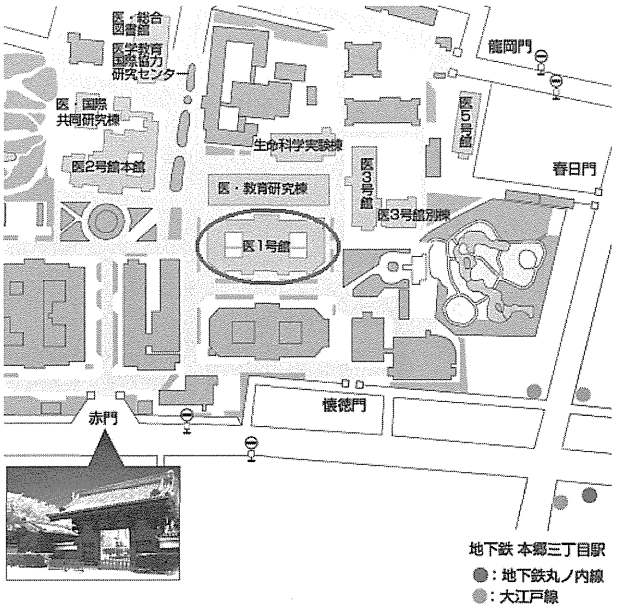
（資料）臨床研究・治験のグローバル化プログラム

臨床研究・治験の国際化に向けたシンポジウム

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

日　時：2013年2月6日(水)
場　所：東京大学医学部1号館3階 講堂
定員と参加費： 200名 無料（ただし懇親会は6000円）

申込方法及び問い合わせ
お名前、ご所属、電話番号、emailアドレス、懇親会参加の有無をご記入の上、cbi-secretary@umin.ac.jpにお送りください。
申込締切は2013年1月31日迄とします。



〈プログラム〉

9:30 開場
10:00-10:10（10分） ご挨拶
　厚生労働省　治験推進室長 山田 雅信
　自治医科大学 学長 永井 良三

10:10-10:50（40分） 基調講演：「臨床研究・治験のための生物統計ステップ・アップ」
　東京大学大学院医学系研究科 公共健康医学専攻 生物統計学分野 教授 大橋 靖雄

メインセッション：日米からの実例に基づく発表

10:50-11:50（60分）
(1)Overview of trial experience & recent experience with ROCET AF Study
（臨床研究の運営とスタッフの指導（ROCKET AFスタディの経験から））
Dr. Manesh R. Patel, MD, FACC (Assistant Professor of Medicine, Duke University Medical Center)

11:50-13:30（100分） 昼食

13:30-14:30（60分）
(2) Overview of Registry Studies（登録研究について）
Dr. Adrian F. Hernandez, MD, MHS (Associate Professor of Medicine, Duke University Medical Center)

14:30-15:30（60分）
(3)Best practice for conducting and reporting clinical studies using large database
（大規模データベースを用いた臨床研究の実施と報告について）
Dr. Soko Setoguchi, MD, MPH (Associate Professor of Medicine, Duke Clinical Research Institute)

15:30-16:00（30分） 休憩

16:00-16:40（40分）
(4)臨床研究の戦略（HOP, JAMP, SPREAD研究を例に）
自治医科大学　内科学講座循環器内科学 主任教授　苅尾 七臣

16:40-16:45（5分） 閉会の辞
東京大学大学院医学系研究科 臨床疫学研究システム講座 特任准教授　小出 大介

17:00-19:30 懇親会（東京大学 伊藤国際学術研究センター内 レストラン）

注：英語の発表には通訳をつける予定です。また本シンポジウムは今後のeラーニングのコンテンツのために撮影を行いますことをご了承ください。なお聴衆はビデオに収録されないように配慮致します。
主催：厚生労働科学研究費補助金 医療技術実用化総合研究事業（H24-臨研基-一般-002）代表：小出大介（東京大学）
共催：同上（H24-臨研基-一般-001）代表：山本精一郎（国立がん研究センター）

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

Outline

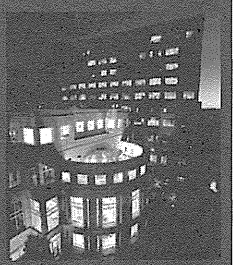
- Background DCRI – ARO and clinical trials
- Review of ROCKET AF trial
- Quiz Questions

DCRI Mission

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

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



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

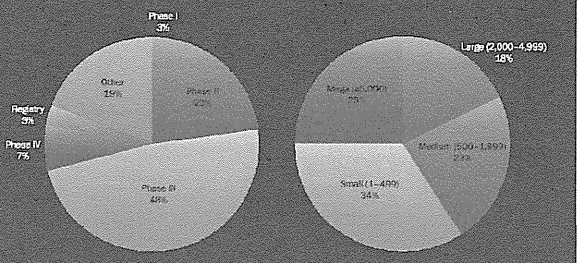
DCRI Facts

- 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

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

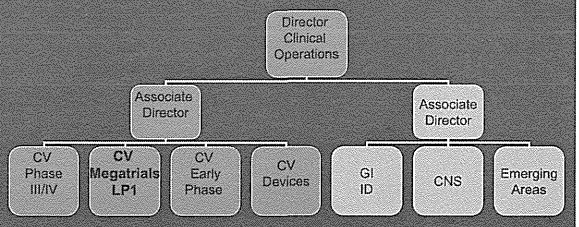
DCRI – Trials Experience by Phase and Size



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.

DCRI Clinical Operations Structure



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

DCRI Global Reach

- Trials conducted in 64 countries

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

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?

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

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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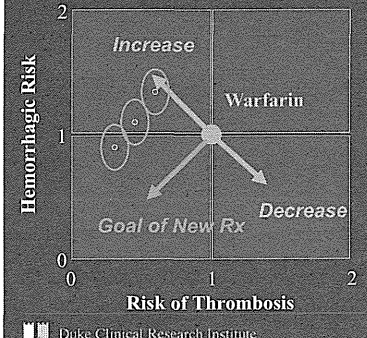
DUKE UNIVERSITY MEDICAL CENTER

Efficacy vs. Safety: Antithrombotic Drug Development



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

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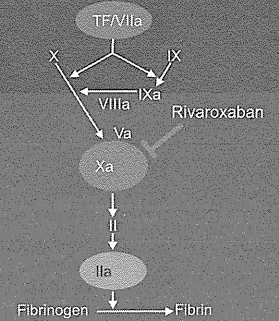
Background
Rivaroxaban

- 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

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: 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

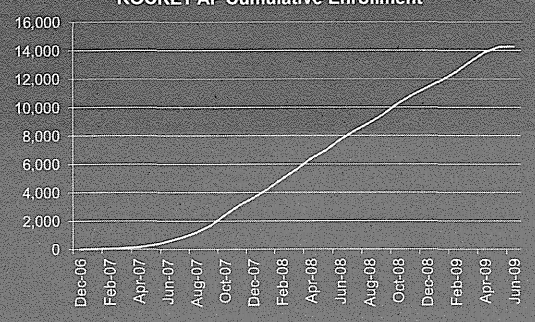
ROCKET Enrollment by Country

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	368	TOTAL	14269
Germany	530	Poland	528		
Greece	29	Romania	783		

Celebrating 14,000 Patients Randomized

Enrollment Over Time

ROCKET AF Cumulative Enrollment



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 Daus	57
Hungary	036007	Andras Vertes	Fovarosi Onkormanyzat Szent Istvan Korhaza	56

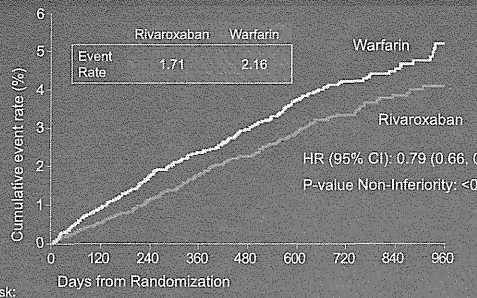
Time in Therapeutic Range (TTR)
INR Data

INR range	Warfarin 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

ROCKET AF

Primary Efficacy Outcome
Stroke and non-CNS Embolism



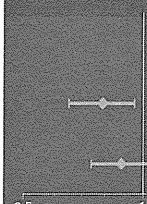
No. at risk:

Rivaroxaban	6958	6211	5786	5468	4406	3407	2472	1496	634
Warfarin	7004	6327	5911	5542	4461	3478	2539	1538	655

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

ROCKET AF

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

ROCKET AF

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)		

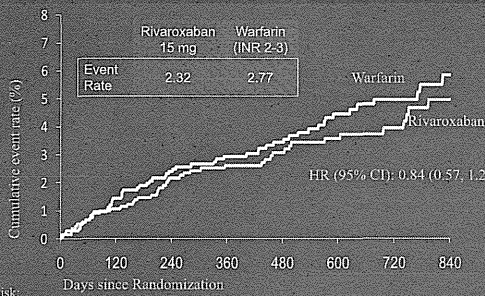
Event Rates are per 100 patient-years
Based on Safety on Treatment Population

ROCKET AF

Renal Insufficiency Patients

ROCKET AF

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



No. at risk:

✓Rivaroxaban	1434	1226	1103	1027	806	621	442	275
✓Warfarin	1439	1261	1140	1052	832	656	455	272

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

ROCKET AF

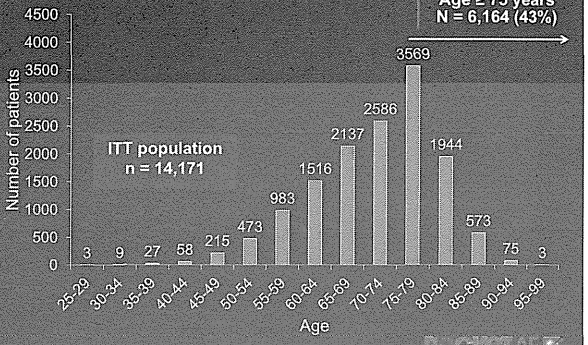
Efficacy endpoints on treatment

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 (FE)
†Rivaroxaban 20 mg od. ‡Rivaroxaban 15 mg od

ROCKET AF

Rivaroxaban vs Warfarin in the Elderly
Age Distribution at Entry



ROCKET AF

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.

Duke Clinical Research Institute

The Role for Registries

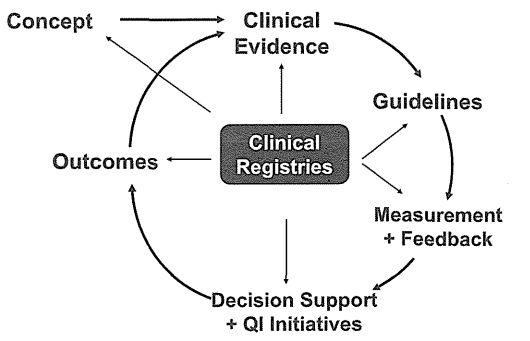
Adrian F. Hernandez, MD, MHS
Associate Professor of Medicine
Duke University Medical Center

Director of Outcomes Research
Duke Clinical Research Institute

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

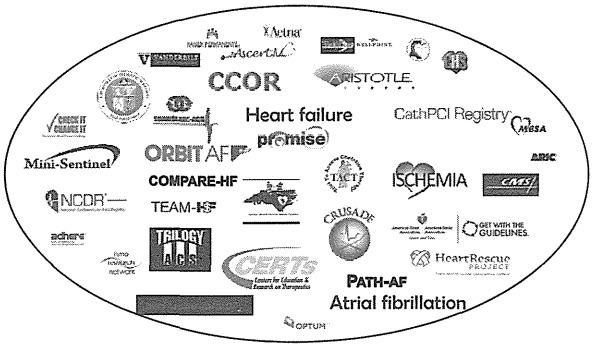


Adapted from Califf RM, Peterson ED et al. JACC 2002;40:1895-901

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

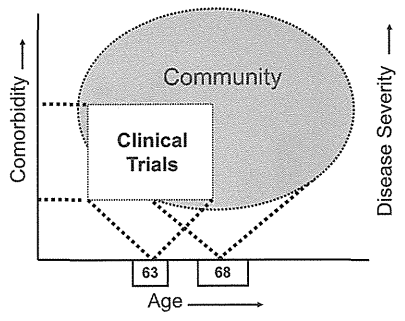
Health Services and Outcomes Research



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

Translating Evidence to Routine Practice



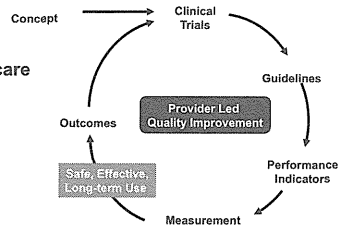
Registries A Tool to Improve Quality of Care

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

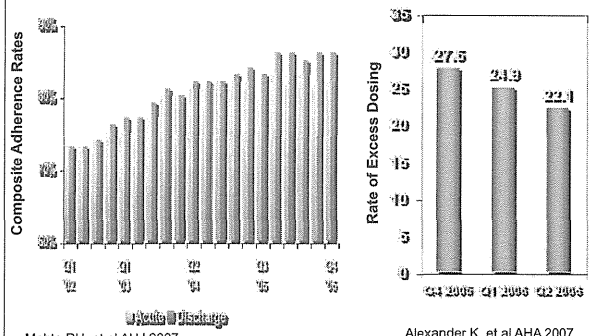
- Are we doing the right things? (evidence)
- Are we doing the right things right? (application)
- Are our patients better off for it? (outcomes)

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



Feedback Driven Improvements in Evidence Based Care Over Time



Mehta RH, et al AHJ 2007

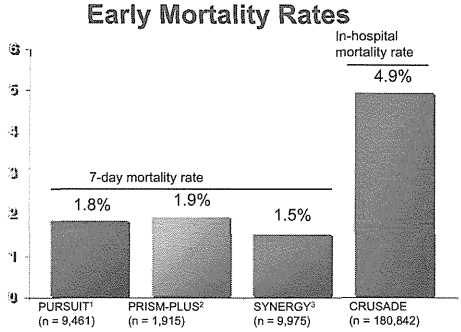
Alexander K, et al AHA 2007

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

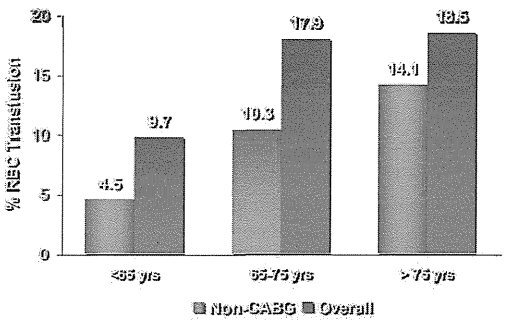
NEJM 1998;339:436-43
NEJM 2001;345:494-502
JAMA 2004:292:45-54
CRUSADE 2006

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

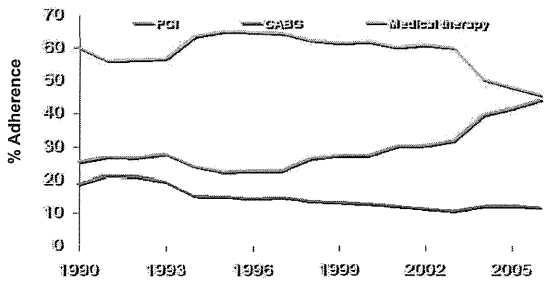


Yang X, et al. J Am Coll Cardiol. 2005;46:1490-5.

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

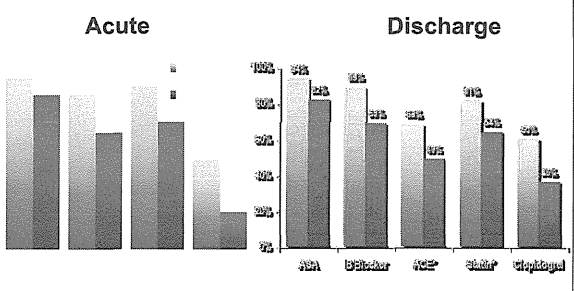
15 Year Trends in MI care and Outcomes: Results from NRMI



Peterson E et al, AHJ 2009

Use of EBM among US Hospitals

430 US hospitals



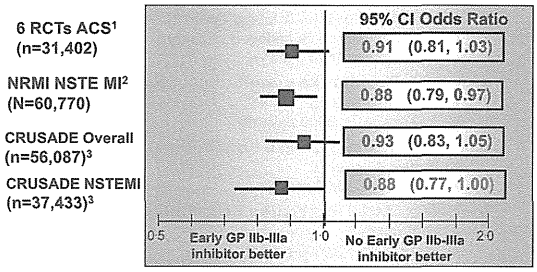
Peterson JAMA 2006

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

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, MSc
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 current at 6, 12, and 24 months through September 7, 2006. Study population included 4666 patients undergoing initial percutaneous coronary intervention with BMS (n = 2169) or DES (n = 2497). Landmark analyses were performed among patients who were event-free for 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.

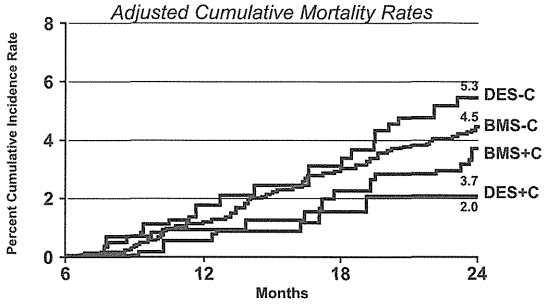
Main Outcome Measures Death, nonfatal MI, and the composite of death or MI at 24-month follow-up.

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

JAMA. 2007;297:159-168

Duke Database: 6-Month Landmark Analysis

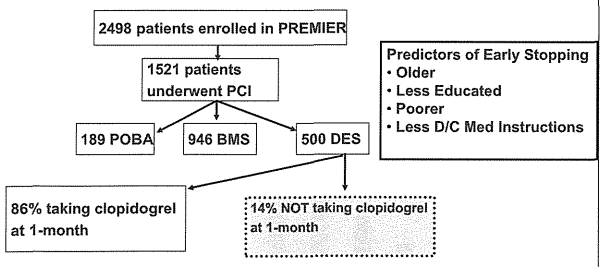
Adjusted Cumulative Mortality Rates



-Eisenstein et al. JAMA 2006

Continuity of Care

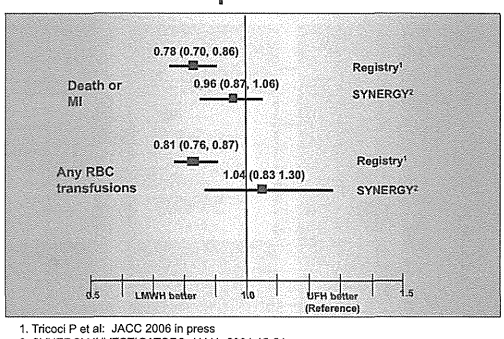
Early Clopidogrel Discontinuation of within 30 Days After DES



Mortality increased nearly 10X

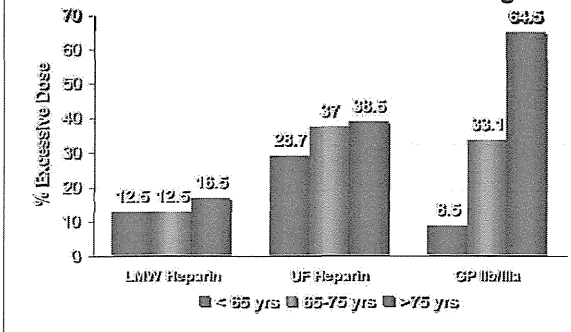
Spertus JA Circ 2006:113: 2803

Comparative Effectiveness: LMHW VS UF Heparin



1. Tricoci P et al: JACC 2006 in press
2. SYNERGY INVESTIGATORS *JAMA* ;2004:45-54

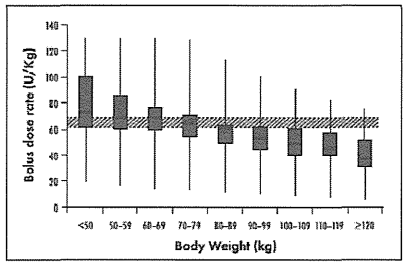
Safe Care? Errors of Commission Excessive Antithrombotic Dosing



Alexander KA, et al. *JAMA* 2005;294:3108-3116

Failure to Individualize Care: Weight and Dosing

Unfractionated Heparin Bolus by Weight in Kg



Melloni, Circulation 2007; Am Heart J 2008

Pharmaceutical Partnerships

- **CRUSADE: ACS Hospitalizations**
  - Partners Millennium, Schering Plough, BMS, Sanofi
  - 500+ hospitals, 200,000 ACS patients
- **MAINTAIN: Post ACS Longitudinal Study**
  - Partners: Merck- Schering, BMS/Sanofi
  - 40 hospitals, 1500 patients
- **AVAIL: Post Stroke Longitudinal Study**
  - AHA GWTG, BMS
  - 100 hospitals, 3000 patients
- **PREVAIL: Pre-Diabetes Longitudinal Study**
  - Tethys Bioscience
  - 40 centers, 3,000 patients
- **ORBIT: Atrial Fibrillation Longitudinal Study**
  - Ortho-McNeil
  - 400 centers, 10,000 patients (initial)
- **TRANSLATE ACS: ACS Longitudinal Study**
  - Lilly
  - 400 centers, 15,000 patients

Other Clinical Registries Coordinated at DCRI

- **Washington State PCI/CABG Registry**
- **SABG: Staph A registry**
- **ICE: International Collaboration on Endocarditis**
- **CATCH: Heparin Induced Thrombocytopenia Registry**
- **SCVIR: Uterine Artery Embolism Registry**
- **Longitudinal Initiatives**
  - **CMS Linkages**
  - **Long-term follow-up for subset of GWTG-Stroke (AVAIL) and CRUSADE (MAINTAIN) patients**

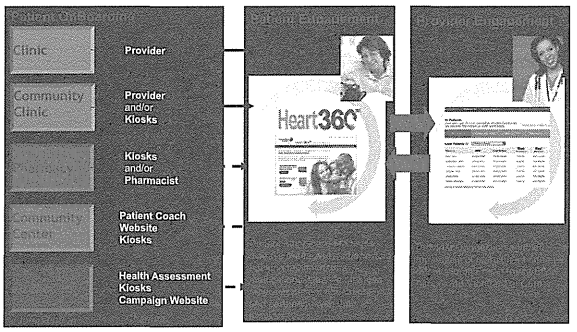
Who Sponsors DCRI Registry Research?

- **Government Agencies**
  - National Institutes of Health (NIH)
  - Agency for Healthcare Research and Quality (AHRQ)
  - Food and Drug Administration (FDA)
- **Professional Societies**
  - AHA, ACC, STS
- **Private Industry**
  - Pharmaceutical companies
  - Biotechnology companies
  - Medical device companies

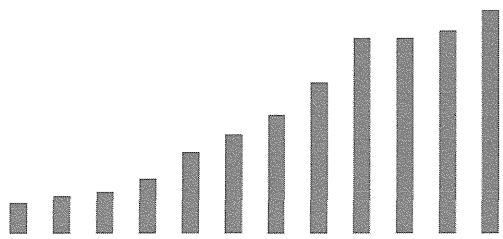
Potential Roles of Registries in the Development and Implementation of Evidence

- **Disease Characterization & Surveillance**
  - Community-based event rates
- **Clinical and comparative 'Effectiveness'**
  - Real world look at therapy' s benefits, risks and costs
- **Quality Measurement**
  - Is community adopting and implementing evidence-based care?
- **Quality Improvement**
  - Use measurement to stimulate practice change
  - Track impact of changes in health policy
- **Identify the unmet needs…**
  - Defining the 'denominator'

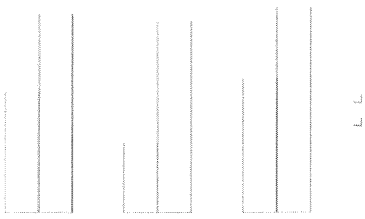
Collaborative Community Care



Health Services Research and Outcomes Publications

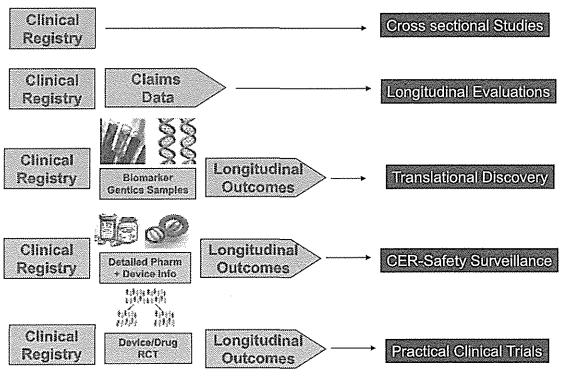


Publication Impact



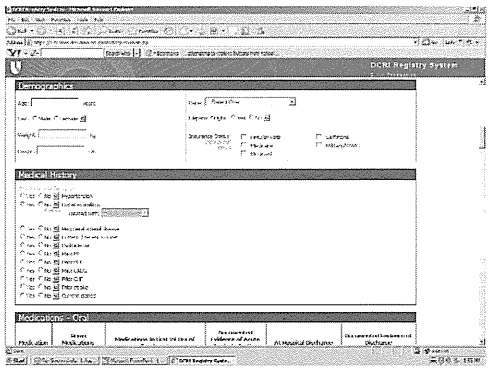
High Impact: NEJM, JAMA, Annals
CV Impact: Circulation, JACC

Expanding Capacity and Use of Clinical Registries



Some Examples...

User-friendly Web-based Data Submission



Data Quality Assurance

- **Site Data Collection Training**
  - Virtual Meetings - webinars, teleconferences
  - Multimedia training modules
  - FAQs, newsletters
- **Data Edit Checks**
- **Data Quality Feedback**
  - Iterative process
  - Highly automated
  - Record-specific and aggregate views
- **On-site QA audits**
  - Do-able but costly, not recommended

Follow-up Strategy

entails....

Site-conducted:

- Site training
- Patient return visit
- Site payment for out-of-pocket
- Site communication
- Site monitoring
- Annual site IRB renewal
- Data QA

Centralized:

- Central personnel training
- Telephone/Web-based follow-up
- Central payment for FU
- Central IRB

Follow-up Alternatives

- **Endpoints collectible without face-face visit**
  - Minimize loss to follow-up
- **Advantages of centralized follow-up?**
  - Consistent data collection
  - Eases site burden
  - Short-term study more appealing to sites
  - Reduces site management/monitoring activities
  - Coordinating center already contacting patients to conduct health outcomes interview

Endpoint Collection/Validation

"Bottom Line: COST"

Collected Endpoints:

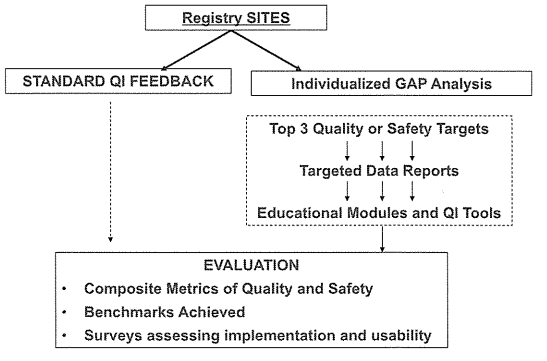
- Death
- Myocardial infarction
- Revascularization
- Bleeding

- **Three potential approaches:**
  - Patient-reported outcomes
  - Obtain medical records with clinical event adjudication
  - Obtain billing data – ICD9 codes
- **Validation**
  - Limited adjudication of early events
  - Annual "check-in" with sites for verification of hospitalization

Follow-up and EQOL

- **Integrated with main study follow-up plan**
  - Patient interviews at 6 month intervals
- **Experienced Follow-up Services Group**
  - Duke Databank for Cardiovascular Disease
    - *> 30 years of routine patient contact after cath/revasc*
  - Long-term follow-up for many global trials
    - *Follow-up rates >90%*
- **Health Economics/QOL Group**
  - Centralized data collection
  - Experts in EQOL methodologies
    - *– randomized sampling for QOL study population*

Clinical Trials:
Personalized And Targeted QI



Duke Clinical Research Institute

Best Practice in Conducting and Reporting Clinical Studies using Large Databases

International Symposium, Tokyo, Japan

Soko Setoguchi, MD, DrPH, MSPE
Associate Professor of Medicine
Duke Clinical Research Institute and Duke University School of Medicine

Outline

- Databases
- What can you do using databases?
- Conducting database studies
  - Database Research and Epidemiology
  - Important concepts in Epidemiology
- Reporting (very briefly)
- Summary

Databases

- Electronic health record data
- Administrative data (claims data)
- Registries
- Cohort study data

Computerization of Health-care Related Records

- Records for billing purposes were standardized/computerized
  - 1970's in pharmacoepidemiology and health service research
- Computerization of health information is rapidly developing and being used

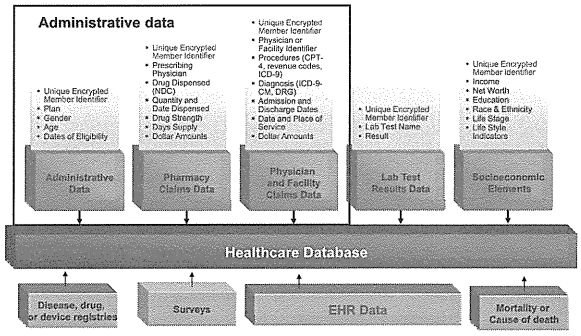
Administrative Databases

- **'Claims databases' or health care utilization databases'**
- **Examples**
  - Medicaid
  - Medicare + State Pharmacy Assistance Programs or Part D
  - Commercial insurance companies
    - United Health
    - Blue Cross Blue Shield
  - Canadian Provincial claims data
    - Ontario
    - Quebec
    - British Columbia
    - Saskatchewan

Electronic Health Record (EHR) Database

- Examples
  - Single provider
    - DEDUCE (Duke)
    - RPRD (Brigham and Women's Hospital)
  - Multiple providers
    - Geisinger Clinic Electronic Health Records- 41 Clinics covering ~3 million patients
  - EHR combined with administrative data
    - Kaiser Permanente

Better Healthcare Data



Secondary Analysis – Database Studies

- **Definition**
  - Any analysis using existing data
  - Some disciplines, such as health services research and pharmacoepidemiology, rely almost entirely on data collected for other purposes

Types of Database Studies

- Disease burden
- Health services research
- Outcome research
- Rick factor studies
- Pharmacoepidemiology (drug and device safety)
- Comparative effectiveness research

Examples of Studies Using Large Databases

Disease Burden

Trends in Out-of-Hospital Deaths Due to Coronary Heart Disease in Sweden (1991 to 2006)

Kerstin Dudas, PhD; Georg Lappas, BSc; Simon Stewart, PhD; Annika Rosengren, MD, PhD

Background—Case fatality associated with a first coronary event is often underestimated when only those who survive to reach a hospital are considered. Few studies have examined long-term trends in case fatality associated with a major coronary event that occurs out of the hospital.

Methods and Results—Record linkage documented all case subjects 35 to 84 years of age in Sweden during 1991 to 2006 with a first major coronary event (out-of-hospital coronary death or hospitalization for acute myocardial infarction). Of the 384 597 cases identified, 111 319 (28.9%) died out of the hospital, and another 36 552 (9.5%) died in the hospital or within 28 days of hospitaliza
events declined from 30.5% to
however, with a larger decline i
confidence interval 5.5% to 6.0
out-of-hospital deaths to overall
54 years of age, no more than 1
sex (odds ratio 0.85, 95% confi
0.971 to 0.974 per year) were as
was associated with increased r

Conclusions—The great majority
particularly among younger ind

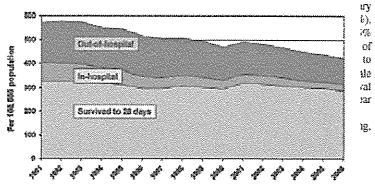
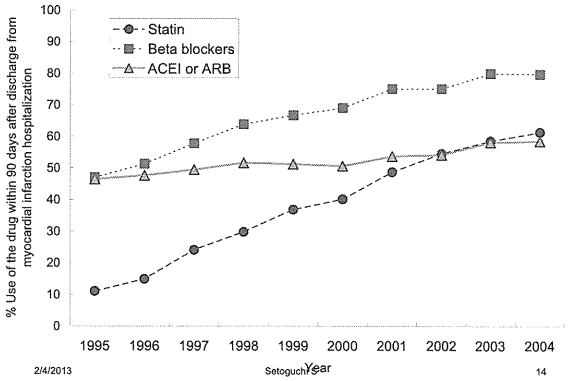


Figure 3. Mortality due to CHD in the hospital (within 28 days) and out of the hospital per 100 000 population 35 to 84 years of age, 1991 to 2006.

Health Services Research

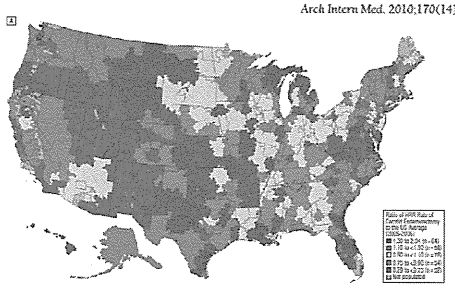


Setoguchi AJC 2007

Geographic Variation in Carotid Revascularization Among Medicare Beneficiaries, 2003-2006

Manesh R. Patel, MD; Melissa A. Greiner, MS; Lisa D. DiMartino, MPH; Kevin A. Schulman, MD; Pamela W. Duncan, PhD, PT; David B. Matchar, MD; Lesley H. Curtis, PhD

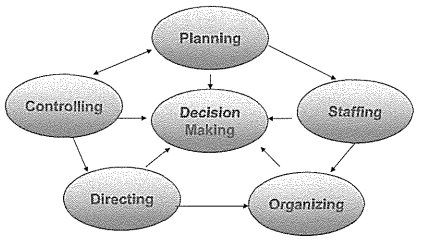
Arch Intern Med. 2010;170(14):1218-1225



Outcomes Research

Utility of Database Studies in Hospital Setting

Hospital management and Quality of Care



Rakich, Longest, and Darr, 1992

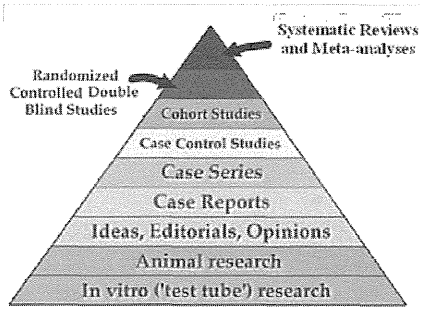
Data

Information needs to be put together and interpreted in a meaningful way

Anticipated challenges in database studies

- Not all important data components to control confounding or selection bias may exist in databases
- Common problems with databases
  - Information bias (in accurate data)
  - Missing data

The Evidence Pyramid



Study design choices

Explanatory RCT	Large Simple or Pragmatic Trial	Observational Studies
'Gold standard'; selected study population, unusual settings	Randomized ; usual setting of care; non-selected study population	Cohort Study Case-Control Study Case-Cohort Study Case Cross Over Study

Effectiveness
- Does it work in the 'real world'?

Internal Validity ⟷ External Validity

Sound Methodology is Needed to Provide Useful Information from Databases

- The integration of clinical expertise, patient values, and the best research evidence into the decision making process for patient care. .....**The best evidence is usually found in clinically relevant research that has been conducted using sound methodology**. (Sackett D, 2002)

Epidemiology

- Is the scientific study of factors affecting the health and illness of populations.....It is considered a ***cornerstone methodology*** of public health research, and is highly regarded in evidence-based medicine for identifying risk factors for disease and determining optimal treatment approaches to clinical practice.

Importance of New User Design

- All exposed persons should be new users or initiators
  - RCT is an experimental new user design
  - Follow-up starts after initiation
    - When defining exposure period, consider not only the actual use but also latency period and residual effect

Healthy User Bias

Users of preventive or newer medications or adherers to medications (e.g., statins, hormone replacement therapies)

- Less likely to die and less frail (Glynn, Epidemiology 2001)
- Seek more usual and preventive care (Brookhart, AJE 2007, Setoguchi CPT 2010),
- Follow a healthier life style (Kinjo ICPE Abstract, 2012)
- Have more willingness to live?
- Better social support?

Demonstrated in Assessing the Effect of...

- Occupation related hazardous exposure: healthy worker bias
- Preventive medications: healthy user bias
  - HRT fallacy
    - Results from Nurses Health Study vs. Women's Health Initiatives
  - Statins as a miracle drug that prevent
    - Cancer
    - Heart failure
    - Fracture

Anticipated Selection of Healthier Patients for ICDs – Healthy User Bias

- Clinical decision on who to receive a therapy depends on physician's judgement considering
  - Overall well-being
  - Functional status
  - Cognitive function
  - Social and family support

  All not typically measured in registries or medical records and associated with prognosis
- Better outcomes in patients who received an ICD may not be all due to effect of ICDs but due to selection of healthier patients for the therapy

ICDs Prevent Hip Fracture of SNF Admissions?

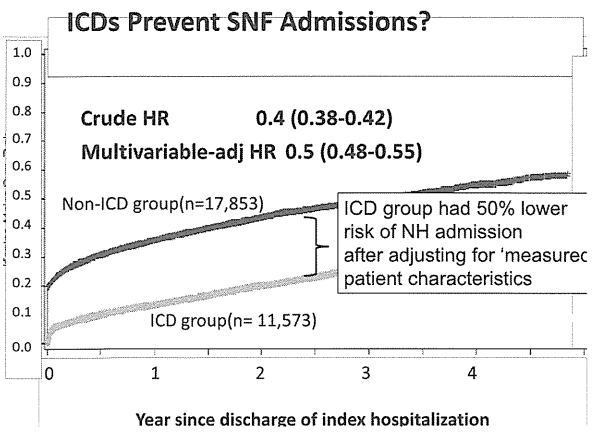
- ICDs
  - Efficacious preventing sudden cardiac deaths in HF patients
  - Do not improve cardiac function

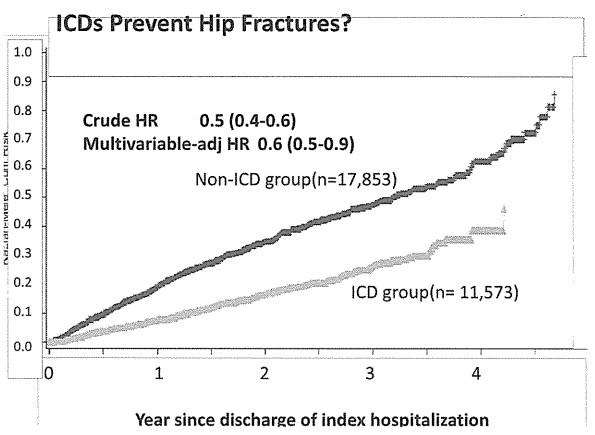
Therefore

- ICDs should not affect rate of admission to nursing home or non-traumatic hip fractures

Bias demonstration analysis

- Assessed outcomes unaffected by ICDs but are associated with unmeasured characteristics
  - Skilled nursing facility (SNF) admission
  - Hip fracture admission
- Any effect in these analyses (hazard ratios, HR < 1.0) suggest 'bias' rather than true effect





III. 研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
特になし							

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
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