は生まれないことが数理的に証明でき、正しい解析が可能である（UMIN e-learning 解説より）

Ⅰ-1-8

原文

8. 以下の臨床研究のそれぞれについて、研究方法論を正しく分類しているものはどれか

□ 199*年 1 月 1 日以降に診断されたステージⅣの胃癌患者全員について、現時点までの治療と予後をカルテから集め、診断時の背景因子と予後の間の関連を調べた　⇒コホート研究

□ ある新薬を患者に投与したところ、これまで報告されていない副作用が 3 例見られたので、学会に報告し、その後、論文にまとめた　⇒臨床試験

□ 外来糖尿病患者の中で、睡眠時無呼吸の患者をケース、そうでない患者をコントロールとして体型を比較した　⇒ケース・コントロール研究

改定後

8. 臨床研究について、研究方法論を正しく分類しているものはどれか。1 つ選べ。

■ 199*年 1 月 1 日以降に診断されたステージⅣの胃癌患者全員について、現時点までの治療と予後をカルテから集め、診断時の背景因子と予後の間の関連を調べた　⇒コホート研究

□ ある新薬を患者に投与したところ、これまで報告されていない副作用が 3 例見られたので、学会に報告し、その後、論文にまとめた　⇒臨床試験

□ 外来糖尿病患者の中で、睡眠時無呼吸の患者をケース、そうでない患者をコントロールとして体型を比較した　⇒ケース・コントロール研究

解説

・ある新薬を患者に投与したところ、これまで報告されていない副作用が 3 例見られたので、学会に報告し、その後、論文にまとめた　⇒臨床試験

→臨床試験とは、臨床研究のうちヒト（患者）に対して行われ、かつある特定の医学的条件に合致する将来の患者に対して最適な治療法を明らかにすべく企画された計画的なものである。安全性・有効性などを確認するためデータの収集を目的とする

・外来糖尿病患者の中で、睡眠時無呼吸の患者をケース、そうでない患者をコントロールとして体型を比較した　⇒ケース・コントロール研究

→ケース・コントロール研究とは、疾病の原因と考えられる要因を、過去にさかのぼ

って調査し、両者で比較する後ろ向きの研究である

Ⅰ-2　臨床研究とは

Ⅰ-2-7

原文

7. 医薬品の臨床試験の実施の基準であるGCPが求めている大きな基本原則は、2つある。それは、次のうちどれか。
   □ 「倫理的妥当性」と「科学的モラル」
   □ 「倫理指針」と「科学的モラル」
   □ 「倫理指針」と「科学的妥当性」
   □ 「倫理的妥当性」と「科学的妥当性」

改定後

7. 医薬品の臨床試験の実施の基準であるGCPが求めている大きな基本原則は2つある。組み合わせが正しいのはどれか。1つ選べ。
   □ 「倫理的妥当性」と「科学的モラル」
   □ 「倫理指針」と「科学的モラル」
   □ 「倫理指針」と「科学的妥当性」
   ■ 「倫理的妥当性」と「科学的妥当性」

改改定後

7. GCPが治験を行う際に重きをおいていないものはどれか。1つ選べ。
   □ 倫理性
   □ 科学性
   □ 信頼性
   ■ 可能性

解説

1997年3月に省令GCP「医薬品の臨床試験の実施の基準に関する省令」（厚生省第28号）が定められた。このGCPは、被験者の人権の保護、安全の保持及び福祉の向上を図り、治験の科学的な質及び成績の信頼性を確保することを目的として、治験および製造販売後臨床試験に関する計画、実施、モニタリング、監査、記録、解析及び報告等に関する遵守事項を定めたものである

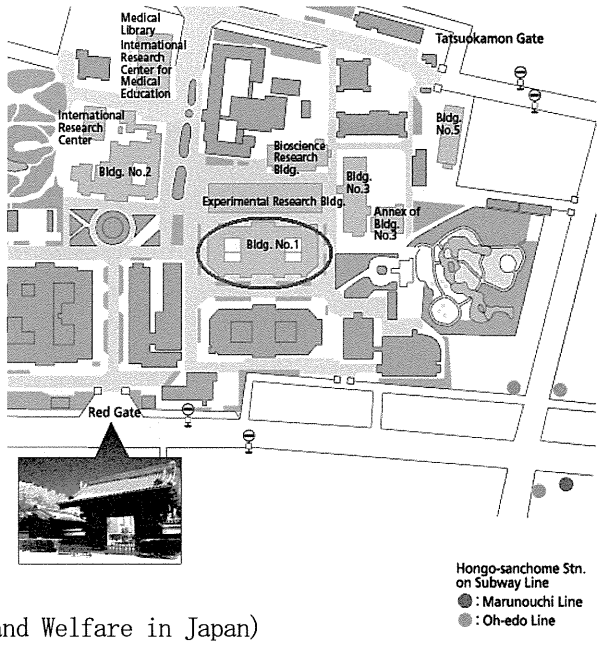
（資料）臨床研究・治験の国際化プログラム

International Symposium on Globalization of Clinical Research and Trial

(http://cbi.umin.ne.jp/dces/isgcrt_e.pdf)

Date: Feb. 6, 2013
Venue: Lecture Hall 3F Bldg #1,
Faculty of Medicine, the University of Tokyo
Registration fees: Free (Reception ¥6000yen or $60)

Registration (No later than Jan.31)
Send the following information to cbi-secretary@umin.ac.jp
Name, Organization, Telephone, Email address, Attending Reception Yes/No



<Program>

9:30 Entrance open
10:00-10:10(10min) Opening remarks
Mr. Masanobu Yamada (The Ministry of Health, Labor and Welfare in Japan)
Prof. Ryozo Nagai (President of Jichi Medical University)

10:10-10:50 (40min) Keynote address: Step-up the knowledge of Biostatistics
Prof. Yasuo Ohashi, PhD (Dept. of Biostatistics, School of Public Health, University of Tokyo)

Main session: Lessons learned from US and Japan

10:50-11:50 (60min)
(1)Overview of trial experience & recent experience with ROCET AF Study
Dr.Manesh R. Patel, MD,FACC (Assistant Professor of Medicine, Duke University Medical Center)

11:50-13:30 (100min) Lunch

13:30-14:30 (60min)
(2) Overview of Registry Studies
Dr.Adrian F. Hernandez, MD, MHS (Associate Professor of Medicine, Duke University Medical Center)

14:30-15:30 (60min)
(3)Best practice for conducting and reporting clinical studies using large database
Dr.Soko Setoguchi, MD,MPH (Associate Professor of Medicine, Duke Clinical Research Institute)

15:30-16:00 (30min) Break

16:00-16:40 (40min)
(4)Strategy of Clinical Study - HOP, JAMP, SPREAD from JAPAN -
Prof. Kazuomi Kario, MD (Dept. of Internal Medicine, Jichi Medical University)

16:40-16:45 (5min) closing remarks
Dr. Daisuke Koide (Assistant Professor of Medicine, the University of Tokyo)

17:00-19:30 reception (Ito International Research Center, the Univ. of Tokyo)

Note: Simultaneous interpretation will be available. Please understand that this symposium will be recorded by a video camera and used for e-learning. We make sure that the audience will not be recorded.

Sponsored by Grant projects of the ministry of Health, labor and welfare in Japan (leaders are Dr.Koide (Univ. of Tokyo) & Dr.Yamamoto (National Cancer Research Center)).

Overview of trial experience & recent experience with ROCET AF Study

Manesh R. Patel, MD

Duke Clinical Research Institute

Disclosures

- Research Grants:
  - *Johnson and Johnson PRD*
  - *NIH – PROMISE trial*
  - *AHRQ – Comparative Effectiveness*
- Advisory Board / Consultant: Ikaria, Cardiostem, Bayer, Genzyme, theheart.org, DukeTV.org, Ortho McNeil Jansen, Pleuristem
- Research Faculty at DCRI

Duke Clinical Research Institute

Outline

- Background DCRI – ARO and clinical trials
- Review of ROCKET AF trial
- Quiz Questions

Duke Clinical Research Institute

DCRI Mission

To develop and share knowledge that improves the care of patients around the world through innovative clinical research

Duke Clinical Research Institute

Duke Clinical Research Institute

- The DCRI is the largest academic clinical research organization (ARO) in the world
- A global coordinating center for multi-center clinical trials that integrates the medical expertise of Duke University Medical Center with the operational capabilities of a full-service CRO

Duke Clinical Research Institute

DCRI: An Academic Research Organization

- Every study:
  - **Duke faculty involvement**
  - **Dedicated project leader**
  - **Customized, cross-functional project team**
- Combined operational and patient bedside experience
- Integrated perspectives - scientific, patient care, regulatory, market
- Global capabilities

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DCRI Facts

- Founded in 1969 with the development of the Duke Databank for Cardiovascular Diseases
- >23 years of experience in coordinating multi-center trials in over 20 therapeutic areas
- >1100 staff and 120 clinical/statistical faculty
- More than 700 clinical trials and outcomes research projects completed in 64 countries enrolling over 1 million subjects
- More than 4,600 publications in peer-reviewed journals

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Clinical Trial Coordinating Center Services

- Scientific Leadership
- Project Leadership
- Biostatistics
- Data Management and Surveillance
- Clinical Events Review
- Regulatory Services
- Site Management and Monitoring
- Safety Surveillance
- Site Contracts + payments
- Medical Writing /Publication
- Clinical Helpline
- Outcomes Research
- Biomarkers, Genetics, eECG Core Lab

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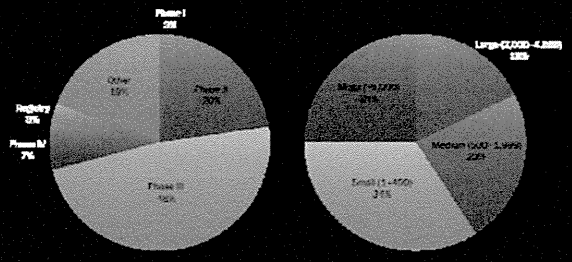
DCRI – Trials Experience by Phase and Size



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Large Pragmatic Trial: A Working Definition

A randomized clinical trial, often involving 2 or more continents and ≥5,000 subjects, that provides a sufficient number of events to reliably estimate the impact of an intervention on relevant clinical outcomes in a clinically representative population in a relevant period of time.

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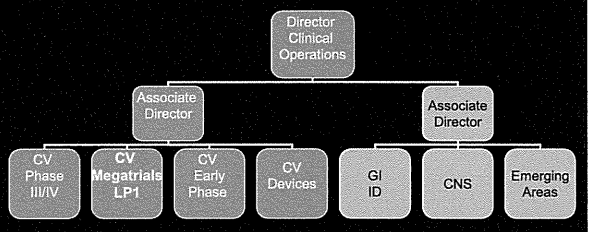
DCRI Clinical Operations Structure



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DCRI MegaTrials > 5000 Patients

GUSTO-I	41,021
GUSTO-IIA/IIB	12,142
GUSTO-III	15,060
ASSENT-II	17,043
HERO-2	17,073
PURSUIT	10,948
SYMPHONY	9,130
2nd SYMPHONY	6,677
PARAGON-B	5,225

All registration trials yellow denotes EDC

REPLACE 2	6,010
SYNERGY	10,027
VALIANT	14,703
EARLY ACS	9,500
APEX AMI	5,745
IMPROVE IT	18,000
ASCEND HF	7,000
ROCKET AF	14,000
TRA*CER	10,000
TECOS	15,000
Total	244,274

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DCRI Global Reach

- Trials conducted in 64 countries

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Global Academic Cardiovascular Collaborations

North America

- Canadian VIGOUR (V) Center-Edmonton
- Montreal Heart
- McMaster- Canada
- Cleveland Clinic-C5
- Henry Ford-Detroit
- TIMI-Boston
- Thomas Jefferson-Philly

Most of World

- Greenland-Auckland
- NHMRC-Sydney
- Flinders-Adelaide
- Singapore-SCRI
- LCC- Brussels
- George Institute-Sydney/China/India
- Uppsala- Sweden
- DTU –UK
- BCRI- Sao Paulo
- ECLA- Argentina
- TANGO-Argentina

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DCRI Guiding Principles: Defining Quality

1. Have we enrolled the right participants according to the protocol with adequate consent?
2. Did participants receive the assigned treatment and did they stay on the treatment?
3. Was there complete ascertainment of primary and secondary efficacy data?
4. Was there complete ascertainment of primary and secondary safety data?
5. Were there any ***major*** GCP related issues?

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Clinical Quiz

- The Large Pragmatic Trial or Mega-Trial definition employed by the DCRI and other organizations is?

1. Trial with over 500 patients
2. Trial with over 500 patients on two continents
3. Trial with over 5000 patients
4. Trial with over 5000 patients on two continents

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Clinical Quiz

- The Large Pragmatic Trial or Mega-Trial definition employed by the DCRI and other organizations is?

1. Trial with over 500 patients
2. Trial with over 500 patients on two continents
3. Trial with over 5000 patients
4. Trial with over 5000 patients on two continents

Generally, by definition mega-trials include over 5000 patients that are geographically diverse (at least two continents)

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Site Level Quality Surveillance Reports

- Enrollment/Data Status/Data Exceptions
- Patient demographics for the site vs. country/global trial
- Adherence to guideline based therapies
- Protocol compliance

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Global Benefits

- Guiding principles drive quality through all parts of the model
- Easily accessible reports allow rapid identification of site/regional global issue
- Integrated CEC workflow allows focused cleaning and expedited review of suspected events
- Aggressive management of cleaning delivers on time data lock

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Functions of Quality Assurance and Regulatory Compliance (QA & RC)

- Consultation with Regulatory Operations and Functional Groups on compliance issues
- Auditing
- SOP administration (Standard Operating Procedures)
- Develop Training on "GXP" (Good ___ Practices)
- Host and prepare for sponsor/FDA audits

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Summary

- Full service research organization integrated with practicing clinicians
  - Focused on lessons learned and design of more efficient operations to support large programs

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Why are VKAs underused?

- **High degree of inter and intra-patient variability in dose-response**
  - Numerous interactions with food and concomitant drugs
  - Genetic polymorphisms
  - Comorbid conditions
- **Narrow therapeutic window (INR 2–3)**
  - Regular coagulation monitoring and dose adjustments required
- **Increased risk of VKA-induced bleeding**
  - Particularly in elderly patients
- **Fear of intracranial haemorrhage, the most devastating bleeding event**

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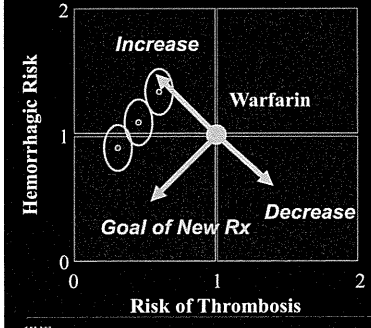
[imaging].mp1-05

Efficacy vs. Safety: Antithrombotic Drug Development



"First, do no harm."
Hippocrates, c 460-370 BC

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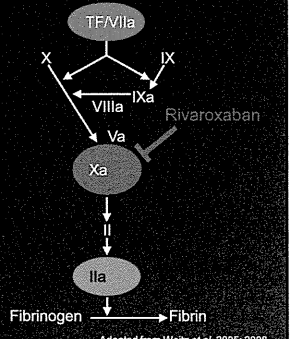
[imaging].mp1-05

Background
Rivaroxaban

- Direct, specific, competitive factor Xa inhibitor
- Half-life 5-13 hours
- Clearance :
  - 1/3 direct renal excretion
  - 2/3 metabolism via CYP 450 enzymes
- Oral, once daily dosing without need for coagulation monitoring
- Studied in >25,000 patients in post-op, DVT, PE and ACS patients



Adapted from Weitz *et al*, 2005; 2008

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Study Design

Atrial Fibrillation

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

} At least 2 or 3 required*

OR
- Stroke, TIA or Systemic embolus

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: Trial Operations & Metrics

Overview for ROCKET AF

ROCKET Sites and Enrollment

- 45 Countries Enrolled
- 1469 Sites with Drug
- 1178 Sites Randomized
- 17,232 Screened
- 14,264 Randomized

Enrollment Timelines

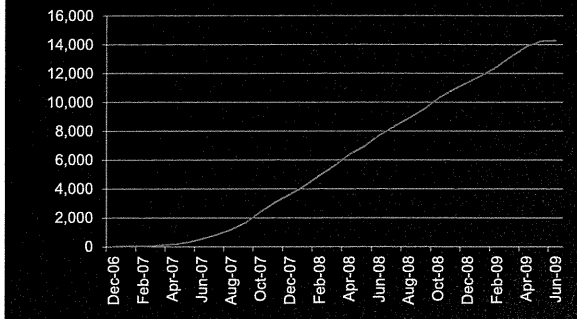
- First Patient Randomized 18 December 2006
  001301 Dr Khaled Ziada
  University of Kentucky Hospital, United States
- Last Patient Randomized 17 June 2009
  086001 Dr Xiao Wei Yan
  Peking Union Medical College Hospital, China

ROCKET Enrollment by Country

Country	Pts	Country	Pts	Country	Pts
Argentina	569	Hong Kong	73	Russia	1292
Australia	243	Hungary	237	Singapore	44
Austria	32	Israel	189	South Africa	245
Belgium	96	India	269	Spain	250
Brazil	483	Italy	139	Sweden	28
Bulgaria	678	Korea	204	Switzerland	7
Chile	287	Lithuania	245	Taiwan	159
China	496	Malaysia	51	Thailand	87
Colombia	268	Mexico	168	Turkey	101
Czech Rep	598	Netherlands	161	Ukraine	1011
Canada	749	New Zealand	116	UK	160
Denmark	123	Norway	49	US	1933
Finland	16	Peru	84	Venezuela	20
France	71	Philippines	388	TOTAL	14269
Germany	530	Poland	528		
Greece	29	Romania	783		

Celebrating 14,000 Patients Randomized

Enrollment Over Time



Top 15 Enrollers - Global

Country	Site Number	PI First Name	Site Name	# of Pts
Philippines	063004	Louie Tirador	Saint Paul's Hospital	129
Bulgaria	359002	Dimitar Raev	MI-Central Clinical Hospital - Ministry of Interior	90
Poland	048037	Grzegorz Kania	NZOZ Przychodnia Zdrowia	72
Germany	049062	Ayham Al-Zoebi	Kardiologische Praxis	72
Romania	040012	Constantin Milataru	Cardiomed	66
Philippines	063006	Elfred Batalla	Davao Doctors Hospital	64
Russia	007040	Yury Shvarts	Clinical Hospital #3	63
Romania	040023	Mariana Tudoran	Spitalul Clinic Judetean de Urgenta Timisoara	61
Spain	034041	Miguel Pelayo	Hospital Virgen del Mar	60
Bulgaria	359011	Konstantin Ramshev	MMA	60
Bulgaria	359019	Valentina Grigorova	1-st MHAT - Sofia	60
Brazil	055030	Jose Kerr Saraiva	Hospital e Maternidade Celso Pierro	59
Bulgaria	359008	Sotir Marchev	V MHAT Sofia	58
Brazil	055018	Euler Manenti	Hospital Mae de Deus	57
Hungary	036007	Andras Vertes	Fovarosi Onkormanyzat Szent Istvan Korhaza	56

Bringing it Home

- End of Trial Notification 28 May 2010
- Last Patient Off Study Drug 22 July 2010
- Last Follow Up Visit Complete 7 September 2010
- Last Casebook Frozen 7 October 2010
- Database Lock 22 October 2010

Data Management Metrics

- How Big Is ROCKET AF??
  - 10,373 Serious Adverse Events
  - 10,895 Clinical Events Triggered for Adjudication
  - 332,627 Concomitant Therapies
  - 478,001 Repeat Visits
  - 2,511,247 eCRF pages
  - 27,252,226 Data Points

20,000 Data Points Entered Every Day!

Megatrial Datalocks 2010

- ROCKET AF locked OCT-2010
  - 17,000 Patients, ~ 500,000 visits
  - ~10,000 events reviewed by CEC
  - Last patient visit to data lock - 4 weeks
  - Data lock to unblinding - 2 weeks
- ASCEND HF locked Oct-2010
  - 7,141 pts, 14,000 visits
  - ~1500 events reviewed by CEC
  - Last patient visit to data lock and unblinding- 3 weeks

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Study Conduct

	Rivaroxaban	Warfarin
Randomized, n	7131	7133
Lost to Follow-up, n	18	18
Premature Discontinuation, n (%)	1693 (23.9%)	1589 (22.4%)
Withdrew Consent, n	626	620
Median (25th, 75th) Exposure (days)	589 (396, 805)	593 (404, 810)
Median (25th, 75th) Follow-up (days)	706 (522, 884)	708 (518, 886)

Study Results

Baseline Demographics

	Rivaroxaban (N=7081)	Warfarin (N=7090)
Age (years)	73 (65, 78)	73 (65, 78)
Female (%)	40	40
Race (%)		
White	83	83
Black	1	1
Asian	13	13
Region (%)		
North America	19	19
Latin America	13	13
Asia-Pacific	15	15
Central Europe	38	38
Western Europe	15	15
Creatinine Clearance (ml/min) (%)		
30 - <50	21	21
50 - ≤80	47	48
> 80	32	31

Values are median (IQR)
Based on Intention-to-Treat Population

ROCKET AF

Baseline Demographics

	Rivaroxaban (N=7081)	Warfarin (N=7090)
$CHADS_2$ Score (mean)	3.48	3.46
2 (%)	13	13
3 (%)	43	44
4 (%)	29	28
5 (%)	13	12
6 (%)	2	2
Prior VKA Use (%)	62	63
Congestive Heart Failure (%)	63	62
Hypertension (%)	90	91
Diabetes Mellitus (%)	40	39
Prior Stroke/TIA/Embolism (%)	55	55
Prior Myocardial Infarction (%)	17	18

Based on Intention-to-Treat Population

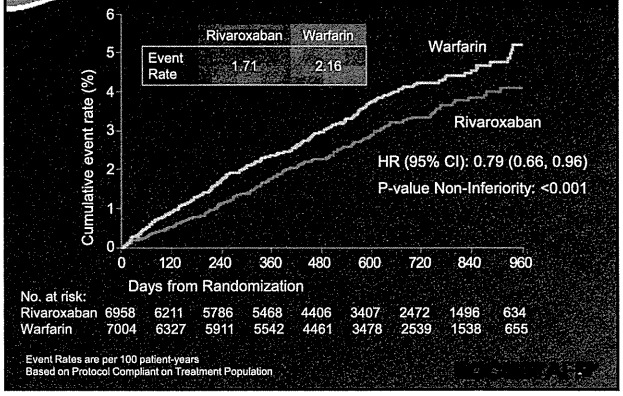
ROCKET AF

Time in Therapeutic Range (TTR)
INR Data

	Warfarin
INR range	Median (25th, 75th)
<1.5	2.7 (0.0 – 9.0)
1.5 to <1.8	7.9 (3.5 – 14.0)
1.8 to <2.0	9.1 (5.3 – 13.6)
2.0 to 3.0	57.8 (43.0 – 70.5)
>3.0 to 3.2	4.0 (1.9 – 6.5)
>3.2 to 5.0	7.9 (3.3 – 13.8)
>5.0	0.0 (0.0 – 0.5)

Based on Rosendaal method with all INR values included
Based on Safety Population

Primary Efficacy Outcome
Stroke and non-CNS Embolism



Event Rates are per 100 patient-years
Based on Protocol Compliant on Treatment Population

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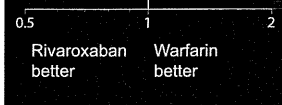
Primary Efficacy Outcome
Stroke and non-CNS Embolism

	Rivaroxaban Event Rate	Warfarin Event Rate	HR (95% CI)	P-value
On Treatment N= 14,143	1.70	2.15	0.79 (0.65,0.95)	0.015
ITT N= 14,171	2.12	2.42	0.88 (0.74,1.03)	0.117



Event Rates are per 100 patient-years
Based on Safety on Treatment or Intention-to-Treat thru Site Notification populations

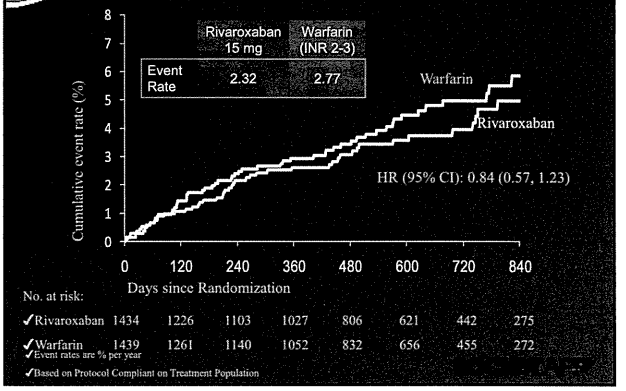
Bleeding Outcomes

	Rivaroxaban Event Rate or N (Rate)	Warfarin Event Rate or N (Rate)	HR (95% CI)	P-value
Major	3.60	3.45	1.04 (0.90, 1.20)	0.576
≥2 g/dL Hgb drop	2.77	2.26	1.22 (1.03, 1.44)	0.019
Transfusion	1.65	1.32	1.25 (1.01, 1.55)	0.044
Critical organ bleeding	0.82	1.18	0.69 (0.53, 0.91)	0.007
Bleeding causing death	0.24	0.48	0.50 (0.31, 0.79)	0.003
Intracranial Hemorrhage	55 (0.49)	84 (0.74)	0.67 (0.47, 0.94)	0.019
Intraparenchymal	37 (0.33)	56 (0.49)	0.67 (0.44, 1.02)	0.060
Intraventricular	2 (0.02)	4 (0.04)		
Subdural	14 (0.13)	27 (0.27)	0.53 (0.28, 1.00)	0.051
Subarachnoid	4 (0.04)	1 (0.01)		

Event Rates are per 100 patient-years
Based on Safety on Treatment Population

Renal Insufficiency Patients

Stroke or non-CNS embolism among those with CrCl 30–49 mL/min



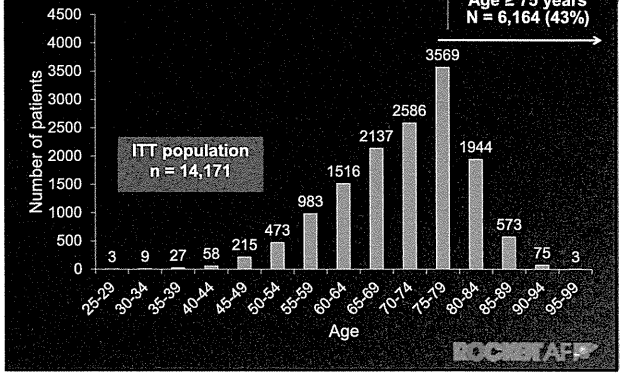
✓Event rates are % per year
✓Based on Protocol Compliant on Treatment Population

Efficacy endpoints on treatment

Clinical endpoint (% per year)	Rivaroxaban (N=7111)	Warfarin (N=7116)	HR (95% CI) Rivaroxaban vs warfarin	P (interaction)
Primary efficacy endpoint*	1.57 2.32	2.00 2.77	0.78 (0.63–0.98) 0.84 (0.57–1.23)	0.76
PE + vascular death	2.76 4.64	3.32 4.83	0.83 (0.70–0.98) 0.96 (0.73–1.27)	0.38
PE + MI, vascular death	3.55 5.58	4.16 6.54	0.85 (0.73–0.99) 0.85 (0.67–1.09)	0.98
Stroke				
Ischaemic	1.20 1.98	1.34 1.78	0.90 (0.69–1.16) 1.11 (0.71–1.73)	0.41
Haemorrhagic	0.26 0.29	0.42 0.52	0.62 (0.37–1.03) 0.56 (0.21–1.51)	0.88
Undetermined	0.07 0.05	0.10 0.09	0.68 (0.24–1.90) 0.51 (0.05–5.67)	0.84

✓Based on per-protocol population on treatment
*Stroke and systemic embolism (PE)
†Rivaroxaban 20 mg od, ‡Rivaroxaban 15 mg od

Rivaroxaban vs Warfarin in the Elderly
Age Distribution at Entry



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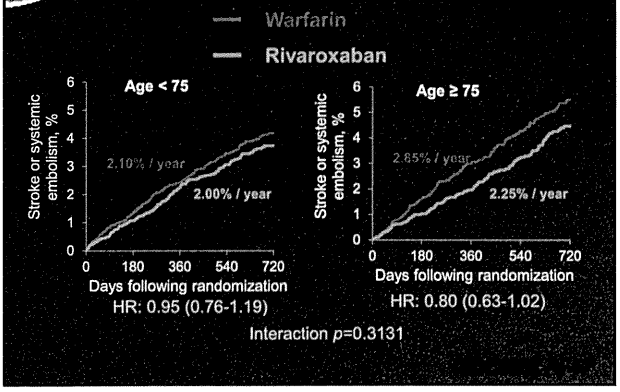
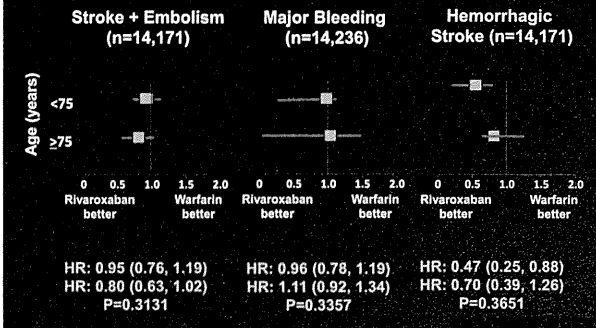
Stroke and Systemic Embolism
Intention-to-treat Analysis



Relative Risks of Major Events
Rivaroxaban vs. Warfarin

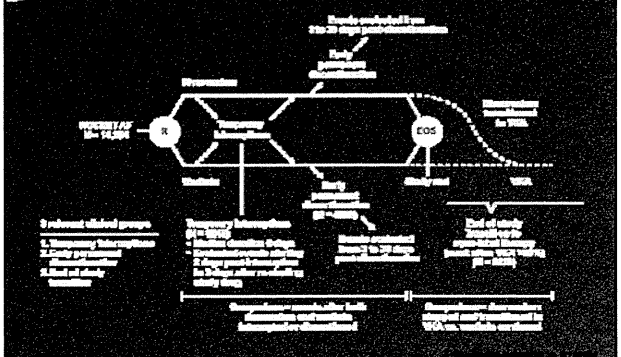


Summary

- **Efficacy**:
  - Rivaroxaban was non-inferior to warfarin for prevention of stroke and non-CNS embolism.
  - Rivaroxaban was superior to warfarin while patients were taking study drug.
  - By intention-to-treat, rivaroxaban was non-inferior to warfarin but did not achieve superiority.
- **Safety**:
  - Similar rates of bleeding and adverse events.
  - Less ICH and fatal bleeding with rivaroxaban.
- **Conclusion**:
  - Rivaroxaban is a proven alternative to warfarin for moderate or high risk patients with AF.

How about the Discontinuation?

ROCKET AF
Relevant populations for effect after discontinuation/interruptions



Results: Discontinuations

	Overall	Rivaroxaban	Warfarin
Patients who took at least 1 dose of study drug	14,143	7061	7082
Median treatment exposure (days)	593 (402, 809)	590 (398, 806)	595 (408, 811)
Temporary interruptions (%)	8245 (58)	3734 (53)	4511 (64)
Early permanent discontinuation (%)	4895 (35)	2470 (35)	2425 (34)
Completion of the study (%)*	9239 (65)	4578 (65)	4652 (66)

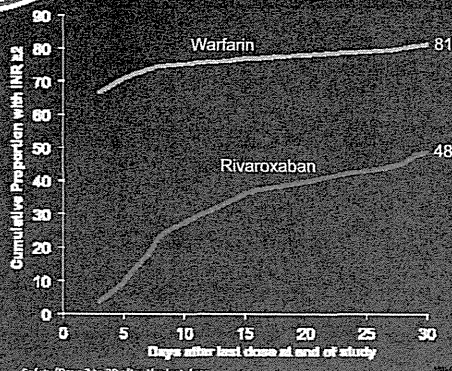
*Without an investigator suspected primary endpoint, death, or early permanent discontinuation.

Stroke or non-CNS embolism after any interruption or discontinuation

	Event Rate (per 100 pt yrs)			
	Rivaroxaban	Warfarin	HR (95% CI)	P-value
All discontinuations and interruptions (prior to end of study)	16.49	14.05	1.21 (0.81, 1.81)	0.35
Temporary interruptions	6.20	5.05	1.28 (0.49, 3.31)	0.62
Permanent discontinuations	25.60	23.28	1.10 (0.71, 1.72)	0.66
After end of study	6.42	1.73	3.72 (1.51, 9.16)	0.0044
All discontinuations and interruptions (prior to end of study) + After end of study events	11.20	7.57	1.50 (1.05, 2.15)	0.026

0.1 1 10
Rivaroxaban better
Warfarin better

Cumulative proportion of subjects with INR ≥2 who completed the study



Safety/Days 3 to 30 after the last dose

ROCKET AF

Conclusions

- In AF patients temporarily interrupting or permanently discontinuing anticoagulation, the risk or stroke or non-CNS embolism is high and similar with rivaroxaban or warfarin.
- An increased risk of stroke and non-CNS embolism was observed in rivaroxaban- compared with warfarin-treated patients undergoing transition to open label therapy after the end of study:
  - Warfarin ——— VKA
  - Rivaroxaban ——— VKA

ROCKET AF

Clinical Implications

- The risk of thrombotic events is significant when anticoagulation is stopped (temporary or permanently)
  - Careful consideration should be given to anticoagulation coverage in patients with moderate to high risk AF
- After the end of study transition to warfarin, an increased risk of stroke was observed for patients transitioned from rivaroxaban versus warfarin
  - These findings argue for continued anticoagulation coverage if patients are transitioned from one anticoagulant to another (rivaroxaban to warfarin in ROCKET AF)

ROCKET AF

Clinical Quiz (2)

- Which one of the following is NOT a guiding principle for quality in large clinical trial design management

1. Ensure the Right Patient (those meeting criteria) are enrolled
2. Ensure Randomization Occurs
3. Ensure Blinding is held
4. Ensure All sites randomize at least one patient
5. Ensure that endpoints are captures and patients are followed until the end of the study

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Clinical Quiz (2)

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1. Ensure the Right Patient (those meeting criteria) are enrolled
2. Ensure Randomization Occurs
3. Ensure Blinding is held
4. Ensure All sites randomize at least one patient
5. Ensure that endpoints are captures and patients are followed until the end of the study

All of the above are guiding principles except #4. It would be nice to have all sites enroll but does not invalidate a trial if not. Few trials accomplish this

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Clinical Quiz (3)

- Which one of the following caused the unbalance in clinical events after discontinuation in ROCKET AF?

1. Differential treatment with unfractionated heparin
2. Differential follow up (different follow up periods for the two groups)
3. Transition from blinded study drug to open lable study drug – where warfarin was still used but rivaroxaban was not possible open label
4. Differential (uneven or unbalanced) capture of events in the two treatment arms

Clinical Quiz (3)

- Which one of the following caused the unbalance in clinical events after discontinuation in ROCKET AF?

1. Differential treatment with unfractionated heparin
2. Differential follow up (different follow up periods for the two groups)
3. Transition from blinded study drug to open label study drug – where warfarin was still used but rivaroxaban was not possible open label
4. Differential (uneven or unbalanced) capture of events in the two treatment arms

Transition from blinded study to open label study with one arm changing and the other study arm staying on same drug

Clinical Quiz (4)

- The term "double-dummy" in trials like ROCKET AF refers to the following:

1. The need for patients to take two different therapies (one active and one placebo) due to either differences in dosing schedule or in order manage one therapy differently than another (dose adjustment)
2. The type of blinding that includes the CEC
3. The type of study where for a short period of time some patients only get placebo

Clinical Quiz (4)

- The term "double-dummy" in trials like ROCKET AF refers to the following:

1. The need for patients to take two different therapies (one active and one placebo) due to either differences in dosing schedule or in order manage one therapy differently than another (dose adjustment)
2. The type of blinding that includes the CEC
3. The type of study where for a short period of time some patients only get placebo

Double dummy refers to two different therapies (two bottles for each patient)

Systems Integration: Operational Efficiencies

- Randomization: Upload IVR data into InForm on a regular basis, i.e., minutes to hours
- Site Management Data: Import site user demographic data
- SAE: Incorporate SAE reporting into InForm
- SDV Tracking: Incorporate targeting/tracking of patients/forms source verified
- CEC: Incorporate adjudication triggers, tracking and results into InForm
- Data Status Reports: By patient, site, country, overall

Outcome: Enhanced Data Quality via Data Surveillance by providing feedback to sites, CRAs, Study Operations and Clinical Leadership to deliver a Quality dataset.

The Role for Registries

Adrian F. Hernandez, MD, MHS
Associate Professor of Medicine
Duke University Medical Center

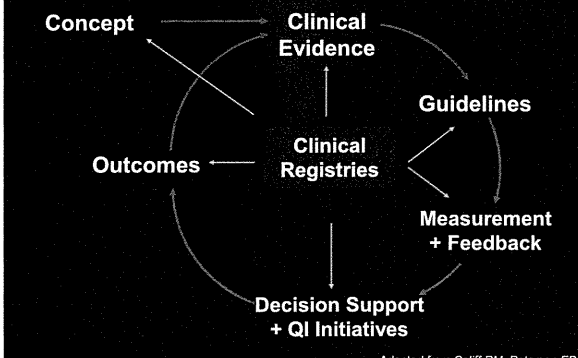
Director of Outcomes Research
Duke Clinical Research Institute

Duke Clinical Research Institute

Our Mission: Health Services and Outcomes Research

To lead and advance innovative health services research that improves the quality, value, and outcomes of patient-centered care.

Cycle of Discovery and Adoption



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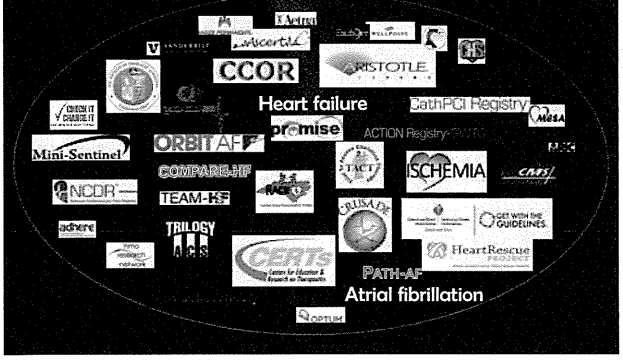
Adapted from Califf RM, Peterson ED et al. JACC 2002:40:1895-901

What we do

- Outcomes research
- Quality improvement
- Implementation science
- Comparative effectiveness research
- Medical decision making
- Cluster randomized trials
- Empirical bioethics
- Drug and device safety
- Health economics
- Health policy
- Methods development
- Patient-reported outcomes
- Decision modeling
- Pharmacoepidemiology

Health Services and Outcomes Research



Question 1

Which of the following questions can a registry not address?

A. Is a drug definitively better than standard of care (efficacy)?
B. Are we doing the right things? (evidence)
C. Are we doing the right things right? (application)
D. Are our patients better off for it? (outcomes)

Roles for Clinical Registries Identify the Challenges:

- **Define epidemiology and temporal trends in community-based practice**
  - Disease presentation
  - Risk factors
  - Prognostication
  - Treatment and utilization patterns
  - Patient outcomes

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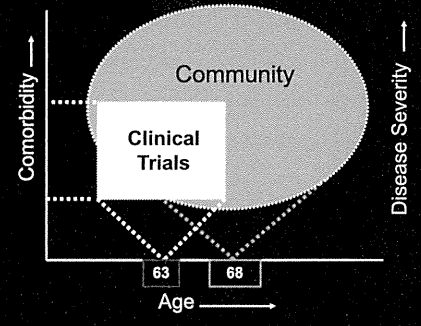
Translating Evidence to Routine Practice



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Registries A Tool to Improve Quality of Care

"Degree to which health care services increase the likelihood of desired health outcomes and are consistent with current professional knowledge"

- Are we doing the right things? (evidence)
- Are we doing the right things right? (application)
- Are our patients better off for it? (outcomes)

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Question 2

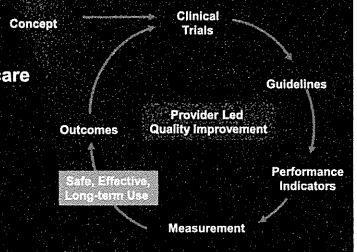
- **Can a registry improve quality of care?**

A. **Yes, data from a registry can be used to inform healthcare providers on best care**

B. **No, registry data is limited to patient information only**

How To Improve Provider Led QI Works vs P4P

- **Participation in provider-led quality improvement (QI) efforts can improve CV care!**
  - NRMI, CRUSADE
  - AHA GWTG
  - ACC-NCDR
- **Means to Achieve better care**
  - Motivated local champions
  - Timely, valued feedback
  - Simple tools
    - *Standard orders, CPOE*
    - *Pt-MD contract*
    - *Chart documentation*
  - Collaborative Teams



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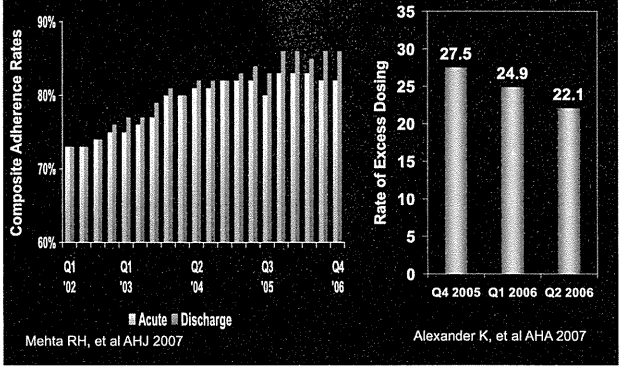
Feedback Driven Improvements in Evidence Based Care Over Time



Mehta RH, et al AHJ 2007

Alexander K, et al AHA 2007

ACS Clinical Trials vs Real World Patients

Variable	PURSUIT (n = 9461)	CURE (n = 12,562)	SYNERGY (n = 9975)	CRUSADE (n = 180,842)
Mean age ± SD (yrs)	63 ± 11	63 ± 12	67 ± 11	69 ± 14
Female sex (%)	36	39	34	40
Diabetes mellitus (%)	23	23	29	33
Prior MI (%)	32	25	28	30
Prior CHF (%)	11	8	9	18
Prior PCI (%)	13	18*	20	21
Prior CABG (%)	12	18*	17	19

NEJM 1998;339:436-43
NEJM 2001;345:494-502
JAMA 2004;292:45-54
CRUSADE 2006

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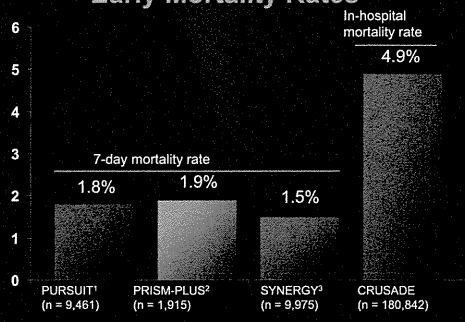
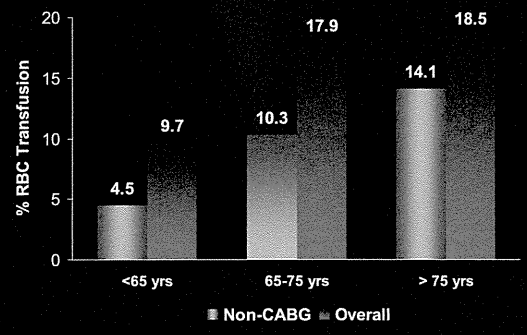
CRUSADE vs. ACS Clinical Trials: Early Mortality Rates



1.The PURSUIT Trial Investigators. N Engl J Med 1998
2.The PRISM-PLUS Study Investigators. N Engl J Med 1998
3. The Synergy Study JAMA 2004
CRUSADE cumulative data through 6/30/2006

CRUSADE Bleeding Risks - Transfusion by Age



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Yang X, et al. J Am Coll Cardiol. 2005;46:1490-5.

The IOM Definition of Quality Care

- **Timely:** Rapid diagnosis and treatment
- **Effective:** with right drugs / procedures
- **Safe:** at the right dose and / or done right
- **Equitable:** in all eligible pts
- **Patient centered:** But considering the risks and benefits and desires of the individual patient
- **Cost-effective:** avoiding over-treatment

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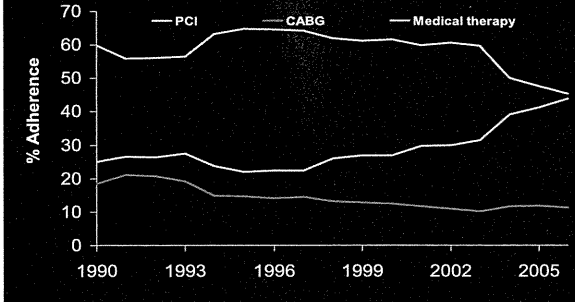
15 Year Trends in MI care and Outcomes: Results from NRMI



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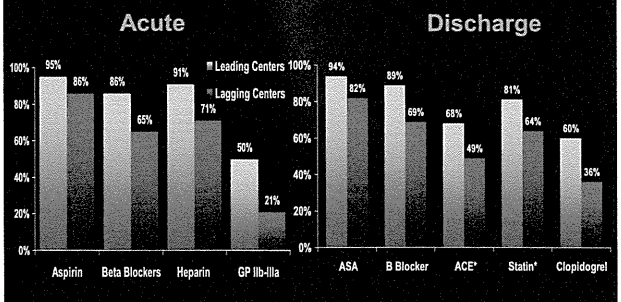
Peterson E et al, AHJ 2009

Use of EBM among US Hospitals

430 US hospitals



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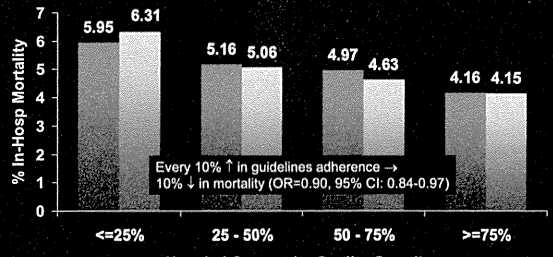
Peterson JAMA 2006

Association Between Hospital Guidelines Adherence and Mortality



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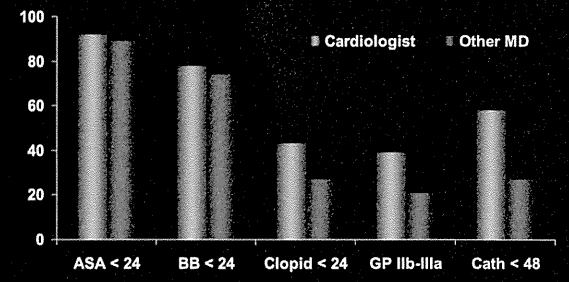
Peterson et al, JAMA 2006;295:1863-1912

Variability in Care By Primary Treating MD Specialty



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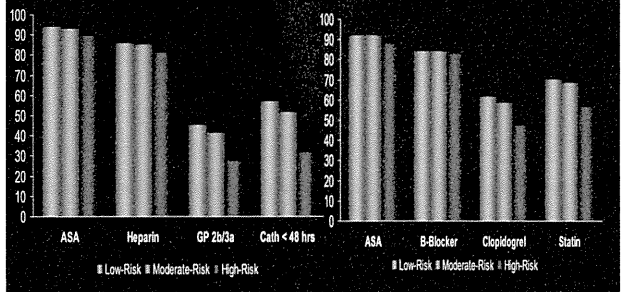
Roe MT et al *Circulation 2007 :116:1153-1161*

Paradoxical Acute and Discharge Care Patterns: CRUSADE



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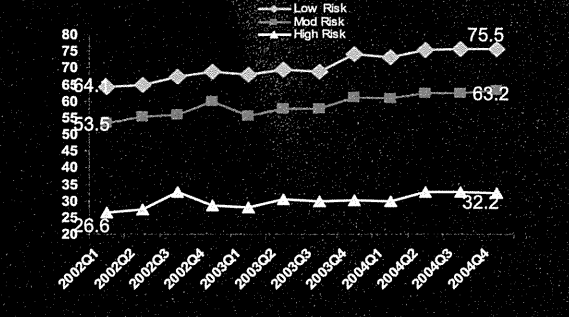
Roe M et al Arch Intern Med 2005;165:1870-6

Interventional Care Trends in Early Cath Use by Risk Status



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Tricoci et al, Am J Cardiol 2006;98:1172-1176.

Disparities in Care

GET WITH THE GUIDELINES

Sex and Racial Differences in the Use of Implantable Cardioverter-Defibrillators Among Patients Hospitalized With Heart Failure

Adrian F. Hernandez, MD, MHS
Gregg C. Fonarow, MD
Li Liang, PhD
Sam M. Al-Khatib, MD, MHS
Lesley H. Curtis, PhD
Kenneth A. LaBresh, MD
Clyde W. Yancy, MD
Nancy M. Albert, PhD
Eric D. Peterson, MD, MPH

Context Practice guidelines recommend implantable cardioverter-defibrillator (ICD) therapy for patients with heart failure and left ventricular ejection fraction of 30% or less. The influence of sex and race on ICD use among eligible patients is unknown.

Objective To examine sex and racial differences in the use of ICD therapy.

Design, Setting, and Patients Observational analysis of 15 034 patients admitted with heart failure and left ventricular ejection fraction of 30% or less and discharged alive from hospitals in the American Heart Association's Get With the Guidelines–Heart Failure quality-improvement program. Patients were treated between January 2005 and June 2007 at 219 participating hospitals.

Main Outcome Measures Use of ICD therapy or planned ICD therapy at discharge.

Results Among patients eligible for ICD therapy, 4515 (35.4%) had ICD therapy at

Only 35% of eligible HF patients receive an ICD.

OR for ICD (relative to White Males)

Black Male:	0.73
White Female:	0.62
Black Female:	0.54

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Hernandez AF et al. *JAMA* 2007;298:1525-1532

Disparities in Care: Impact of Insurance on Treatment

	Medicaid	HMO/Private	Adj. OR (95%CI)*
Aspirin	90	94	0.78 (0.68, 0.90)
Beta-Blocker	76	81	0.86 (0.77, 0.95)
Clopidogrel	39	49	0.89 (0.82, 0.97)
Gp IIb-IIIa	36	49	0.84 (0.76, 0.94)

* Comparison adjusted for gender, race, comorbidity, cardiac markers, insurance status, hospital features, and clustering effects

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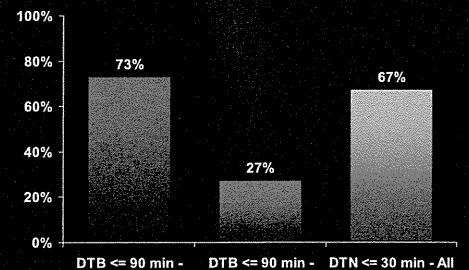
Calvin JE Annals Int Med 2006

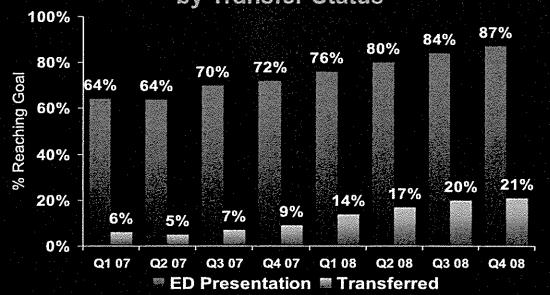
Timely Care: STEMI – Door to Balloon and Door to Needle Times: Cumulative 12 Month Data



ACTION Registry-GWTG DATA: January 1,2009 – December 31, 2009

DTB = 1st Door to Balloon for Primary PCI
DTN = Door to Needle for Lytics

Improving Trends in DTB ≤ 90 min by Transfer Status



Non-transfer patients represent 67% of primary PCI population

Question 3

- **A registry can be used for comparative effectiveness or safety evaluations of 'real-world' treatments?**
  - A. Yes
  - B. No

Roles for Clinical Registries Comparative Effectiveness and Safety Evaluation:

- **Comparative Effectiveness Research**
  - Compare competing treatment options
- **Support Post market Safety evaluation:**
  - Off-label uses and outcomes
  - Track late treatment outcomes (beyond trials)
  - Drug-drug and drug-device interactions

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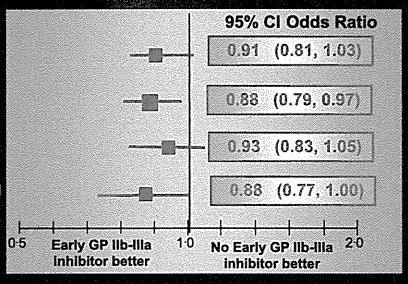
Comparative Effectiveness: Early GP IIb-IIIa Inhibitor:

Results from Clinical Trials, NRMI, and CRUSADE



1. Boersma et al. *Lancet.* 2002;359:189.
2. Peterson et al. *J Am Coll Cardiol.* 2003;42:45.
3. Hoekstra et al. *Acad Emerg Med* 2005;12:431-438

Identifying Safety Concerns DES vs BMS Debates

ORIGINAL CONTRIBUTION

Clopidogrel Use and Long-term Clinical Outcomes After Drug-Eluting Stent Implantation

Eric L. Eisenstein, DBA
Kevin J. Anstrom, PhD
David F. Kong, MD
Linda K. Shaw, MS
Robert H. Tuttle, MSPH
Daniel B. Mark, MD, MPH
Judith M. Kramer, MD, MS
Robert A. Harrington, MD
David B. Matchar, MD
David E. Kandzari, MD
Eric D. Peterson, MD, MPH
Kevin A. Schulman, MD
Robert M. Califf, MD

Context Recent studies of drug-eluting intracoronary stents suggest that current antiplatelet regimens may not be sufficient to prevent late stent thrombosis.

Objective To assess the association between clopidogrel use and long-term clinical outcomes of patients receiving drug-eluting stents (DES) and bare-metal stents (BMS) for treatment of coronary artery disease.

Design, Setting, and Patients An observational study examining consecutive patients receiving intracoronary stents at Duke Heart Center, a tertiary care medical center in Durham, NC, between January 1, 2000, and July 31, 2005, with follow-up contact at 6, 12, and 24 months through September 7, 2006. Study population included 4666 patients undergoing initial percutaneous coronary intervention with BMS (n = 3165) or DES (n = 1501). Landmark analyses were performed among patients who were event-free (no death, myocardial infarction [MI], or revascularization) at 6- and 12-month follow-up. At these points, patients were divided into 4 groups based on stent type and self-reported clopidogrel use: DES with clopidogrel, DES without clopidogrel, BMS with clopidogrel, and BMS without clopidogrel.

Main Outcome Measures Death, nonfatal MI, and the composite of death or MI at 24-month follow-up.

Conclusions: The early discontinuation of clopidogrel in patients with DES was associated with increased risk for bad outcomes.

JAMA. 2007;297:159-168