Duke Clinical Research Institute

Lessons Learned from Cardiovascular Clinical Trials

March 3, 2016

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Director, Health Services & Outcomes Research
Associate Director, DCRI

1

What problems are we trying to solve?

Cultural Demand:
A Persistent Problem – Closing Major Gaps in Evidence

ORIGINAL CONTRIBUTION

Scientific Evidence Underlying the ACC/AHA Clinical Practice Guidelines

Pierluigi Tricoci, MD, MHS, PhD
Joseph M. Allen, MA
Judith M. Kramer, MD, MS
Robert M. Califf, MD
Sidney C. Smith Jr, MD

CLINICAL PRACTICE GUIDELINES are systematically developed statements to assist practitioners with decisions about appropriate health care for spe-

Context The joint cardiovascular practice guidelines of the American College of Cardiology (ACC) and the American Heart Association (AHA) have become important documents for guiding cardiology practice and establishing benchmarks for quality of care.

Objective To describe the evolution of recommendations in ACC/AHA cardiovascular guidelines and the distribution of recommendations across classes of recommendations and levels of evidence.

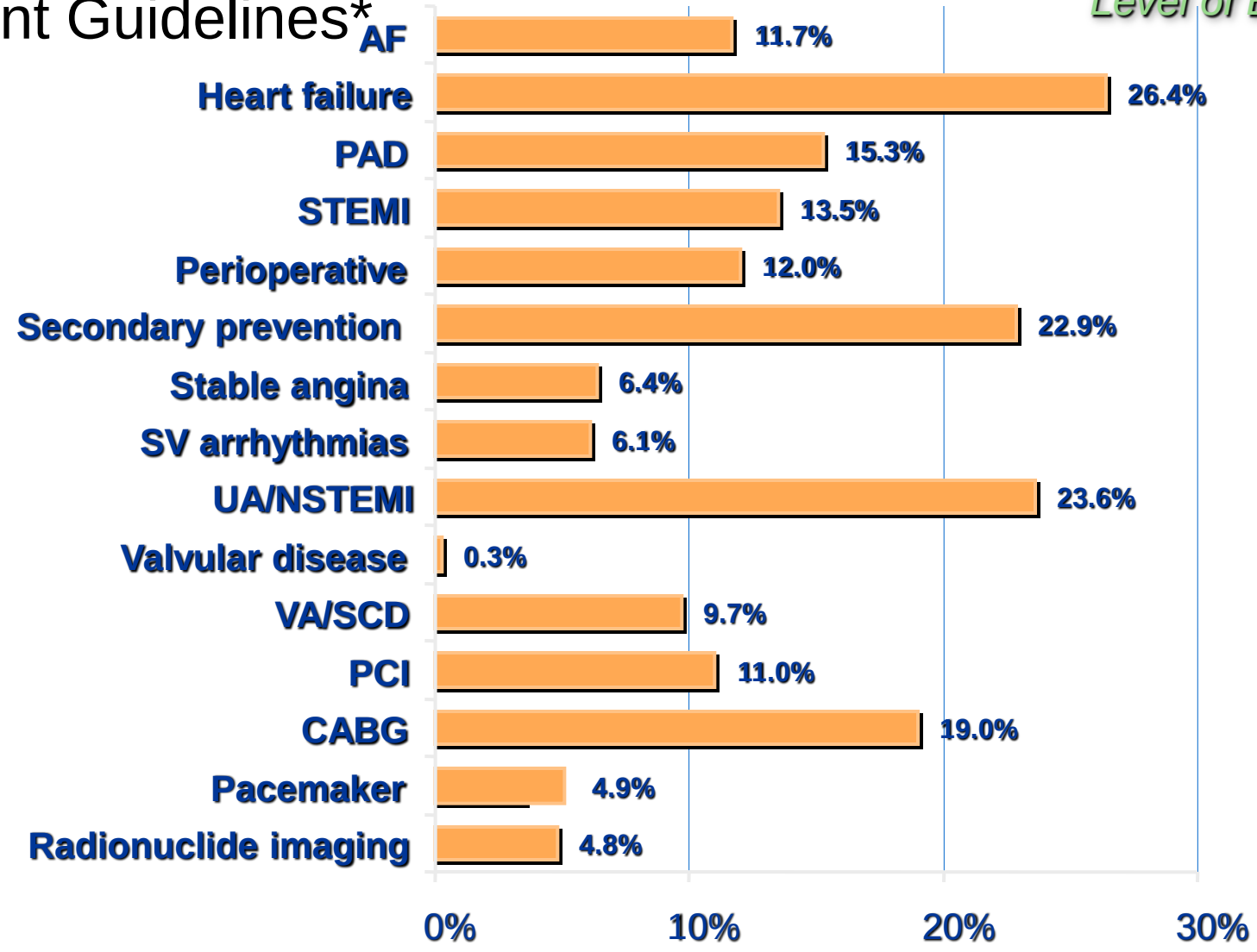
Data Sources and Study Selection Data from all ACC/AHA practice guidelines issued from 1984 to September 2008 were abstracted by personnel in the ACC Science and Quality Division. Fifty-three guidelines on 22 topics, including a total of 7196 recommendations, were abstracted.

Tricoci P et al. JAMA 2009;301:831-41

Level of Evidence A

Current Guidelines*

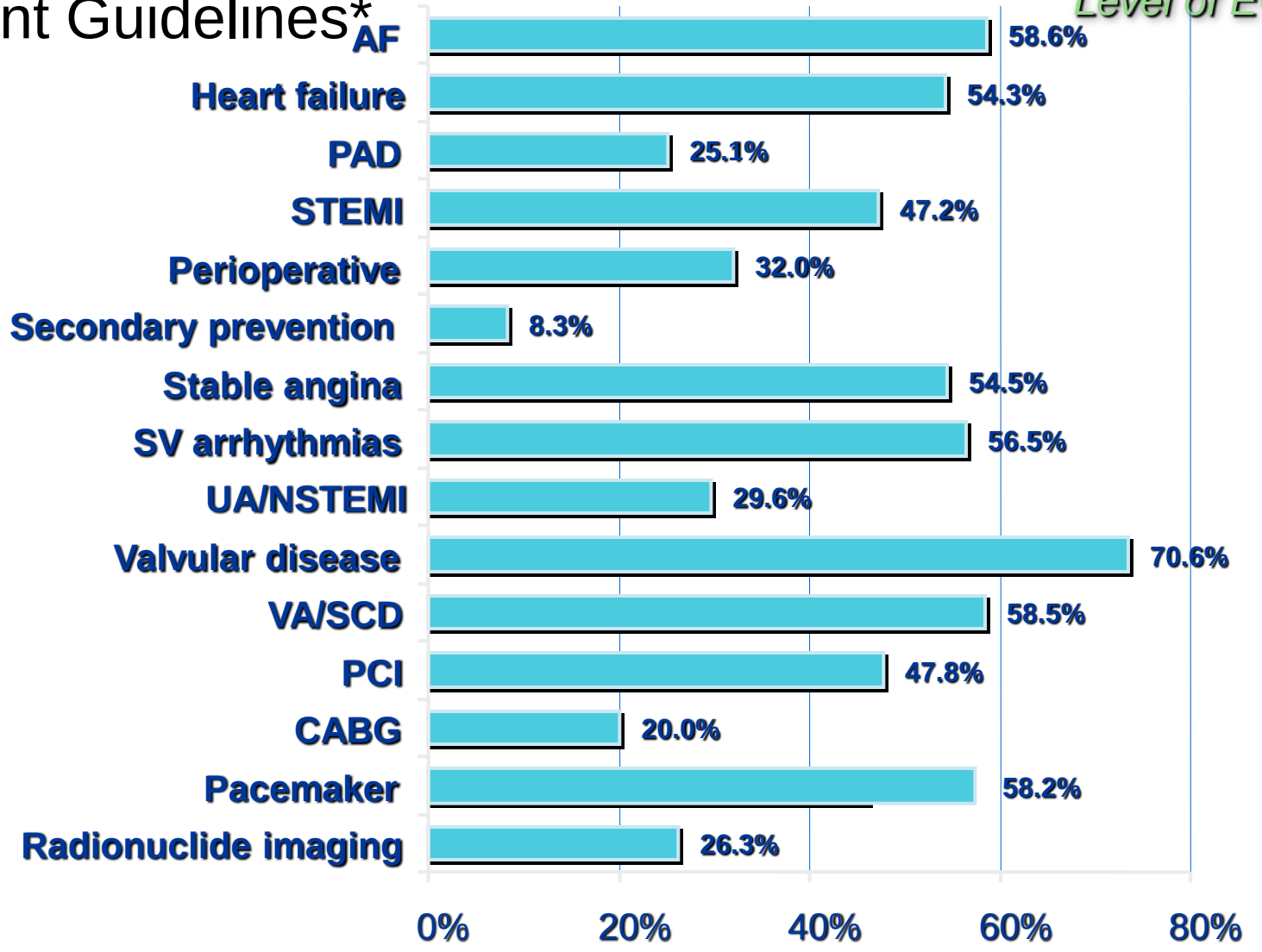
**Guidelines expressing Level of Evidence*



Level of Evidence C

Current Guidelines*

*Guidelines expressing Level of Evidence



2

How do we fill in the knowledge gaps?

Looking Back at a Disruptive Technology

EFFECTIVENESS OF INTRAVENOUS THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION

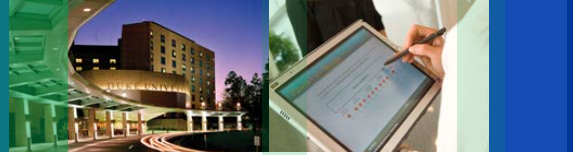
GRUPPO ITALIANO PER LO STUDIO DELLA STREPTOCHINASI NELL'INFARTO MIOCARDICO (GISSI)*

Summary In an unblinded trial of intravenous streptokinase (SK) in early acute myocardial infarction, 11 806 patients in one hundred and seventy-six coronary care units were enrolled over 17 months. Patients admitted within 12 h after the onset of symptoms and with no contraindications to SK were randomised to receive SK in addition to usual treatment and complete data were obtained in 11 712. At 21 days overall hospital mortality was 10·7% in SK recipients versus 13% in controls, an 18% reduction ($p=0·0002$, relative risk 0·81). The extent of the beneficial effect appears to be a function of time from onset of pain to SK infusion (relative risks 0·74, 0·80, 0·87, and 1·19 for the 0–3, 3–6, 6–9, and 9–12 h subgroups). SK seems to be a safe drug for routine administration in acute myocardial infarction.

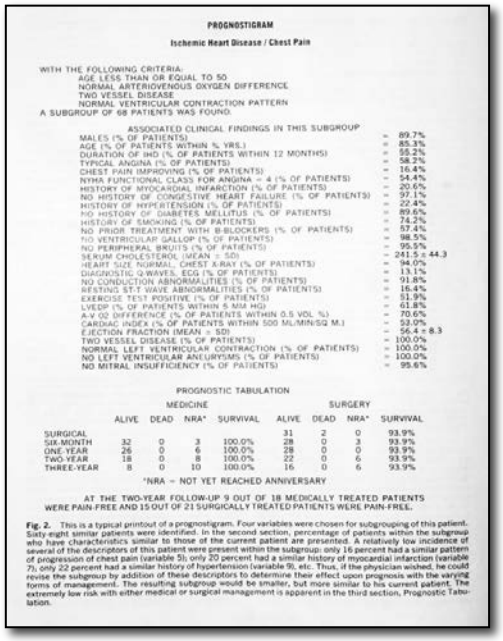
The Lancet · Saturday 22 February 1986

"It started with no funding and skepticism in some quarters but today GISSI is recognized as an Italian achievement that has changed cardiology treatment worldwide."

http://eurheartj.oxfordjournals.org/content/31/9/1023.full



Evolving Technology!



PROGNOSTIGRAM

Ischemic Heart Disease / Chest Pain

WITH THE FOLLOWING CRITERIA:
AGE LESS THAN OR EQUAL TO 50
NORMAL ARTERIOVENOUS OXYGEN DIFFERENCE
TWO VESSEL DISEASE
NORMAL VENTRICULAR CONTRACTION PATTERN
A SUBGROUP OF 68 PATIENTS WAS FOUND.

ASSOCIATED CLINICAL FINDINGS IN THIS SUBGROUP

MALES (% OF PATIENTS)	= 89.7%
AGE (% OF PATIENTS WITHIN ± YRS.)	= 85.3%
DURATION OF IHD (% OF PATIENTS WITHIN 12 MONTHS)	= 58.2%
TYPICAL ANGINA (% OF PATIENTS)	= 58.2%
CHEST PAIN IMPROVING (% OF PATIENTS)	= 16.4%
NYHA FUNCTIONAL CLASS FOR ANGINA = 4 (% OF PATIENTS)	= 54.4%
HISTORY OF MYOCARDIAL INFARCTION (% OF PATIENTS)	= 20.6%
NO HISTORY OF CONGESTIVE HEART FAILURE (% OF PATIENTS)	= 97.1%
HISTORY OF HYPERTENSION (% OF PATIENTS)	= 22.4%
NO HISTORY OF DIABETES MELLITUS (% OF PATIENTS)	= 89.6%
HISTORY OF SMOKING (% OF PATIENTS)	= 74.2%
NO PRIOR TREATMENT WITH B-BLOCKERS (% OF PATIENTS)	= 57.4%
NO VENTRICULAR GALLOP (% OF PATIENTS)	= 98.5%
NO PERIPHERAL BRUITS (% OF PATIENTS)	= 95.5%
SERUM CHOLESTEROL (MEAN ± SD)	= 241.5 ± 44.3
HEART SIZE NORMAL, CHEST X-RAY (% OF PATIENTS)	= 94.0%
DIAGNOSTIC Q WAVES, ECG (% OF PATIENTS)	= 13.1%
NO CONDUCTION ABNORMALITIES (% OF PATIENTS)	= 91.8%
RESTING ST-T WAVE ABNORMALITIES (% OF PATIENTS)	= 16.4%
EXERCISE TEST POSITIVE (% OF PATIENTS)	= 51.9%
LVEDP (% OF PATIENTS WITHIN 5 MM HG)	= 61.8%
A-V O2 DIFFERENCE (% OF PATIENTS WITHIN 0.5 VOL %)	= 70.6%
CARDIAC INDEX (% OF PATIENTS WITHIN 500 ML/MIN/SQ M.)	= 53.0%
EJECTION FRACTION (MEAN ± SD)	= 56.4 ± 8.3
TWO VESSEL DISEASE (% OF PATIENTS)	= 100.0%
NORMAL LEFT VENTRICULAR CONTRACTION (% OF PATIENTS)	= 100.0%
NO LEFT VENTRICULAR ANEURYSMS (% OF PATIENTS)	= 100.0%
NO MITRAL INSUFFICIENCY (% OF PATIENTS)	= 95.6%

PROGNOSTIC TABULATION

	MEDICINE				SURGERY			
	ALIVE	DEAD	NRA*	SURVIVAL	ALIVE	DEAD	NRA*	SURVIVAL
SURGICAL					31	2	0	93.9%
SIX-MONTH	32	0	3	100.0%	28	0	3	93.9%
ONE-YEAR	26	0	6	100.0%	28	0	0	93.9%
TWO-YEAR	18	0	8	100.0%	22	0	6	93.9%
THREE-YEAR	8	0	10	100.0%	16	0	6	93.9%

*NRA – NOT YET REACHED ANNIVERSARY

AT THE TWO-YEAR FOLLOW-UP 9 OUT OF 18 MEDICALLY TREATED PATIENTS WERE PAIN-FREE AND 15 OUT OF 21 SURGICALLY TREATED PATIENTS WERE PAIN-FREE.

Fig. 2. This is a typical printout of a prognostigram. Four variables were chosen for subgrouping of this patient. Sixty-eight similar patients were identified. In the second section, percentage of patients within the subgroup who have characteristics similar to those of the current patient are presented. A relatively low incidence of several of the descriptors of this patient were present within the subgroup: only 16 percent had a similar pattern of progression of chest pain (variable 5); only 20 percent had a similar history of myocardial infarction (variable 7); only 22 percent had a similar history of hypertension (variable 9), etc. Thus, if the physician wished, he could revise the subgroup by addition of these descriptors to determine their effect upon prognosis with the varying forms of management. The resulting subgroup would be smaller, but more similar to his current patient. The extremely low risk with either medical or surgical management is apparent in the third section, Prognostic Tabulation.

1969
Duke Databank
1st and largest CV clinical registry

1989
GUSTO
40,000+ pts
3-page faxed CRF
100's of papers!

pcornet
The National Patient-Centered Clinical Research Network

2016
ADAPTABLE
Patient Centric RCT
20,000 pts; EHR driven
Mobile based pt follow-up

Enabling Pragmatic Research: eScreening, eEnrollment and eFollowup

ADAPTABLE Enrollee

Baseline Data

OR

Adaptable
The Aspirin Study

DCRI FOLLOW-UP
- *Patient Reported Outcomes*
- *Medication use*
- *Health outcomes*

Portal FOLLOW-UP
- *Patient Reported Outcomes*
- *Medication use*
- *Health outcomes*

4 8 12 16 20 …. 30

PCORNet Coordinating Center FOLLOW-UP
- *Via Common Data Model*
- *Longitudinal health outcomes*

CMS & Payer Virtual Data Warehouse FOLLOW-UP
- *Longitudinal health outcomes*

Adaptable

pcornet

3

Relevant Question?

NATRECOR®

FDA approved on Aug 10, 2001

- Intravenous treatment of patients with acutely decompensated congestive heart failure who have dyspnea at rest or with minimal activity

Real World Challenges- Equipoise?

Short-term Risk of Death After Treatment With Nesiritide for Decompensated Heart Failure

A Pooled Analysis of Randomized Controlled Trials

Jonathan D. Sackner-Bernstein, MD
Marcin Kowalski,
Marshal Fox, MD
Keith Aaronson,

Context Nesiritide improves symptoms in patients with acutely decompensated heart

Heart Failure

Risk of Worsenir
Patients With A

Jonathan D. Sackner-Bernstein,

Perspective
JULY 14, 2005

Nesiritide — Not Verified

Eric J. Topol, M.D.

The New York Times
nytimes.com

August 9, 2005

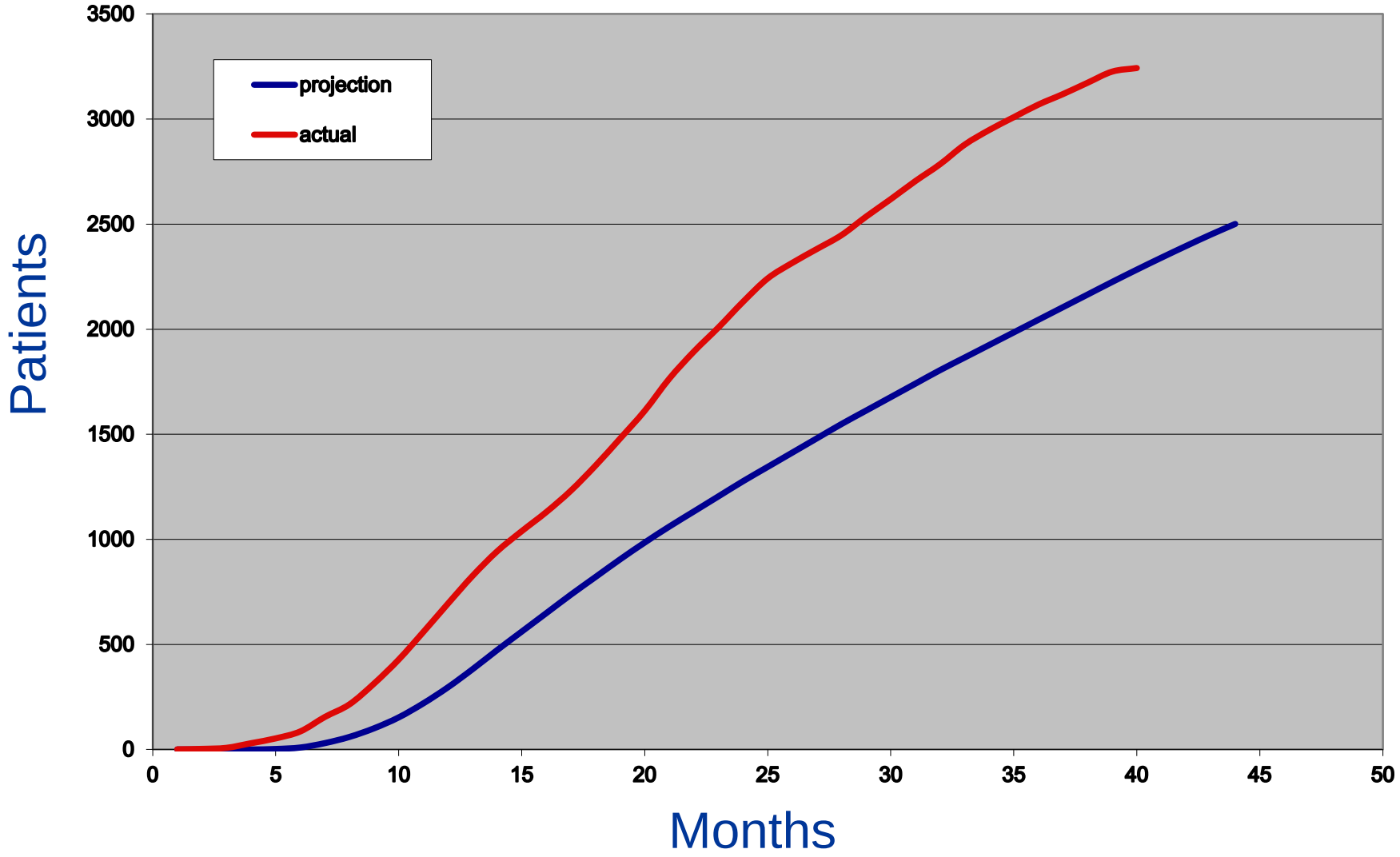
Expert Panel Gives Advice That Surprises A Drug Maker

By STEPHANIE SAUL

Design of ASCEND-HF: Guiding Principles

- Investigator independence in context of joint Executive Committee/large Steering Committee
- Large, pragmatic trial model
  - Focused
  - Efficient study design
  - Streamlined procedures
  - Simple follow-up
- Enroll clinical heart failure
- Meaningful outcomes
- ‘Real world’ treatment (standard of care)
- Feasible sub-studies to advance knowledge in acute heart failure

ASCEND-HF North American Enrollment

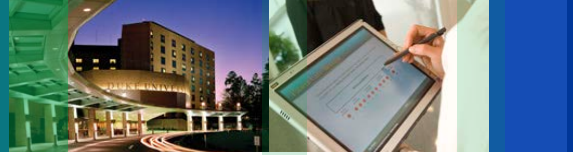


Benchmarking…

	XXXXXX (>10,000)	ASCEND-HF (n=7142)
Type of Trial	Chronic CV	Acute Heart Failure
Traditionally Reported SAEs	10,373	964
Triggered Events	10,895	1480
Coded AEs	65,296	386
Concomitant Therapies	332,677	<50,000
Visits	478,001	14,200
eCRF pages	>2.5 million	<200,000
Data Points	>30 million	<3 million
Costs	+++++++++	++

3

Right Treatment?



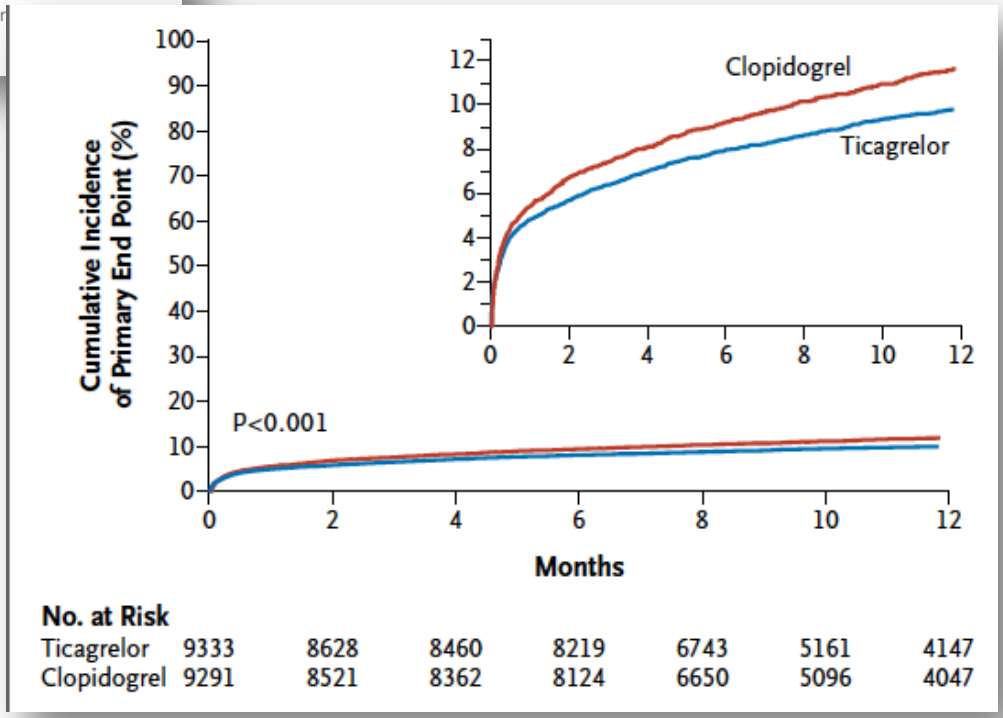
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Har
for the PLATO Investigators*

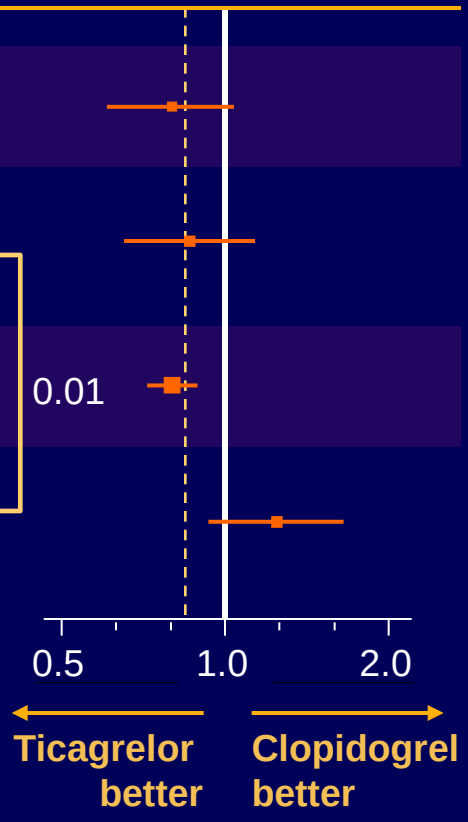
HR 0.84 (95% CI 0.77–0.92), p=0.0003



Geographic Regions
CV Death, MI, Stroke

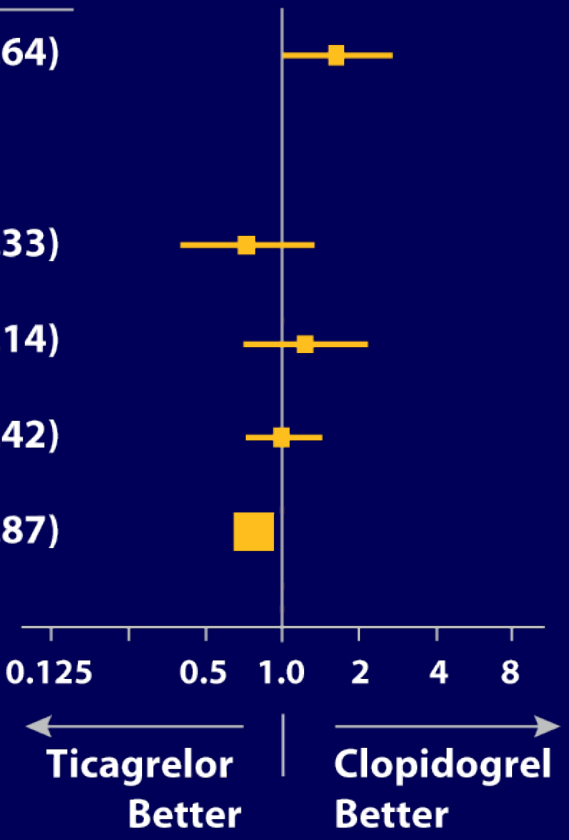
PLATO

Geographic region	Total patients	KM at month 12 Tic	KM at month 12 Clop	HR (95% CI)	Interaction p-values
Asia / Australia	1714	11.4	14.8	0.80 (0.61, 1.04)	
Central America / South America	1237	15.2	17.9	0.86 (0.65, 1.13)	
Europe / Middle East / Africa	13859	8.8	11.0	0.80 (0.72, 0.90)	
North America	1814	11.9	9.6	1.25 (0.93, 1.67)	



Primary Efficacy Outcome
US and Non-US and by ASA Dose

Region	ASA Dose (mg)	Ticagrelor N	Ticagrelor E	Clopidogrel N	Clopidogrel E	HR (95% CI)
US	≥300	324	40	352	27	1.62 (0.99, 2.64)
	>100–<300	22	2	16	2	*
	≤100	284	19	263	24	0.73 (0.40, 1.33)
Non-US	≥300	140	28	140	23	1.23 (0.71, 2.14)
	>100–<300	503	62	511	63	1.00 (0.71, 1.42)
	≤100	7449	546	7443	699	0.78 (0.69, 0.87)



Hazard ratio not calculated due to small number of events.

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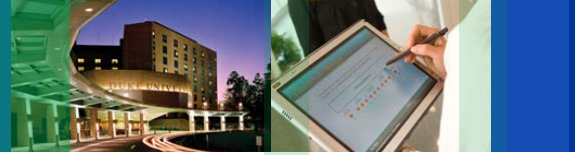
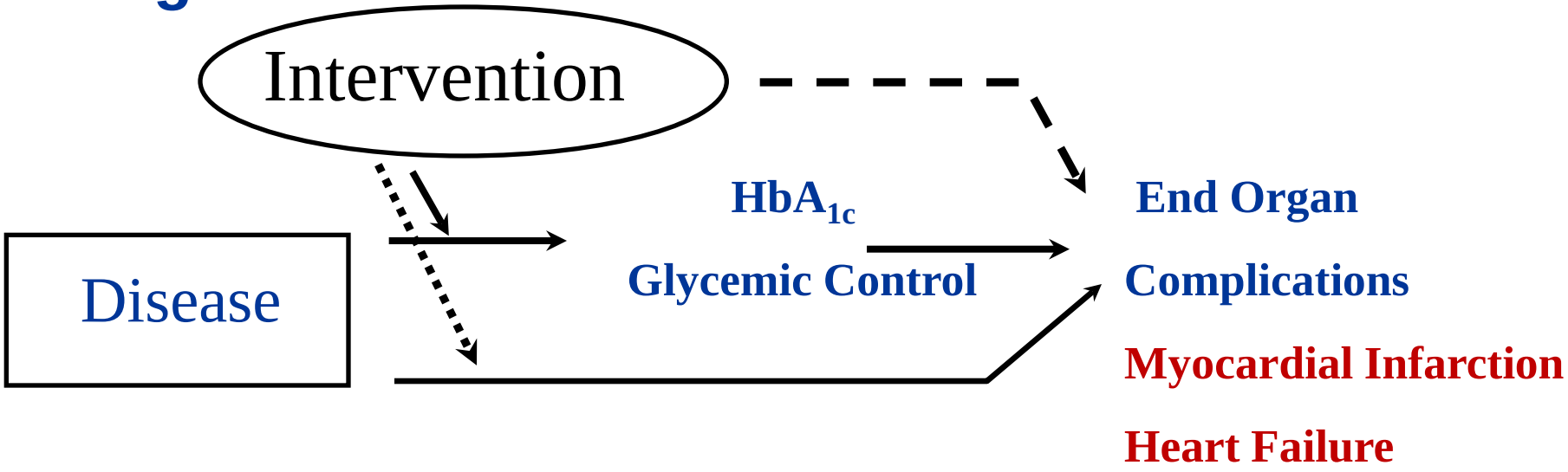
Right Outcome?



Diabetes and Cardiovascular Outcomes: Surrogate vs. Outcomes

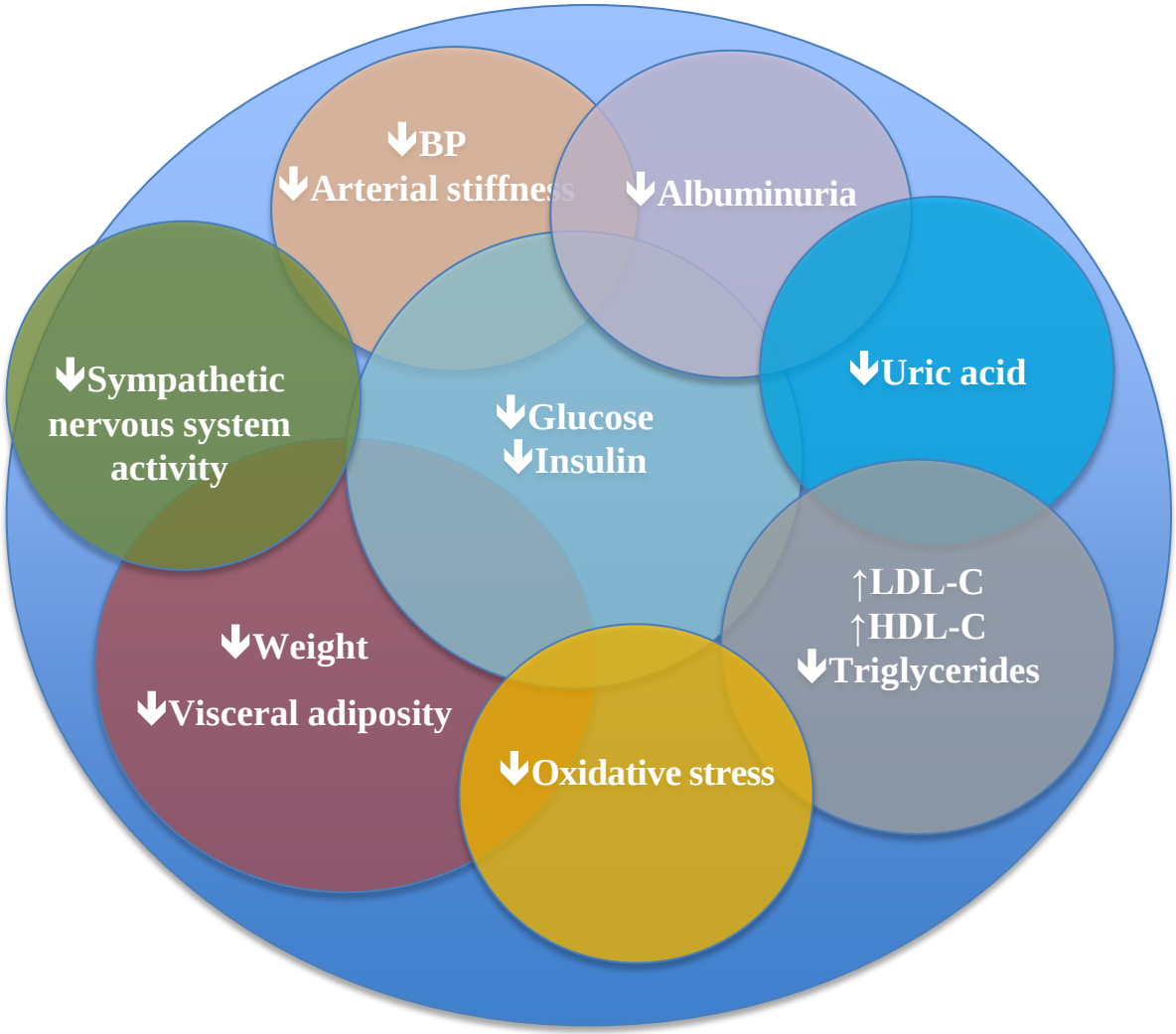


Unintended negative effects

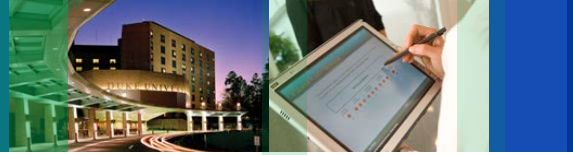
e.g., **Hypoglycemic Events**

Alternative beneficial effects

Potential Modifiable factors related to CV risk



Inzucchi SE,Zinman, B, Wanner, C et al. Diab Vasc Dis Res 2015;12:90-100

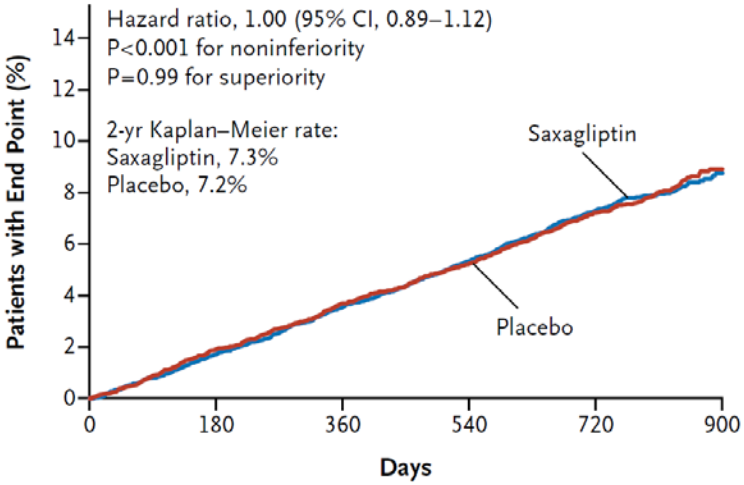


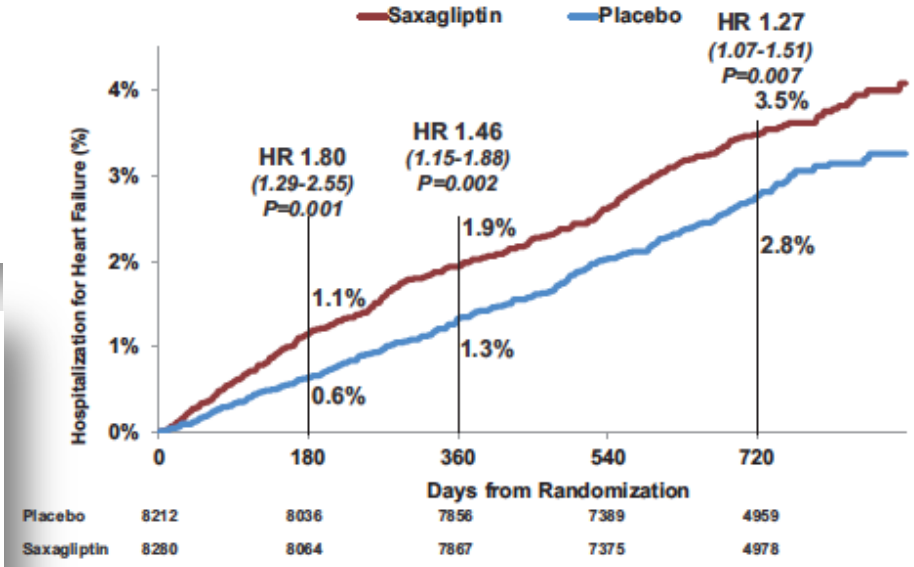
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

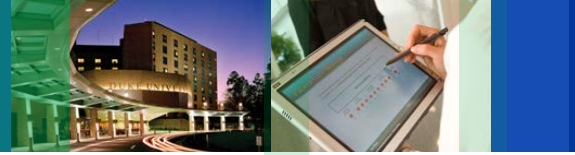
Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. Udell, M.D., M.P.H., Nihar R. Desai, M.D., M.P.H., Ofri Mozenson, M.D., Darren K. McGuire, M.D., Kausik K. Ray, M.D., Lawrence A. Leiter, M.D., and Itamar Raz, M.D., for the SAVOR-TIMI 53 Steering Committee and Investigators*

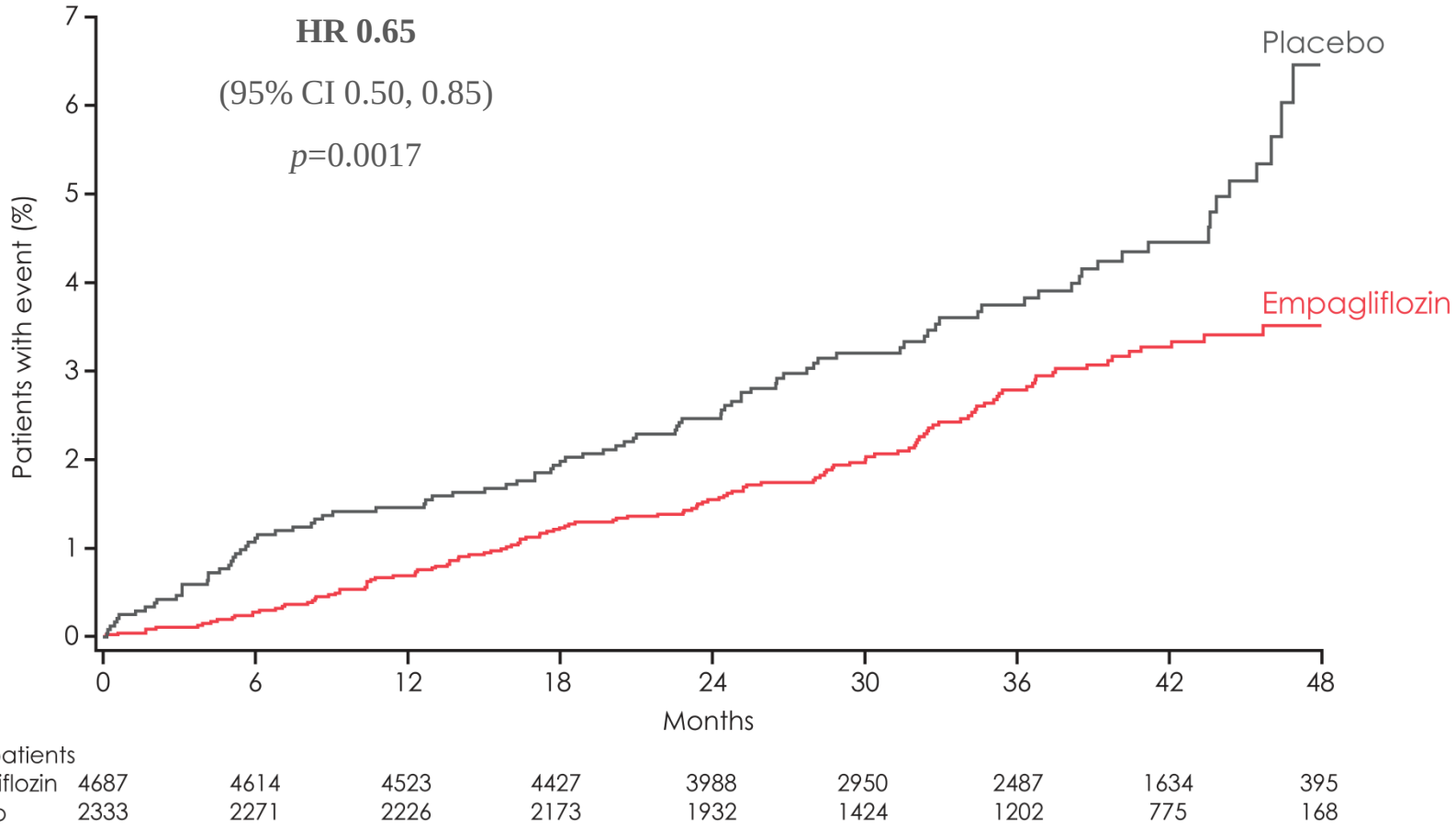




Scirica BM et al NEJM 2013Scirica BM et al Circ 2014



EMPA-REG-Outcomes: Hospitalisation for heart failure



Zinman B et al N Engl J Med 2015; 373:2117-2128

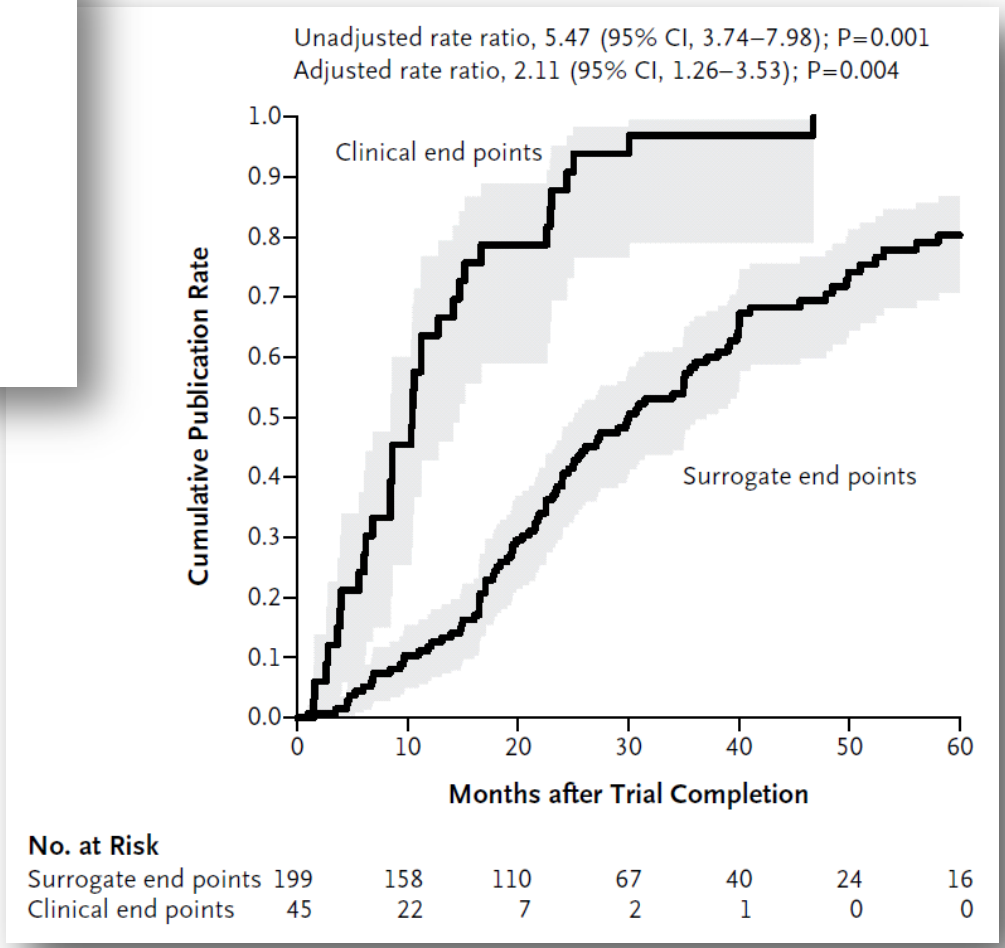
Impact of Endpoints on Dissemination…

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Publication of Trials Funded by the National Heart, Lung, and Blood Institute

David Gordon, M.D., Ph.D., Wendy Taddei-Peters, Ph.D., Alice Mascette, M.D., Melissa Antman, Ph.D., Peter G. Kaufmann, Ph.D., and Michael S. Lauer, M.D.



Gordon D, Lauer M et al. N Engl J Med 2013;369:1926-34

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Real World Integration?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2013 VOL. 369 NO. 17

Thrombus Aspiration during ST-Segment Elevation Myocardial Infarction

Ole Fröbert, M.D., Ph.D., Bo Lagerqvist, M.D., Ph.D., Göran K. Olivecrona, M.D., Ph.D., Elmir Omerovic, M.D., Thorarinn Gudnason, M.D., Ph.D., Michael Maeng, M.D., Ph.D., Mikael Aasa, M.D., Ph.D., Oskar Angerå Fredrik Calais, M.D., Mikael Danielewicz, M.D., David Erlinge, M.D., Ph.D., Lars Hellsten, M.D., Ulf Jensen, M.D., Ph.D., Agneta C. Johansson, M.D., Amra Kåregren, M.D., Johan Nilsson, M.D., Ph. Lotta Robertson, M.D., Lennart Sandhall, M.D., Iwar Sjögren, M.D., Ollie Östlund, Ph.D., Jan Harnek, M.D., Ph.D., and Stefan K. James, M.D., Ph.D.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 7, NO. 8, 2014

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcin.2014.04.007

A Registry-Based Randomized Trial Comparing Radial and Femoral Approaches in Women Undergoing Percutaneous Coronary Intervention

The SAFE-PCI for Women (Study of Access Site for Enhancement of PCI for Women) Trial

Sunil V. Rao, MD,* Connie N. Hess, MD, MHS,* Britt Barham, BA,* Laura H. Aberle, BSPH,* Kevin J. Anstrom, PhD,* Tejan B. Patel, MD,† Jesse P. Jorgensen, MD,‡ Ernest L. Mazzaferri Jr., MD,§ Sanjit S. Jolly, MD,‖ Alice Jacobs, MD,¶ L. Kristin Newby, MD,* C. Michael Gibson, MD,# David F. Kong, MD,* Roxana Mehran, MD,** Ron Waksman, MD,†† Ian C. Gilchrist, MD,‡‡ Brian J. McCourt,* John C. Messenger, MD,§§ Eric D. Peterson, MD, MPH,* Robert A. Harrington, MD,‖‖ Mitchell W. Krucoff, MD*

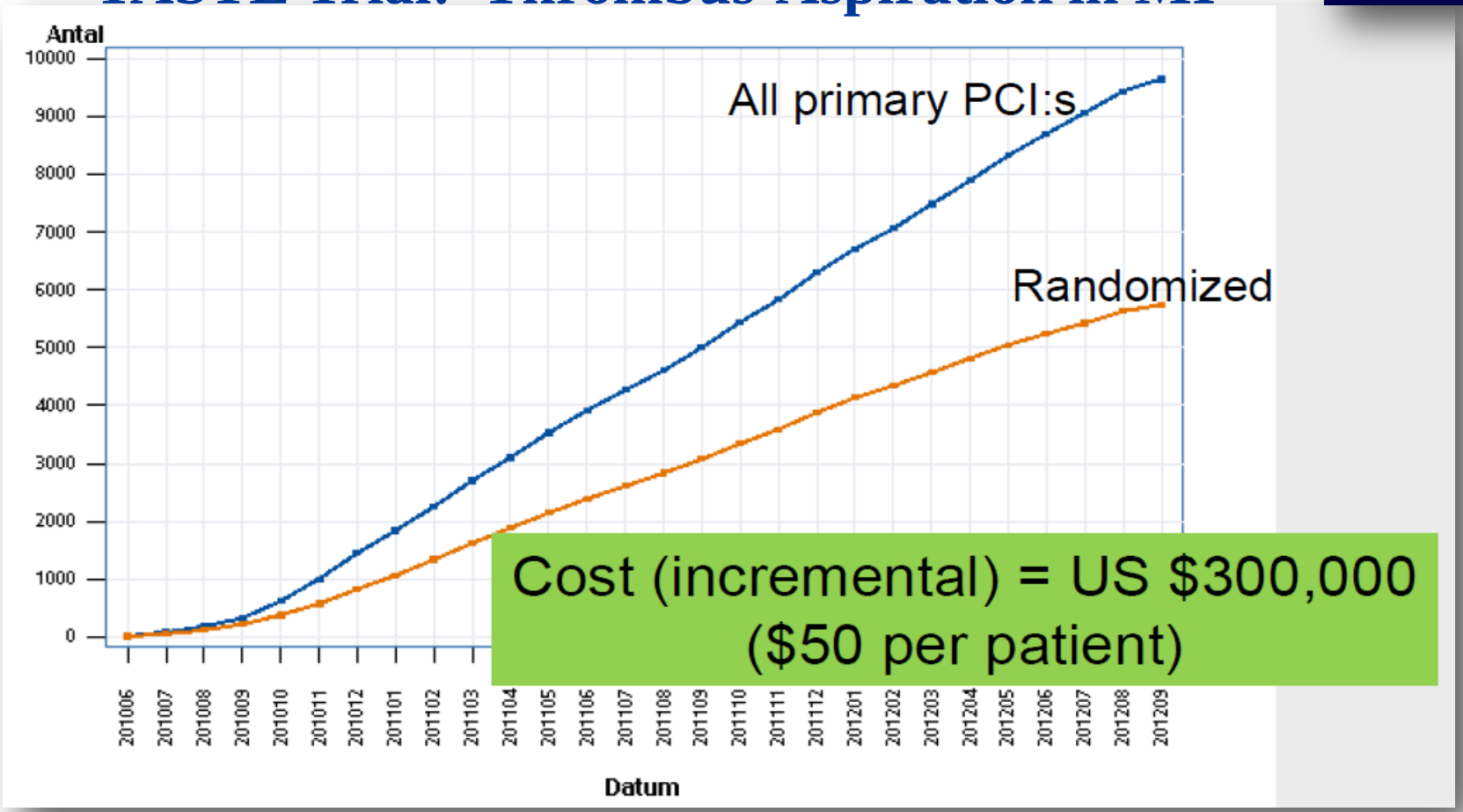
The Randomized Registry Trial — The Next Disruptive Technology in Clinical Research?

Michael S. Lauer, M.D., and Ralph B. D'Agostino, Sr., Ph.D.

SCAAR
SWEDEHEART

Swedish Registry-Trial Hybrids

TASTE Trial: Thrombus-Aspiration in MI



Frobert O et al NEJM 2013

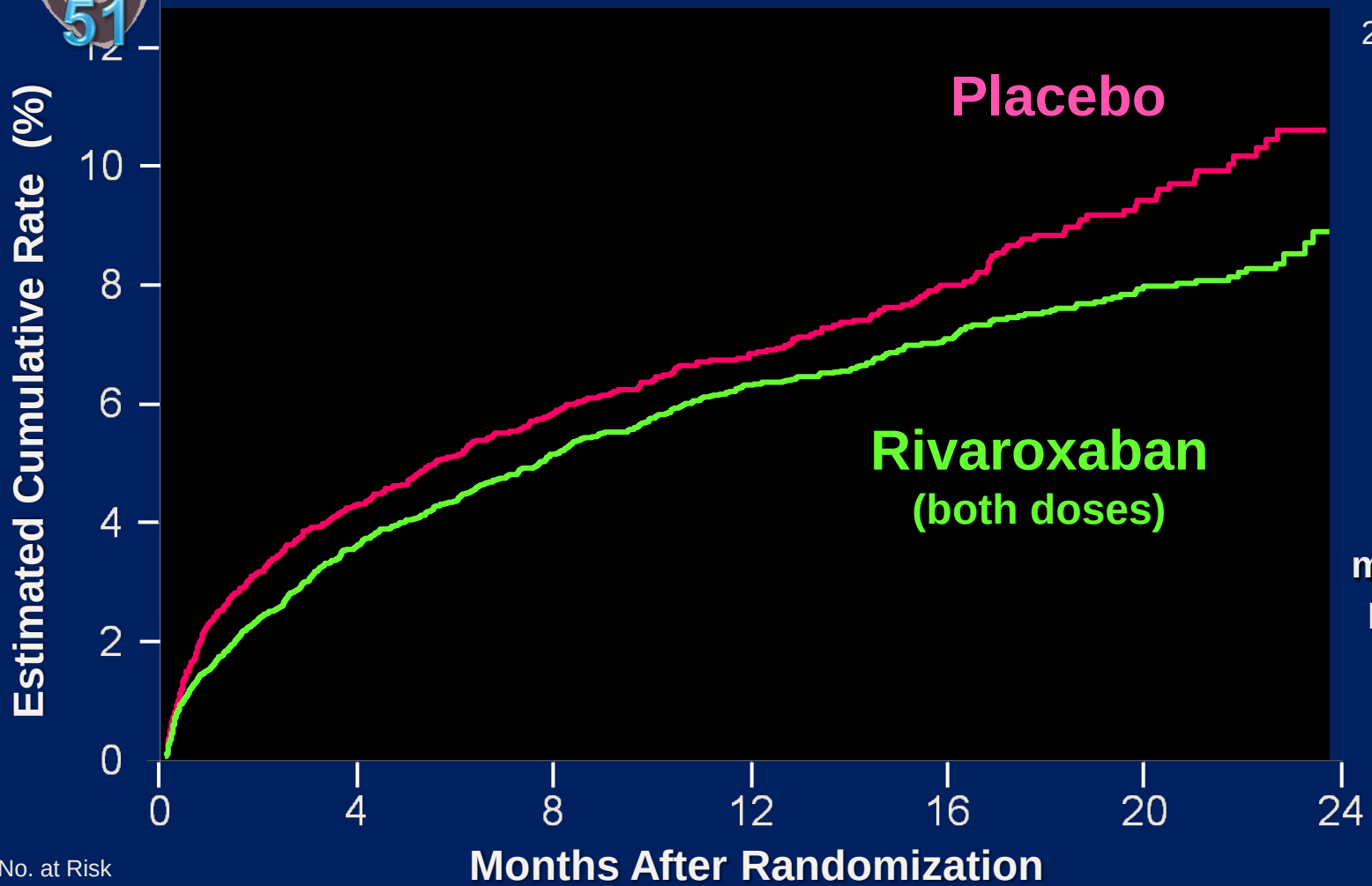
5

Retention!

ATLAS ACS 2 TIMI 51

PRIMARY EFFICACY ENDPOINT:

CV Death / MI / Stroke* (Ischemic + Hemg.)



2 Yr KM Estimate

10.7%

8.9%

HR 0.84
(0.74-0.96)
ARR 1.7%

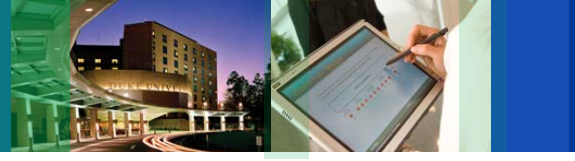
mITT p = 0.008
ITT p = 0.002

NNT = 59

No. at Risk

Placebo	5113	4307	3470	2664	1831	1079	421
Rivaroxaban	10229	8502	6753	5137	3554	2084	831

*: First occurrence of cardiovascular death, MI, stroke (ischemic, hemorrhagic, and uncertain) as adjudicated by the CEC across thienopyridine use strata
Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches; ARR=Absolute Relative Reduction; NNT=Number needed to treat; Rivaroxaban=Pooled Rivaroxaban 2.5 mg BID and 5 mg BID.



VIEWPOINT

The ATLAS ACS 2–TIMI 51 Trial and the Burden of Missing Data

(Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2–Thrombolysis In Myocardial Infarction 51)

Mori J. Krantz, MD,*†‡ Sanjay Kaul, MD§‖

Aurora and Denver, Colorado; and Los Angeles, California

Trial	Enrolled (N)	Median Follow-up (days)	Incomplete F/U	Withdrawal of consent	Vital Status Unknown
ATLAS-ACS-2 TIMI 51	15,526	484	2402 (15.5%)	1294 (8.3%)	1117 (7.2%)
PLATO	18,624	277	562 (3.0%)	545 (2.9%)	2 (0.01%)
APPRAISE-2	7,392	241	131 (1.8%)	81 (1.1%)	N/A

Krantz MJ, Kaul S. J Am Coll Cardiol. 2013;62(9):777-781

5

Final Thoughts

What is A Quality Clinical Trial?

1. Relevant question being addressed
2. A protocol that is clear, practical, focused
3. Adequate number of events to answer question with confidence
4. In a general practice setting to make results generalizable
5. With proper randomization
6. With reasonable assurance that patients receive (and stay on) assigned treatment
7. With reasonably complete follow-up and ascertainment of primary outcome (and other key outcomes like death)
8. With a plan for ongoing measurement, feedback, improvement of quality measures during trial conduct
9. With safeguards against bias in determining clinically relevant outcomes
10. With protection of rights of research patients