Principles of GCP

- **2.11** The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- **2.12** Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
- **2.13** Systems with procedures that assure the quality of every aspect of the trial should be implemented.

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Quality System

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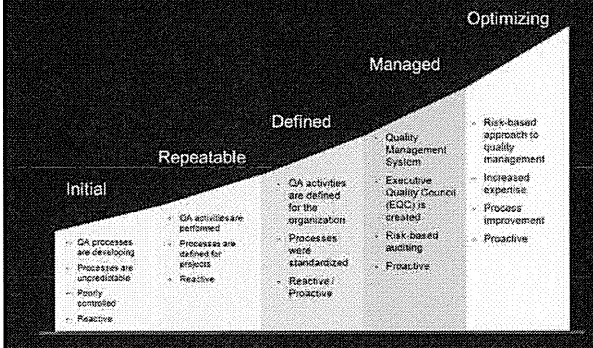
QA Maturity Model



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Quality Systems

- A dynamic engine for driving the business
- A method to facilitate oversight and control by management
- A method to drive toward continuous improvement
- Running a clinical trial or clinical program today is tantamount to running a small company
- As such, it should be run as the best company with the best quality system to ensure the highest success of high quality data and regulatory compliance

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Quality System

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Quality System Documents

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Conclusion

- Quality should be built into each step of conducting a clinical study
- Quality Assurance is a necessary function to ensure patient safety, and integrity of data are under control
- In investigator-initiated clinical study, if data integrity is compromised, not only will the safety of patients be jeopardized, but the reputation of the investigator could also be destroyed
- Only quality-driven clinical research can be reliable and sustainable through time

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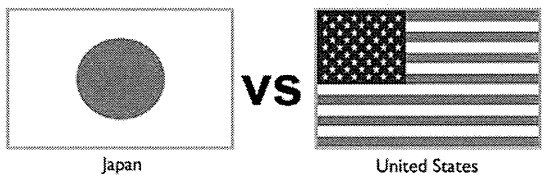
日米の相違

医療機器評価とデータベース研究

Soko Setoguchi, MD DrPH, FISPE
Associate Professor

Duke University School of Medicine
University of Tokyo Graduate School of Medicine

研究者主導臨床研究 日米比較



いろいろな臨床研究

- Randomized trials vs. observational studies
- Primary data collection vs. database studies
- Qualitative vs. quantitative studies
- Descriptive vs. etiologic studies
- Small hospital based vs. large population based studies
- Questions related to patients vs. health care policy or economics
- Multiple disciplines involved: clinical medicine, pharmacology, epidemiology, biostatistics, medical informatics, behavioral and social sciences health services and outcome research, health economics

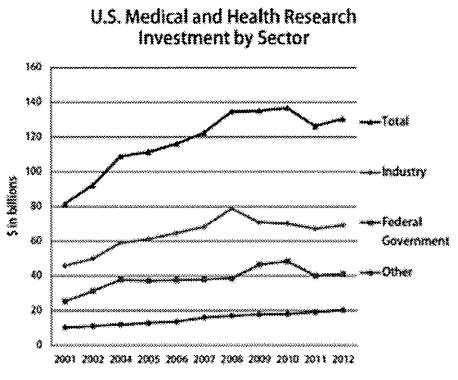
資金

USA

- $130 billion dollars (約1300億ドル) in 2012 per year including basic and clinical research
- Funding sources
  - Industry>government> others

JAPAN

- ?? 円



http://www.researchamerica.org/uploads/healthdollar12.pdf

2012 Total: Estimated U.S. Medical and Health Research Expenditures 130,383

	2010	'10-'11 Change	2011	'11-'12 Change	2012
National Institutes of Health	34,829	-14.4%	29,831	0.6%	30,012
Department of Defense (medical research, chemical and biological defense)	2,667	-12%	2,346	2.8%	2,412
Department of Homeland Security (biodefense)	2,372	-91.0%	213	9.9%	234
Department of Agriculture (Agricultural Research Service, National Institute of Food and Agriculture, Economic Research Service)	2,168	-19.8%	1,754	11.3%	1,953
National Science Foundation (biological sciences, bioengineering, behavioral sciences, computer and information science and engineering)	1,753	0.4%	1,760	17.9%	2,075
Department of Energy (biological and environmental research, advanced scientific computing research)	1,037	-3.1%	1,005	1.5%	1,020
Environmental Protection Agency (clean air, clean water, health and human ecosystems, pesticides and toxics)	596	-2.3%	582	-2.4%	568
National Institute of Standards and Technology	588	-9.5%	532	4.7%	557
Department of Veterans Affairs (medical and prosthetic research)	581	-0.2%	580	0%	580
Agency for Healthcare Research and Quality	420	-5.2%	398	-1.0%	394
Centers for Disease Control and Prevention (disease control, research and training)	363	25.9%	457	-10.7%	408
Food and Drug Administration	248	2.4%	254	59.8%	406
NASA (Human Research Program)	182	-14.8%	155	1.9%	158
U.S. Agency for International Development	158	0%	158	19.0%	188
Administration for Children and Families (children's research)	43	-4.7%	41	-75.6%	10
Ctrs. for Medicare & Medicaid Services (health services research, demonstration, evaluation)	27	33.3%	36	-47.1%	21
Health Resources and Services Administration	8	42.9%	12	0%	12
Patient Centered Outcomes Research Institute	—	–	1	700%	8
Subtotal	48,222	-16.8%	40,115	2.2%	41,016

Patient-Centered Outcome Research Institute (PCORI)

- With the Patient Protection and Affordable Care Act, the Patient-Centered Outcomes Research Institute (PCORI) was established (March 2010)
- Funding for FYs 2014-2019 averages $650 million(65億ドル) per year.
- PCORI just announced for >$200 million (20億ドル) funding opportunities for Spring 2014 cycle

Other Sources					
Universities (institutional funds) (2011)	11,198	6.2%	11,897	4.6%	12,445
State and Local Government (2011)	3,647	5.7%	3,854	-0.9%	3,819
Independent Research Institutes (institutional funds)	1,259	2.1%	1,285	19.7%	1,538
Philanthropic Foundations (2011)	854	-13.7%	737	79.4%	1,322
Voluntary Health Associations	887	14.9%	1,008	6.5%	1,074
Subtotal	**17,835**	**5.3%**	**18,781**	**7.5%**	**20,198**

データソース

USA

- クレームデータ、レジストリ、コホートデータなどいろいろなデータが存在
- Big Dataは、はやり言葉
  - データリンケージ、ゲノムデータ、電子カルテの普及でデータはどんどん大きくなっている

JAPAN

- NDB
- レジストリ
- コホートデータ

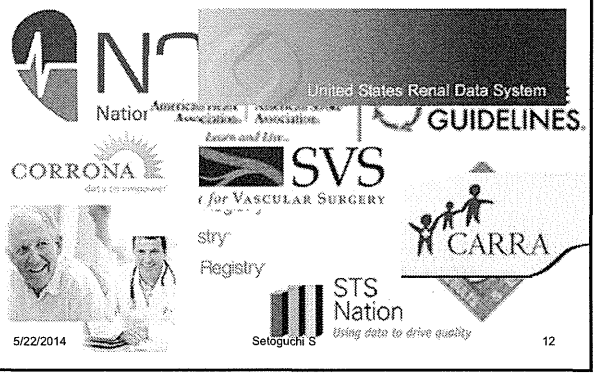
Administrative Databases

- **Claims databases or health care utilization databases'**
- **Examples in North America**
  - 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

電子カルテ(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
    - Kaiser Permanente

レジストリ- 例



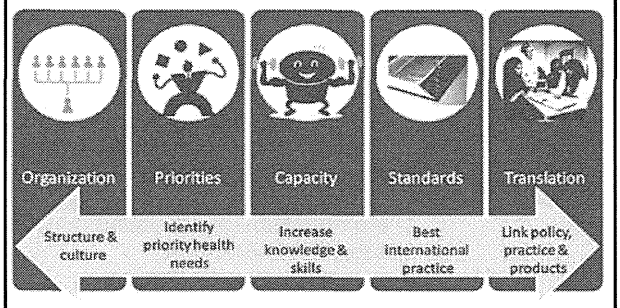
経験、人材
(データベース研究に関して)

USA

- 1970年代からデータベース研究が行われてきている
- 多数の関連分野の大学院があり(例:>44の公衆衛生大学院、75の医療管理学校)があり関連分野の研究者を要請してきている
- 研究をサポートするスタッフを育成、雇用するだけのリソースがある

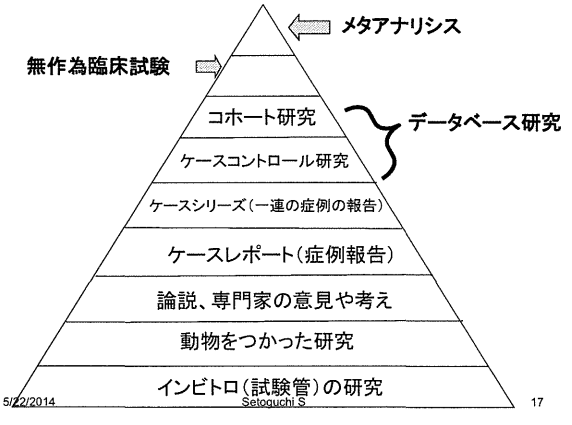
JAPAN

- クレームデータベースの構築と使用は過去10年程度？
- 公衆衛生大学院は10以下？
- リソース不足でサポートスタッフが少ない？



医療機器評価における
データベースの役割

市販前臨床試験と
医療機器の効果と安全性



RCTの長所と短所

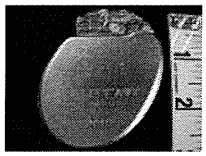
無作為臨床試験

長所	短所
無作為化により比較グループが似通っており交絡のリスクがほとんどない	費用や手間がかかる
確立された手法に基づいておこなうことができる	倫理的問題のため行えない場合もある
薬の効果を証明するためのゴールドスタンダードと考えられている	比較的小規模、短期間である 患者や併用療法の多いもの、子供、妊婦などが除外されやすい 通常の現場での医療とRCTの環境が異なる プラセボ比較はしばしば臨床の経験には不適切 臨床アウトカム(死亡やイベント)でなくサロゲートアウトカム(例えば血圧、コレステロール値)を比較することも多い

Avorn, NEJM 2009より抜粋、一部変更

埋め込み型除細動器

Implantable Cardioverter Defibrillator (ICD)



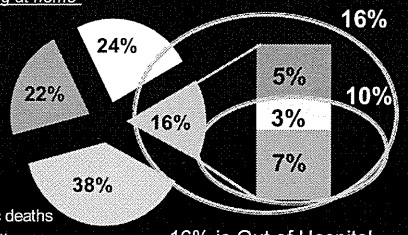
- 心不全の患者は不整脈による突然死のリスクが高い
- ICDは、臨床試験で収縮器障害のある心不全患者で突然死の予防に効果があることがしめされている
- CMS は2005年にメディケアの心不全患者でで突然死の一次予防の為のICDのしよををカバーすることを決定
- ICDの臨床効果は、はっきりしない
  - 高齢者
  - 多発併発疾患患者
  - 実際の医療の現場での使用

Patients in RCT vs. Medicare

	SCD-HeFT (n=829)	Medicare (n=68,087)
Median Age	60	76
Male	77%	73%
White	77%	88%
Median EF %	24	25
Systolic BP	118	130
Diabetes	31%	50%
Atrial fibrillation	17%	51%
Pulmonary disease	21%	46%
Ischemic cause HF	52%	73%
NYHA I	0	6%
NYHA II	70%	30%
NYHA III	30%	59%
NYHA IV	0	5%

Causes of 7,401 Deaths

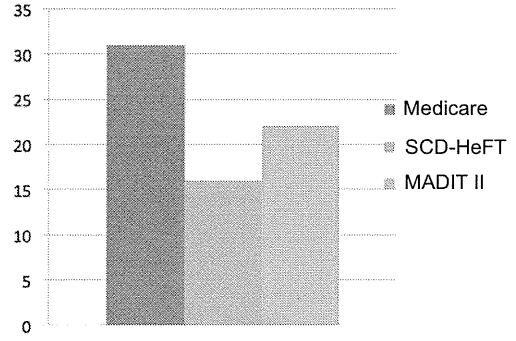
Only 10% of all deaths occurred from presumed cardiac causes in patients living at home



- IH non-cardiac deaths
- IH cardiac deaths
- OOH non-cardiac deaths
- OOH death presumed cardiac occuring in residential nursing home
- OOH death presumed cardiac deaths in home support/other
- OOH death presumed cardiac occuring in independent living settings

16% is Out of Hospital (OOH) Cardiac Death

3-Year Morality in Medicare vs. Trials Patients



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Quiz 1

- RCTのエビデンスを適応する場合考慮しなければならないことは何か？
  - a. *患者が選択的である*
  - b. *比較的小規模でフォローアップが短い場合ある*
  - c. *老人や併発疾患を含むものを除外する傾向がある*
  - d. *臨床的に意味のあるアウトカムを評価してるかどうか*
- 答え
  - *上記すべて*

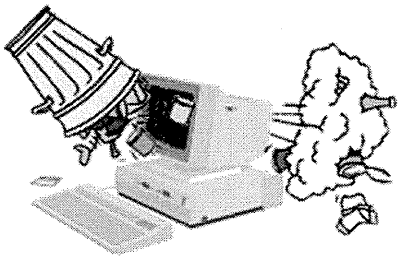
データベース研究と医療機器評価

観察研究	
長所	**短所**
臨床の現場で見られるような患者を数多く数調査できる	交絡バイアスの可能性がある（データ、デザイン、分析方法に大きく影響される）
コスト、時間ともに無作為臨床試験と比べて低い	選択バイアスの可能性がある（データ、デザイン、分析方法に大きく影響される）
稀な副作用を同定できる	誤分類によるバイアスの可能性がある（データ、デザイン、分析方法に大きく影響される）
長期にわたって観察調査可能である	手法が単純でなく、よい研究を行うのは容易でない
プラセボではなく、他の薬剤との比較が可能である	
死亡や入院など臨床アウトカムを観察することができる	

Avorn, NEJM 2009より抜粋、一部変更

アメリカのレセプトデータベース＝クレームデータ

Garbage-In Garbage-Out ??



クレームデータに対する誤った認識

- データの特性と疫学手法の原理の理解不足
- 他のデータ（電子カルテデータ、臨床試験データなど）の問題点を認識していないか過小評価
  - –臨床データ＝よいデータ
  - –それ以外はダメ

医薬品・医療機器評価に望ましいデータの特徴

1. 大規模かつ長期にわたる
2. ポピュレーションベースである（RCTのように選択的な患者層でない） Mostly OK
3. 詳細、正確、かつ時系列な治療や診断のデータ（暴露データ）

1. 正確なイベントやアウトカムのデータ Partly OK
2. 正確な交絡因子にや効果修飾因子関するデータ

クレームデータの欠点

- データは、医療費の支払い目的で作られたもの
  - – 生のデータをそのままつかえない
- 臨床データがない
  - – 検査の結果、診察の所見、症状など

完璧なデータベースはある？

レジストリ

	Registry data	
Pros	-Detailed information on the target device -Detailed clinical information relevant to the target device -Probably representative of populations for large, national registries	重要な臨床の情報を詳細に含む（特に標的疾患や手技に関して）
Cons	-No or few follow-up data -No or limited information on health conditions that is not relevant to the target device -Data quality depends on the resource available -Missing data	フォローアップデータが限られている 薬剤や医療機器の情報が不完全 標的疾患・手技外の情報が限られている

電子カルテにおける薬剤の情報の例 (N=16,599)

薬品名	Identified by non-NDC codes
処方日・調剤日	(no missing)
投与量	(8,411 missing)
投与期間	Not included

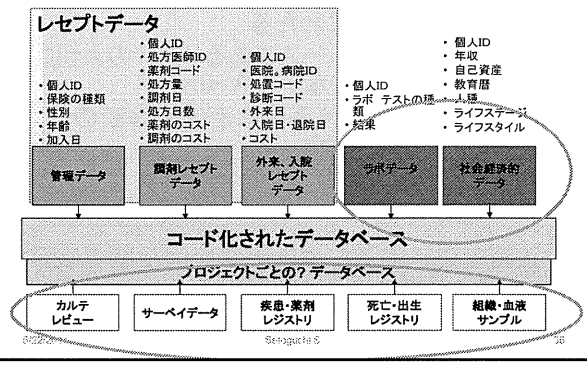
どのようにしてデータベースの欠点を克服するか？

- データを知る
- デザインの創意工夫
- 分析方法の適切な選択と創意工夫
- データの改善

データの改善

- すべてのデータベースには利点と欠点があり完璧なデータはない
- より完璧なデータベースをつくるにはお金と時間がかかる
  - 現存のデータベースをリンクすることで新しいよりよいデータベースをつくる。（データベースのリンケージ）
  - 既存のデータベースに追加情報をつけくわえる。（カルテ照合、患者サーベイ、追加のラボデータ）
- それぞれ利点を生かした（欠点をカバーする）複合データベースがよりよい研究を生み出す

レセプトデータを超えて



レコードリンケージ

- Deterministic or exact record linkage
  - 1つ以上のマッチする項目(例えば、SSNとMedicare ID)が完全に一致するレコードをリンクする。
  - SSNなどのUnique Personal identifiersが必要
  - SSNにタイプミスなどがあれば、間違ったリンケージになる、あるいはリンクできなくなる
- Probabilistic linkage
  - 複数の項目がある一定の確率で一致するという条件でレコードをリンクする。
  - レジストリでは、タイプミスは良くあることなので、実際にはこの方法のほうがリンケージ率がよくなる可能性が高い。

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リンケージに患者特有のIDが必ずしも必要か？

- 患者特有のID
  - *SSN, Medicare ID etc*
- 入院レコードは複数の非特有のIDを使ってリンクできる
  - *生年月日、性別*
  - *診療情報: 入院日、退院日、入院診断、手技、病院や医師の情報*
  - *ポイントは、レコードを'ユニーク'にする為に必要な情報を組み合わせること*

特有のIDがない場合とある場合のレコードリンケージを比較

Linkage Rules	# of 1-1 linkage	Sen.	Spec.	PPV
R1: Gender, DOB, Adm. Date, Provider ID	136,117	95	98	98
R3: Gender, DOB, Adm. Date, **Provider State**	135,537	89	91	93
R4: Gender, DOB, Adm. Date	5	0	100	0
Gold-Standard: SSN, Provider ID, Adm. Date	136,511	ref	ref	ref

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Quiz 2

- レコードリンケージについて正しいものを選びなさい
  - a. *レコードリンケージはデータを改善し、よりよい臨床研究を可能にするかもしれない*
  - b. *レコードリンケージには、大きく分けて、確定的リンケージと確率的リンケージの2つがある*
  - c. *レコードは、固有IDがなければ、高い精度で突合することはできない*

a. 答え
  - *a とb*

医療機器評価手法の特殊性

医療機器評価の手法の特殊性

- データベースにおけるデバイスの同定
- 医療機器評価で気をつけるべきバイアス
  - 適応という交絡
  - 選択バイアスーhealthy candidate bias
- プロバイダーに関する考慮

データベースにおける医療機器の同定

クレームデータでの薬剤の同定

NDC	Disp_dt	Days supply	Qty dispensed
62794014501	2-Feb-04	30	30
62794014501	12-Mar-04	30	30
62794014501	7-Apr-04	30	30
62794014501	27-Jul-04	25	25

クレームデータでの薬剤の同定

NDC	NDC description	Disp_dt	Days supply	Qty dispensed
62794014501	Digitek 125mcg Tablet	2-Feb-04	30	30
62794014501	Digitek 125mcg Tablet	12-Mar-04	30	30
62794014501	Digitek 125mcg Tablet	7-Apr-04	30	30
62794014501	Digitek 125mcg Tablet	27-Jul-04	25	25

National Drug Code (NDC) でわかること

- Dosage form
- Route of administration
- Active and inactive ingredients
- Manufacture
- Strength
- Package size and type
- Major drug class

etc....

クレームデータでの医療機器を同定

ICD-9 Procedure codes	CPT codes	Admission Date	Procedure Date
37.94	33249	25-May-04	25-May-08

医療機器の同定

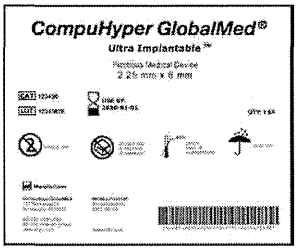
ICD-9 Procedure codes	CPT codes	Admission Date	Procedure Date
Implantation or replacement of automatic cardioverter-defibrillator, total system	Insertion or replacement of permanent pacing cardioverter-defibrillator system with transvenous lead(s), single or dual chamber	25-May-04	25-May-08

埋め込み型の医療機器のクレームデータにおける同定

- No information on
  - Manufacture
  - Model
- Insertion vs. replacement?
- Single vs. dual chamber?

We Currently Lack Essential System to Identify Devices with Sufficient Accuracy and Details

Unique Device Identifiers (UDIs)



- A UDI is a unique numeric or alphanumeric code
  - a device identifier (DI), a mandatory, fixed portion of a UDI that identifies the labeler and the specific version or model of a device
  - a production identifier (PI)
- FDA released the final rule and will be require for most medical devices

http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/UniqueDeviceIdentification/default.htm

UDIができれば医療機器が正確に同定できるようになる？

1. Will it be recorded in EHR?
2. Will it be recorded in registries?
3. If recorded, will it be complete and accurate?

How Drugs are Identified in National Registries

Registry	Generic name or class	Brand name	Dose	Quantity	Formulation	Longitudinal?	NDC
ACC NCDR ICD Registry	√	No	No	No	No	At discharge	No
AHA GWTG HF Registry	√	No	No	No	No	On admission	No
	√	No	optional	No	No	At discharge	No
ACC NCDR CARE Registry	√	No	No	No	No	Pre, intra, and post-procedural	No
SVS Vascular Registry	√	No	No	No	No	Pre procedural	No

Missing or Invalid Values in A Device Registry are More Common for Long Strings of Digits

	ICD Registry (N=264,918)
UDI has to be machine-read into a hospital data system And transferred to a registry directly from EHR	
Social security number (9 digits)	11,089 (4.3%)
Provider ID (10 digits)	17,881 (6.7%)
Date of birth	7 (< 0.01%)
Gender	381 (< 0.01%)

電子カルテにおける薬剤の情報の例 (N=16,599)

薬品名	Identified by non-NDC codes
処方日・調剤日	(no missing)
投与量	(8,411 missing)
投与期間	Not included

Duke Clinical Research Institute

Quiz 3

- データベースにおける医療機器の同定について正しいものを選びなさい。
  - a. *現状では、すべての電子カルテやレジストリで、医療機器の詳細が標準コード化されて記録されている。*
  - b. *現在のシステムでは、クレームデータでは、ブランド名、モデルなど、細かい情報は同定できない。*
  - c. *現状では、医療機器では、薬品におけるNDCのような標準化されたコードが存在しない*

a. 答え
- *b と c*

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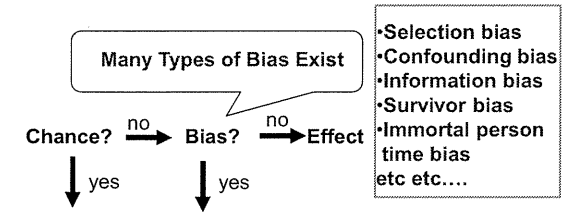
医療機器評価で考慮すべきバイアス

とくに
Confounding by indication
Healthy user biasについて

医療機器評価においても、疫学全般で問題とされているバイアスはすべて考慮するべき



Does not reflect effectiveness!

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埋め込み型除細動器は、老人や併発疾患の多い患者でも効果があるか?

- Study design: データベースを使った後ろ向きコホート研究
- 特に問題になる可能性がある2つのバイアス
  - Patients selected for ICDs have severer HF e.g., lower EF, worse NYHA class, etc. (confounding by indication)
  - Patients selected for ICDs are healthier in general? (healthy user effect– a form of selection bias or unmeasured confounding)

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Confounding by indication

- Do patients receiving ICDs have severer heart failure?
  - ICDs are indicated for HF with low ejection fraction, <35%
  - Compare patients with ICDs vs. no ICDs before or after applying indication criteria for primary ICDs (restriction)
    - Age > 65, 1 year Medicare eligibility
    - EF <35%, no prior cardiac arrest, no other life-threatening diseases

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Confounding by indication with and without indication criteria

	Without eligibility criteria	
	ICD=0 (N=535,885)	ICD=1 (N=4,990)
Age	70	76
Male	56%	71%
White	76%	75%
Ejection fraction	48%	25%
Systolic BP	138	127
BNP	524	561

Healthy User Bias

Users of preventive or newly marketed 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?

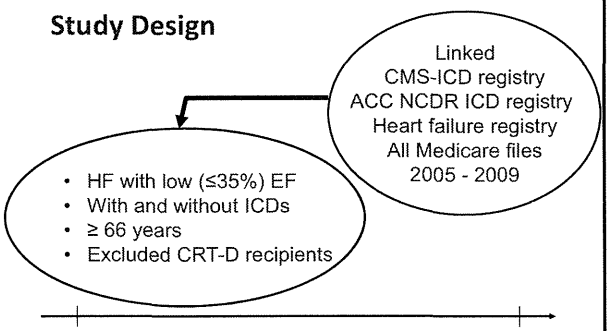
ICDが大腿骨骨折と老人ホーム入院を防ぐ?

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

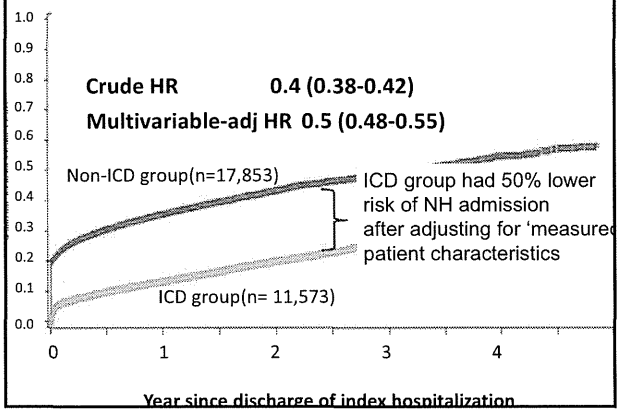
Therefore

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

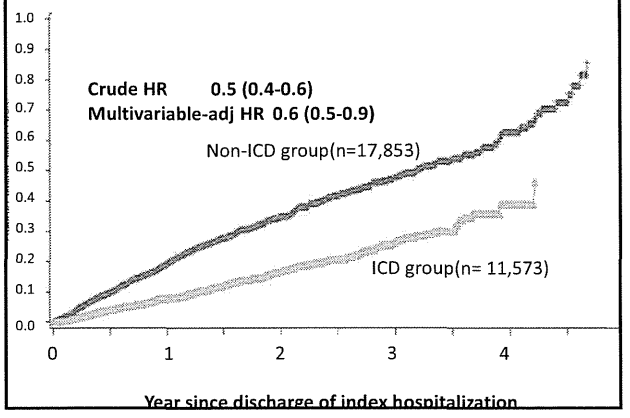
Study Design



ICDと老人ホーム入院の関係?



ICDs と大腿骨骨折



プロバイダーの特徴と技量をどう評価して考慮するか?

Potential Effect of Provider on Outcomes for Medical Devices

- Operating Physician
  - Demographics
  - Specialty
  - Training
  - Time since graduation
  - Familiarity with procedure/device
- Intervention Setting: Hospital
  - Hospital type
  - Teaching affiliation
  - Location
  - Familiarity with procedure/device

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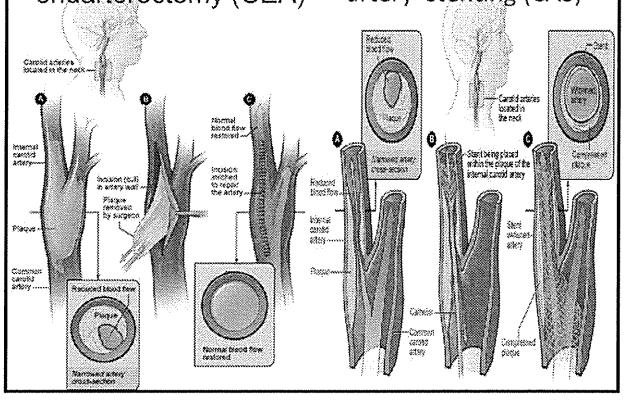
頸動脈剥離術 Carotid endarterectomy (CEA)　頸動脈ステント Carotid artery stenting (CAS)



Provider Experience in RCTs

RCT	Physician Experience	Hospital experience
SAPPHIRE, 2004	CEA: low complication rates (median 30 CEA/year) CAS: low complication rates (median ≥64 CAS)	Not mentioned
ICSS, 2010	Low complication rates for CAS/CEA	Not mentioned
CREST, 2010	CEA: ≥ 12 CEA/year + low complication rates CAS: low complication rates (~30 CAS)	CEA: ≥ 50 CEA/year + low complication rates CAS: Not mentioned

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Real-World vs. RCTs CAS Patients

	Medicare N=33,108	SAPPHIRE N=159	ICSS N=828	CREST N=1262
30-Day Mortality Risk	1.9%	0.6%	1.3%	0.7%
Mean Age +/- SD	76 +/- 6	73 +/-8	70 +/-9	69 +/- 9
% Men	60	67	70	64
% Hypertension	96	86	69	86
% Dyslipidemia	89	79	61	83
% Diabetes Mellitus	56	25	16	31
% Prior CABG	23	43	13	20

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Figure 1: Distribution of Past-Year CAS Volume Among Physicians (N=2,815)

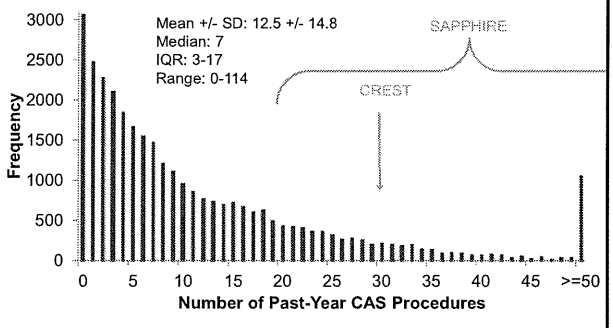

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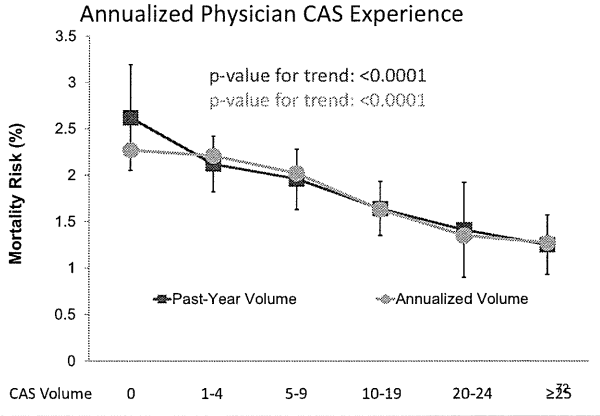
Figure 3: 30-Day Mortality Risk by Past-Year and Annualized Physician CAS Experience



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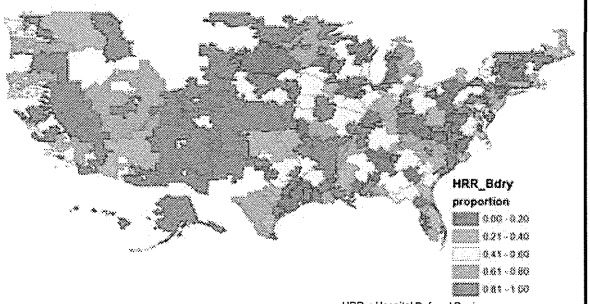
Proportion of CAS Procedures in HRRs
Performed in Hospitals with <20 Past-Year CAS
(2007 – 2008)



HRR = Hospital Referral Regions
From the Dartmouth atlas of health care
http://www.dartmouthatlas.org/data/region/

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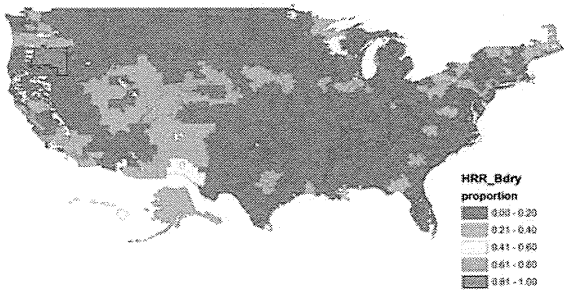
Proportion of CEA Procedures in HRRs
Performed in Hospitals with <20 Past-Year CEA
(2007 – 2008)



HRR = Hospital Referral Regions
From the Dartmouth atlas of health care
http://www.dartmouthatlas.org/data/region/

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CEAとCASではプロバイダーの技量が違う、これらの比較効果をする場合は技量を交絡因子として調整するべきか？

- Failure to evaluate account experience in CER of CAS vs. CEA may result in
  - Residual confounding
  - Treatment effect heterogeneity
- Do you agree?

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2つの手技のプロバイダーの技量の違いは交絡か?

- たとえば、薬剤の効果を評価する場合にコンプライアンスをどう考慮するか？と同様な疑問
- どう扱うかは、分析の目的による

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Quiz 3

- データベース研究で医療機器の安全性や効果を評価する際に考慮すべきバイアスについて正しいものを選びなさい。
  - a. *交絡バイアス*
  - b. *選択バイアス（特に健康志向バイアス）*
  - c. *情報バイアス*
  - d. *Immortal person time bias*
  - e. *サバイバーバイアス*
- 答え
  - *すべて*

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まとめ

- RCTからのエビデンスのギャップを埋めるため、医療機器の評価に、大規模データベースが使用されている
- 研究者は、データベースの利点と欠点を理解し、リンケージによるデータ改善の可能せや、バイアスを考慮しながら、医療器評価の研究を行う必要がある

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まとめ

- 医療機器評価で特に考慮するべき手法の問題点としては
  - データベースにおける医療機器の同定の精度
  - 適応や重症度による交絡
  - 健康は埋め込み手術候補者バイアス
  - プロバイダー情報の評価と取り扱い

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
Takahide Kohro, Tsutomu Yamazaki, Hiroki Sato, Kenji Harada, Kazuhiko Ohe, Issei Komuro, Ryozo Nagai	Trends in Antidiabetic Prescription Patterns in Japan From 2005 to 2011	International Heart Journal	54(2)	93-97	2013
山崎 晶司, 吉尾 卓, 苅尾 七臣, 浜本 敏郎, 星出 聡, 小出 大介	アカデミアにおける治験・臨床研究に関する教育の実態調査.	臨床薬理	44巻Suppl	S315	2013
小出 大介、山崎 力	職種・レベル別に対応した安全な臨床研究・治験のためのe-learningシステムの開発	東大病院先端医療開発フォーラム		p99	2014
小出 大介	e-learning のコンテンツ　何が必要	日本臨床試験研究会 第５回学術集会総会プログラム・抄録集		p28	2014

Trends in Antidiabetic Prescription Patterns in Japan From 2005 to 2011

Impact of the Introduction of Dipeptidyl Peptidase-4 Inhibitors

Takahide KOHRO,[1] MD, Tsutomu YAMAZAKI,[2] MD, Hiroki SATO,[3] MSc, Kenji HARADA,[4] MD, Kazuhiko OHE,[5] MD, Issei KOMURO,[6] MD, *and* Ryozo NAGAI,[7] MD

SUMMARY

There have been few reports concerning the trends in antidiabetic drug use in Japan. In 2009, a dipeptidyl peptidase-4 inhibitor (DPP4I), an antidiabetic with a new mechanism of action, was made available. This study was conducted to analyze the antidiabetic prescription trends in Japan in recent years and the influence of DPP4Is on those trends. We used monthly claims data obtained from a database company. Data from patients 20 years of age or older and who were prescribed antidiabetics were extracted and analyzed. A total of 18,457 patients were prescribed antidiabetics (mean age, 53.6 ± 11.0). The sulfonylurea prescription rate decreased while that of biguanides increased. After the introduction of DPP4Is, use of these agents rapidly increased and the rate further increased one year after DPP4I introduction. DP-P4Is also became the most prescribed antidiabetics for those prescribed antidiabetics for the first time. The decrease in the use of sulfonylureas and the increase in the use of biguanides are in accordance with trends observed in the United States and Europe, and probably reflect Japanese physicians' awareness of cumulating evidence gained from studies such as the UK Prospective Diabetes Study (UKPDS). The rapid increase in the DPP4I prescription rate might be the result of several factors including their safety profiles, which were highlighted in clinical studies published just prior to the drugs becoming available. However, there is little data regarding the efficacy of DPP4Is in reducing diabetes related complications, which should be determined in future studies. (Int Heart J 2013; 54: 93-97)

Key words: Clinical guidelines, Antidiabetics, Dipeptidyl peptidase-4 inhibitor, Prescription trends

The goals of diabetes mellitus (DM) therapy are to prevent microvascular and macrovascular complications of hyperglycemia. Numerous clinical studies have been performed to compare the effectiveness of different drugs or to investigate the optimum level of blood glucose, and clinical guidelines have been built upon this evidence. However, there have been difficulties in the history of DM treatment. For example, sulfonylureas (SUs) are the oldest and most widely used oral antidiabetic agents because of their demonstrated blood glucose lowering effect, but there is some evidence that they can potentially damage pancreatic beta-cells,[1-3] which may cause secondary failure over time.[4] Several studies have shown that biguanides are also effective at lowering blood sugar and that they preserve beta-cell function.[5-8] It was also shown that metformin may be associated with fewer DM-related adverse events compared with other antidiabetics,[9] although it is still controversial. However, phenformin, which was the only biguanide available in the United States, was withdrawn from the market in the late 1970s because it was found to be associated with lactic acidosis with a high fatality rate. The withdrawal of phenformin negatively affected the use of biguanides in Japan. Biguanides were re-introduced into the US after a study demonstrated the safety and efficacy of metformin.[10] Thiazolidinediones (TZDs) were introduced in the 1990s, but each had its own problems. Troglitazone was withdrawn from the market because of the associated side effect of severe hepatitis. Recently, an association was suspected between rosiglitazone and increased myocardial infarction,[11] and while rosiglitazone has not been withdrawn from the market in the US, its use has been limited. In addition, pioglitazone was reported to be associated with an increased risk of bladder cancer.[12]

There have been several reports addressing the optimal blood sugar target level, and these reports have suggested that maintaining strict blood sugar control results in a smaller risk of microvascular complications.[13,14] However, no study has shown definitively that intensive lowering of blood glucose reduces the incidence of macrovascular complications such as

From the [1] Department of Translational Research for Healthcare and Clinical Science, Graduate School of Medicine, The University of Tokyo, [2] Clinical Research Support Center, The University of Tokyo Hospital, [3] Department of Preventive Medicine and Public Health, National Defense Medical College, Departments of [4] Health Care Safety Management, [5] Medical Informatics and Economics, Division of Social Medicine, and [6] Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, and [7] Jichi Medical University, Tochigi, Japan.

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Address for correspondence: Takahide Kohro, MD, Department of Translational Research for Healthcare and Clinical Science, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo, Tokyo 113-8655, Japan.

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myocardial infarction or stroke. Three recent studies compared normal versus intensive blood glucose lowering, and these studies questioned the effectiveness of strict blood glucose control.[15-17]

In 2009, and for the first time in 10 years, antidiabetic agents with a new mechanism of action were introduced; these agents were dipeptidyl peptidase-4 inhibitors (DPP4Is) and glucagon-like peptide-1 (GLP-1) analogues.

Unlike the guidelines published by the American Diabetes Association (ADA) or the European Association for the Study of Diabetes (EASD),[18,19] the clinical guidelines published by the Japan Diabetes Society (JDS) do not explicitly state which oral agent should be used as first line therapy for newly diagnosed type 2 DM patients. Thus, we investigated the prescribing trends for antidiabetic agents in recent years in Japan, and the impact of DPP4Is on these trends. To perform this research, we analyzed information, collected in Japan from 2005 to 2011, in a large claims database.

Methods

Data source and management: Monthly claims data (from January 2005 to October 2011) were obtained from a database company called Japan Medical Data Center (JMDC).[20,21] The population covered by the database consisted of insurees and their dependents belonging to one of several health insurance unions in Japan. The database was expanded in 2008, 2009 and 2010, and subjects from different health insurance unions were added. For each patient, the data consisted of an encrypted personal identifier, age and gender, a description of the procedures performed, diagnosis name and diagnosis code according to the World Health Organization's International Classification of Diseases (ICD10), and prescribed drugs. Drug information included the month and year of prescription, brand name and generic name, dosage, and number of days prescribed. Of the total one million patients in the database, information on those patients whose diagnosis name included 'diabetes mellitus' at least once and who were 20 years of age or older was initially extracted. However, not all patients with a DM diagnosis were prescribed antidiabetics, so the group was restricted to those who were prescribed any kind of antidiabetic agent for at least one month (n = 18,457). Most prescription periods ranged from 14 days to 3 months. We determined the prescription rates for each class of antidiabetic per patient per month. To do this, multiple prescriptions for a given drug during a single month were counted only once. For prescription periods of two months' duration, data were generated for the month following the first month and they were added to the original database. For prescription periods of 3 or more months' duration, data were generated for the two months following the initial month and they were added to the original database. Patients who were treated for DM for the first time were identified as those who were insured for more than 3 months without any antidiabetic prescriptions and then were prescribed at least one type of antidiabetic agent for at least 3 months. Data from patients who had undergone coronary revascularization were extracted by searching the procedure database using codes representing either a form of percutaneous coronary intervention or coronary artery bypass graft operation. Data from patients who were on maintenance dialysis were extracted by searching the procedure database using a code representing a special fee for maintenance dialysis. Data from patients who were prescribed at least one type of antihypertensive drug or any of the statin drugs were extracted by searching the prescription database.

Statistical analysis: Analysis of covariance (ANCOVA) was used to test the slope equality of DPP4I usage trends between clinics and academic hospitals.

The average of continuous variables is shown as the average ± standard deviation. All P values for statistical tests were two-sided. All statistical analyses were performed using Stata 12.1 (Stata Corporation, College Station, TX, USA).

Ethical considerations: The data used in this study were completely de-identified and informed consent from the subjects was not necessary. This study was approved by the ethics committee of the University of Tokyo.

Results

Table I shows the patient background information. The mean age of the overall population was 53.6 ± 11.0 years, and the average age of females was slightly but significantly higher than that of males (P = 0.0001). There was a similar proportion of male (0.8%) and female patients (0.9%) who were on chronic hemodialysis (P = 0.417). The rate of coronary revascularization for males was nearly 3 times (2.2%) that of females (0.8%). A similar proportion of patients were prescribed at least one type of antihypertensive (51.0% for males, 50.1% for females, P = 0.233).

As shown in Figure 1, the use of SUs was declining and the use of biguanides was gradually increasing during the observation period. The use of alpha glucosidase inhibitors (GIs) abruptly decreased in January 2008, which is the result of adding a different population to the database. When addition of the new population was taken into account, the use of alpha-GIs remained almost constant until the end of 2009 and gradually

Table I. Patient Characteristics

	Total	Male	Female	P^a
n	18457	11991	6466	
Mean age	53.6 ± 11.0	52.3 ± 10.5	53.2 ± 12.8	< 0.0001[b]
Chronic hemodialysis	152 (0.8)	94 (0.8)	58 (0.9)	0.417[c]
Coronary revascularization	312 (1.7)	263 (2.2)	49 (0.8)	< 0.0001[c]
Antihypertensives	9356 (50.7)	6117 (51.0)	3239 (50.1)	0.233[c]
Statin	7531 (40.8)	4612 (38.5)	2919 (45.1)	< 0.0001[c]

Numbers in parentheses show the percentage of subjects in each group. a: test for the difference between male and female, b: tested by unpaired t-test, and c: tested by chi-square test.