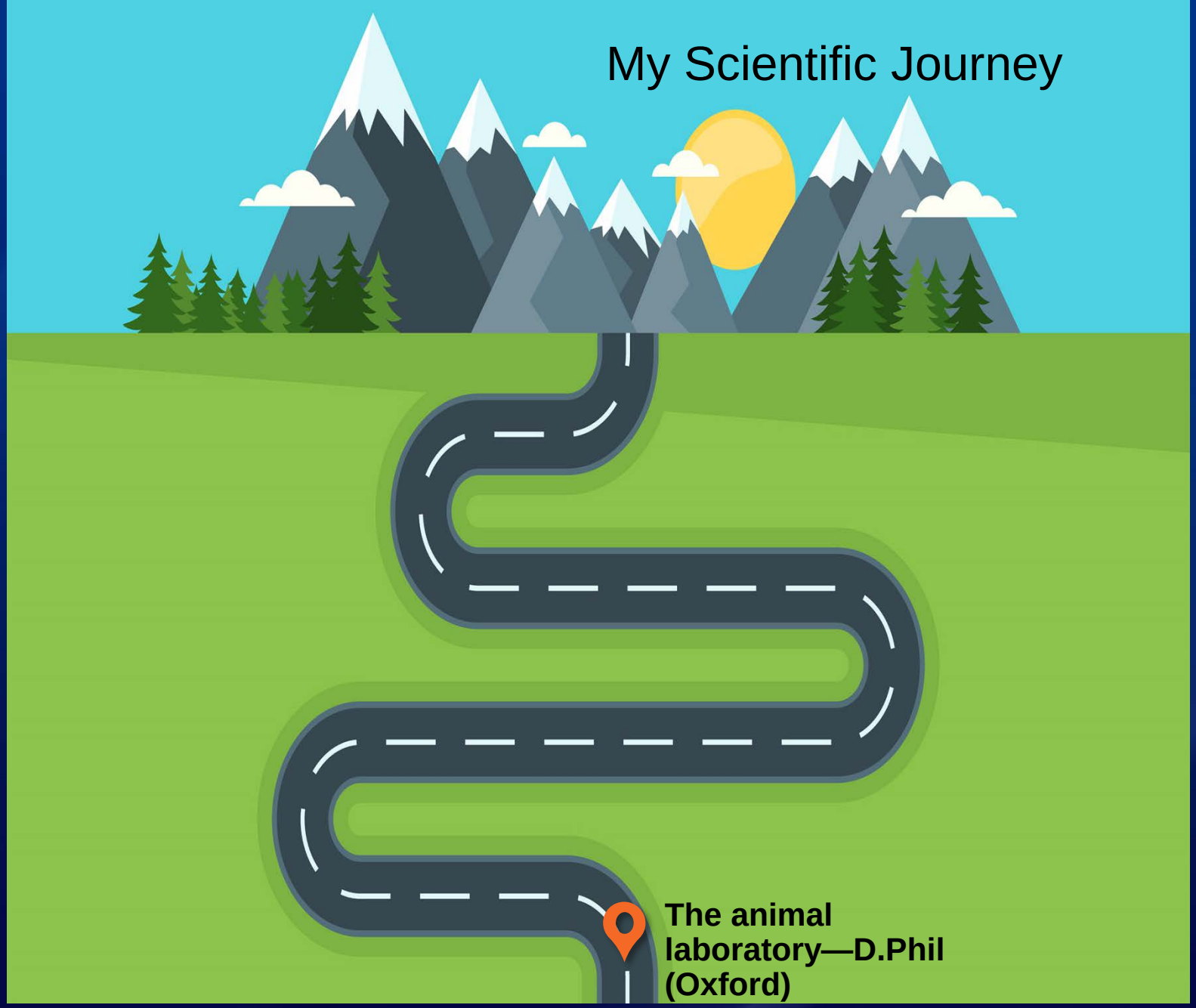
My Scientific Journey



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D.Phil Thesis, Oxford University---Lessons Learned
Ventricular function and Hemodynamics in the Dog During Anesthesia

Meticulous experimental methodology is the key to good data

- Measuring indices of myocardial contractility is a waste of time
- The failing ventricle cannot deal with an increased afterload
- The fascination of asking questions and analyzing data

To read and write in English and make it all look effortless even when working extremely hard:

Cultivate an air of superiority:

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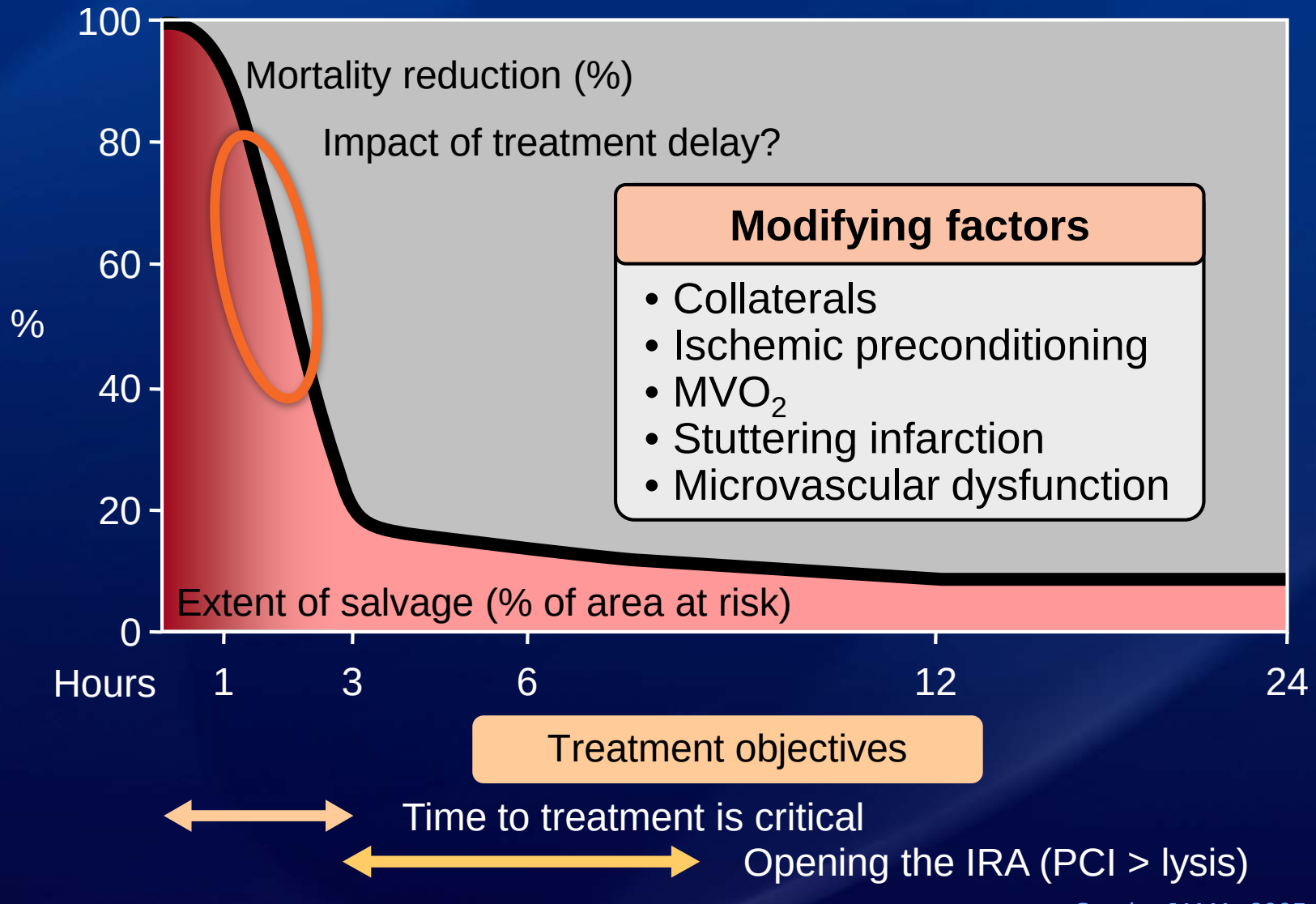
Relationship Between Mortality Reduction and Extent of Salvage



Gersh: JAMA, 2005

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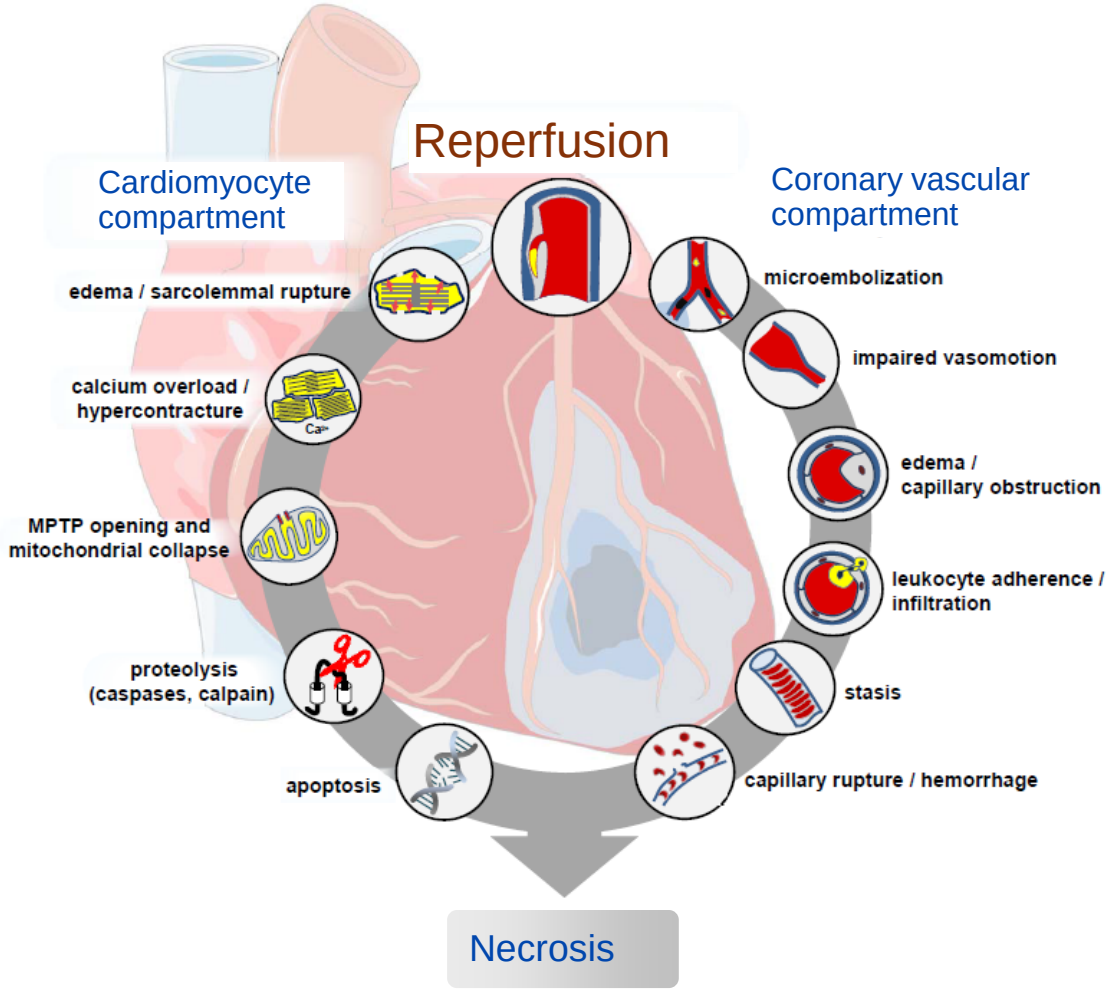
Pathophysiology of Reperfusion Injury and Microvascular Dysfunction

Large agenda-disappointing results



Heusch and Gersh: EHJ, 2016

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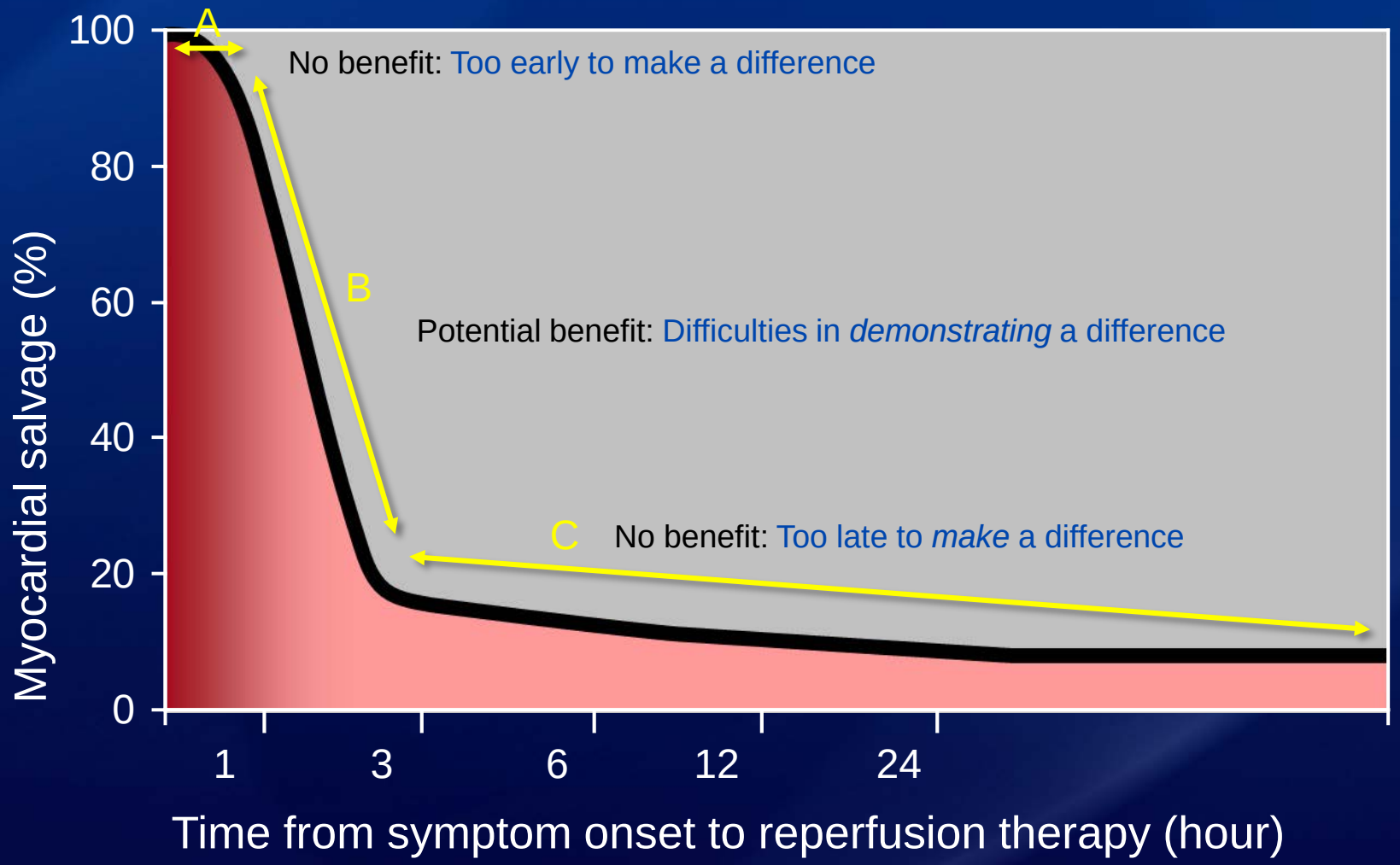
Windows of Opportunity



Gersh: JAMA, 2005

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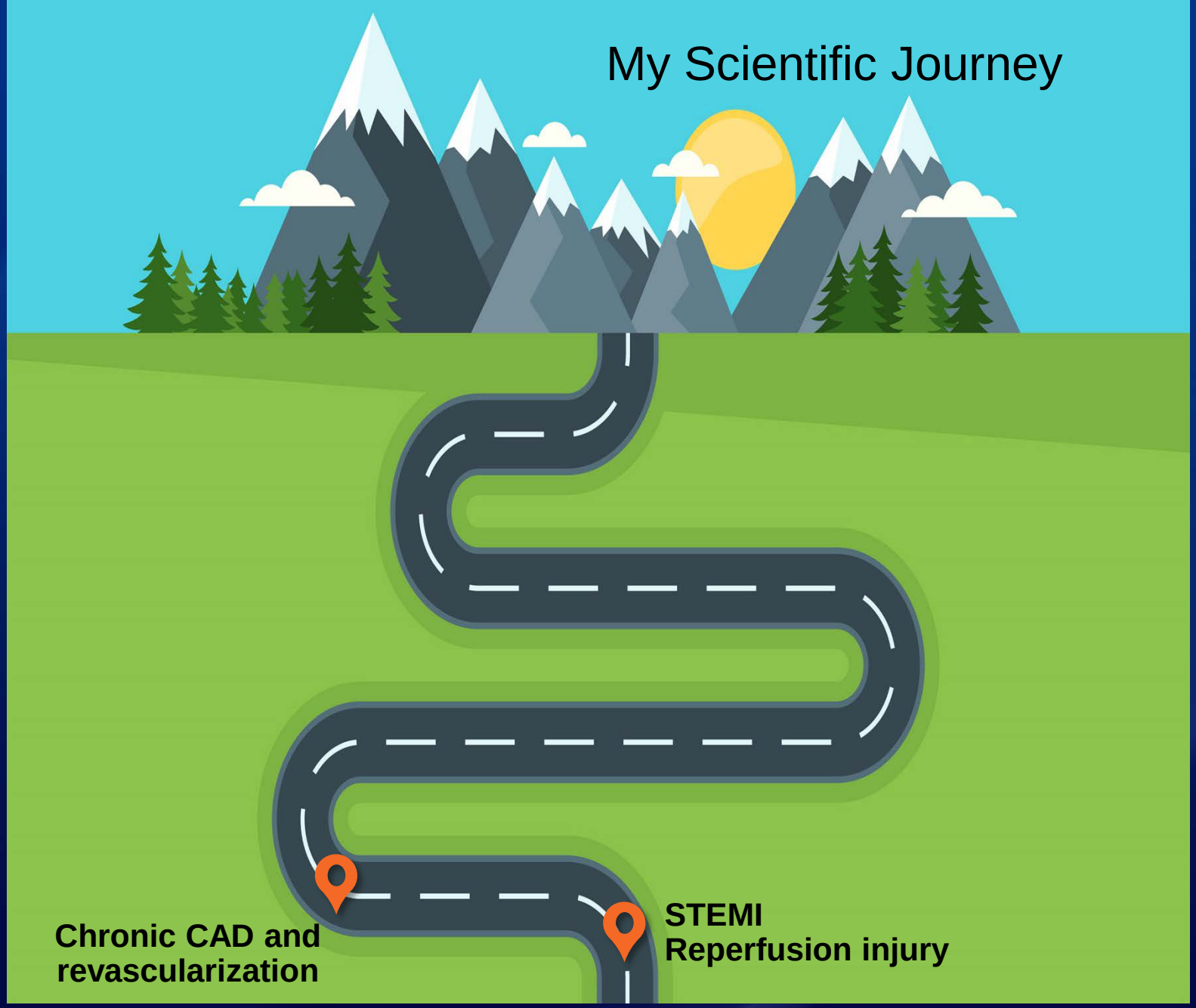

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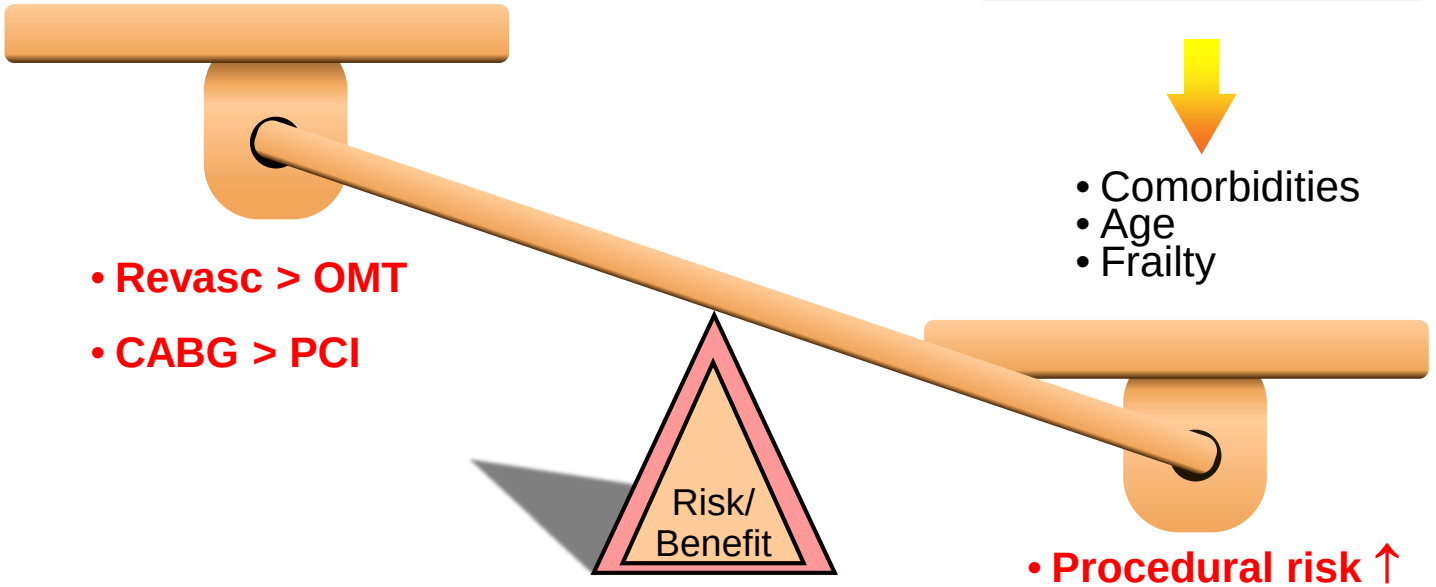
Benefits and Risks of Revascularization in Stable CAD

Guidelines driven by RCT

"Sicker Patients"
- Location and extent of coronary disease
- Diffuse disease
- Severe symptoms
- LV dysfunction
- Diabetes

Registry driven data

- Comorbidities
- Age
- Frailty



- **Revasc > OMT**
- **CABG > PCI**

- **Procedural risk ↑**
- **Long-term benefits ↓**

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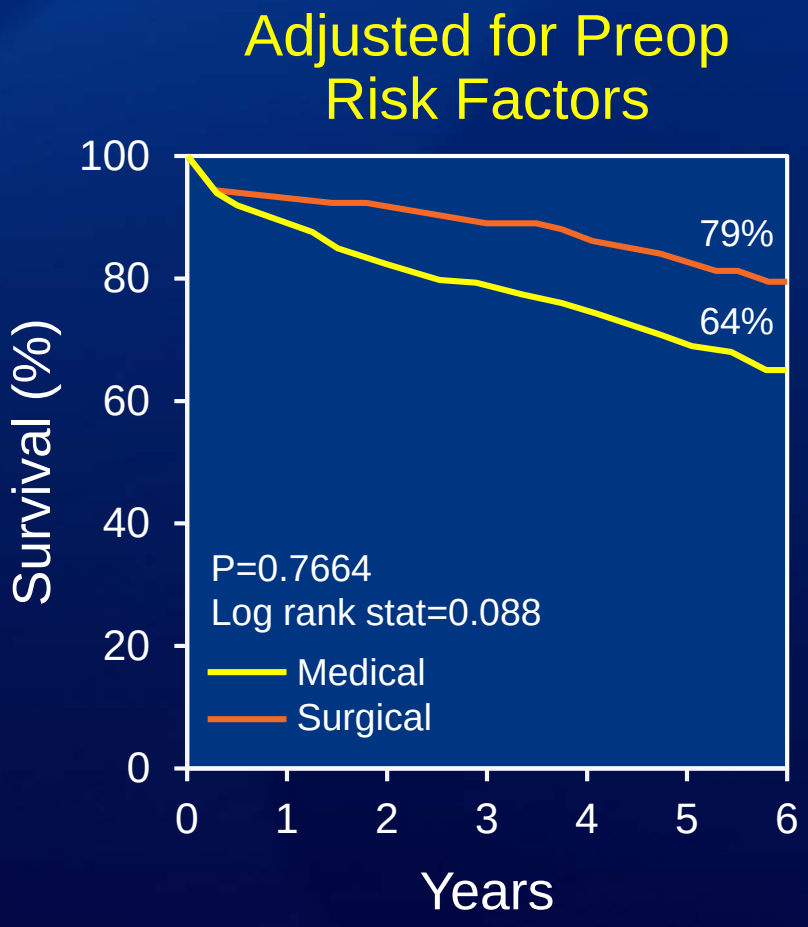
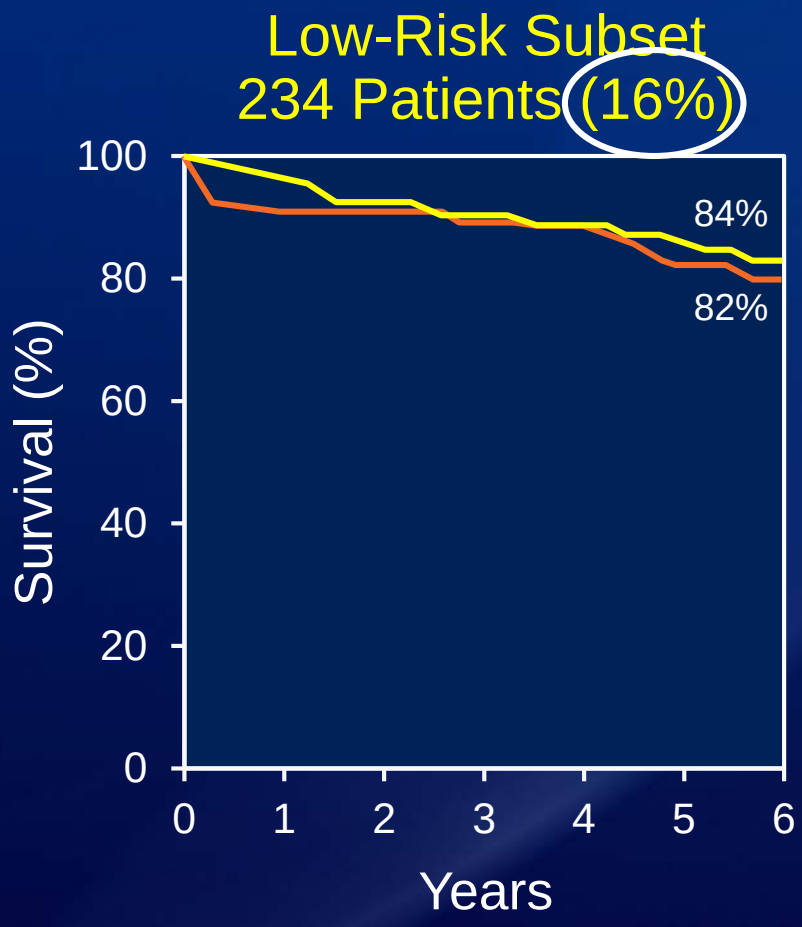
Cumulative Survival With Medical and Surgical Therapy

1491 Patients ≥65 Years Old – CASS Registry





Gersh: NEJM, 1985

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Chronic Stable I.H.D. and the Potential Role of Microvascular Dysfunction

Simple Questions Without Clear Cut Answers

Severity of stenoses and angina

Complex relationships

- Absence of obstructive disease in pts with evidence of ischemia and angina

- Absence of angina in pts with severe coronary atherosclerosis

- **High frequency of MVD in pts with ACS without pre-existing angina** – ? Preserved microvascular function and collaterals

Continued symptoms and events after coronary revascularization

Progressive epicardial disease

Microvascular dysfunction

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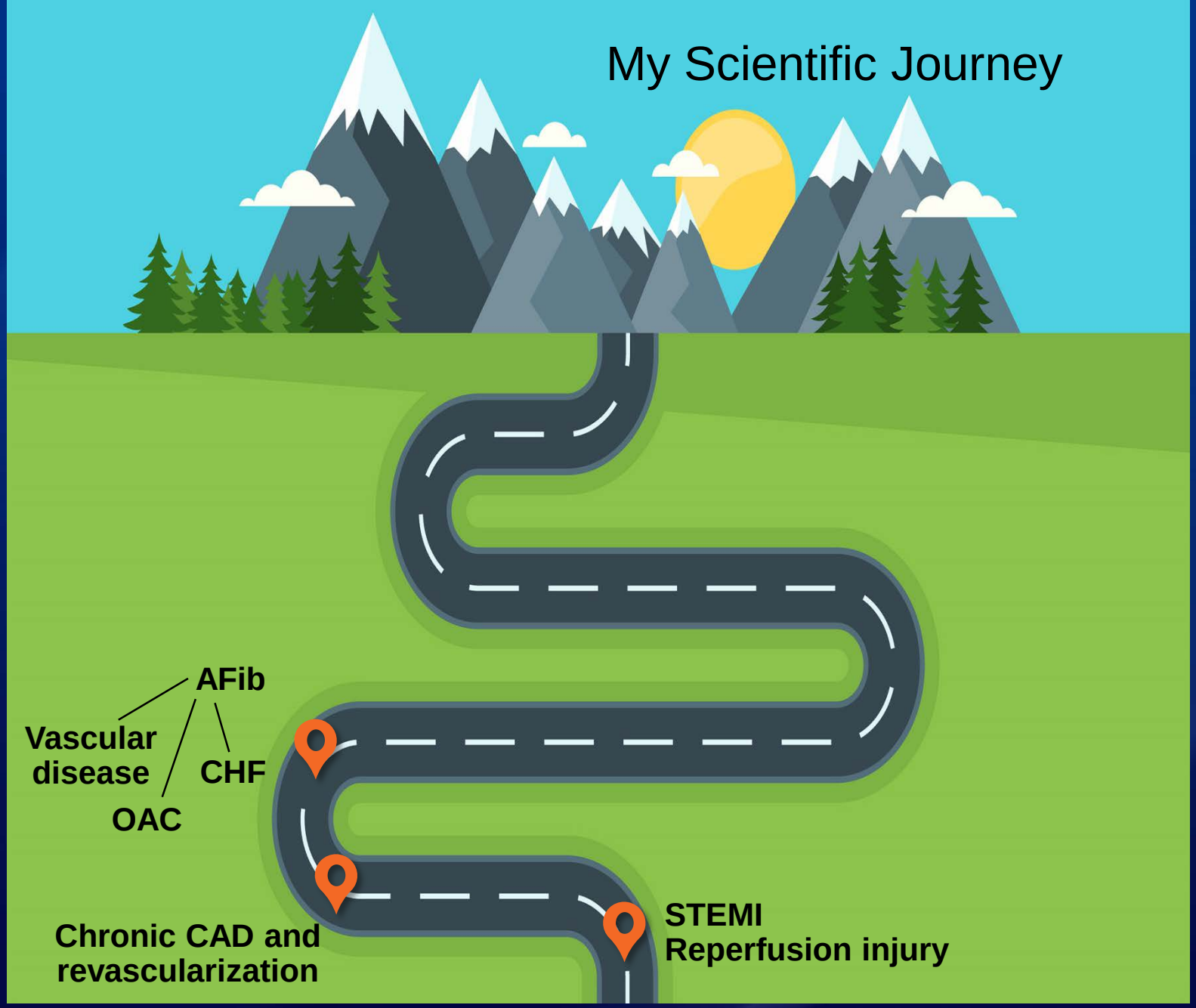

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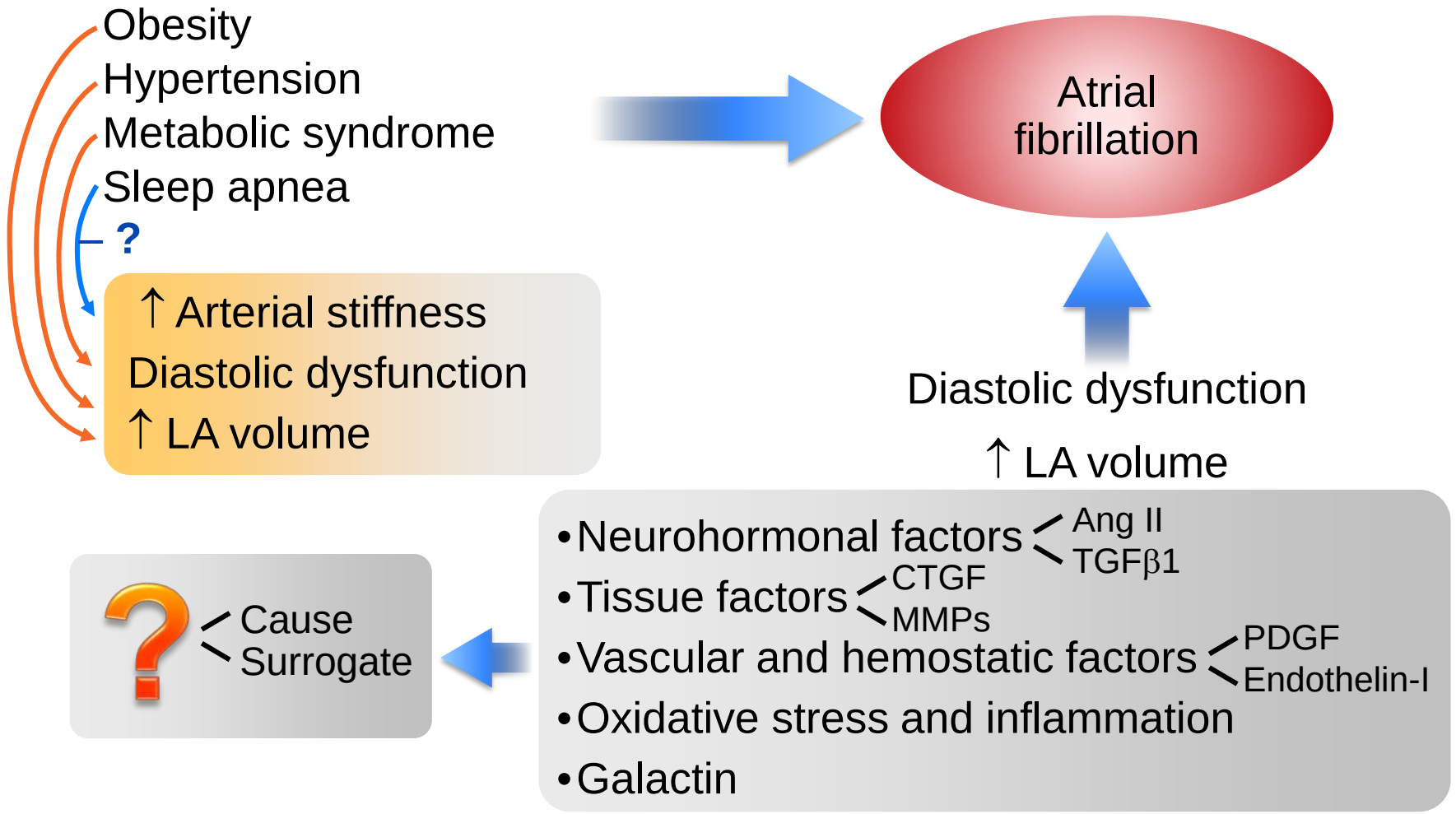
AFib as a Vascular Disease

Suggestive Evidence



Tsang and Gersh: EHJ 2008; JACC 2008; AJC 2008; AJC 2006; JACC 2006; JACC 2003; JACC 2002

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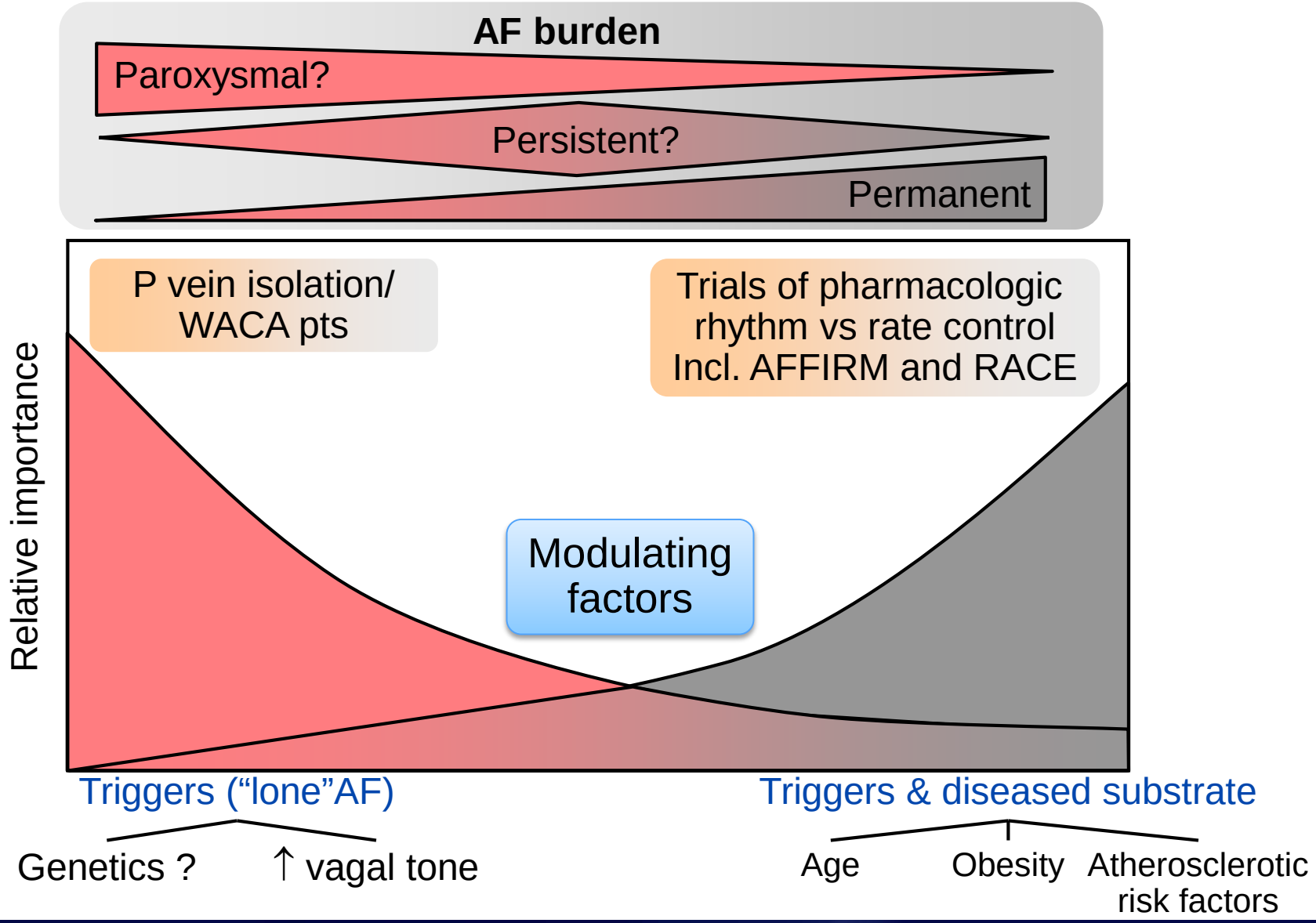
Triggers vs Substrate in Pathophysiology of AF



Wyse & Gersh: Circ, 2004

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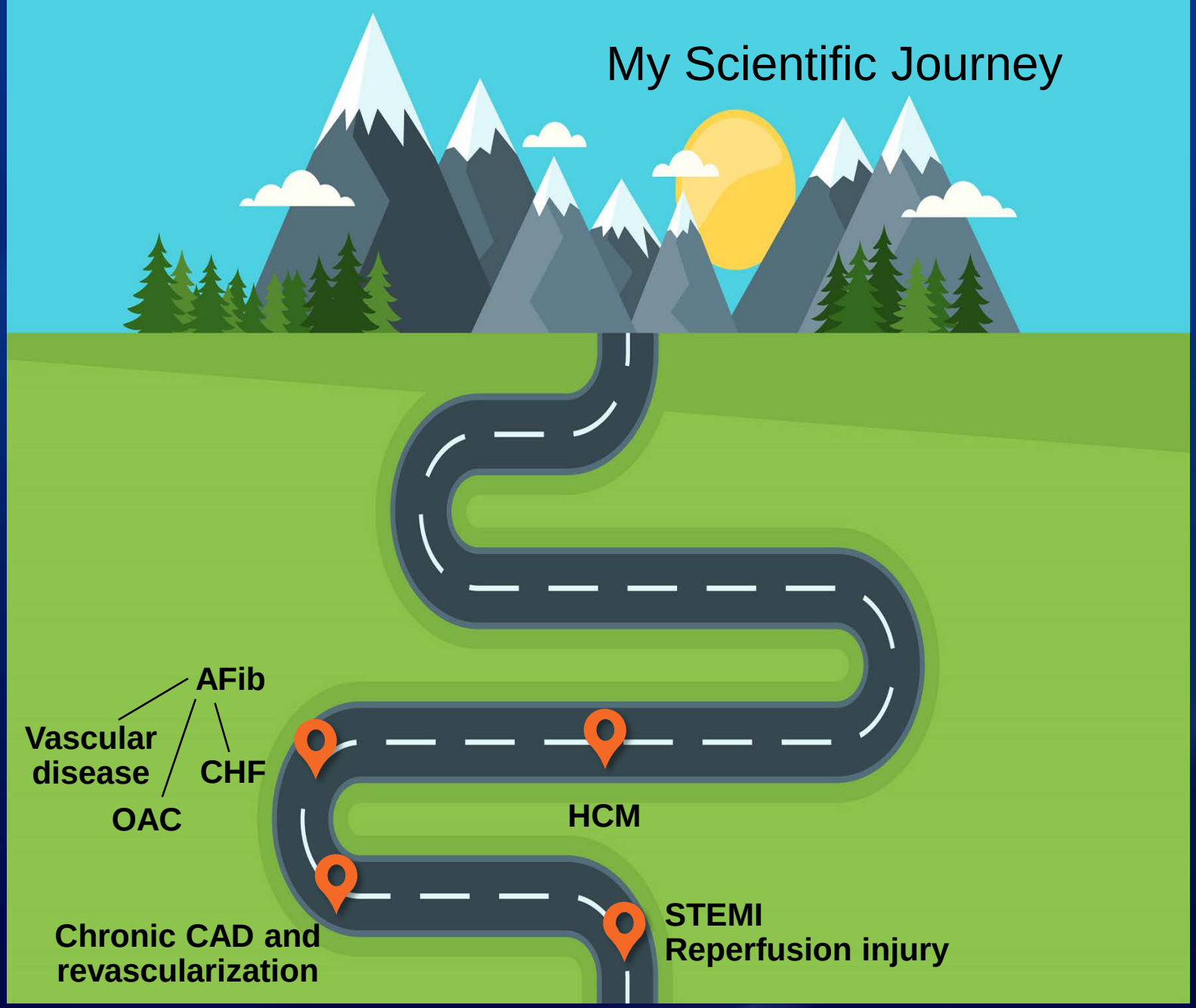

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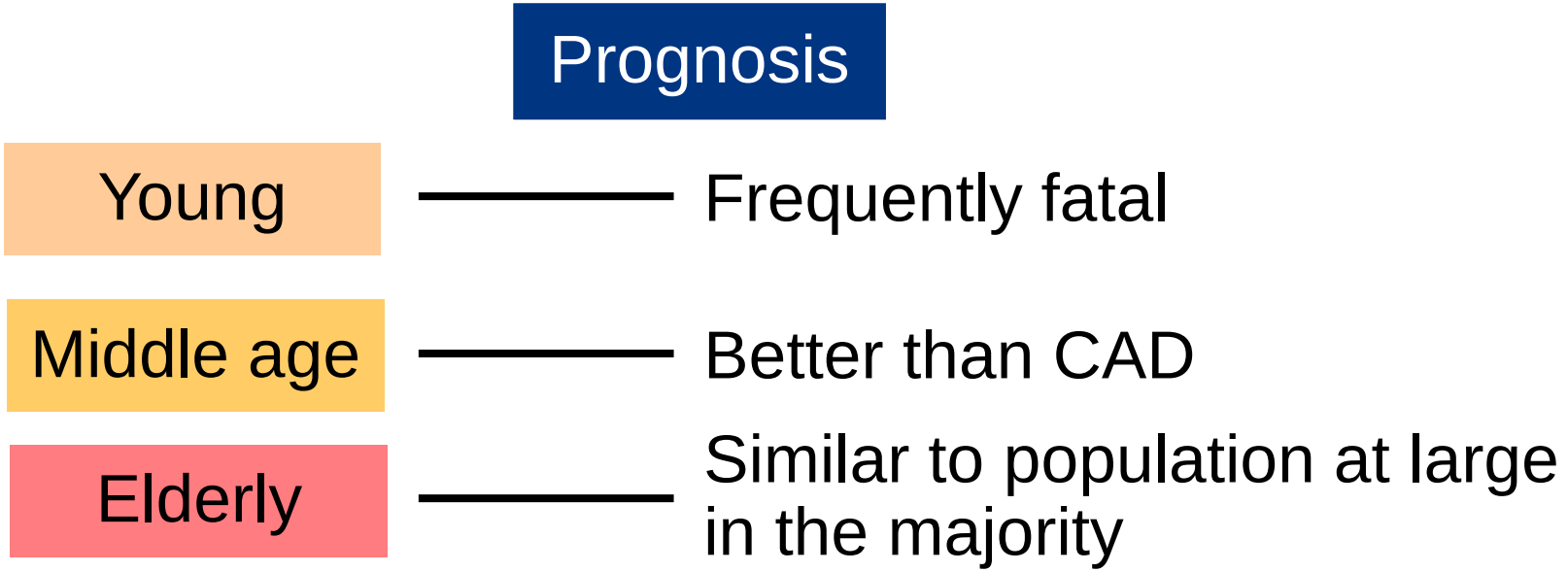
HCM – Changing Natural History and the Impact of Referral Bias

- Rare disease in young people
- Relatively common in older patients in community hospitals



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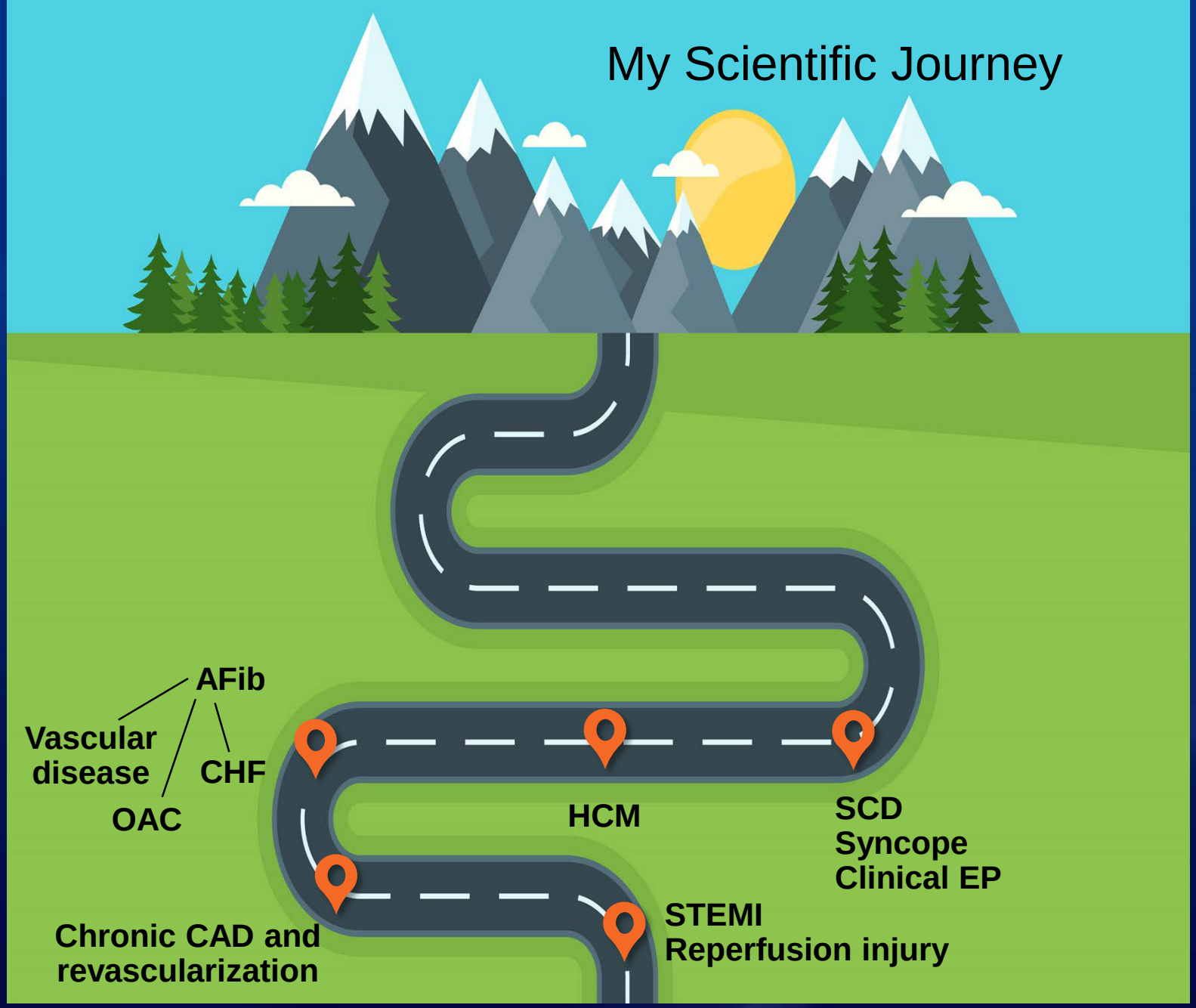

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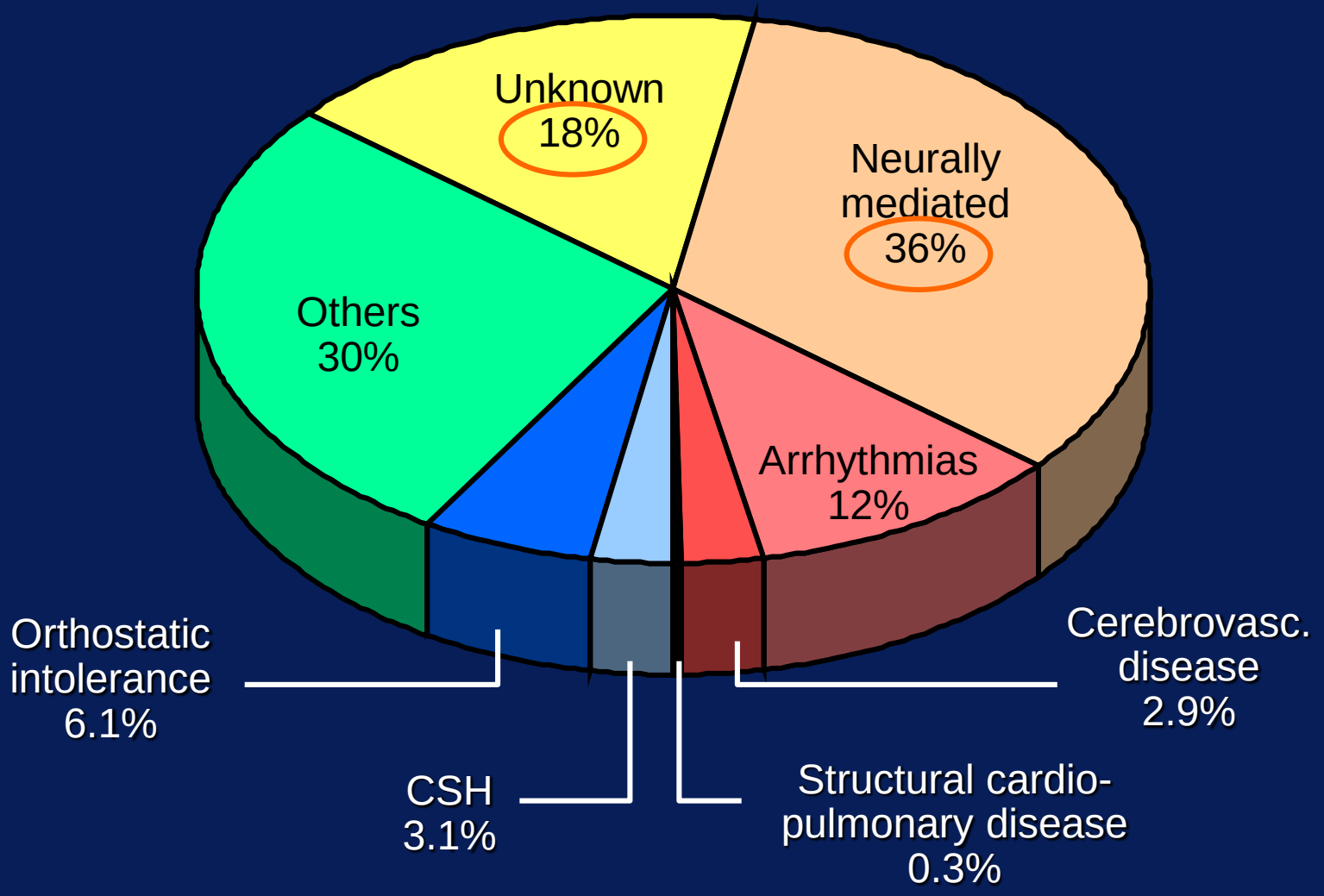
Causes of Syncope: Mayo Clinic 1996-1998

3,496 Patients



Sorajja: Circ, 2009

The clinical history is the single most important diagnostic aid

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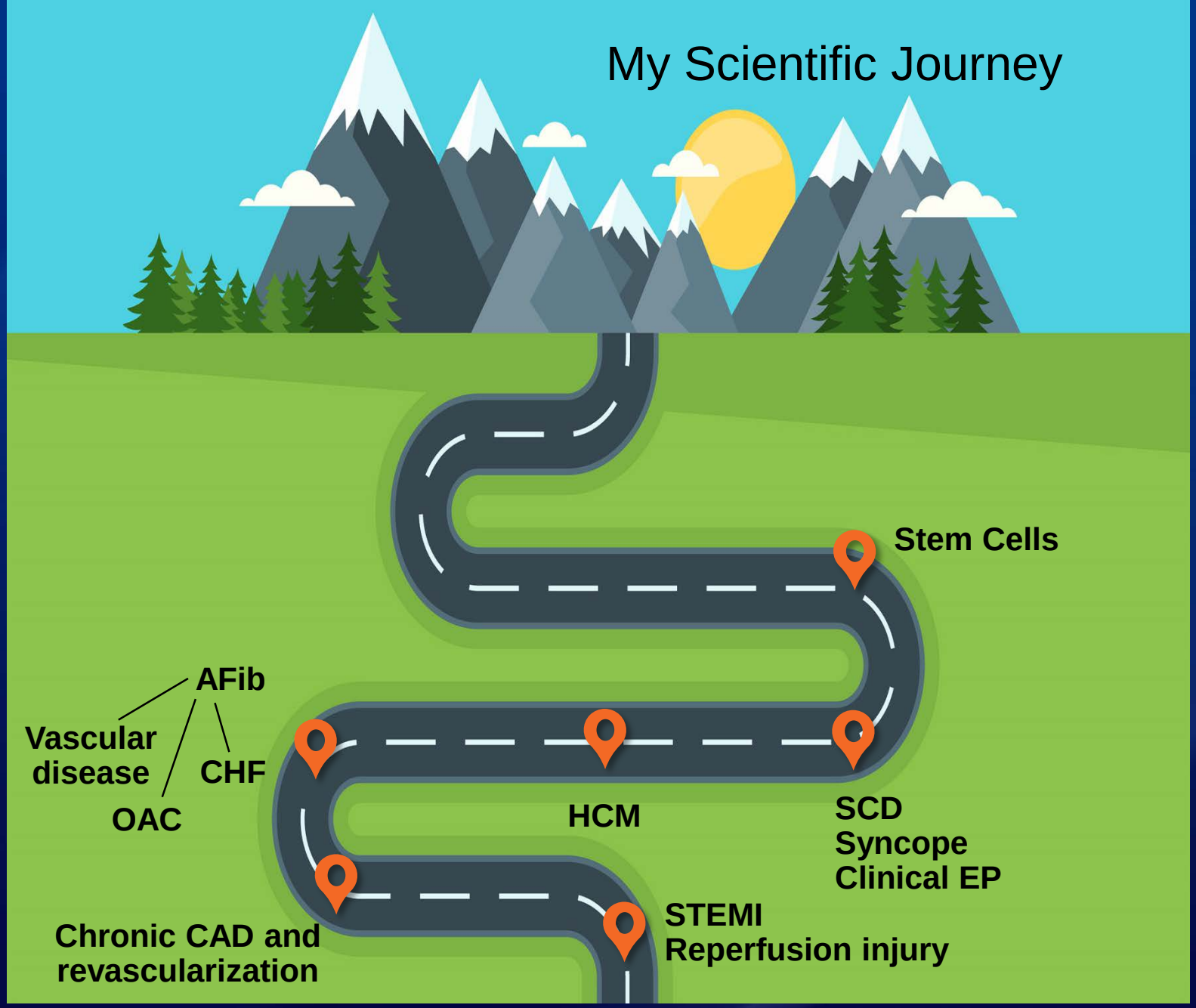

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Cardiac Cell Repair Therapy is at a Crossroads

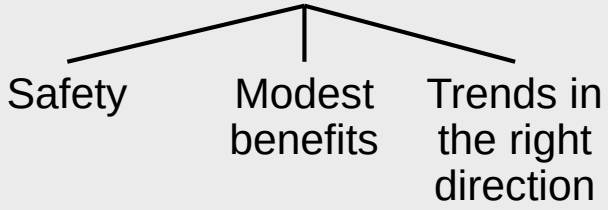
"The end of the beginning or the beginning of the end"?

-*Winston Churchill*

Grounds for cautious optimism

- Ongoing basic research on multiple fronts and countries but "lost in clinical translation"

Clinical trial results



- Improved clinical trial design

Concerns

- Benefits – modest
- Neutral trials

- Unrealistic expectations < Physicians, Public/media

- Overreaction to neutral trial results

- Perceptions in scientific community over extent of stem cell research funding

- Concerns re scientific credibility – *justified and unjustified*

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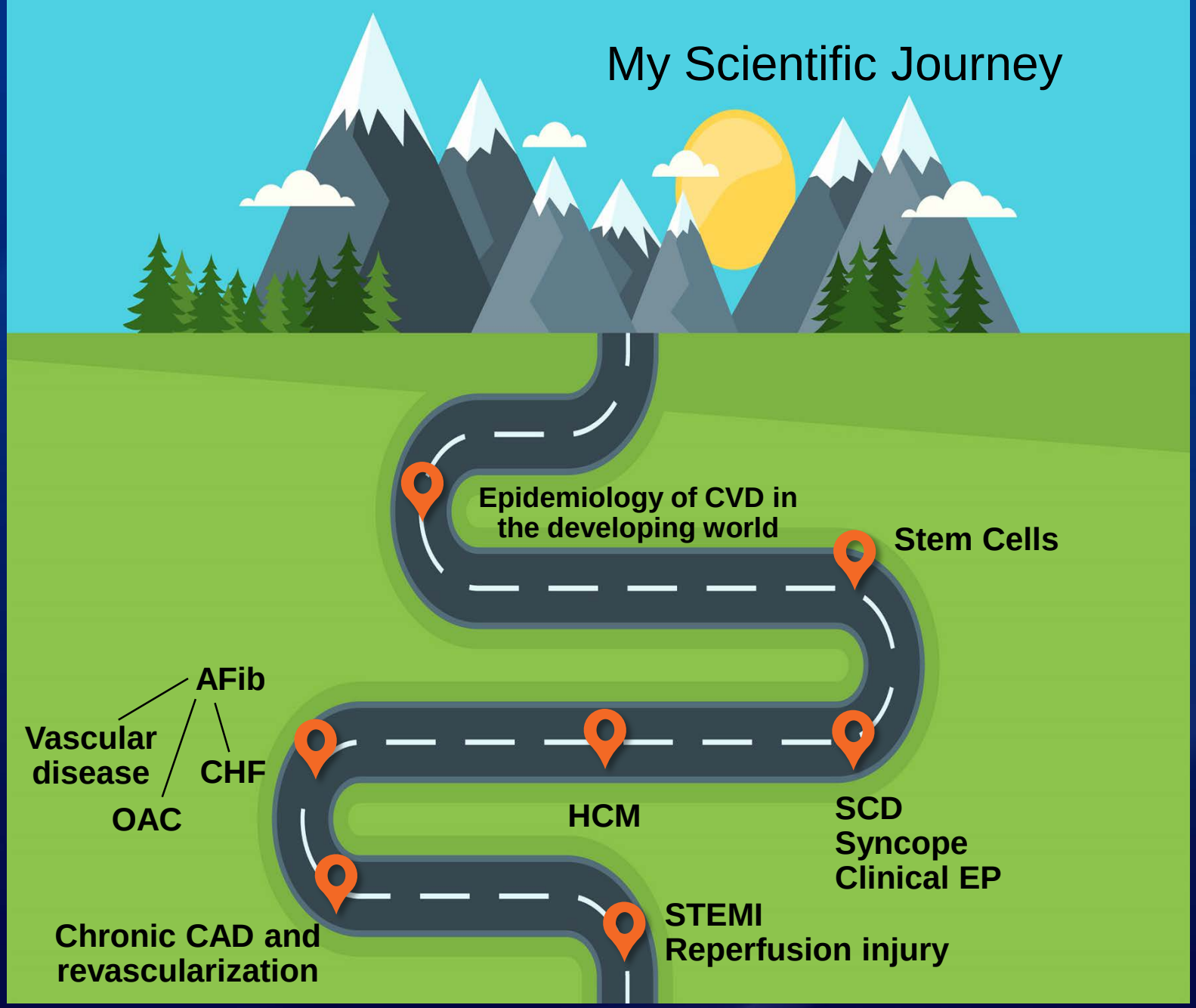

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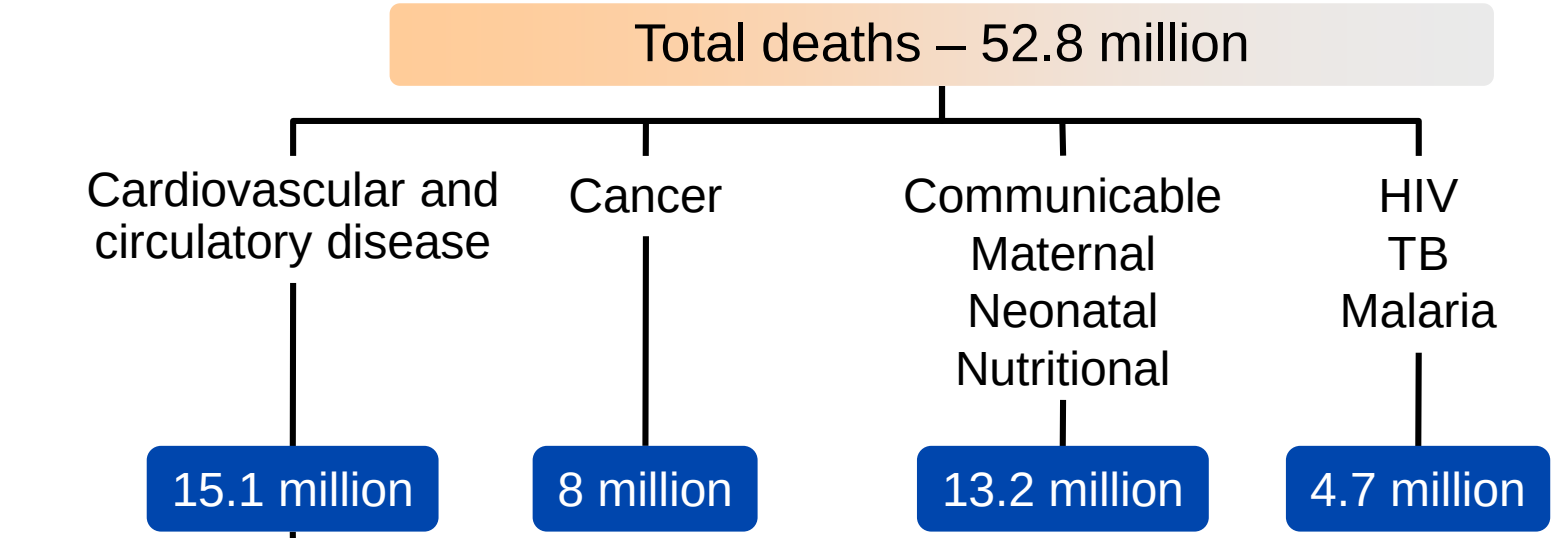
Global Burden of Cardiovascular Disease – 2010



Developing (LIMC) Countries

- 80% of worldwide CV deaths
- Occur at a younger age – impact on workforce,productiviy and families.
- 2010 – 70% of the elderly living in the developing world

Lopez: Lancet, 2006; Reddy: NEJM, 2004
Lozano: Lancet, 2012

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The Potential Epidemic of CVD in Developing Countries

Hostile CV environment

- Diet/lack of exercise
- Tobacco incl second-hand smoke
- Aging society
- HIV survivors- Statins in Primary Prev. ?
- Air pollution
- Rural → urban migration
  Psychosocial/economic stressors
- Culture
  - Obesity
  - Traditional healers

88/g2

- Limited national resources
- Lack of infrastructure

Genetic/phenotypic vulnerability? – thrifty gene concept?

- Salt sensitivity
- Insulin resistance
- Lipid/fat metabolism
- Low birth weights

Gersh et al: EHJ, 2010

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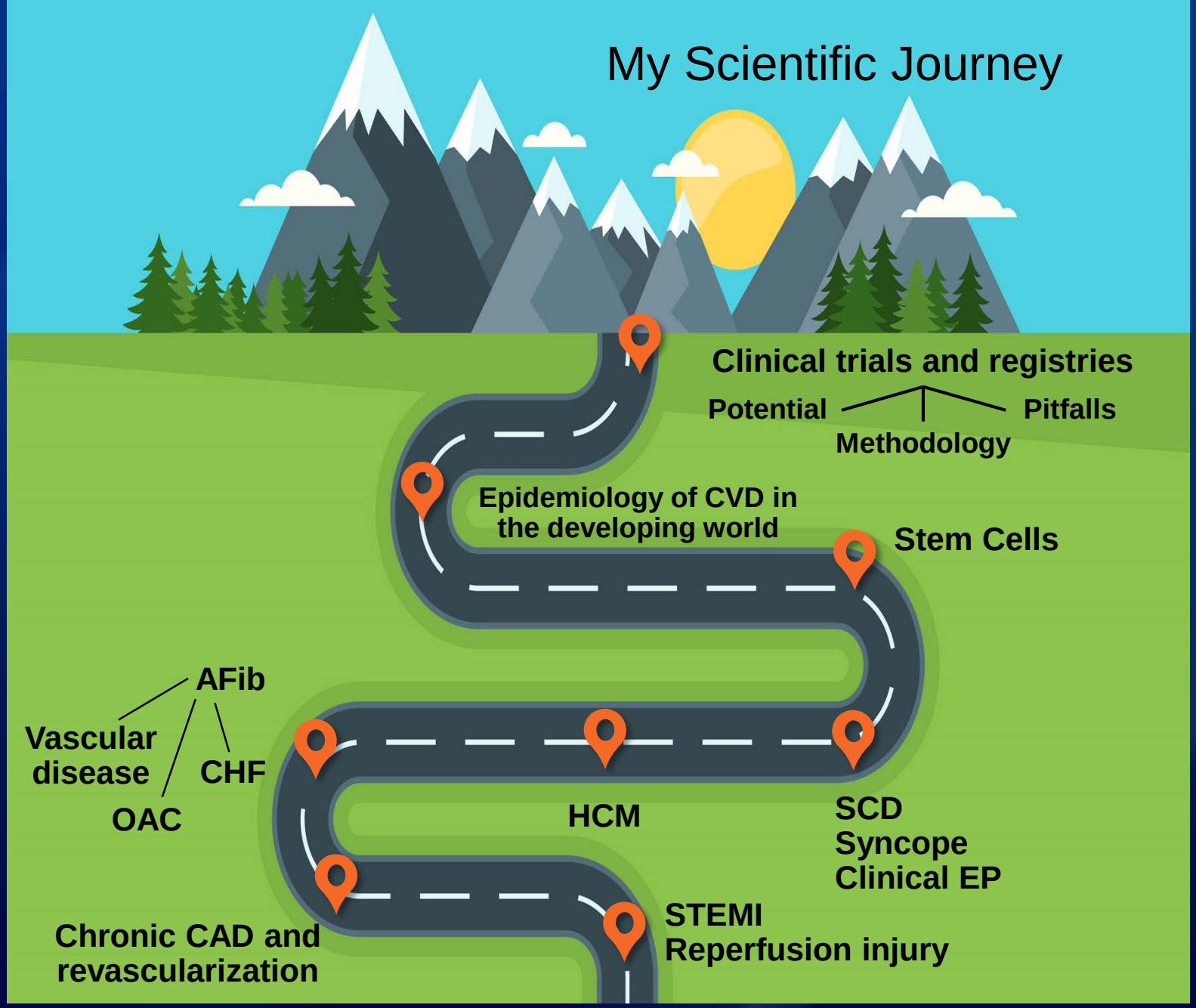

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Limitations of Randomized Trials and Registry Studies of C. Revascularization

Registry studies

- Selection bias
- Greater relevance to practice at large

Randomized trials

- Entry bias (Inclusion criteria mandate clinical equipoise and eligibility for both forms of therapy

  Brown, Gersh et al: Nature CV Med, 2005
- Prolonged duration of trials introduces a risk of "obsolesence"

"Things may not be as they seem"

Gersh and Frye: NEJM, 2005

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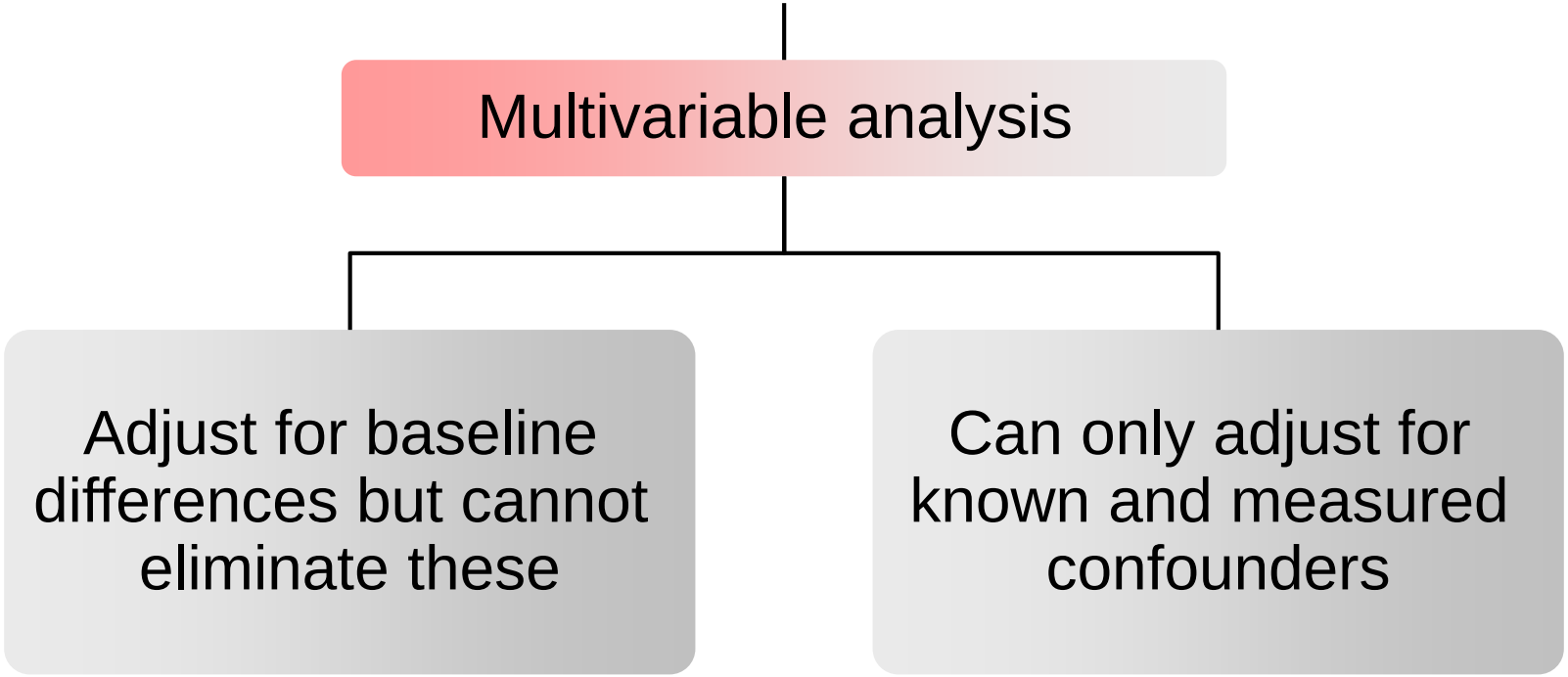
Every Database is Vulnerable to Confounders



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Placebo Effect

"you have to believe it to see it"

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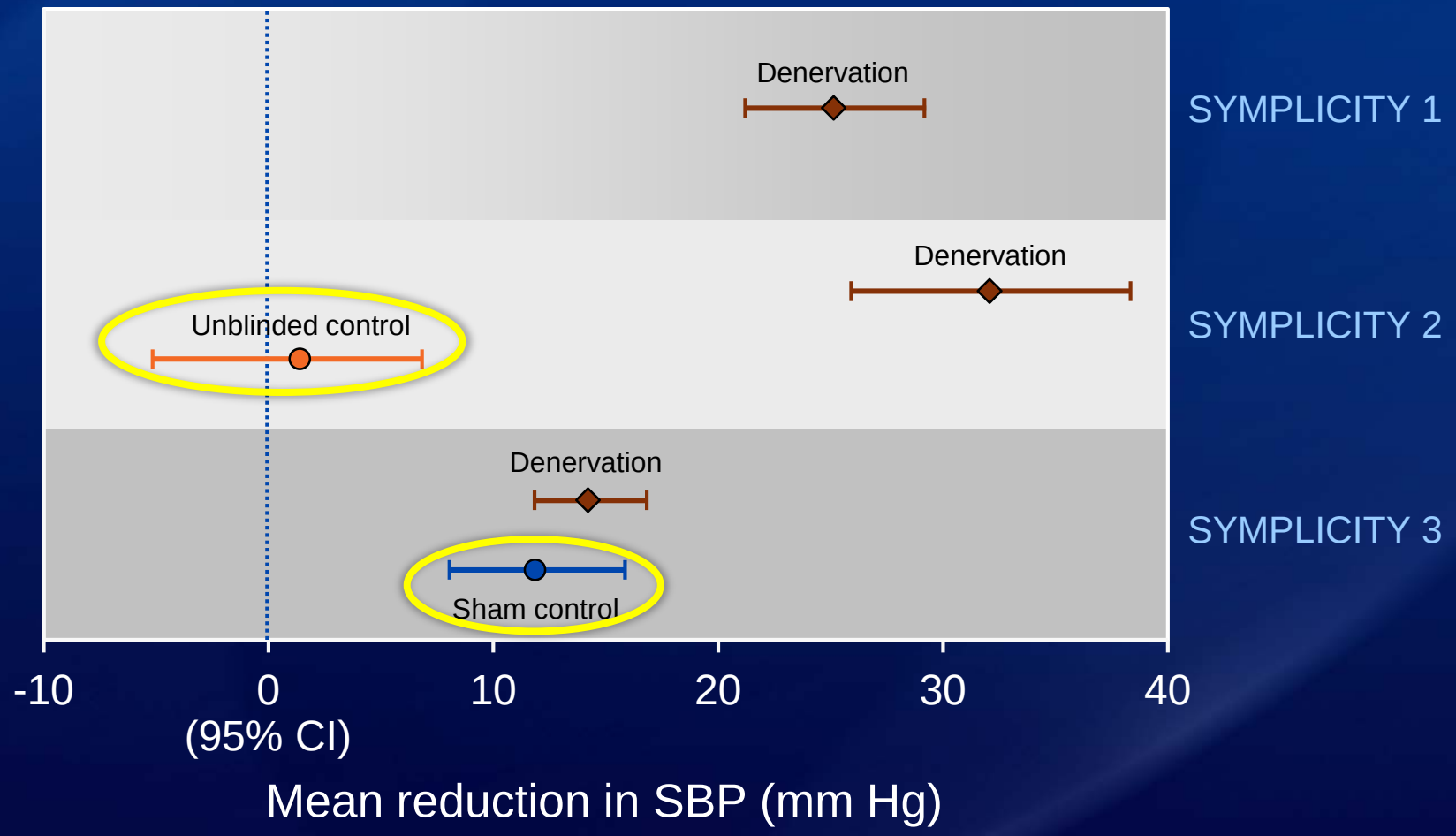
Comparison of Changes in SBP at 6 Months in 3 Trials of Renal Denervation



Pocock and Gersh: JACC, 2014

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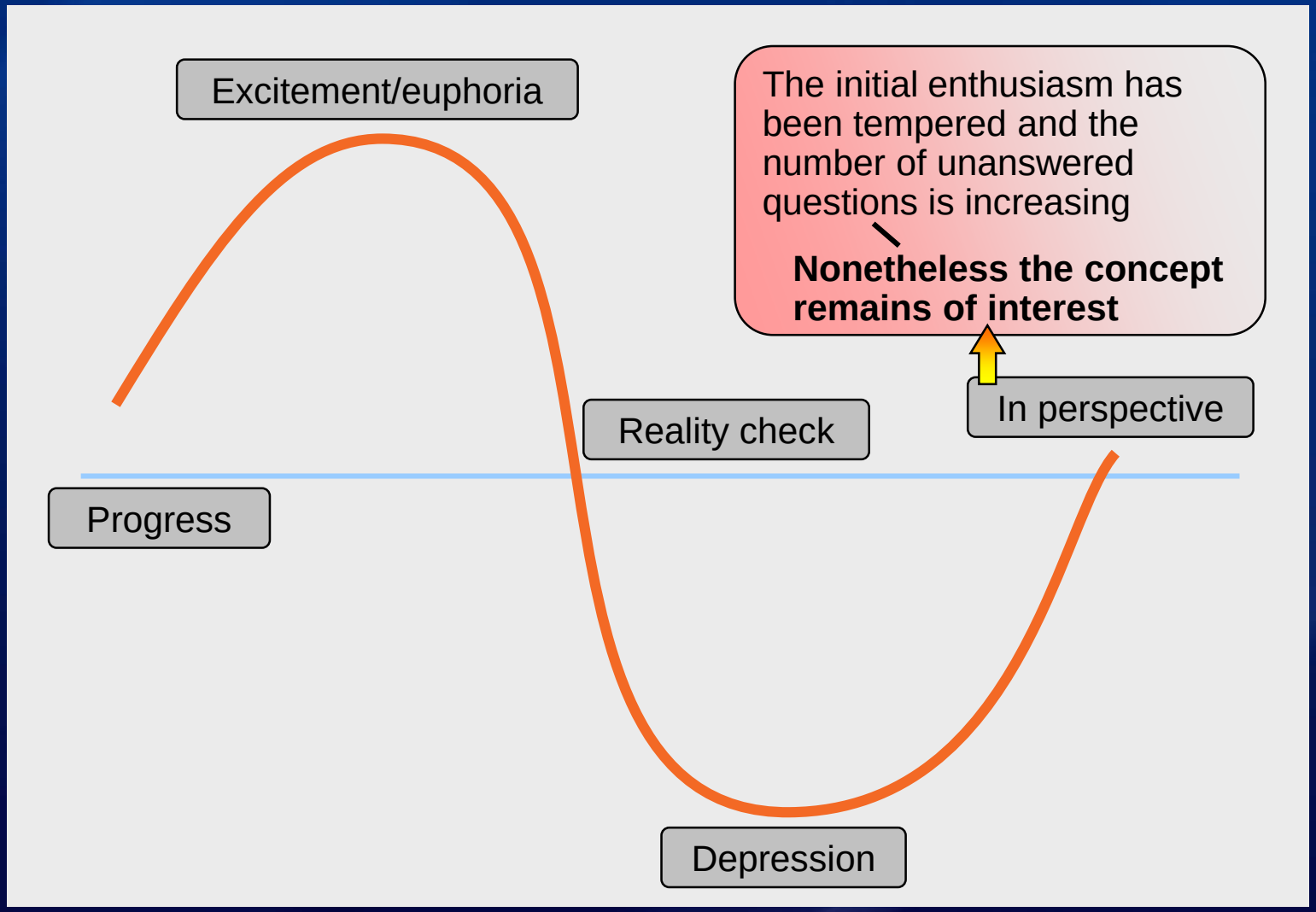
The Natural History of Evolving Therapies



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A Story about Mark Twain in "Drugs and Behavior"

By Fred Leavitt

Sage Publications 1994

"Twain was convinced that he could only sleep in well-ventilated rooms. Finding himself in a small hotel room with a window that was stuck shut, he tried in vain to fall asleep. Finally unable to bear it any longer, he reached under his bed, picked up a shoe, and heaved it at the window. The ensuing crash relieved him and he quickly fell asleep.

He awoke refreshed, only to find that he had missed the window and shattered a mirror instead.

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Composite Endpoints – Potential Pitfalls

Advantages

- ↑ statistical power
- ↑ frequency of events

Convenient
impact on sample size and costs

Caveat

"but a danger of oversimplifying the evidence by putting too much emphasis on the composite"

Pocock: and Gersh JACC, 2015

Summary of Key 1- and 5-Year Findings From the SYNTAX Trial

	1-year event rates		
Endpoint	**CABG (n=897)**	**DES (n=903)**	**P**
MACCE composite	12.1	17.8	0.002
Death	3.5	4.4	0.37
MI	3.3	4.8	0.11
Stroke	2.2	0.6	0.003
Death/MI/stroke	7.6	7.5	0.98
Repeat revascularization	5.9	13.7	<0.001
PCI	4.7	11.4	<0.001
CABG	1.3	2.8	0.03

Pocock: JACC, 2015; Serruys: NEJM, 2009; Mohr: Lancet, 2013

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Differential Magnitude of Composite Endpoints

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Small Studies with Highly Positive Results

Can be misleading

Non-inferiority and inadequate power
are two very different entities

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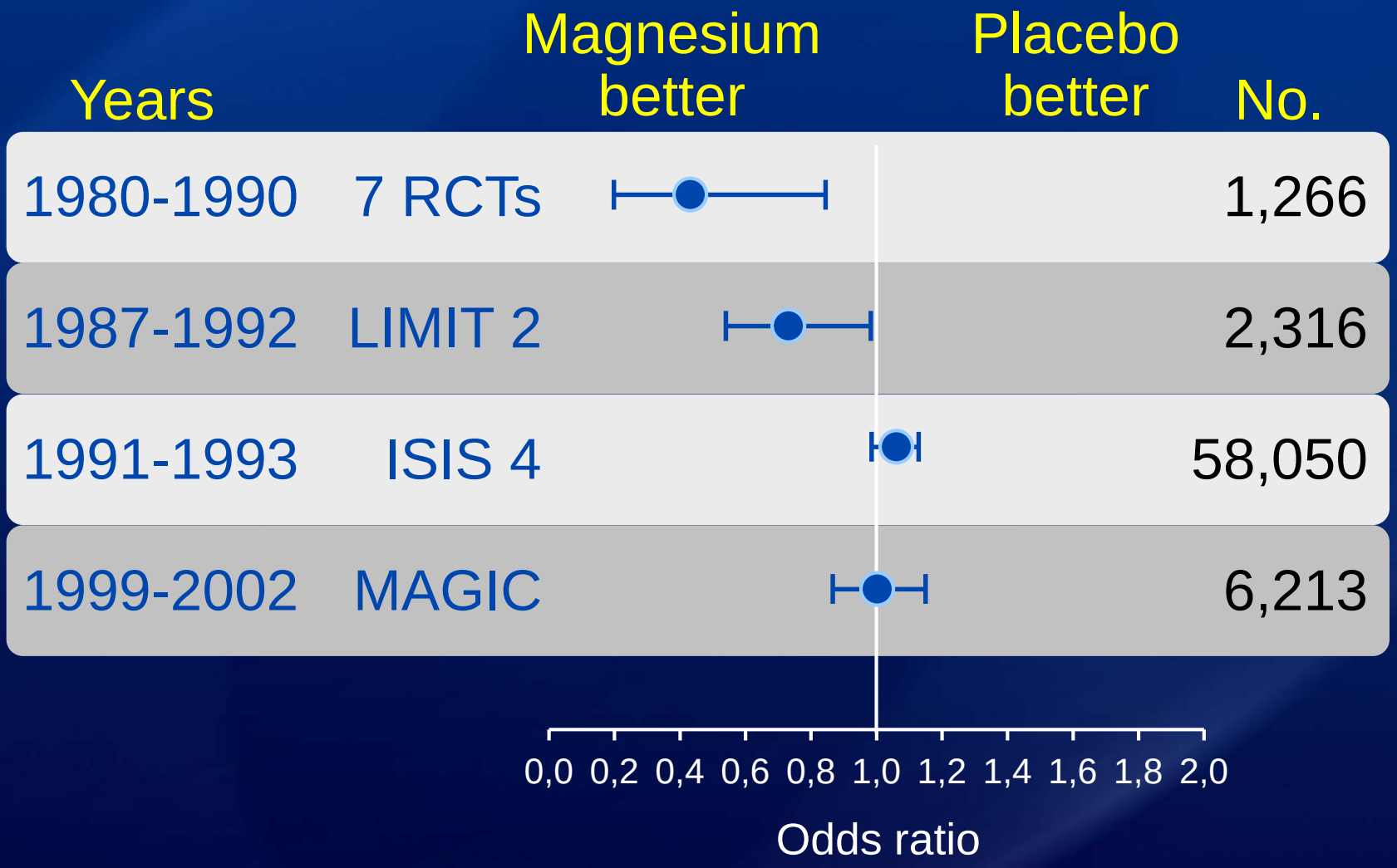
Trials of Magnesium for Acute MI



Antman E: Lancet 360:1189, 2002

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Type II Error in a Randomized Trial

Improved	33%
Unchanged	33%
Escaped	Monkey no. 3

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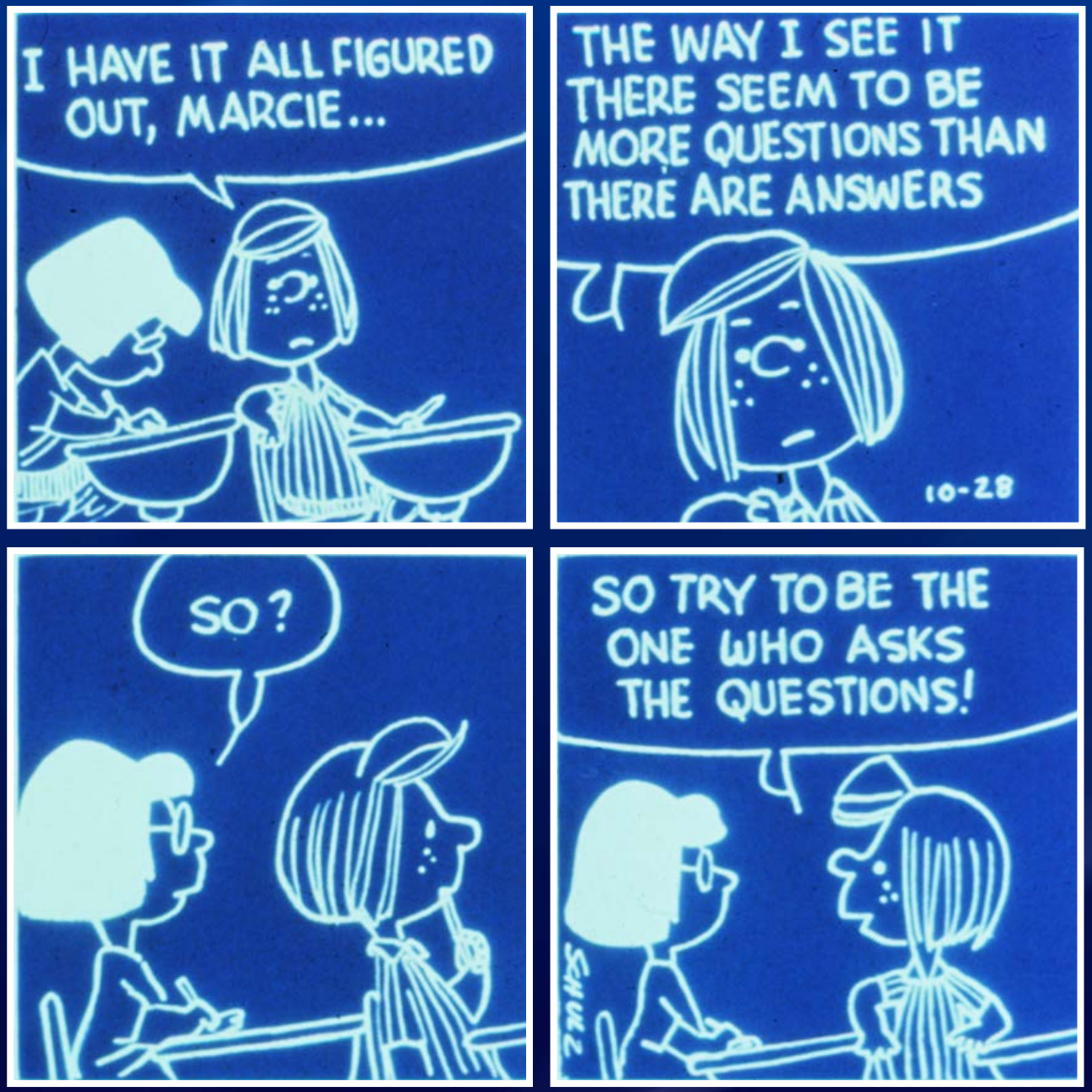

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Eminence-Based Medicine

"The more senior the colleague the less importance placed upon anything as mundane as evidence."

Isaacs: BMJ, 1999

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The “sicker” the patient

- Coronary artery
- Symptoms
- LV dysfunction
- Diabetes

The greater the benefit of revascularization vs medical therapy

The greater the benefit of CABG vs PCI-comorbidities?

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