Symposium for Research Administrators

Continuous Improvement in a Time of Change

Clinical Trials are the Answer. What's the Question?

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Director, Heart Center SBR
Co-Director, Cardiovascular Research DCRI
Duke UNIVERSITY

Thank You

Disclosures available:
https://dcri.org/about-us/conflict-of-interest

Nomenclature

- **Research:** A systematic evaluation to develop generalizable knowledge
- **Clinical Research:** Research involving human subjects or their protected health information (PHI)
- **Clinical Trial:** Clinical research where a specific research intervention is applied
- **Observational Study:** Clinical research without a specific research intervention where research subjects are "observed"

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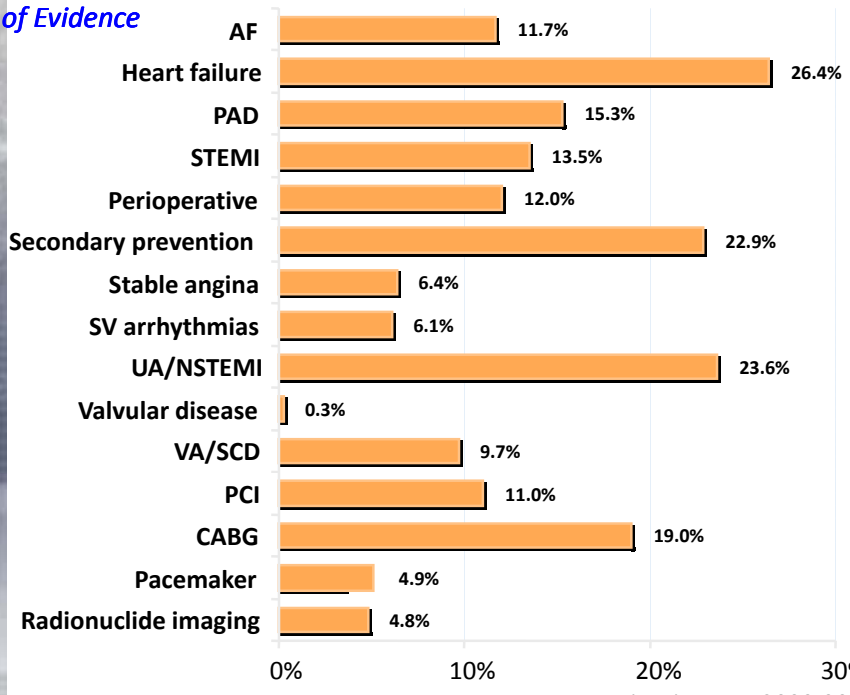
Medical Decision Making

Reality

For most medical decisions we simply do not know whether recommendations regarding therapies lead to better patient outcomes

Level of Evidence A

*Guidelines expressing Level of Evidence



Tricoci JAMA. 2009;301:831-41.

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Life's Questions

Artificial Sweeteners

versus

Sugar

Life's Questions

Reading

versus

Television

Quality of Evidence for Modestly Effective Therapies

Method	Reliability
Common sense	Nearly Worthless
Targeting disease process with surrogate endpoints	Terrible
Observational database analysis	Poor
Case-control study	Poor
Meta-analysis	Good (66%)
Large randomized clinical trial	Best

Good Clinical Trial

Key Elements

- Relevant population included
- Randomized and Blinded
- Clinically meaningful endpoints
- Adequate size
- Quality
  - Protection of human subjects
  - Integrity of clinical trial data

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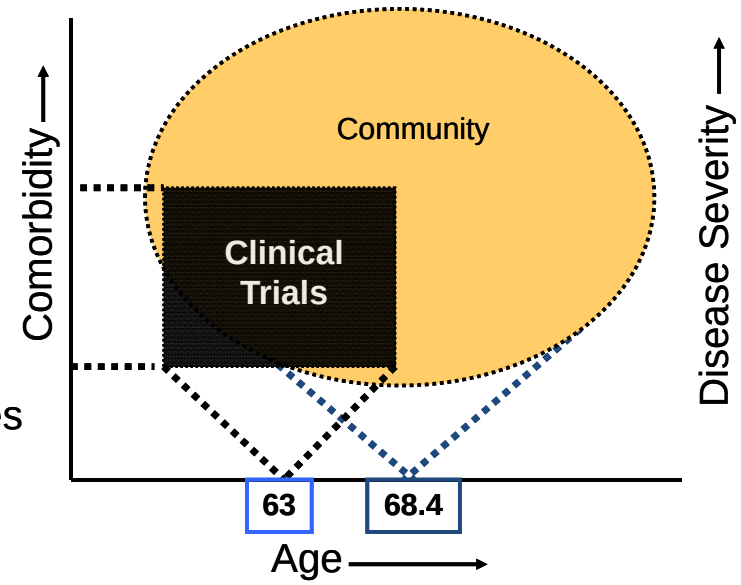
Clinical Trials vs The Community

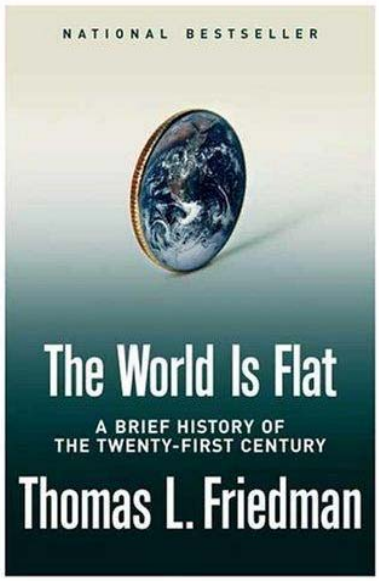
Clinical Trials

- White
- Male
- Adult
- Non-elderly
- Few comorbidities



"Flattening" of Clinical Research

- Conducting high quality clinical research in the US is an increasing challenge
  - Public Perception
  - Complexity / Regulation
  - Speed and Cost
- Clinical research is being "outsourced" from the US to India, China, Eastern Europe, and South America



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Hormone Replacement Therapy

Background

CHD in Women is Common and Often Fatal

Multiple Observational Studies Suggest:

- 35–50% Lower Risk for CHD in Estrogen Users
- Stronger Protection in Women with CHD
- Similar Benefit for Estrogen and Estrogen/Progestin
- Observed Benefit Could Be Due to Selection Bias

Millions of American Women using HRT

Randomized Trials Needed

HERS Study Overview

Post-menopausal women with CAD with an intact uterus
n=2763

RANDOMIZED!

0.625 mg conjugated equine estrogens + 2.5 mg medroxyprogesterone acetate qd
n=1380

Placebo qd
n=1383

4.1 years treatment; clinic visits q 4 months

Completed Closeout Contact (n=1222)
Alive, But No Closeout (n=27)
Lost-to-Follow-Up (n=0)
Died (n=131)

Completed Closeout Contact (n=1228)
Alive, But No Closeout (n=32)
Lost-to-Follow-Up (n=0)
Died (n=123)

Primary endpoint: CHD death or non-fatal myocardial infarction

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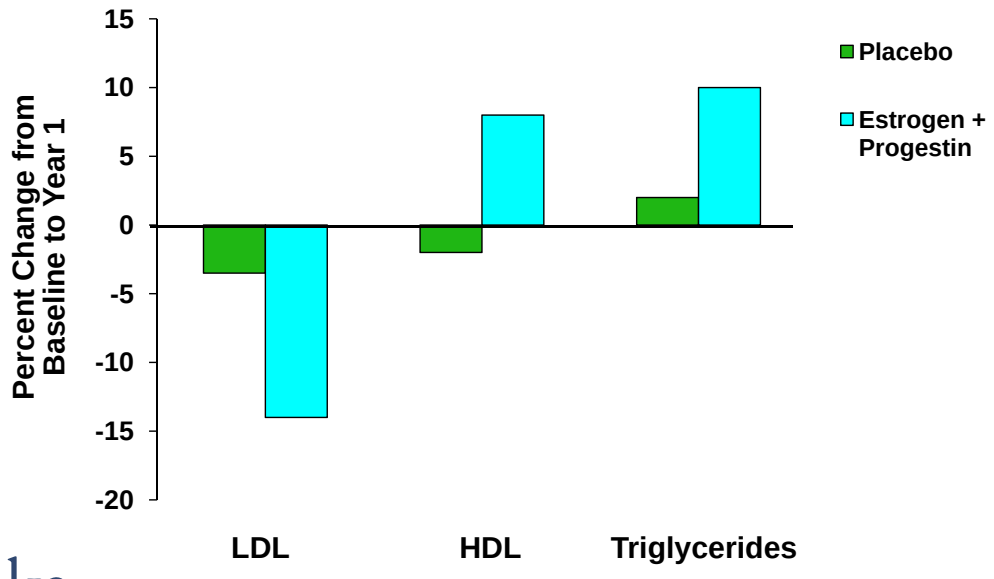
HERS Changes In Lipids



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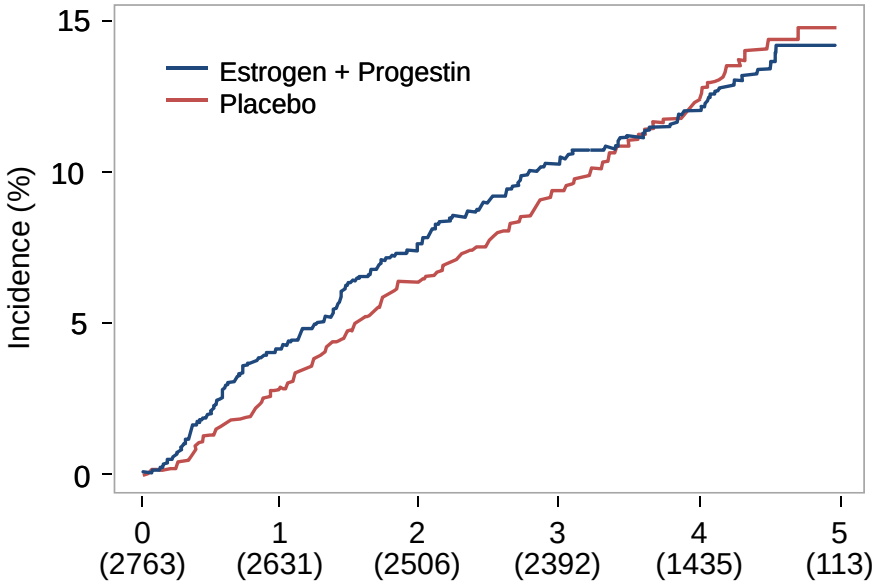
HERS Cardiovascular Events



Log Rank p=0.91

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Good Clinical Trial

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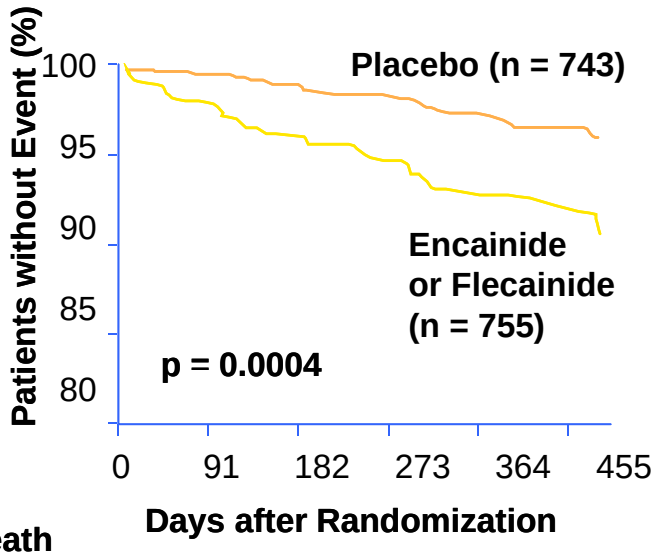
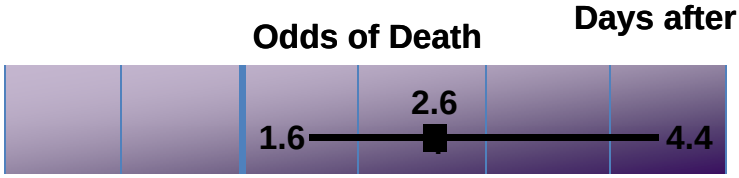
The CAST Trial

Important Outcomes

- Longer life
- Better quality of life
- Less cost





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—Echt, NEJM, 1991

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Sample Size

Treatment Effect = 25%

Events	Patients Randomized (Risk = 10%)	Chance of Type II Error*	Comments on Sample Size
0-50	< 500	> 90%	Utterly inadequate
50-150	1000	70-90%	Probably inadequate
150-350	3000	30-70%	Possibly inadequate
350-650	6000	10-30%	Probably adequate
> 650	10000	< 10%	Adequate

Multicenter

*Probability of failing to detect an important treatment effect if one exists.

— Yusuf, Prog in CV Disease, 1985

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Good Clinical Trial

Key Elements

- Relevant population included
- Randomized and Blinded
- Clinically meaningful endpoints
- Adequate size
- Quality ≠ Complexity
  - Protection of human subjects
  - Integrity of clinical trial data

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605 BC

King Nebuchadnezzar II ordered children of royal blood to eat only meat and wine. Several other children ate only legumes and porridge. After ten days the other children were noticeably healthier than those who ate meat and wine.

Key Clinical Trial Elements	Assessment
Relevant population included	No
Randomized and Blinded	No and no
Clinically meaningful endpoints	No
Adequate size	No
Quality	
Protection of human subjects	No
Integrity of clinical trial data	Unknown

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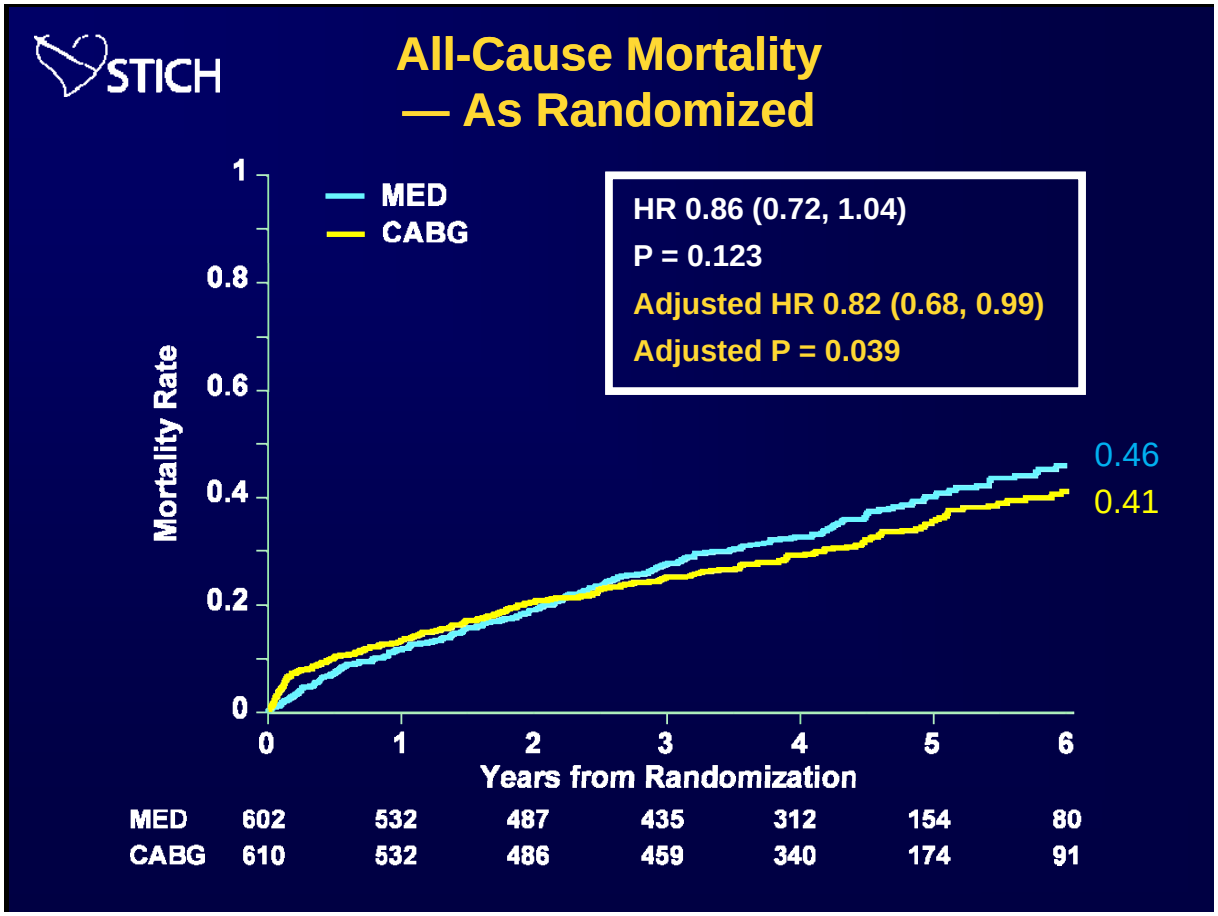
STICH

Coronary Artery Bypass Graft Surgery in Patients with Ischemic Heart Failure

Eric J. Velazquez, MD
on behalf of the STICH Investigators

April 4, 2011



Study population

ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure

Randomized (n=7141)

Placebo (n=3577)
- Did not receive study drug (n=66)
  - Hypotension (n=28)
  - Exclusion criteria (n=8)
  - Physician decision (n=6)
  - Participant withdrew consent (n=14)
  - Other reason (n=10)

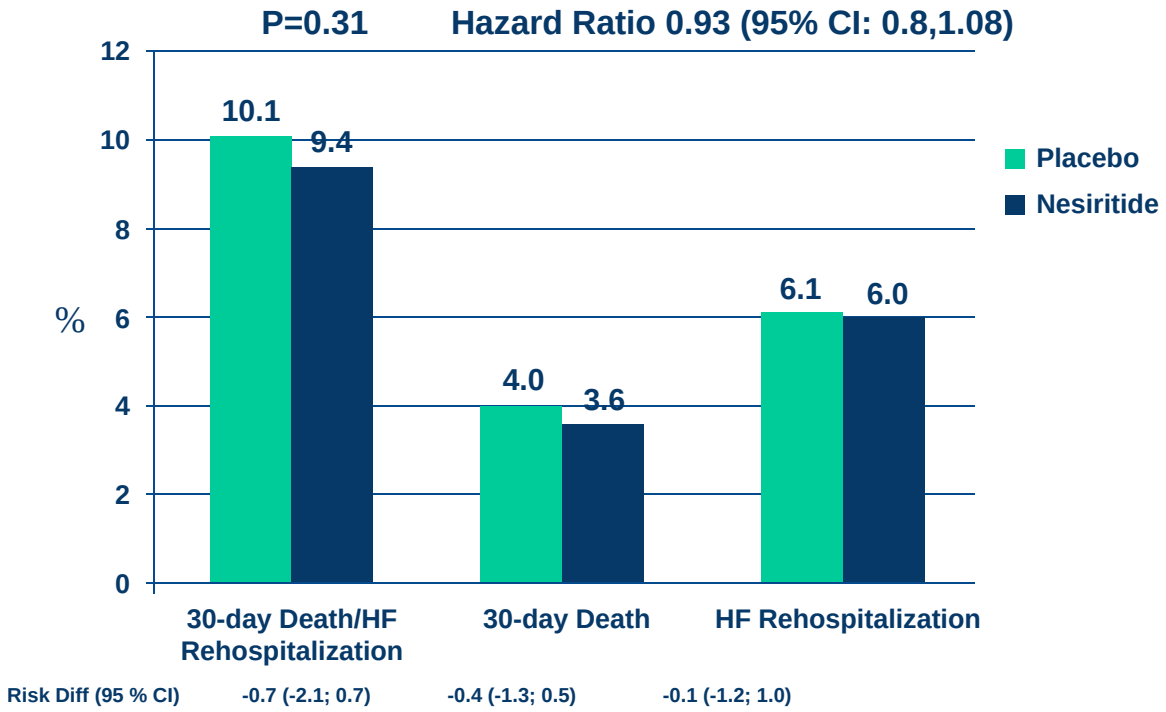
Nesiritide (n=3564)
- Did not receive study drug (n=68)
  - Hypotension (n=26)
  - Exclusion criteria identified (n=9)
  - Physician decision (n=6)
  - Participant withdrew consent (n=16)
  - Other reason (n=11)

Placebo MITT=3511

Nesiritide MITT=3496

Co-Primary outcome: 30-day all-cause mortality or HF rehospitalization

ASCEND-HF
Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure



Study Design

Risk Factors
- CHF
- Hypertension
- Age ≥ 75
- Diabetes

At least 2 or 3 required*

OR
- Stroke, TIA or Systemic embolus

Atrial Fibrillation

Rivaroxaban
20 mg daily
15 mg for Cr Cl 30-49 ml/min

Randomize
Double Blind / Double Dummy
(n ~ 14,000)

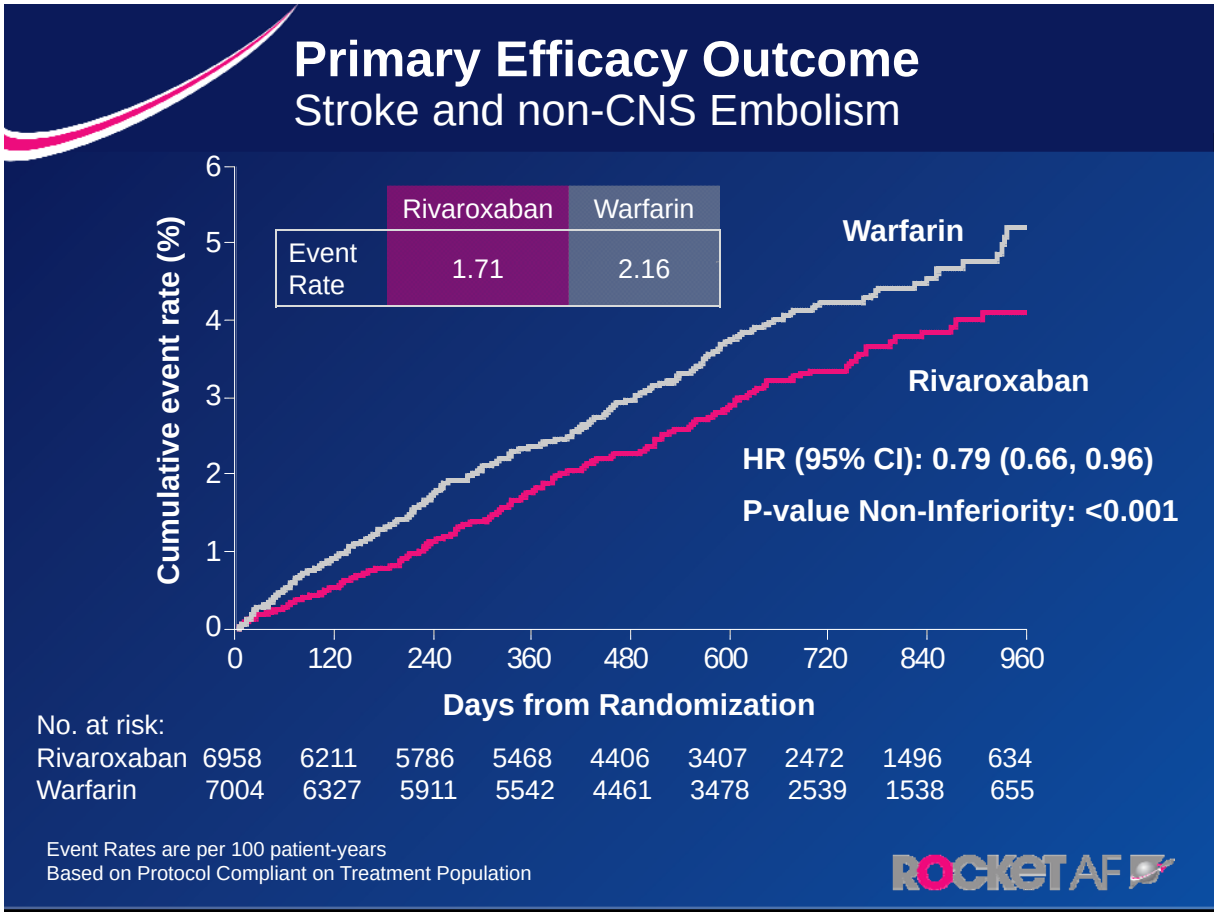
Warfarin
INR target - 2.5
(2.0-3.0 inclusive)

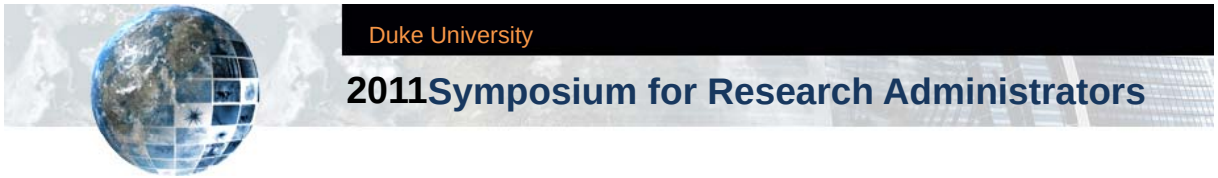
Monthly Monitoring
Adherence to standard of care guidelines

Primary Endpoint: Stroke or non-CNS Systemic Embolism

* Enrollment of patients without prior Stroke, TIA or systemic embolism and only 2 factors capped at 10%

ROCKET AF





Costs of Clinical Trials

- Large Global Phase III Clinical Trial
  - 18,000 patients w/ atrial fibrillation
  - Randomized to warfarin vs. oral fXa inhibitor
  - Outcome = stroke or systemic embolism
- Time (enrollment / follow-up) > 4 years
- Cost > $400,000,000 (almost half a billion!)
- Result = definitive answer to 1 question
- Is something wrong with this picture?

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The Medical / Academic Community

Our Responsibilities in Clinical Research

- Demand (on behalf of our patients) adequate evidence to support the use of new therapies
- Participate (as investigators) in the generation of evidence through participation in clinical trials
- Educate other physicians, medical institutions and the public about the importance of collaboration and participation in clinical research

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"Science is organized common sense where many a beautiful theory was killed by an ugly fact."

Thomas Huxley

Thank You

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