The Cosmic Implications of ORBITA

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Professor of Medicine
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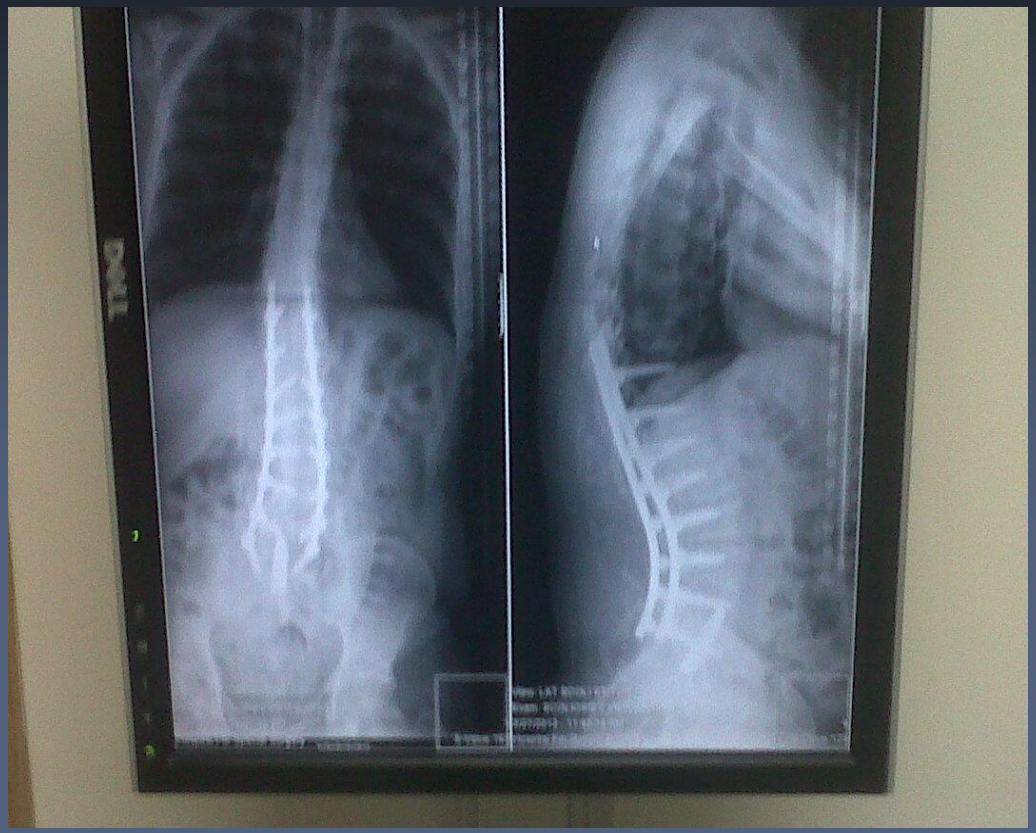
Coronary Vasomotion Disorders International Study Group (COVADIS) Summit
Munich, Germany
August 29, 2018

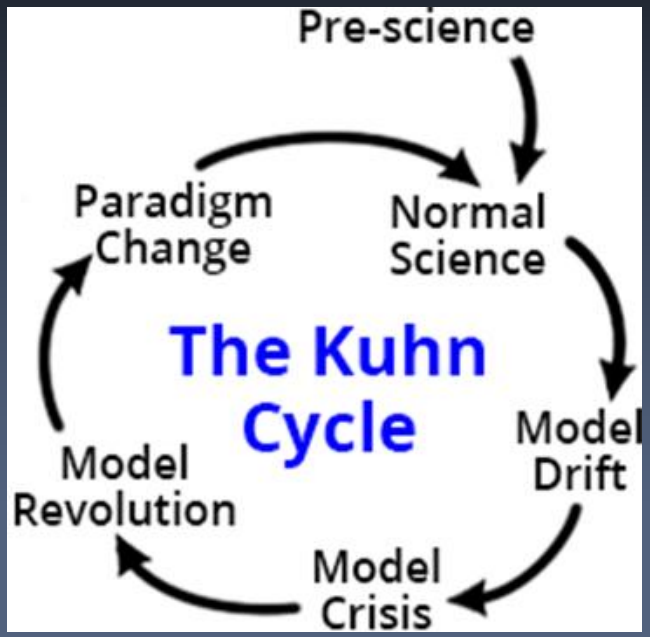
Washington University in St. Louis
School of Medicine

Disclosure

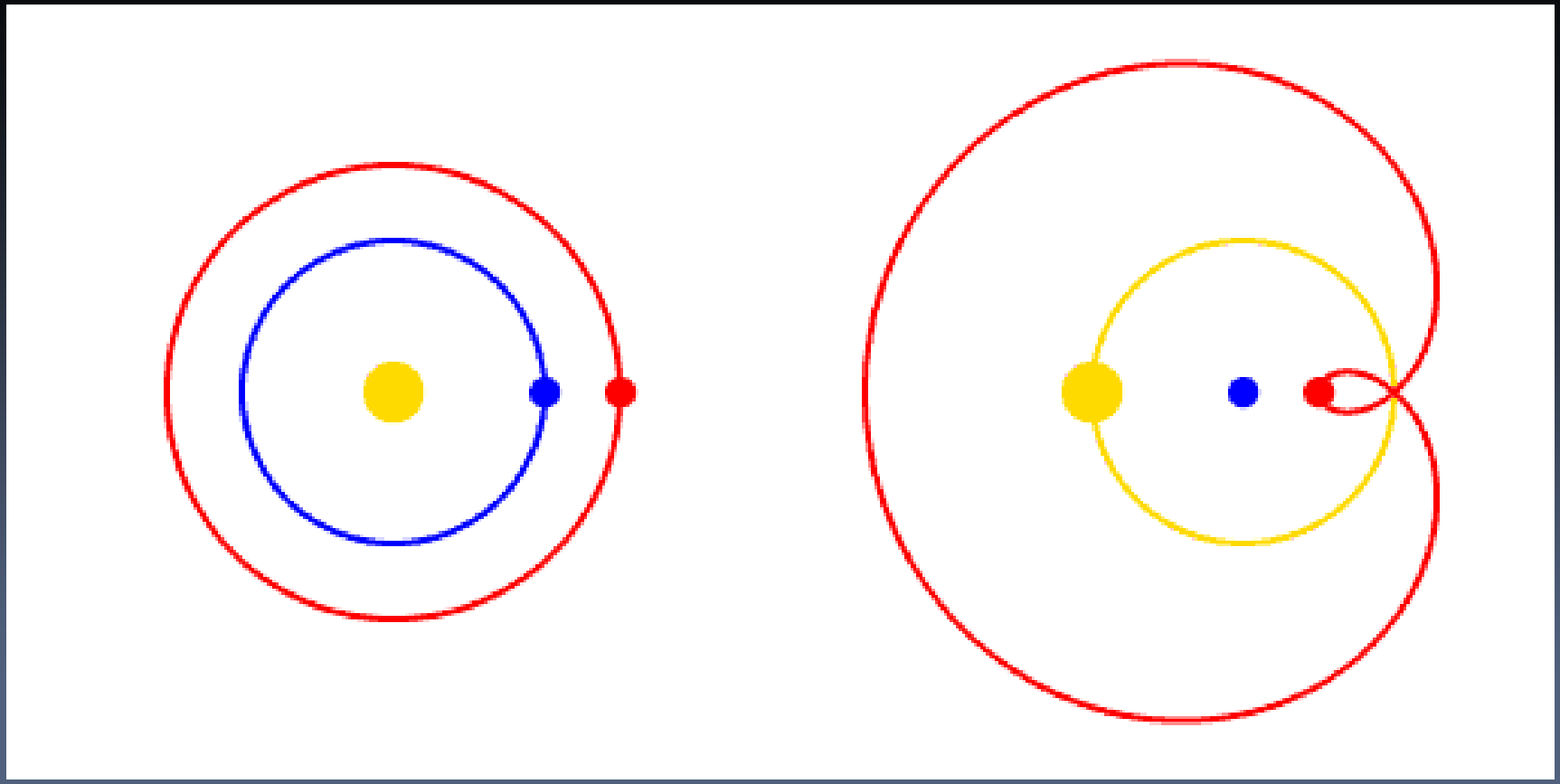
I practiced interventional cardiology for 19 years before becoming a general cardiologist in 2012



The Structure of Scientific Revolutions

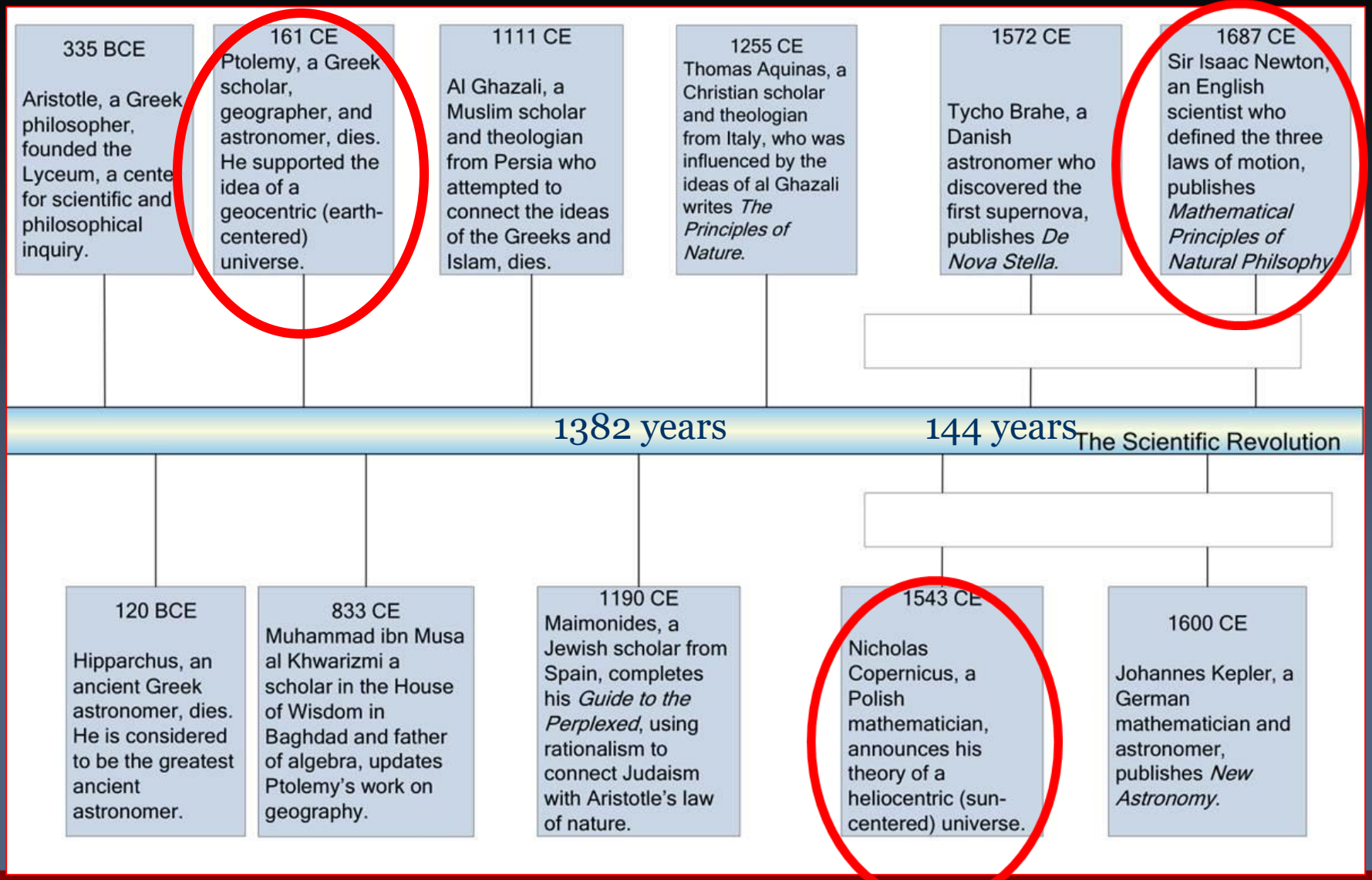


The Copernican Revolution

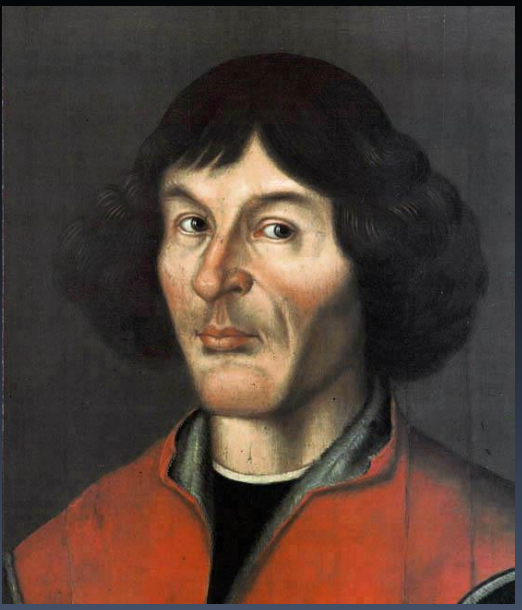


The Copernican Revolution was the paradigm shift from the Ptolemaic model of the heavens, which described the cosmos as having Earth stationary at the center of the universe, to the heliocentric model with the Sun at the center of the Solar System.

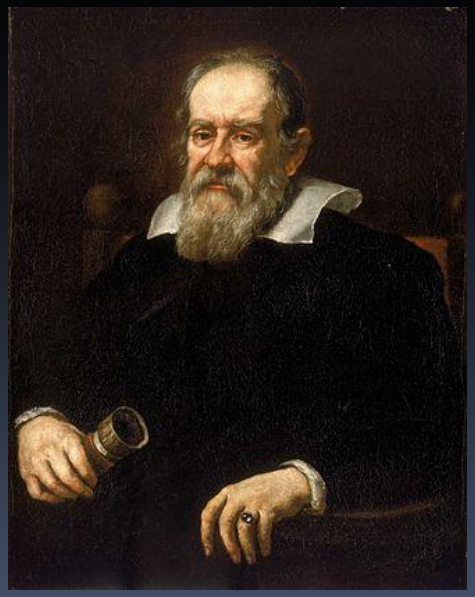
2000-Year Timeline of the Copernican Revolution



Major Figures of the Copernican Revolution

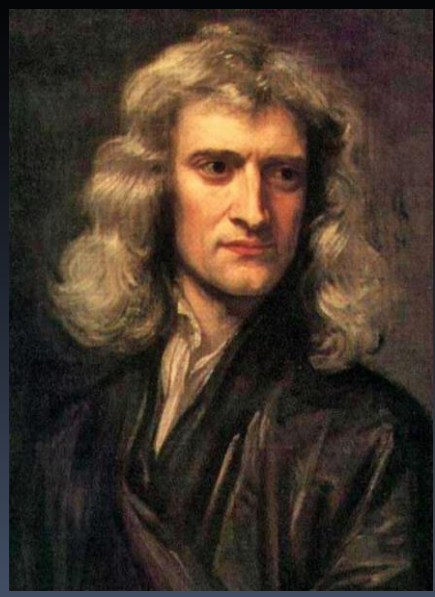


Copernicus-a Renaissance-era mathematician and astronomer who formulated a model of the universe that placed the Sun rather than the Earth at the center of the universe.



Galileo-the "father of modern observational astronomy" supported Copernicus and was tried by the Roman Inquisition, found "foolish and absurd in philosophy, and formally heretical ", and forced to recant. He spent the rest of his life under house arrest.

Pope Paul V- ordered Galileo to abandon completely the opinion that the sun stands still at the center of the world and the earth moves and not to teach, or defend it in any way.



Isaac Newton-an English physicist and mathematician. Newton's 3 laws published in Mathematical Principles of Natural Philosophy ended the Copernican Revolution

2012-First Call for of a Copernican Revolution in SIHD

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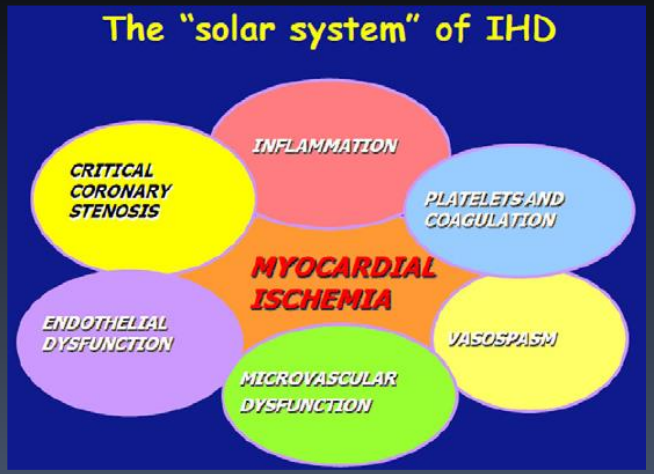
STATE-OF-THE-ART REVIEW AND COMMENTARY

Obstructive Coronary Atherosclerosis and Ischemic Heart Disease: An Elusive Link!

Mario Marzilli, MD,* C. Noel Bairey Merz, MD,† William E. Boden, MD,‡ Robert O. Bonow, MD,§ Paola G. Capozza, MD,* William M. Chilian, PHD,‖ Anthony N. DeMaria, MD,¶ Giacinta Guarini, MD,* Alda Huqi, MD,* Doralisa Morrone, MD,* Manesh R. Patel, MD,# William S. Weintraub, MD**

Pisa, Italy; Los Angeles, and San Diego, California; Albany, New York; Chicago, Illinois; Rootstown, Ohio; Durham, North Carolina; and Newark, Delaware



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http://dx.doi.org/10.1016/j.jacc.2012.04.046

Rethinking Stable Ischemic Heart Disease

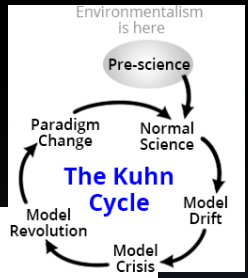
Is This the Beginning of a New Era?

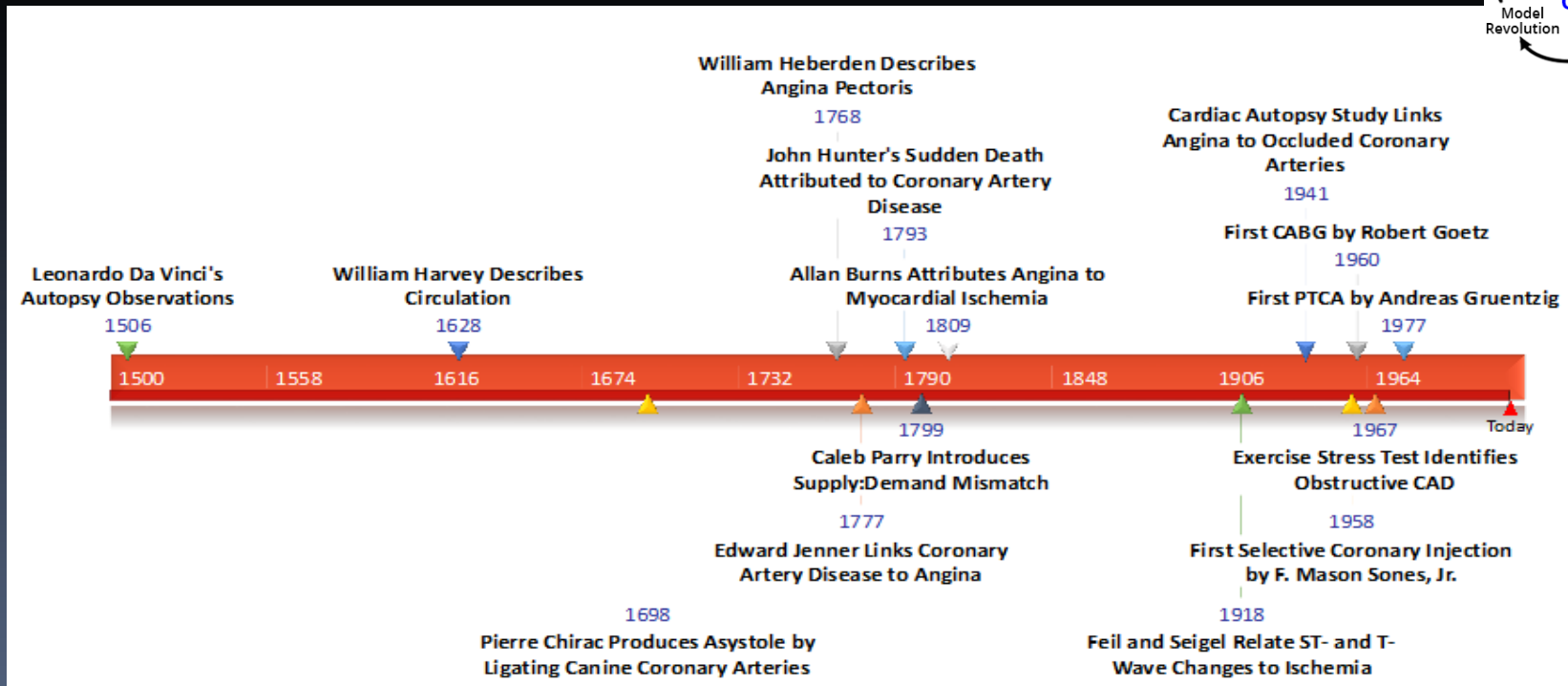
Carl J. Pepine, MD,* Pamela S. Douglas, MD†

Gainesville, Florida; and Durham, North Carolina

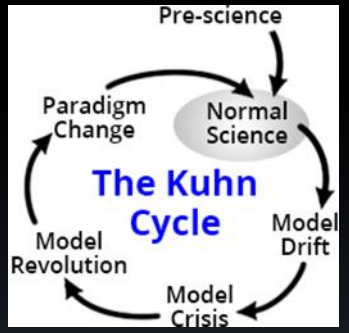
Pre-Science:

Origins of the Epicardial Stenosis-Ischemia-Revascularization Paradigm





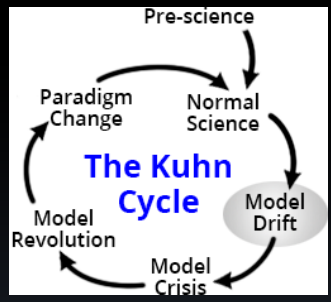
Normal Science 1977-2007
"Clogged Pipe" Paradigm of SIHD



- Any inconsistencies are solved within the context of the dominant paradigm
- As long as there is consensus within a discipline, normal science continues

Dilating or bypassing the narrowed arteries will change the natural history of the disease by preventing death and heart attack while relieving ischemia and angina

Model Drift



- Failure of the current paradigm to explain observed phenomena-anomalies
- Usually resolved or rationalized
  - Studies unfairly designed
    - Patients too low risk
  - Results misinterpreted
  - Results not generalizable to "my" patients
  - Results not consistent with "my" (anecdotal) experience
  - Anomalies are rare
- In some cases, anomalies accumulate to the point where normal science becomes difficult and weaknesses in the paradigm are exposed

COURAGE- The First Anomaly
April 12, 2007

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 12, 2007 VOL. 356 NO. 15

Optimal Medical Therapy with or without PCI for Stable Coronary Disease

William E. Boden, M.D., Robert A. O'Rourke, M.D., Koon K. Teo, M.B., B.Ch., Ph.D., Pamela M. Hartigan, Ph.D., David J. Maron, M.D., William J. Kostuk, M.D., Merril Knudtson, M.D., Marcin Dada, M.D., Paul Casperson, Ph.D., Crystal L. Harris, Pharm.D., Bernard R. Chaitman, M.D., Leslee Shaw, Ph.D., Gilbert Gosselin, M.D., Shah Nawaz, M.D., Lawrence M. Title, M.D., Gerald Gau, M.D., Alvin S. Blaustein, M.D., David C. Booth, M.D., Eric R. Bates, M.D., John A. Spertus, M.D., M.P.H., Daniel S. Berman, M.D., G.B. John Mancini, M.D., and William S. Weintraub, M.D., for the COURAGE Trial Research Group*

Rationalizing Anomalies Before Social Media
October 16, 2007
(6 Months of Peace)

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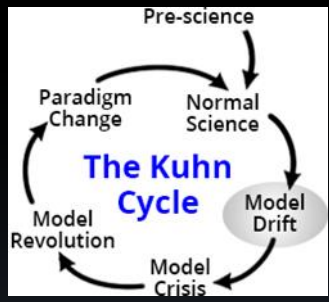
EXPEDITED PUBLICATIONS **Viewpoint**

The Truth and Consequences of the COURAGE Trial

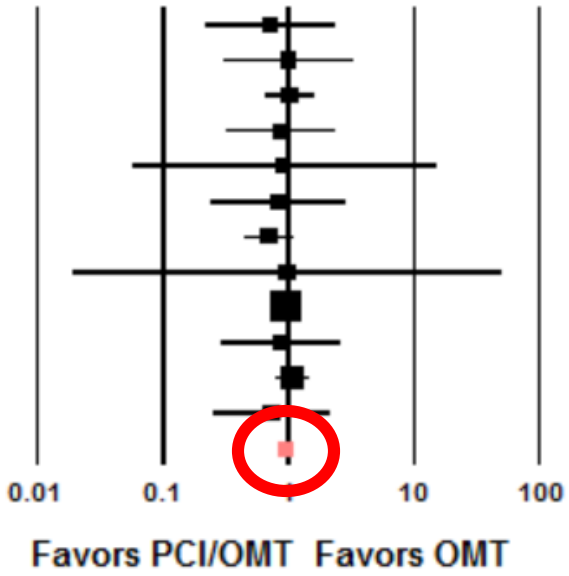
Dean J. Kereiakes, MD, FACC,* Paul S. Teirstein, MD, FACC,† Ian J. Sarembock, MB, ChB, MD,‡ David R. Holmes, Jr, MD,§ Mitchell W. Krucoff, MD, FACC,¶ William W. O'Neill, MD,‖ Ron Waksman, MD, FACC,# David O. Williams, MD,** Jeffrey J. Popma, MD, FACC,†† Maurice Buchbinder, MD, FACC,† Roxana Mehran, MD,†† Ian T. Meredith, MBBS, PhD, FACC,‡‡ Jeffrey W. Moses, MD, FACC,†† Gregg W. Stone, MD, FACC††

Cincinnati, Ohio; La Jolla, California; Rochester, Minnesota; Durham, North Carolina; Miami, Florida; Washington, DC; Providence, Rhode Island; Boston, Massachusetts; New York, New York; and Clayton, Australia

Model Drift:
PCI + OMT vs. OMT in Stable CAD
Mortality



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Events / Total Group-A	Events / Total Group-B
ACME-1 1992	0.714	0.219	2.326	-0.559	0.576	5 / 105	7 / 107
MASS I (PCI) 1995	1.000	0.307	3.261	0.000	1.000	6 / 72	6 / 72
RITA-2 1997	1.022	0.657	1.589	0.095	0.924	43 / 504	43 / 514
ACME-2 1997	0.857	0.316	2.328	-0.302	0.762	9 / 51	10 / 50
AVERT 1999	0.926	0.057	14.928	-0.054	0.957	1 / 177	1 / 164
DEFER 2001	0.833	0.245	2.835	-0.292	0.770	5 / 90	6 / 91
MASS II (PCI) 2004	0.698	0.451	1.081	-1.611	0.107	49 / 205	63 / 203
Hambrecht 2004	0.980	0.019	50.374	-0.010	0.992	1 / 51	1 / 50
COURAGE 2007	0.958	0.763	1.204	-0.365	0.715	253 / 613	253 / 598
JSAP 2008	0.867	0.286	2.628	-0.253	0.800	6 / 188	7 / 191
BARI 2D PCI 2009	1.085	0.806	1.462	0.540	0.589	102 / 798	96 / 807
FAME 2 2012	0.736	0.253	2.140	-0.562	0.574	6 / 447	8 / 441
	0.945	0.815	1.096	-0.745	0.456	486 / 3301	501 / 3288

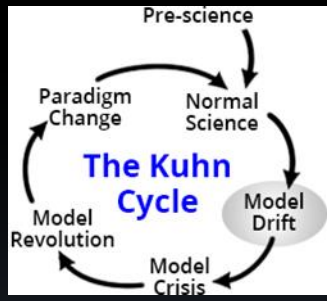


12 RCT's; N=6589.

Mitchell JD, Brown DL. JAHA. 2017.

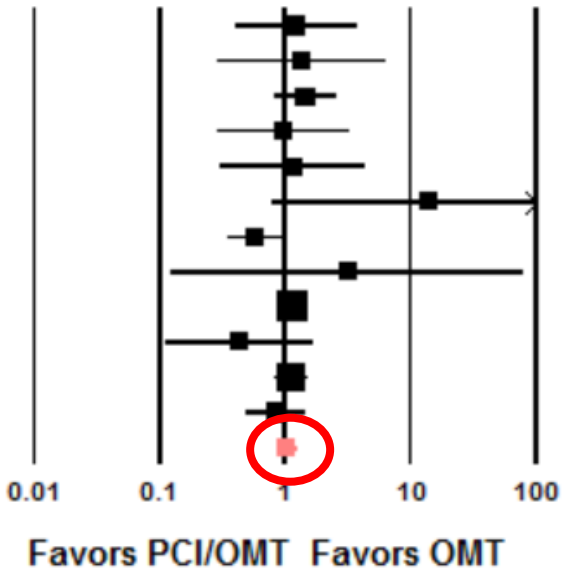
Model Drift: Challenges to the Paradigm: PCI + OMT vs. OMT in Stable CAD

MI



Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	MI / Total PCI+OMT	MI / Total OMT
ACME 1992	1.202	0.390	3.705	0.321	0.748	7 / 105	6 / 107
MASS 1995	1.353	0.292	6.273	0.386	0.699	4 / 72	3 / 72
RITA-2 1997	1.447	0.835	2.510	1.316	0.188	32 / 504	23 / 514
ACME-2 1997	0.978	0.293	3.264	-0.037	0.971	6 / 51	6 / 50
AVERT 1999	1.163	0.307	4.407	0.222	0.824	5 / 177	4 / 164
DEFER 2001	14.077	0.781	253.696	1.793	0.073	6 / 90	0 / 91
MASS-II 2004	0.581	0.343	0.986	-2.011	0.044	27 / 205	42 / 203
Hambrecht 2004	3.121	0.124	78.454	0.692	0.489	1 / 50	0 / 51
COURAGE 2007	1.122	0.870	1.446	0.886	0.376	143 / 1149	128 / 1138
JSAP 2008	0.426	0.109	1.674	-1.222	0.222	3 / 188	7 / 191
BARI 2D 2009	1.124	0.819	1.543	0.723	0.470	90 / 798	82 / 807
FAME 2 2012	0.846	0.492	1.455	-0.604	0.546	26 / 447	30 / 441
	1.037	0.855	1.258	0.369	0.712	350 / 3836	331 / 3829

Odds ratio and 95% CI



12 RCT's; N=7665.

Mitchell JD, Brown DL. JAHA 2017.

More Model Drift: No High-Risk Subgroups Benefit from PCI

High-Risk Subsets	Worse Outcomes (Death, MI)	Outcomes Improved by PCI
Diabetics	Yes	No
Diabetics with high-risk anatomy	Yes	No
Older patients	Yes	No
Low LVEF	Yes	No
More extensive CAD	Yes	No
3V CAD + low LVEF	Yes	No
Proximal LAD	Yes	No
Chronic kidney disease	Yes	No
Ischemia	Yes	No

But PCI Still Works for Angina!

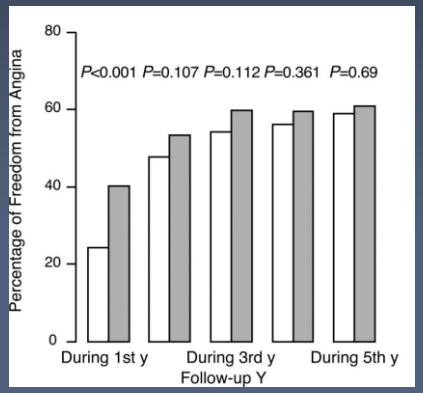
2.3. Revascularization to Improve Symptoms: Recommendations

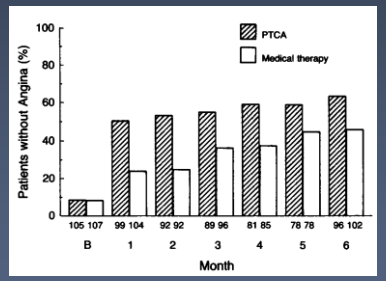
CLASS I

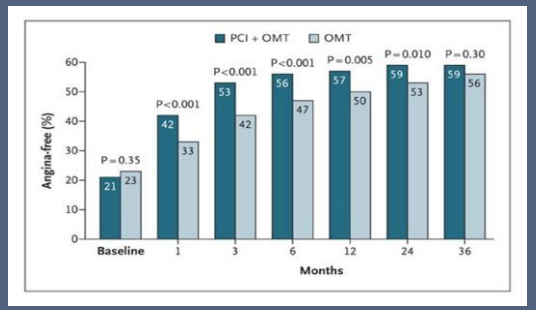
1. CABG or PCI to improve symptoms is beneficial in patients with 1 or more significant (≥70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite GDMT (82,99–108). *(Level of Evidence: A)*

Class I:
Conditions for which there is evidence, general agreement, or both that a given procedure or treatment is useful and effective.

Level of Evidence A:
Data derived from multiple (unblinded) randomized clinical trials







Or Does It?

SEMINARS IN MEDICINE OF THE BETH ISRAEL HOSPITAL, BOSTON ARCHIVE

Angina Pectoris and the Placebo Effect

Herbert Benson, M.D., and David P. McCallie, Jr.

Article

55 References 126 Citing Articles Letters

June 21, 1979
N Engl J Med 1979; 300:1424-1429
DOI: 10.1056/NEJM197906213002508

Editors

Howard L. Bleich, M.D., Editor, Mary Jean Moore, Assistant Editor

THE PLACEBO EFFECT IS A COMPONENT OF ANY THERAPEUTIC intervention, and its influence is seen in many diseases.[1 2 3 4 5] The symptoms of angina pectoris, in particular, are responsive to the placebo effect. Many of the treatments used since Heberden's[6] description of this disease in 1772 are now known to

Sham-Controlled Trials in Stable Angina

Study	Treatment	Control	N	Exercise Time Endpoints	Δ Active-Placebo
Cobb et al; NEJM 1959	Internal Mammary ligation	Sham	17	Pre-post difference	1 vs .3 min 42 seconds
Stone et al; JACC 2002	PTMR	Sham	71	Pre-post difference	10 vs 7 sec 3 seconds P=.73
Salem et al; AJC 2004	PTMR	Sham	82	Final exercise time	620 vs 604 16 seconds P>.1
Leon et al; JACC 2005	PTMR	Sham	200	Final exercise time	431 vs 395 sec 36 seconds
Verheye; NEJM 2015	Coronary sinus reduction	Sham	104	Pre-post difference	59 vs 4 sec 54 seconds P=.07

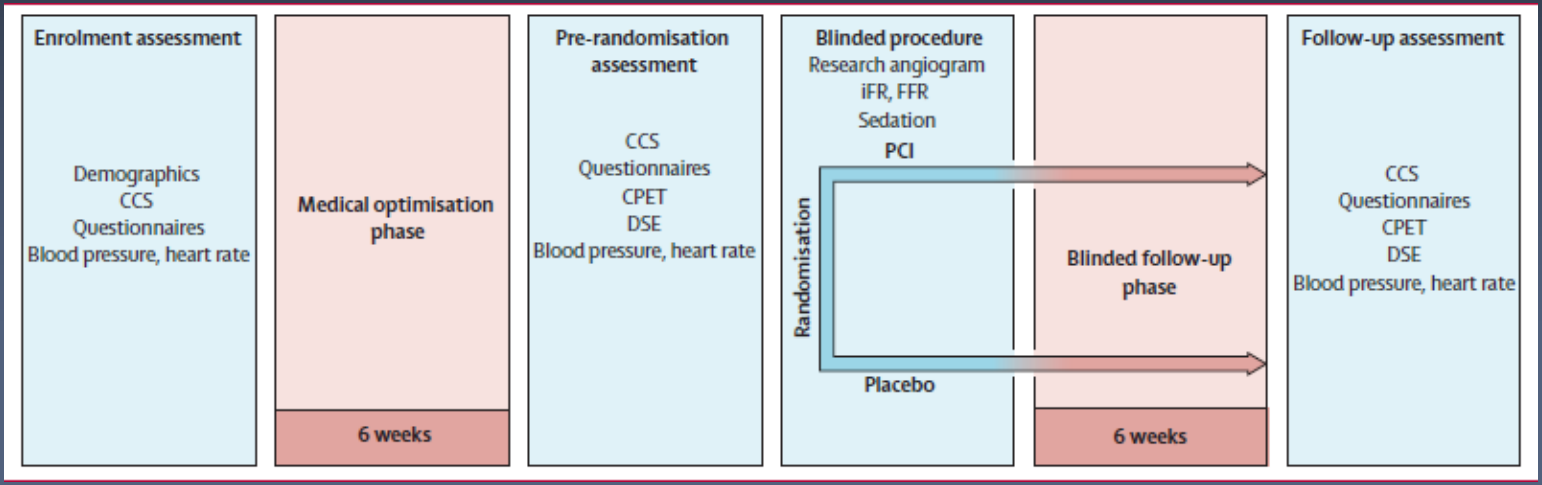
ORBITA-The Newest Anomaly

November 2, 2017

Lancet 2018; 391: 31 - 40

Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial

*Rasha Al-Lamee, David Thompson, Hakim-Moulay Dehbi, Sayan Sen, Kare Tang, John Davies, Thomas Keeble, Michael Mielewczik, Raffi Kaprielian, Iqbal S Malik, Sukhjinder S Nijjer, Ricardo Petraco, Christopher Cook, Yousif Ahmad, James Howard, Christopher Baker, Andrew Sharp, Robert Gerber, Suneel Talwar, Ravi Assomull, Jamil Mayet, Roland Wensel, David Collier, Matthew Shun-Shin, Simon A Thom, Justin E Davies, Darrel P Francis, on behalf of the ORBITA investigators**



Principle Hypothesis: PCI increases exercise time more than a sham procedure
Sample size calculation: To detect an increase in exercise time of 30 seconds with 80% power and a SD of 75 seconds requires 200 randomized patients

ORBITA Results Summarized

- Stent compared to sham
  - **No significant improvement in:**
  - Exercise time (with 2 different statistical methods)
  - Time to 1 mm ST depression
  - Peak oxygen uptake
  - SAQ physical limitation (with 2 different statistical methods)
  - SAQ angina frequency (with 2 different statistical methods)
  - SAQ angina stability
  - SAQ quality of life (with 2 different statistical methods)
  - EQ-5D-5L QoL (with 2 different statistical methods)
  - Duke treadmill score
  - CCS angina grade (with 2 different statistical methods)
  - **Significant improvement in:**
  - Peak stress wall motion index score (with 2 different statistical methods)
  - Freedom from angina at 4 weeks (49.5 vs. 31.5%)

Rationalizing Anomalies in the Era of SoMe

Gregg W. Stone MD @GreggWStone · 2 Nov 2017

Baseline SAQ >70 = monthly angina. Hard to improve upon this with PCI despite significant reduction in ischemia. Like Courage.

Gregg W. Stone MD @GreggWStone · 2 Nov 2017

Corresponds with the ~27% of lesions in this trial with FFR >0.80 for which PCI is inappropriate. Class III to have treated these pts.

Gregg W. Stone MD @GreggWStone · 3 Nov 2017

Problem is wrong cohort enrolled. Should have been SAQ<60 (mod angina), exercise duration <6' w/hypokinesis. Primary EP of ex dur or QOL OK.

Gregg W. Stone MD @GreggWStone · 8 Nov 2017

From ORBITA appendix: While many lesions were "real", many also had DS <50% or supplied a small amount of myocardium (e.g. septal perforators, distal LCX

Sandra and 2 others Retweeted

Gregg W. Stone MD @GreggWStone · 16 Dec 2017

OK, here comes the heresy. I have no doubt that PCI in select patients with stable ischemic heart disease **prevents** MI and improves survival. However, will be impossible to ever prove this in a randomized trial.

Published Critiques

Fallout from the ORBITA trial – is angioplasty in a spin?

Robert A. Byrne*, MB, BCh, PhD, *Deputy Editor*

ESC European Society of Cardiology

European Heart Journal (2018) **0**, 1–3
doi:10.1093/eurheartj/ehx796

VIEWPOINT

ORBITA revisited: what it really means and what it does not?

Bernard R. Chaitman[1], Maria Mori Brooks[2], Kim Fox[3], and Thomas F. Lüscher[4,5]*

Circulation

PERSPECTIVE

Rediscovering the Orbit of Percutaneous Coronary Intervention After ORBITA

The publication of the ORBITA trial (Objective Randomised Blinded Investigation With Optimal Medical Therapy of Angioplasty in Stable Angina) generated an immense amount of discussion, debate, and controversy.[1] The editorialists posed in their title whether the ORBITA trial is the "Last nail in the coffin for PCI [percutaneous coronary intervention] in stable angina?"[2] The ensuing press coverage has been extensive, although mostly 1-sided, and largely following the negative tone set by the editorial. The exchange on social media has been at times vitriolic, both pro and con. The number of tweets of the article (1716 as of February 25, 2018) now exceeds the number of patients enrolled by >7-fold. Thus, ORBITA has disrupted the orbit of PCI.

Deepak L. Bhatt, MD, MPH
Bernard J. Gersh, MB, ChB, DPhil
Ph. Gabriel Steg, MD
Robert A. Harrington, MD
Stephan Windecker, MD

Circulation

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Ph. Gabriel Steg, MD
Robert A. Harrington, MD
Stephan Windecker, MD

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Abstract

ORBITA$_2$: Bringing Some Oxygen Back to PCI in Stable Ischemic Heart Disease?

Ajay J. Kirtane

Originally published 24 Jul 2018 | Circulation. 2018;0:CIRCULATIONAHA.118.03533

Abstract

With the presentation and publication of the ORBITA trial in late 2017,[1] for the first time the cardiology community had the results of a blinded randomized trial examining the efficacy of percutaneous coronary intervention (PCI) for stable ischemic heart disease (SIHD). ORBITA was a mechanistic trial, carefully examining a host of endpoints in order to determine potentially measurable effects of PCI vs. a sham comparator at 6 weeks of

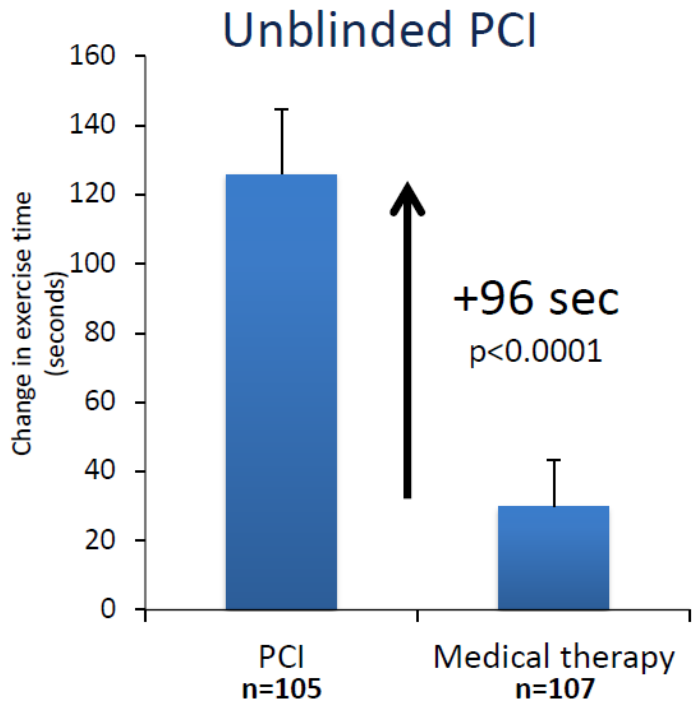
Summary of Published Critiques of ORBITA

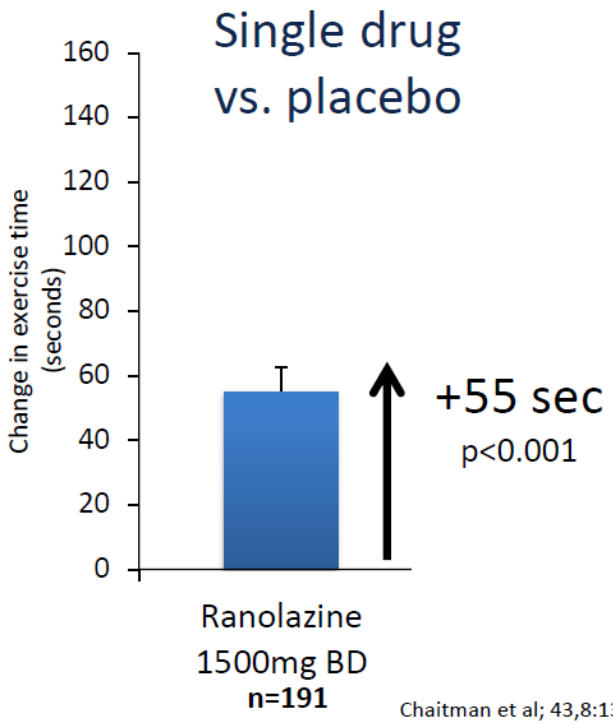
- Patients too fit
- Sample size too small
- Angina too mild
- Wrong primary endpoint
- FFR normal in 29% of patients
- Follow-up too short
- Single-vessel disease not relevant to current interventional practice
- Wrong Paradigm?

“Patients Are Too Fit if They Can Go 8:20 on the Bruce Protocol”

- Modified Bruce Protocol used- 6 minutes of low level warm-up
- 8 minutes≈2 minutes on Bruce protocol

"Sample Size Too Small"
Or Too Large?





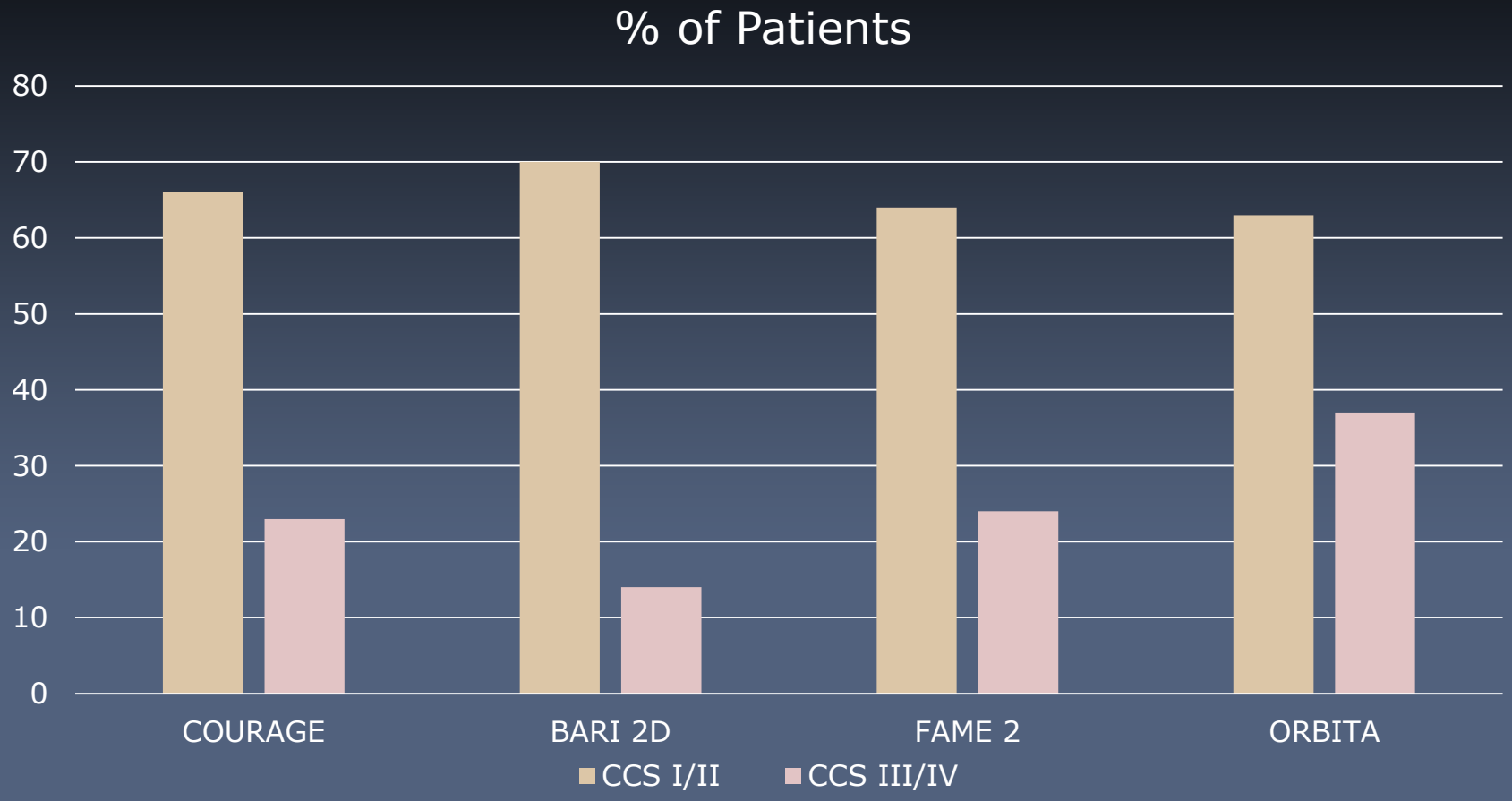
Error bars are standard errors of the mean

Parisi et al; 326:10-6 NEJM 1992

Chaitman et al; 43,8:1375-82 JACC 2004

"Angina Too Mild"

Baseline Angina Severity in Four Landmark RCTs

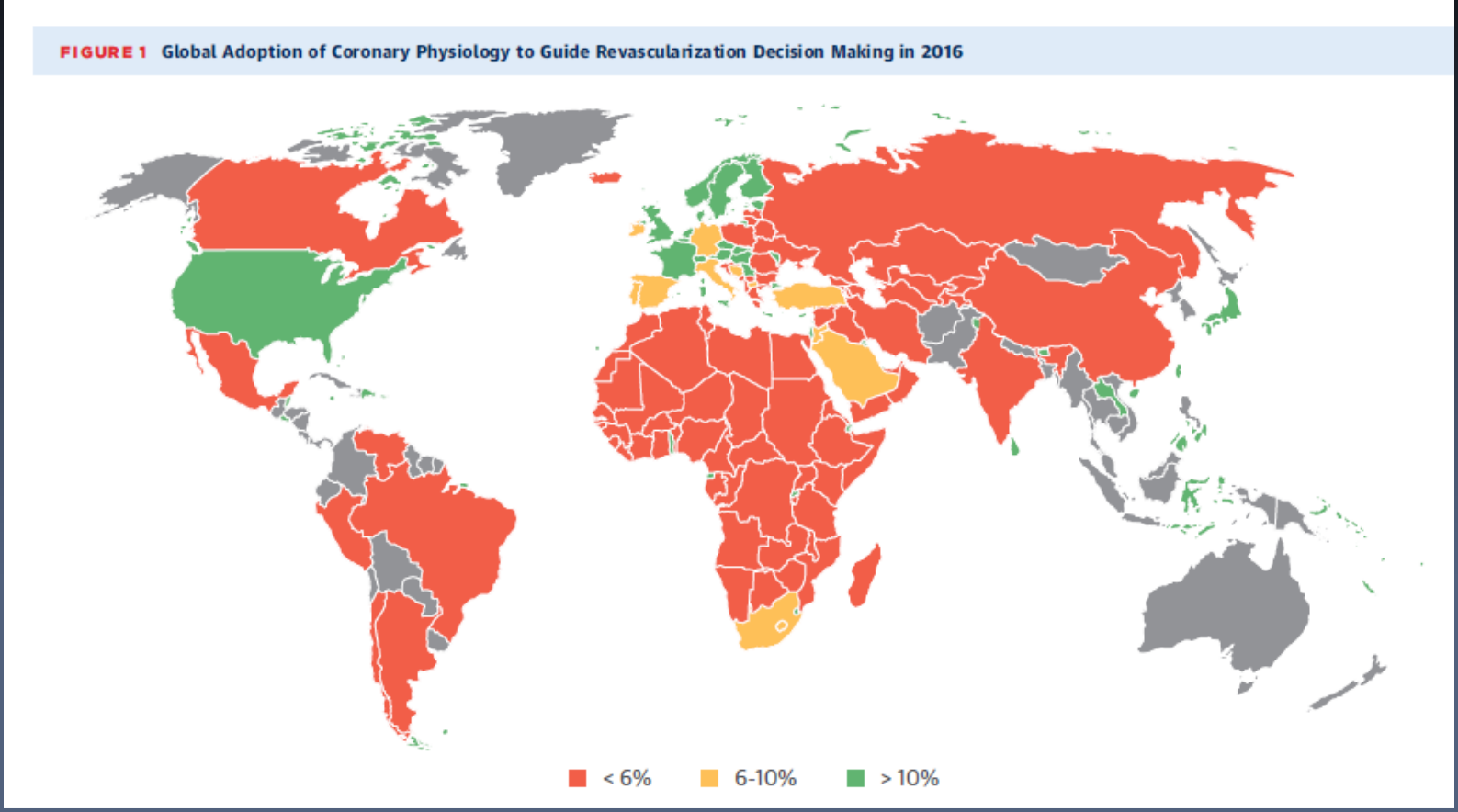


"Wrong Primary Endpoint"

- Treadmill exercise time was chosen to replicate FDA and EMA requirements for anti-anginal medications and too duplicate methods used in all other sham-controlled trials of angina treatments.

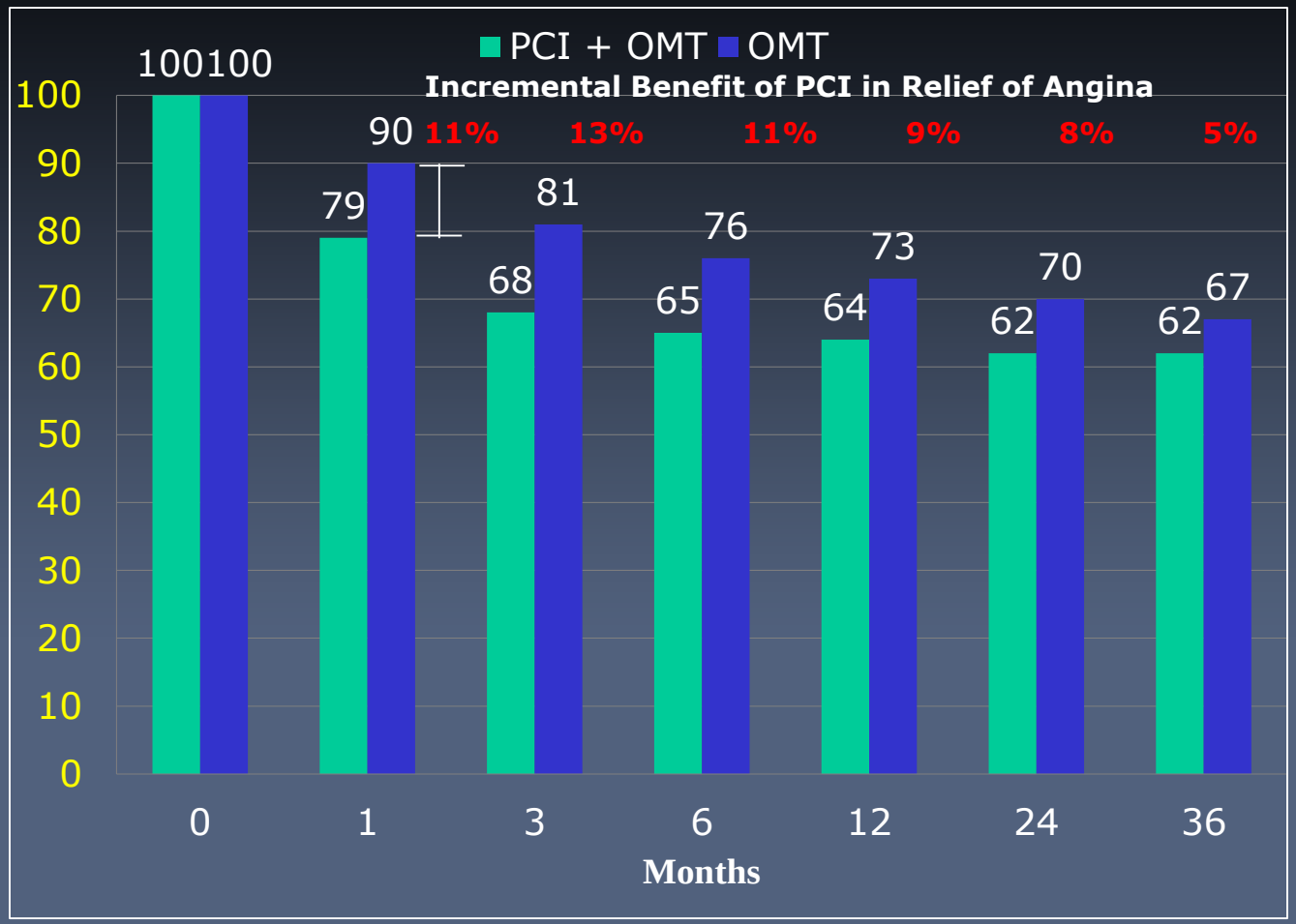
"FFR > 0.8 in 29% of Patients"

Global Use of FFR to Guide PCI



94% of ORBITA patients had at least one test that was positive for ischemia

"Follow-up Not Long Enough"
Angina Relief Over Time in COURAGE

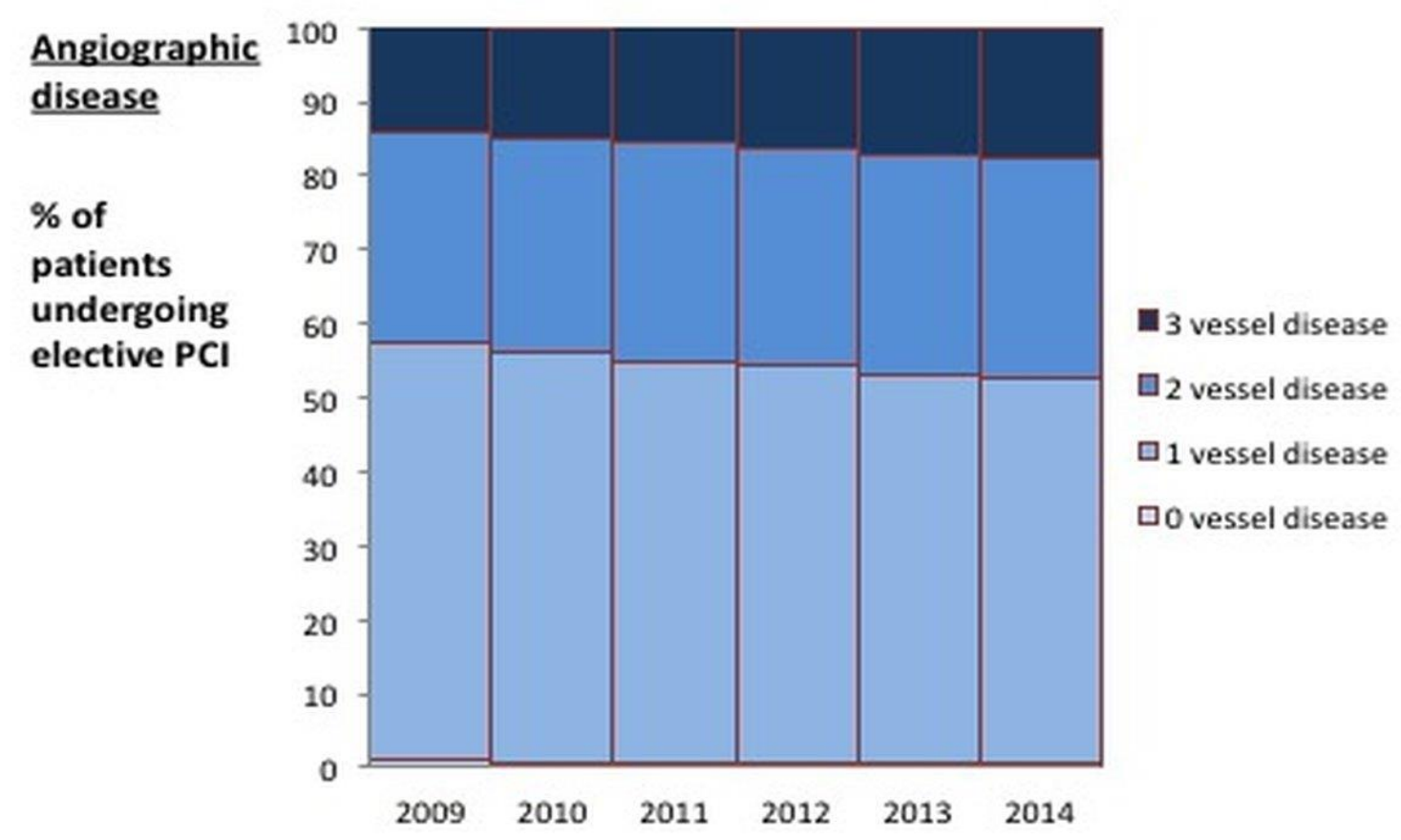


N=1784 patients with angina at the time of randomization

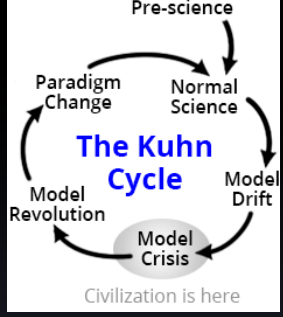
N Engl J Med 2008;359:677-87.

"Single-Vessel PCI Not Relevant to Contemporary Practice"

Elective PCI in the United States



Model Crisis



- If the paradigm proves chronically unable to account for anomalies, the model enters a crisis period.
- Irreconcilable Anomalies-
  - In RCTs, PCI does not reduce death or MI in any identifiable subset of patients with stable CAD beyond what is achieved by OMT
  - PCI improves coronary artery blood flow but appears to be no more effective than OMT and a sham PCI at eliminating angina

The Attack on Facts

"That's so silly because it's somebody's version of the truth," Rudy Giuliani said of allowing President Donald Trump to testify. | Andrew Harnik/AP Photo

Giuliani: 'Truth isn't truth'

By REBECCA MORIN and DAVID COHEN | 08/19/2018 10:27 AM EDT | Updated 08/19/2018 06:16 PM EDT

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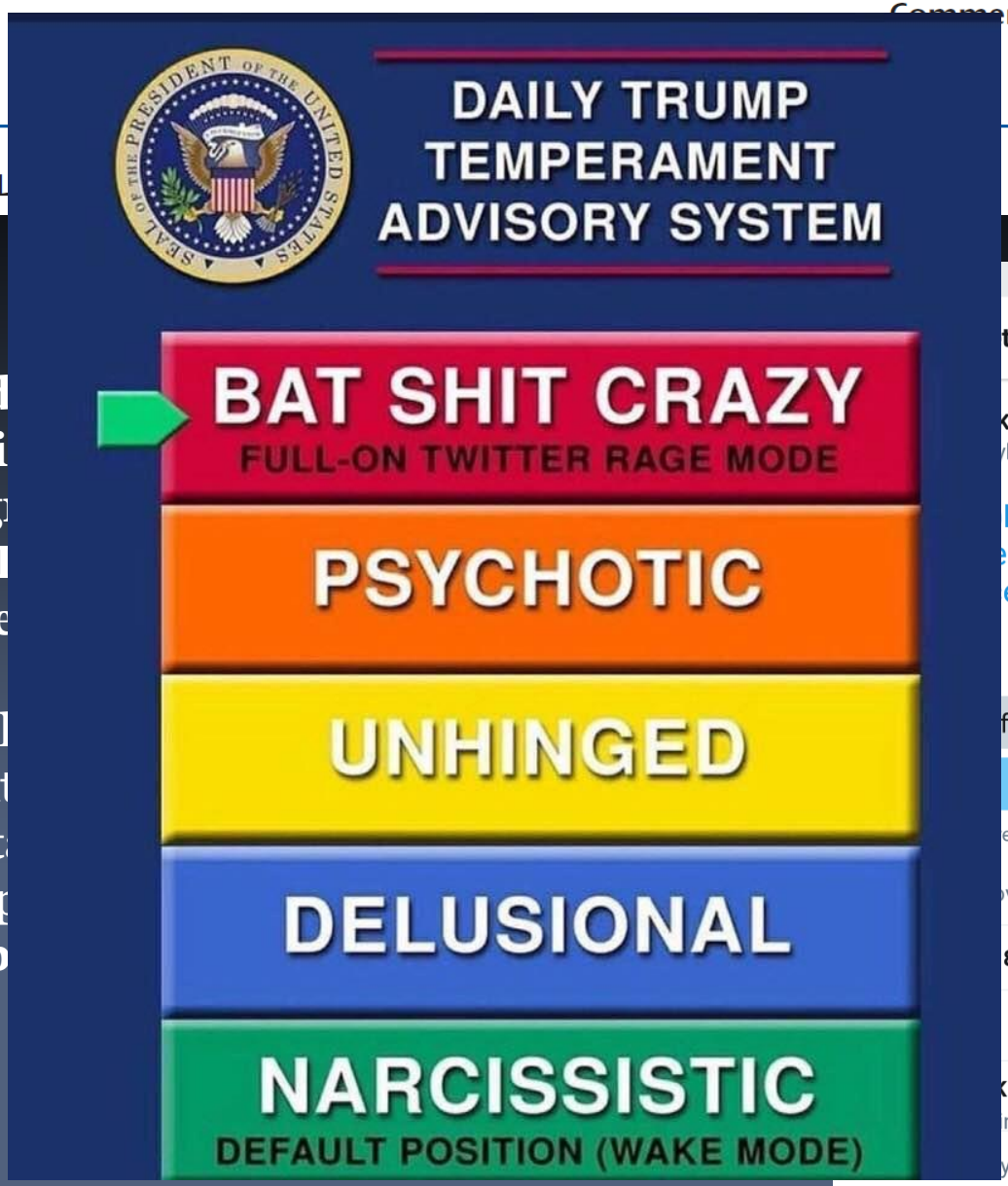
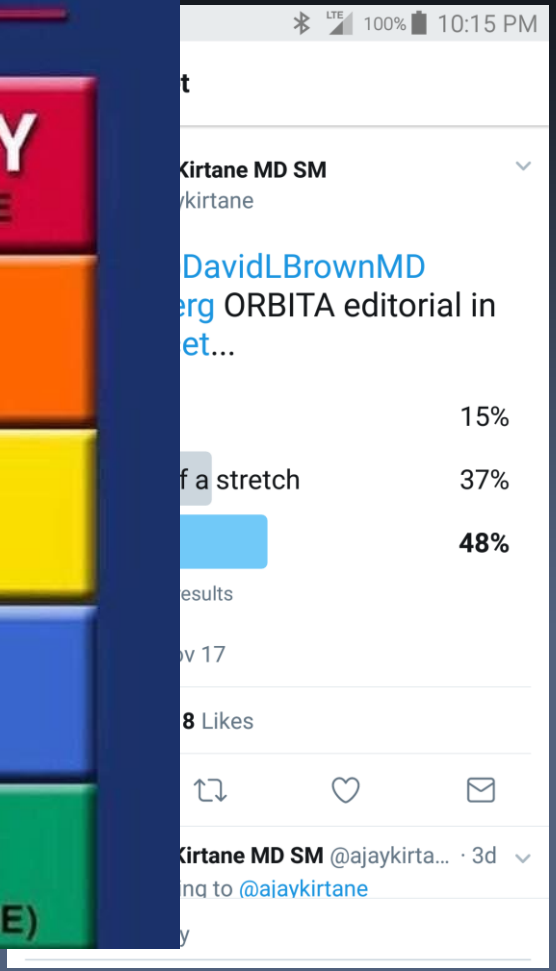
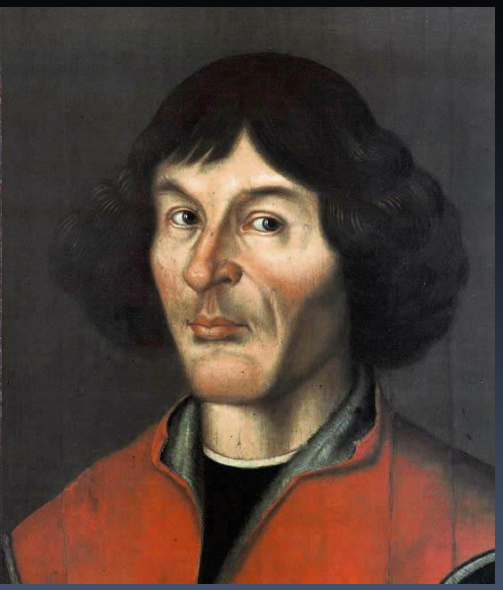
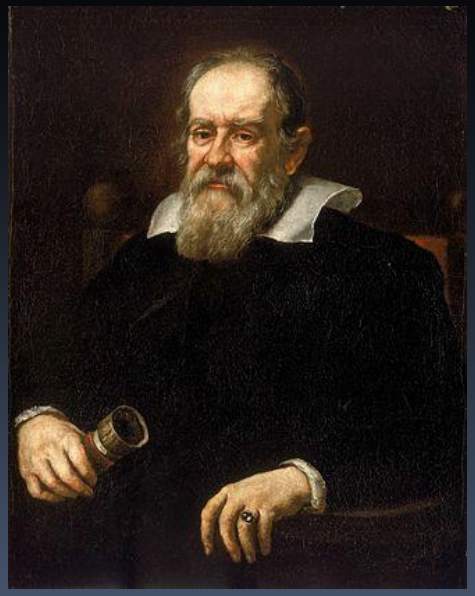
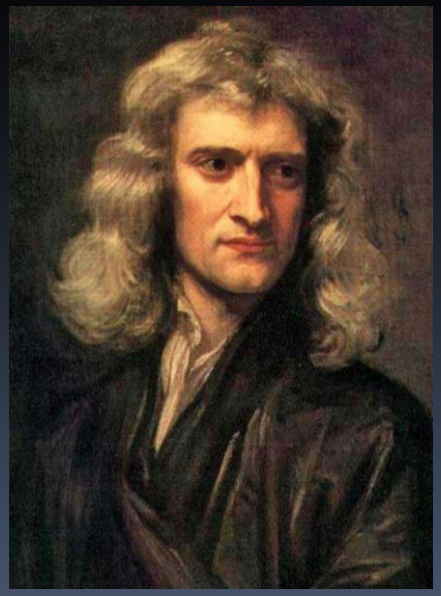


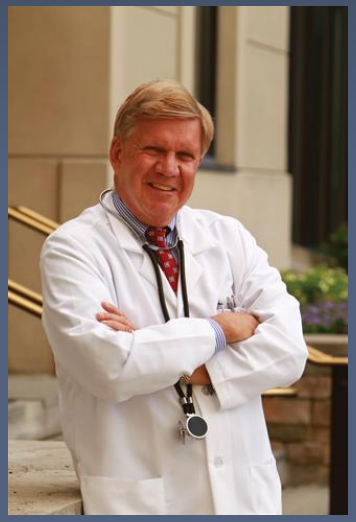


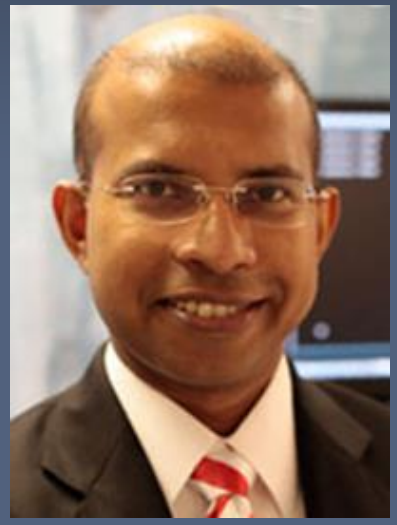
Major Figures of the SIHD Revolution











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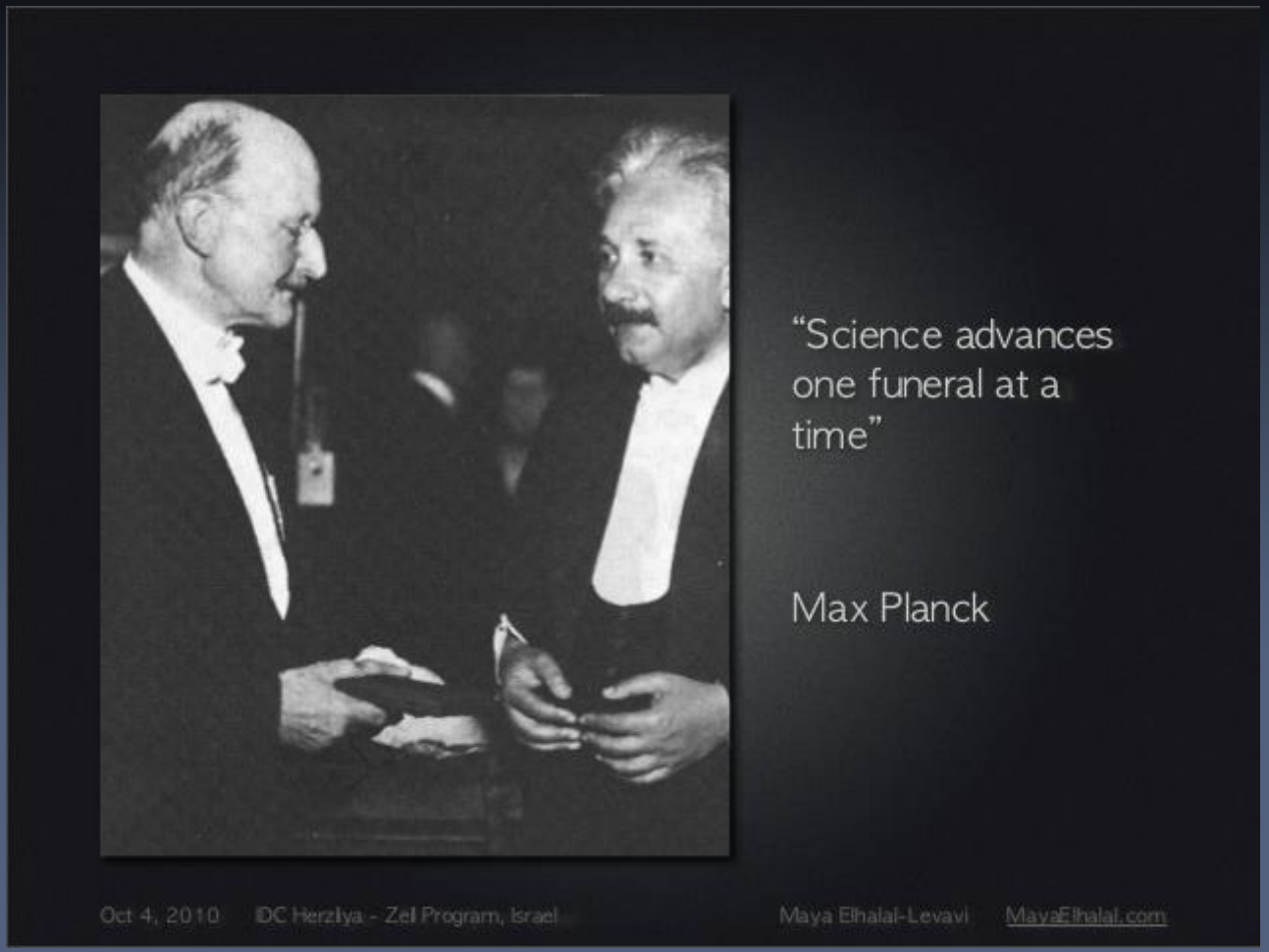
Summary

- Scientific revolutions are slow and resisted by an establishment that benefits from the status quo
- Those that benefit from the prevailing paradigm never seek scientific proof to verify it but they attack those that do
- Paradigm shift is made more difficult by the amplification of anti-science voices by social media
- There will not be a single Isaac Newton who, with one publication, puts the final nail in the coffin of the prevailing SIHD paradigm.
- There will need to be many Newtons working simultaneously to add more anomalies to the existing SIHD paradigm as well as to provide new data to support an alternative paradigm

The arc of the scientific universe is long, but it bends slowly toward truth

With apologies to Dr. Martin Luther King, Jr and President Barack Obama

Thank You


"Science advances one funeral at a time"
Max Planck
Oct 4, 2010 IDC Herzliya - Zell Program, Israel
Maya Elhalal-Levavi MayaElhalal.com