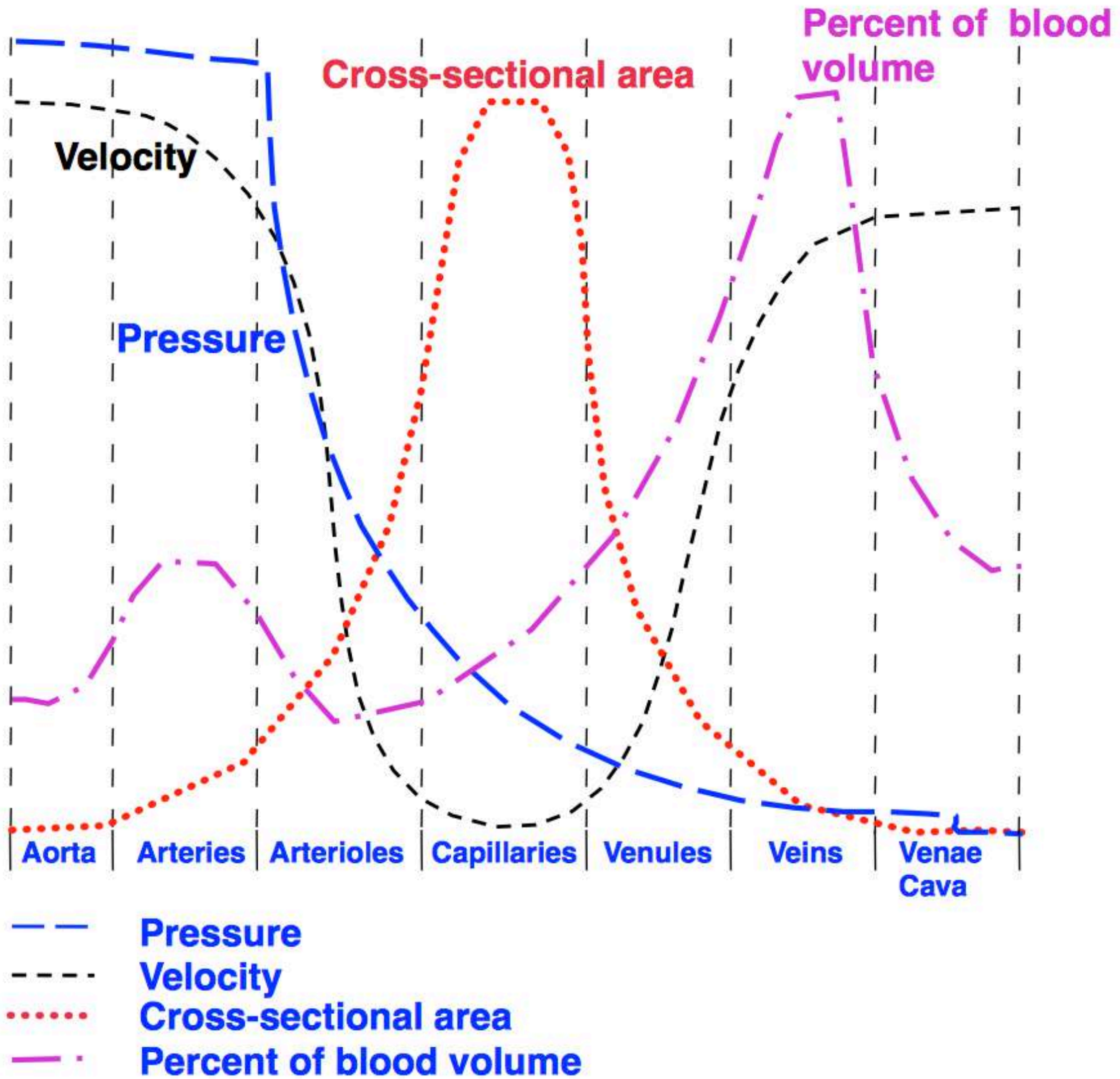
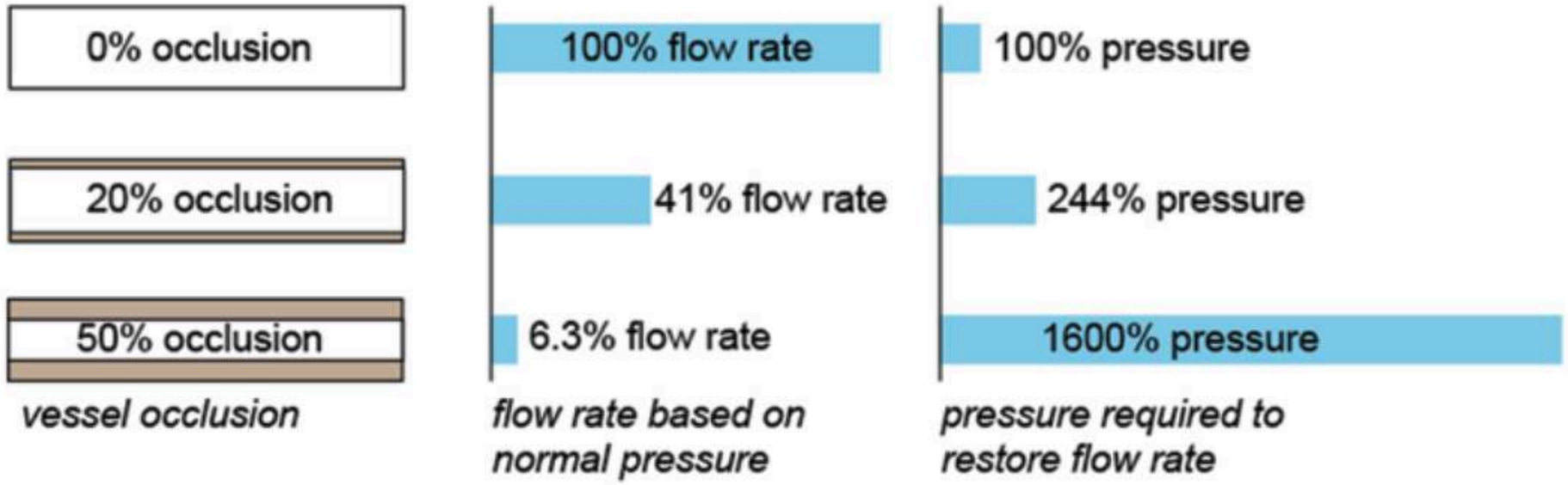
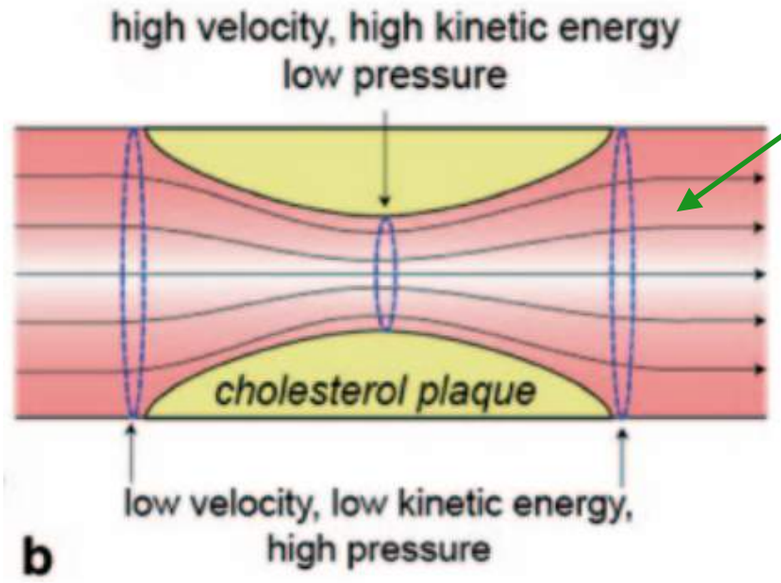
Some hemodynamic variables



Challenge: atherosclerotic plaque + stent





region to be stented

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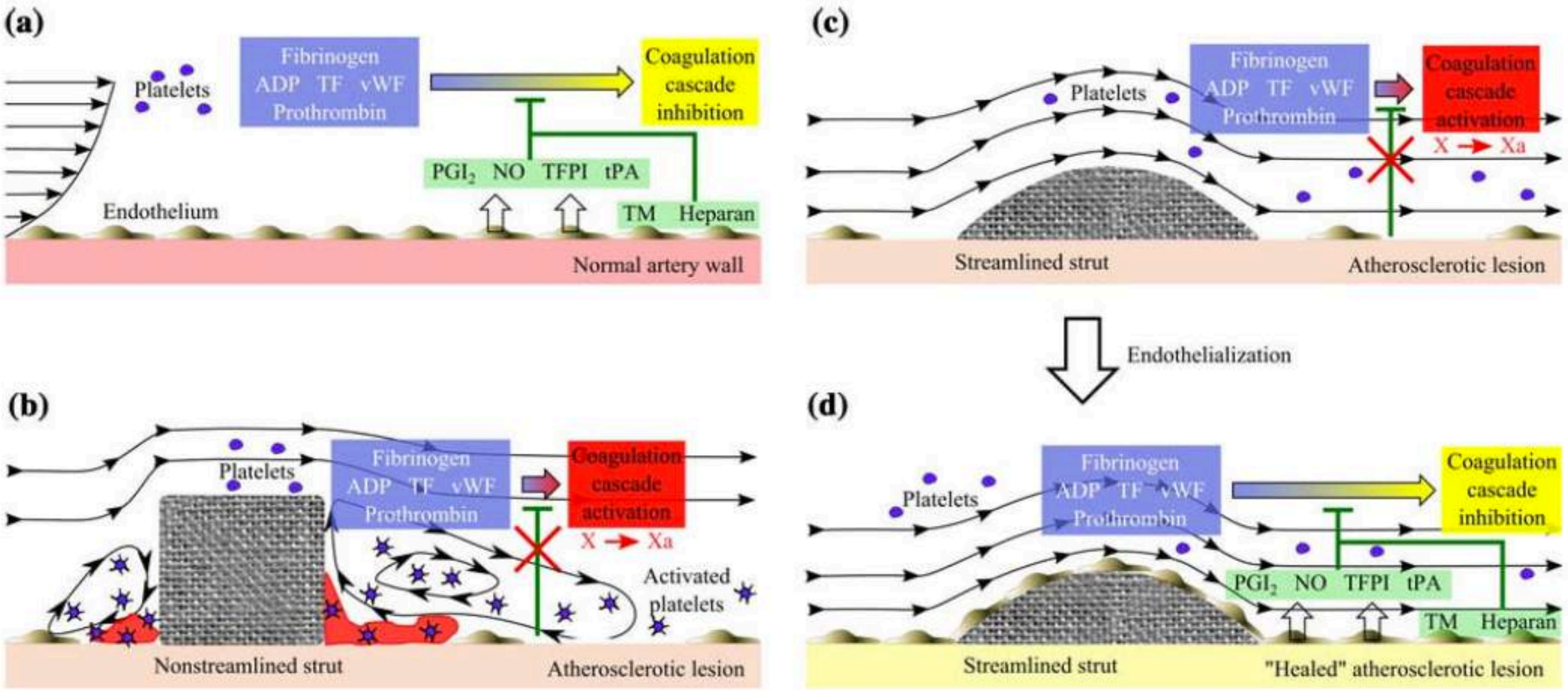
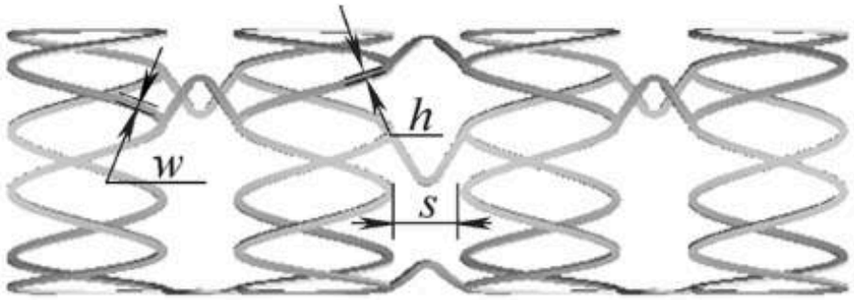
Challenge: flow metrics

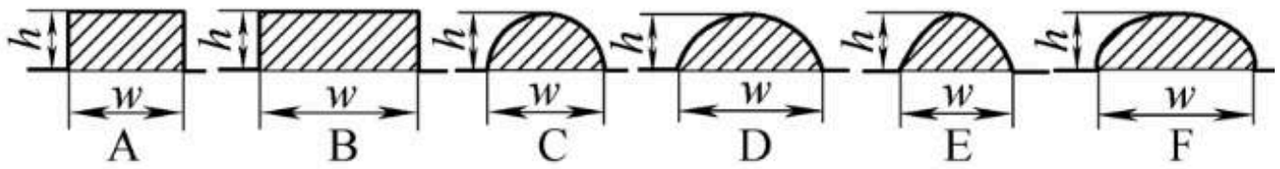
- stent struts: thickness, shape, width, height
- aerodynamic inspiration (boundary-layer; recirculation zone)



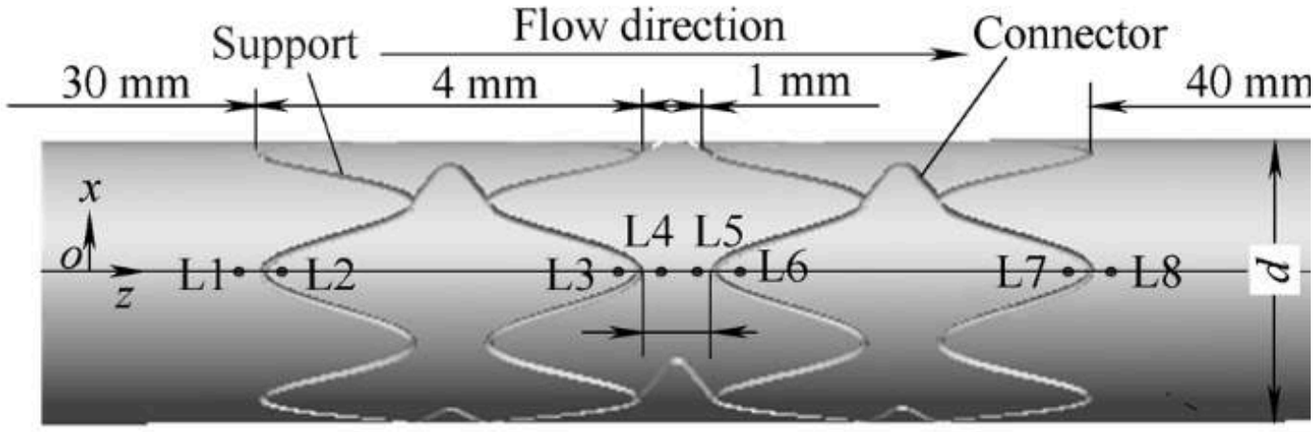
Yongfei et al., Chin. Journ. of Mech. Engg. 29.3 (2016): 624-632.



(a) Stent geometric structrue

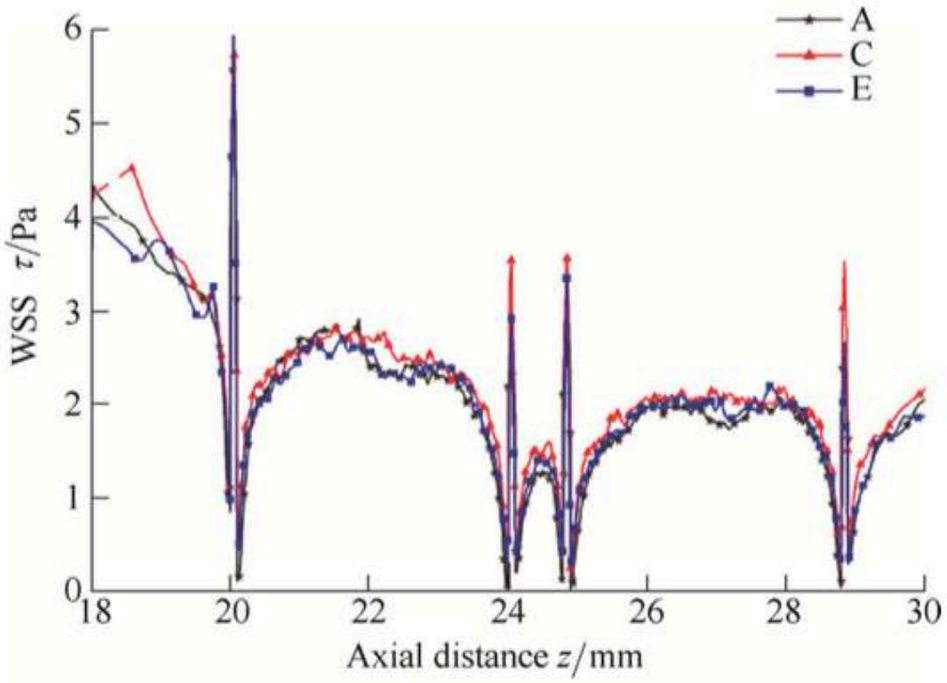


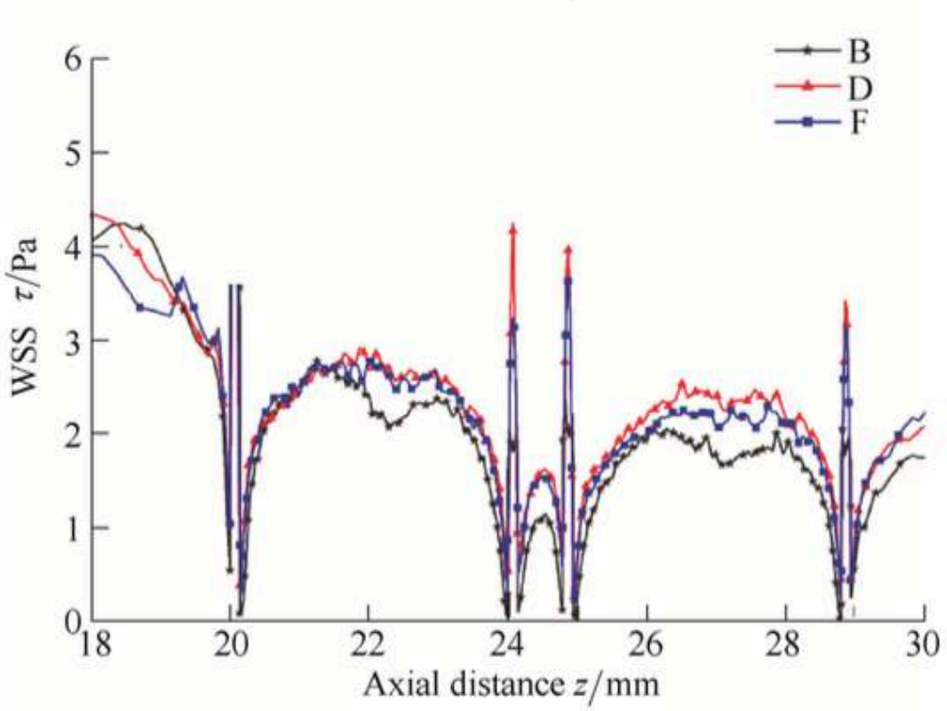
(b) Cross-sectional geometric shapes of the six stent models



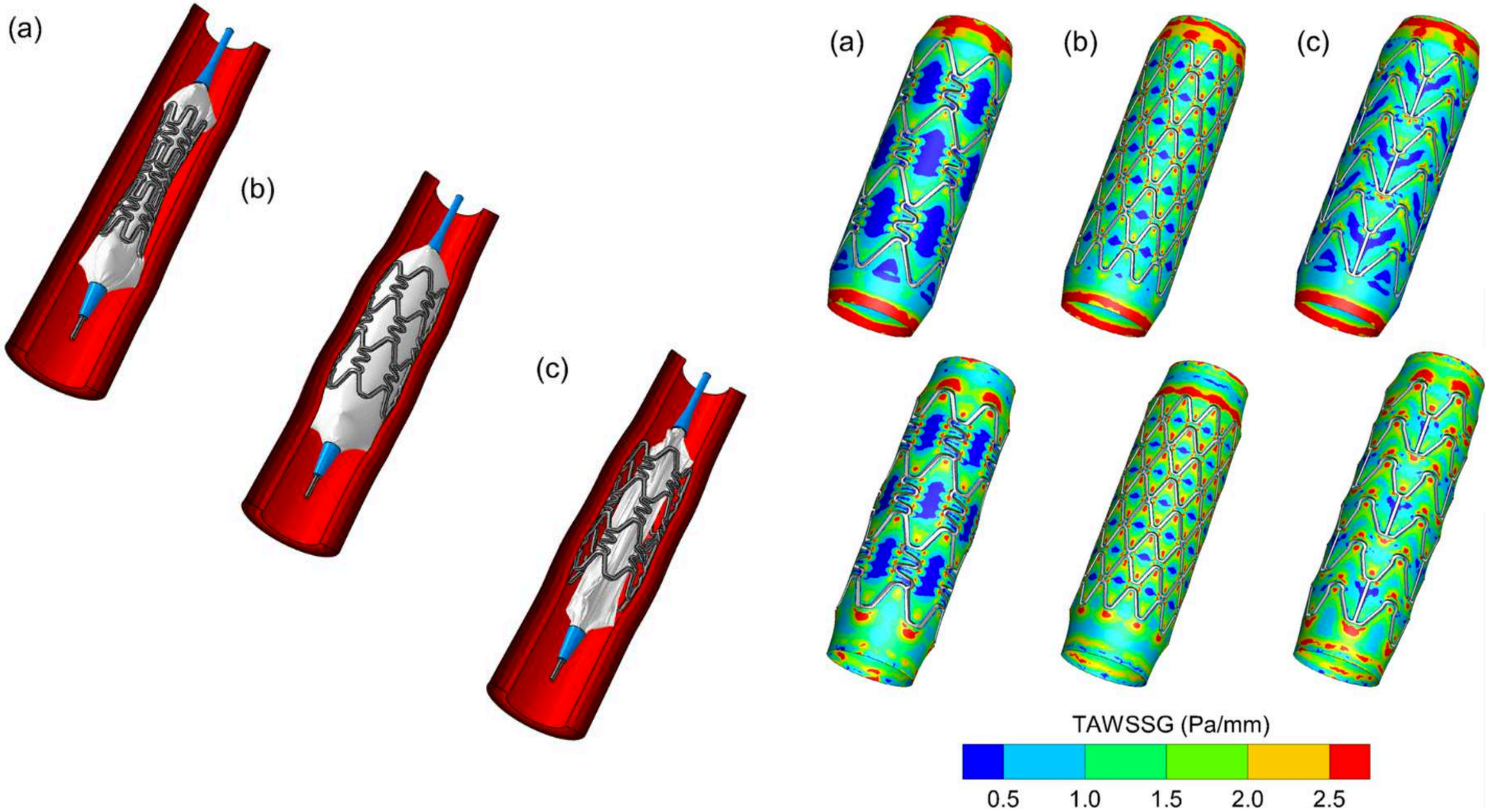
(c) Flow physical model used in the simulations

- increase wall shear stress!





Challenge: vessel deformation + FSI + balloon expansion



Martin et al. 2014, http://dx.doi.org/10.1016/j.medengphy.2014.05.011

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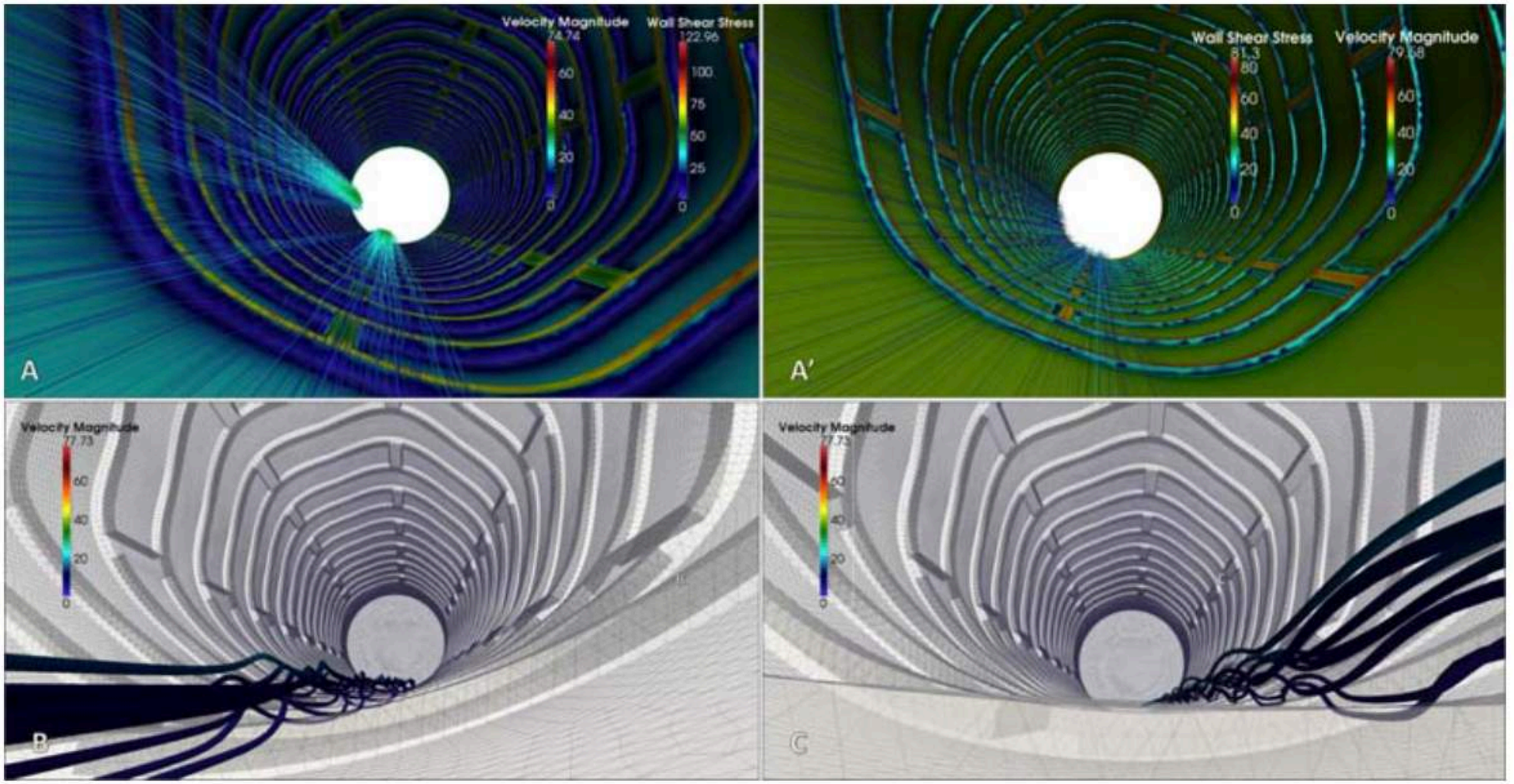
Challenge: Computational Hemodynamics (CHD)

HPC & parallel computing are (almost) imperative today



Gogas BD et al. "Computational fluid dynamics applied to virtually deployed drug-eluting coronary bioresorbable scaffolds(...)" 2014 http://dx.doi.org/10.5339/gcsp.2014.56

Frontline: Design and manufacturing

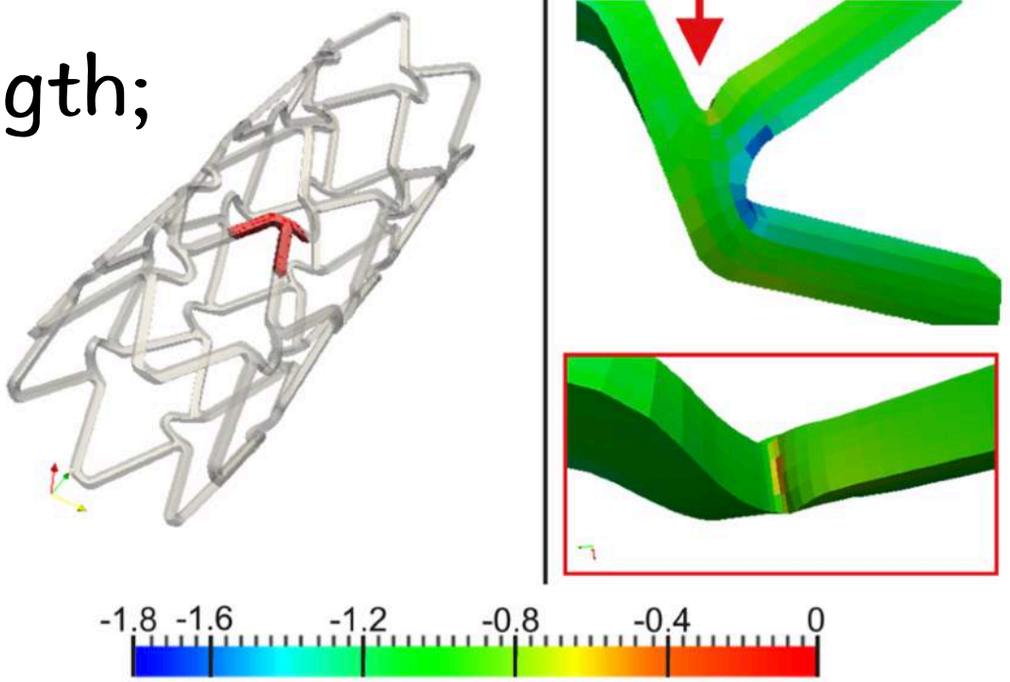
"maximize minimum lumen area by achieving optimal minimal stent area"

other metrics of stent performance:

(a) Radial (and longitudinal) strength;
(b) Fatigue resistance;
(c) Flexibility;
(d) Stent malapposition;
(e) Tissue damage;

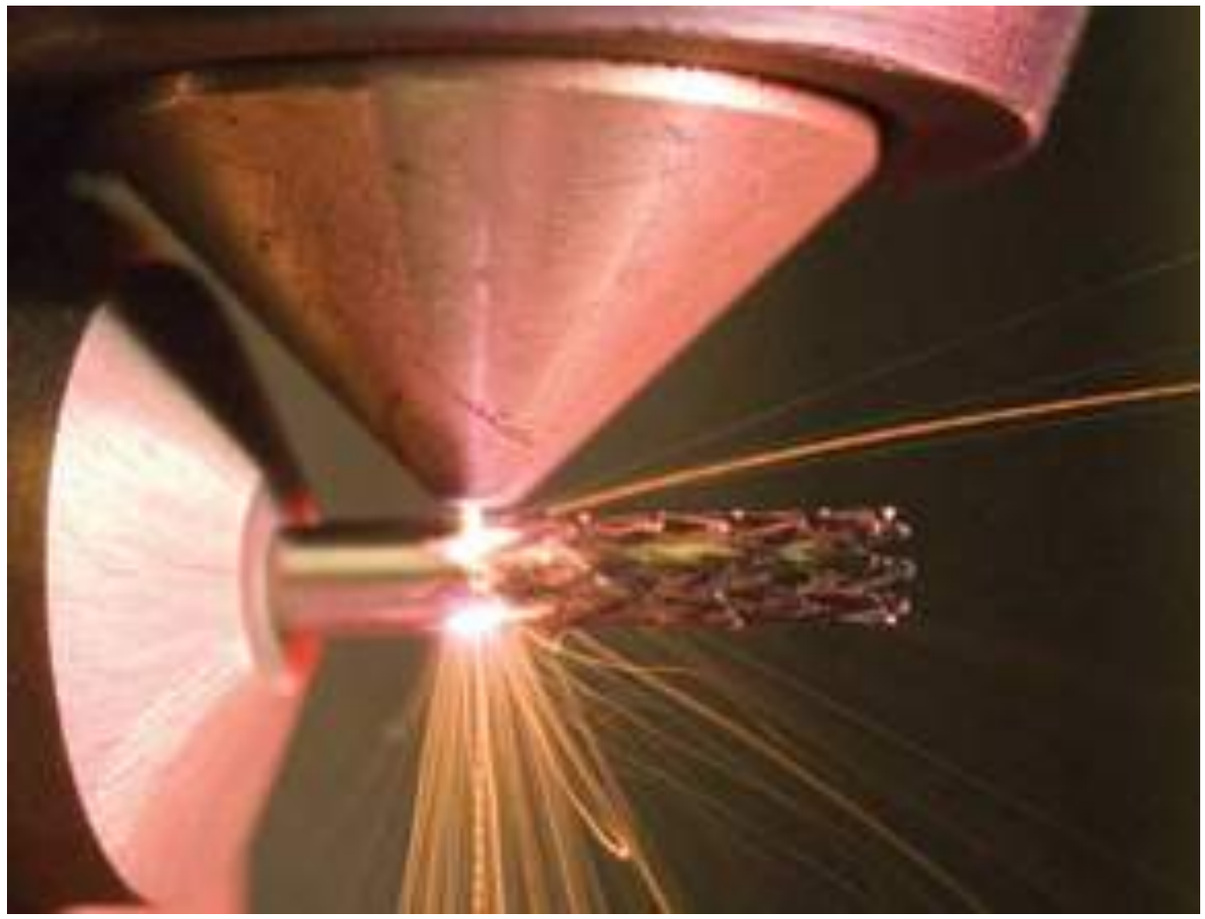
Bressloff et al, Annals of Biomed. Engg. 44.2 (2016): 357-367.

fatigue test simulation



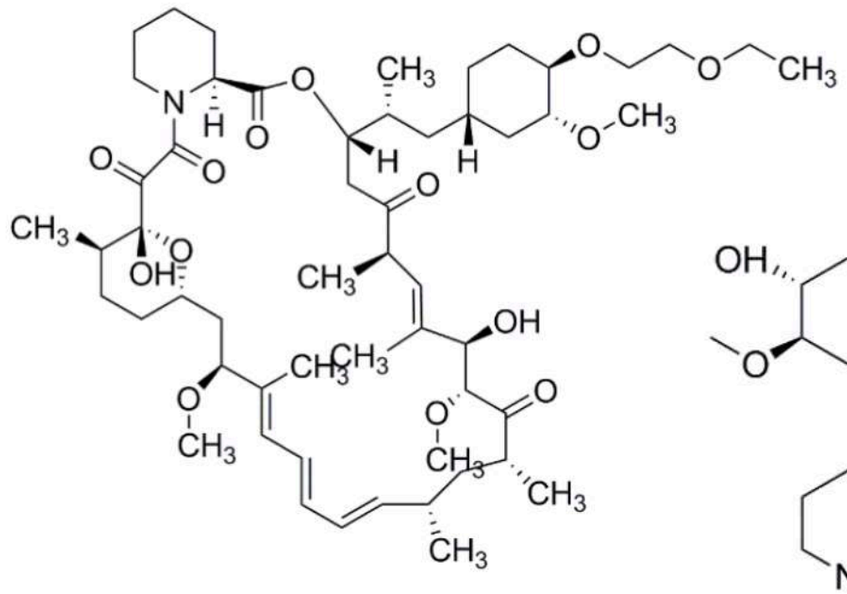
Auricchio et al. Annals of Biomed. Engg. 44.2 (2016): 287-301.

stent manufacturing process
(Innovatech®)

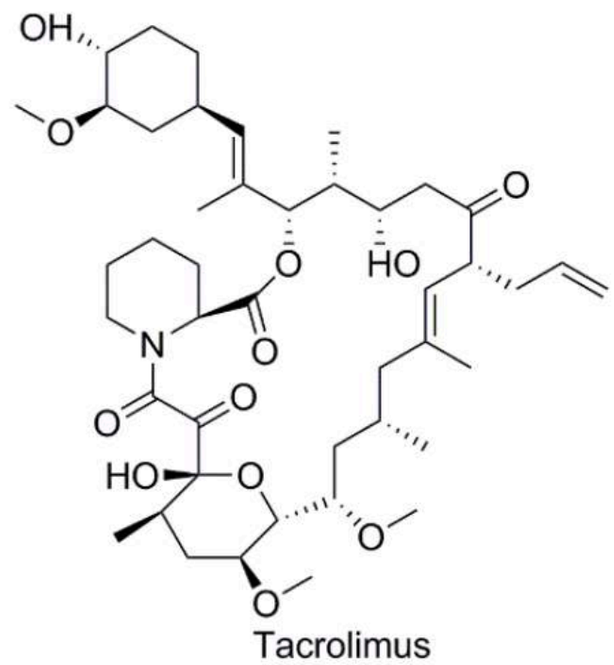


Frontline: Chemistry/Biomaterials

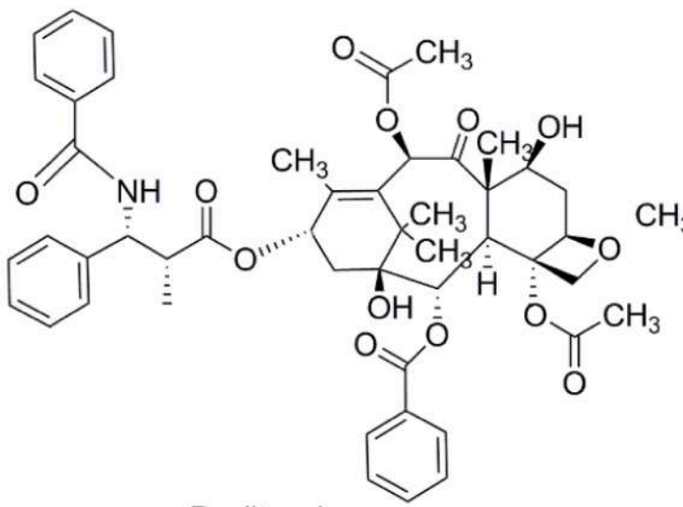
- coating strategies
- new drugs are to come?



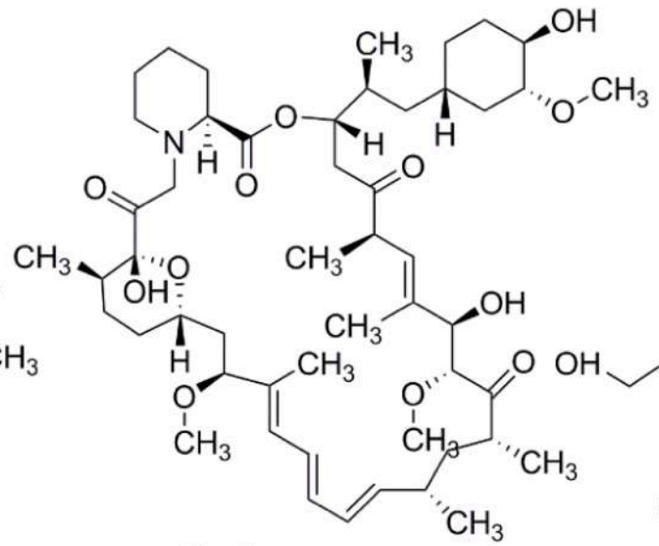
Biolimus



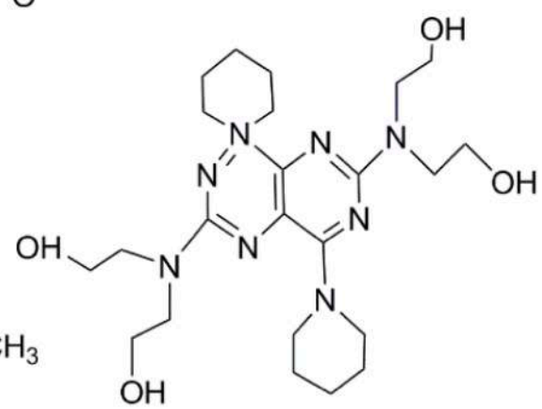
Tacrolimus



Paclitaxel



Sirolimus



Dipyridamole

some molecular structures of polymer-free drugs

Chen et al. *Bioconjugate chemistry* 26.7 (2015): 1277-1288.

current tests on several DES

Table 2. Polymer-free DES and comparison of their *in vivo* results to polymer-coated DES.

Stent	Application	Platform	Drug	Type of study	Outcome*§	References
V-Flex plus	Coronary	Stainless Steel	Direct coating of Paclitaxel	6 months Clinical Trial	-	55
Supra-G	Coronary	Stainless Steel	Direct coating of Paclitaxel	6 months ASPECT (ASian Paclitaxel-Eluting Stent Clinical Trial)	+-	56
Achieve	Coronary	Stainless Steel	Direct coating of Paclitaxel	8 months DELIVER Clinical Trial	-	57
Janus	Coronary	316L	Tacrolimus reservoir	1 year Clinical Trial	-	58
Optima	Coronary	316L	Tacrolimus reservoir	N/A	N/A	52
Yukon	Coronary	316L	Micropores filled with Sirolimus	5 years Clinical Trial	+-	30
Yinyi	Coronary	316L	micropores filled with Paclitaxel	1 year Clinical Trial	+-	59
Biofreedom	Coronary	Stainless Steel	Biolimus A9; textured surface	1 year LEADERS FREE Clinical trial	+	60

See full table in Chen et al. *Bioconjugate chemistry* 26.7 (2015): 1277-1288.

4. Final remarks

- Brazil spends billions with heart diseases
- The country still runs to reduce CVD mortality in some regions
- Diabetes is a highly-rated disease in Brazil
- SUS now offers DES (Thanks God!) :)
- DES research demands joint efforts and expertises: very complex issues

- Brazilian researchers have a sea of opportunity in DES field: the matter is to find an effluent and a boat...
- Mechanical Engineering, especially, would have much to contribute
- **So... Yes, we have a generous dose of interdisciplinary syrup here!**

Last advice

Listen to your cardiologist...

"Eat less fatty food; avoid tobacco and excessive alcohol; do exercises and make yourself and your heart happier."

No heart attacks, please!

NÃO aumente os números do DATASUS!

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