表C2.2.1a
登録時HbA1c7.0%未満、以上の患者の背景,

	ALL	HbA1c <7.0%	HbA1c>=7.0%
年齢　平均(SD)	67(10)	68(10)	66(10)
性別（男性、%）	74%	77%	71%
BMI 平均(SD)	25（4)	25(4)	25(4)
糖尿病罹患歴年、平均(SD)	12(10)	10(10)	13(10)
喫煙者	23%	21%	27%
高血圧	80%	82%	78%
脳卒中既往	15%	16%	15%
心筋梗塞既往	37%	39%	37%
透析	10%	12%	6%
PCI	45%	49%	42%
CABG	10%	12%	10%

表C2.2.1b
危険因子管理状況と心腎機能

	All	HbA1c <7.0%	HbA1c>=7.0%
収縮期血圧mmHg, 平均 (SD)	134(22)	134(22)	134(3)
拡張期血圧	73(13)	73(13)	73(21)
脈拍 bpm, 平均 (SD)	75(14)	73(13)	76(15)
LDL-c mg/dl,平均(SD)	105(33)	101(32)	109(34)
中性脂肪	160(109)	142(89)	174(119)
HDL-c	46(13)	47(13)	46(13)
Hb A1c %, 平均 (SD)	7.3(1.3)	6.3(0.5)	8.2(1.2)
eGFR, 平均(SD)	59.6(26.5)	56.2(26.2)	63.0(26.0)
EF % 平均(SD)	59(13)	61(12)	60(13)
蛋白尿(%)	31%	28%	34%

表C2.2.1c
高脂血症薬と糖尿病薬

	All	HbA1c <7.0%	HbA1c>=7.0%
スタチン	65%	67%	64%
スタチン以外の高脂血症薬	6%	7%	7%
SU	37%	27%	46%
メトフォルミン	13%	9%	18%
ピオグリタゾン	16%	15%	18%
αグルコシダーゼ阻害薬	26%	24%	29%
グリニド	3%	4%	3%
インスリン	20%	12%	28%
DPP4 阻害薬	1.2%	1%	1.5%

表C2.2.1d
心血管薬、抗血小板薬等

	All (n=4248)	HbA1c <7.0% (n=)	HbA1c>=7.0% (n=)
アスピリン	90%	90%	90%
アスピリン以外の抗血小板薬	64%	66%	63%
ワルファリン	9%	10%	8%
Ca拮抗薬	42%	44%	41%
β遮断薬	39%	41%	38%
α遮断薬	3%	4%	2%
アンジオテンシンⅡ受容体拮抗薬	45%	46%	44%
ACE阻害薬	22%	20%	22%
利尿薬	26%	27%	25%
亜硝酸薬	28%	27%	28%
ニコランジル	31%	32%	31%

表C.2.2.1.2
主要評価項目および「個々の評価項目の発症数、率、ハザード比
登録時HbA1c 7.0 %未満と以上の比較

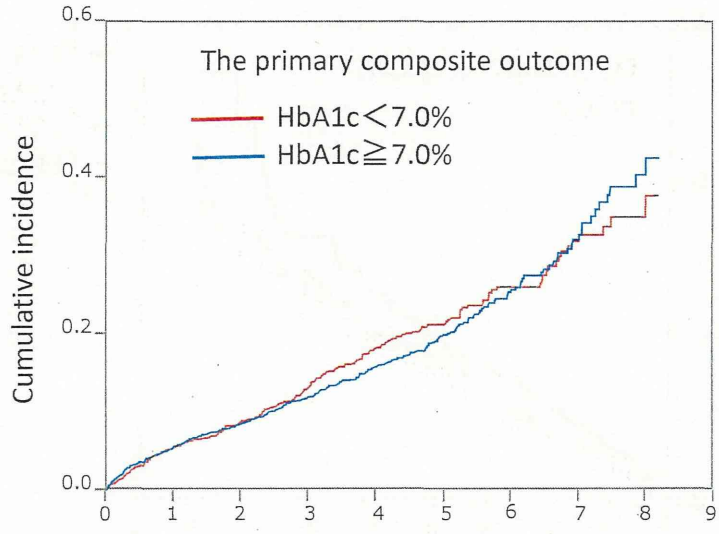
Outcome	All		HbA1c<7.0%		HbA1c≧ 7.0%		Hazard Ratio	95% C.I.	P value
	No. of Events	Event Rate per 1000 patient-year	No. of Events	Event Rate per 100 patients-year	No. of Events	Event Rate per 100 patients-year			
The primary composite outcome	630	49.1	294	50.3	336	48.1	0.95	0.82-1.12	0.5728
All cause death	446	34.8	210	35.9	236	33.8	0.94	0.78-1.13	0.4941
Non-fatal stroke	137	10.7	61	10.4	76	10.9	1.05	0.75-1.48	0.7728
Non-fatal myocardial infarction	91	7.1	40	6.8	51	7.3	1.08	0.71-1.64	0.7279

Abbreviation: C.I., confidence interval;

表2.2.1.3.
主要評価項目および「個々の評価項目の発症数、率、ハザード比
観察期間中の平均HbA1c 6.0 %未満、6.0-7.0%、7.0-8.0%, 8.0%以上の比較

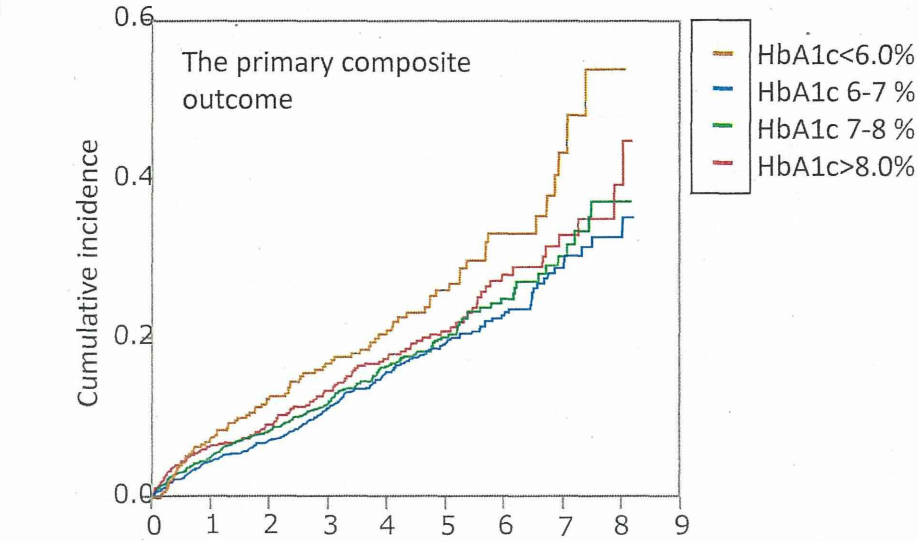
	Very intensive control (HbA_{1c} <6.0%)			Intensive control (HbA_{1c} 6.0-7.0%) Reference		Standard (HbA_{1c} 7.0-8.0%)			Uncontrolled (HbA_{1c} >8.0%)		
	No. of Events	Event Rate per 1000 patient-year	Hazard Ratio (95% C.I.)	No. of Events	Event Rate per 100 patient-year	No. of Events	Event Rate per 100 patient-year	Hazard Ratio (95% C.I.)	No. of Events	Event Rate per 100 patient-year	Hazard Ratio (95% C.I.)
The primary composite outcome	84	66.9	1.52 (1.18-1.94)	247	44.2	198	47.7	1.09 (0.90-1.31)	119	52.9	1.19 (0.95-1.48)
All cause death	60	47.8	1.51 (1.12-2.01)	177	31.7	137	33.0	1.05 (0.84-1.32)	83	36.9	1.15 (0.89-1.49)
Non-fatal stroke	20	15.9	1.72 (1.00-2.83)	52	9.3	45	10.8	1.16 (0.78-1.73)	26	11.6	1.24 (0.76-1.97)
Non-fatal myocardial infarction	10	8.0	1.27 (0.60-2.48)	35	6.3	26	6.3	1.00 (0.60-2.48)	21	9.3	1.49 (0.85-2.53)

図 C2.2.1.1.



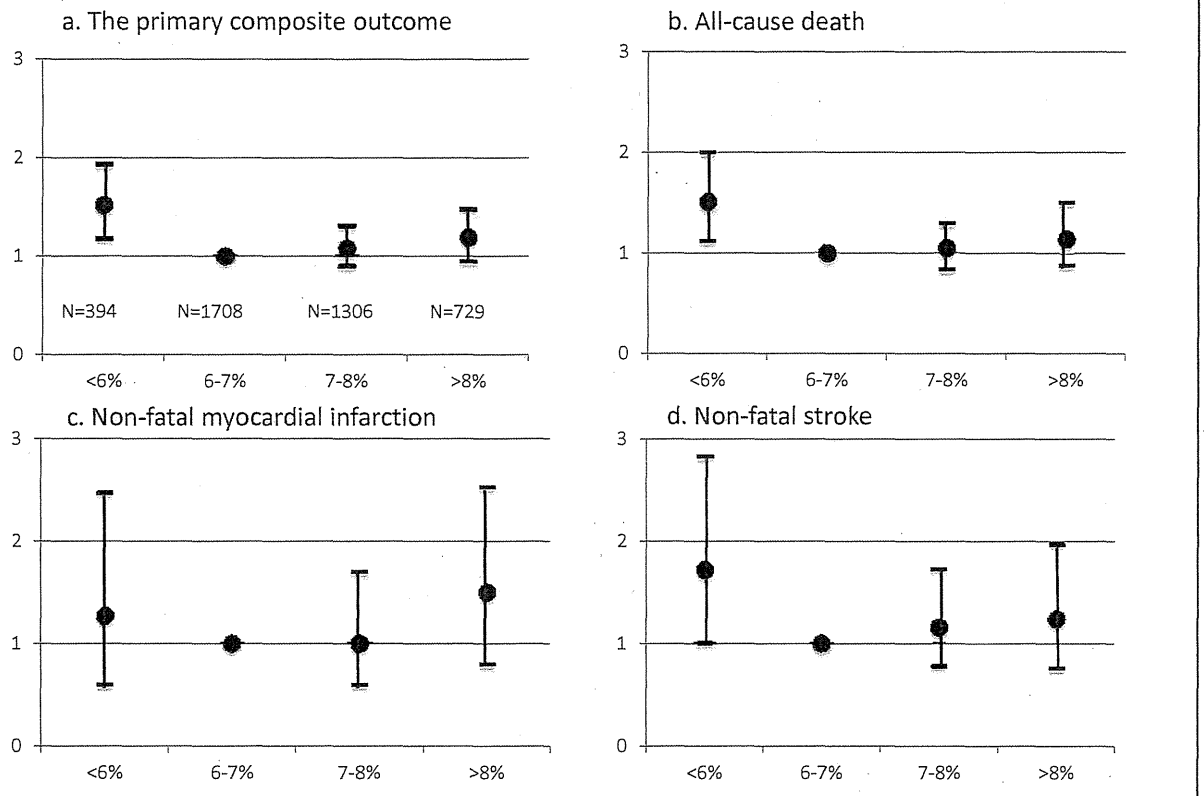
No.at risk									
HbA1c＜ 7.0 %	1878	1459	1206	977	678	408	191	83	21
HbA1c≧ 7.0 %	2153	1678	1437	1175	866	533	247	102	23

図C2.2.1.2a

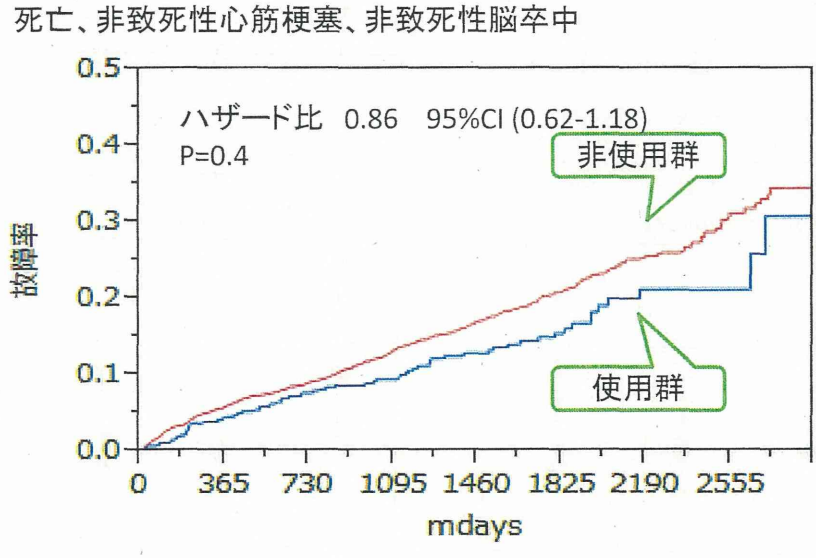


No. at risk									
HbA1c＜6.0%	394	310	252	204	153	94	49	14	1
HbA1c 6–7%	1708	1349	1156	952	657	416	196	87	23
HbA1c 7–8%	1306	1032	862	708	514	288	124	51	13
HbA1c＞8.0%	727	544	464	359	272	172	89	44	7

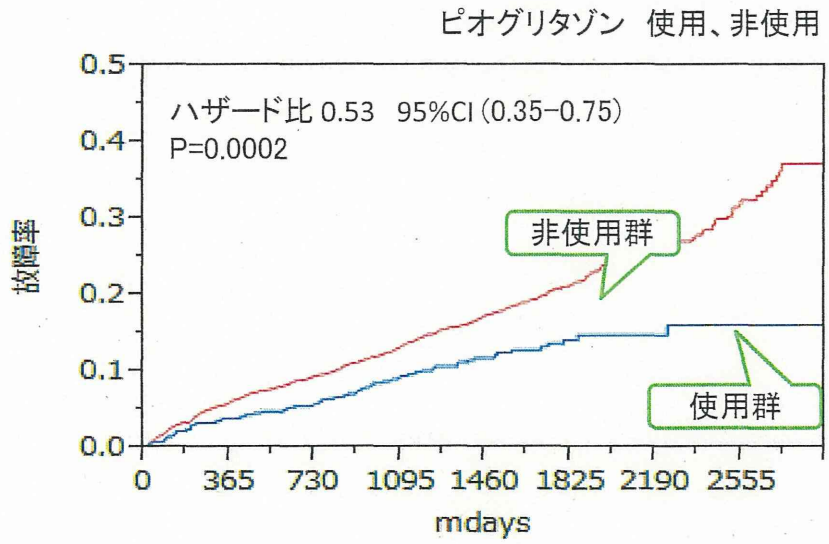
図C.2.2.1.2b


a. The primary composite outcome
b. All-cause death
c. Non-fatal myocardial infarction
d. Non-fatal stroke
3
2
1
0
N=394
N=1708
N=1306
N=729
<6%
6-7%
7-8%
>8%
Averaged hemoglobin A1c during follow-up

図C.2.3.1
メトフォルミン使用、非使用とアウトカム



図C.2.3.2
ピオグリタゾン使用、非使用とアウトカム



発表資料 1

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

EDITORIAL

Non-Statistical Key Issues in Conducting Sensible Observational Studies to Resolve Clinical Questions

Shinichiro Ueda, MD, PhD

"Life Is Not Complex. We Are Complex. Life Is Simple, and the Simple Thing Is the Right Thing." Oscar Wilde

Life is full of questions. Clinical practice is full of clinical questions. Physicians have many questions come across their minds when seeing patients ie 3 questions for every 10 patients they see,[1] although most questions, unfortunately, are left unanswered. To resolve such questions as quickly as possible, the best thing for us is to appropriately conduct clinical research. Some physicians think that observational studies are easier to conduct than randomized controlled trials (RCTs). This is true in some aspects but in other aspects, completely wrong. We have to bear in mind some key issues, which does not necessarily mean complicated multivariate analysis, for conducting sensible observational studies.

Article p2225

In this issue of the Journal, Minakata et al report the possible association of impaired renal function with poor outcome in patients after coronary artery bypass grafting.[2] I would like to emphasize that their success may be attributed to the registry of patients well constructed by the clinical questions they had, the patients and outcome they defined, and the variables they selected. Clinical studies based on registries have been increasingly published recently.[3,4] The key issues for registry-based observational studies are discussed in this editorial review.

Purpose of the Study and Clinical Questions

First of all, the most important issue in conducting any clinical research is to have a clear purpose; that is, sensible clinical questions from clinical practice. The quality of clinical research largely depends on the quality of the clinical questions and subsequent research hypotheses. There are roughly 2 types of clinical research (**Table**). Seeds-driven research examines the efficacy of new drugs for approval by regulatory agencies, whereas needs-driven research is intended to resolve clinical questions. The former needs a very strict study design. Efficacy of drugs should usually be tested in double-blind, RCTs with restrictive criteria for eligible patients and endpoints under the strict regulation and guidance (ICH-GCP) with few exceptions. Observational study design may fit the latter but RCTs also are applicable as pragmatic trials with less restrictive design. Pragmatic RCTs may also be fit for comparisons of strategies of care. For example, intensive control of cardiovascular risk factors such as blood pressure is better to be compared to standard control by a RCT rather than in a cohort study. Therefore, study design should be determined by the purpose of study not by a hierarchical "pyramid of evidence".

Definition of Patients and Outcomes

The target population on which the researchers will focus should be defined clearly according to the purpose of the study. As observational studies usually need a large number of typical clinical practice populations for sufficient statistical power and generalizable results, inclusion and exclusion criteria should be clear, simple but much less restrictive than in a RCT testing the efficacy of new drugs in similar patients. For example, the RELY trial was a phase III trial that the examined efficacy and safety of dabigatran for approval and the exclusion criteria of RELY trial consisted of more than 20 conditions,[5] whereas the cohort study comparing warfarin and dabigatran by FDA sentinel project had only 3 disease-related conditions as exclusion criteria.[6] Selected patient subgroups can also be predefined according to clinical questions but the feasibility of dividing patients into subgroups should be assessed. Outcomes are another part of clinical question. Outcomes in observational studies should be more (or equally) objective and severer than those in RCTs. When patients with atherosclerotic cardiovas-

Table. Types of Research

Seeds-driven research
· Evaluation of efficacy of new drugs for approval
· Principally double-blind randomized controlled trials
· Rigid study design
· Restrictive inclusion and exclusion criteria for maximization of efficacy and minimization of adverse event risk
Needs-driven research
· Clinical question based
· Comparison of effectiveness of treatments outside of clinical trial settings
· Comparison of strategies of care
· Evaluation of association between variables and outcomes
· Observational studies and pragmatic randomized controlled trials
· Less restrictive inclusion and exclusion criteria for representatives of clinical practice

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ISSN-1346-9843 doi:10.1253/circj.CJ-14-0826

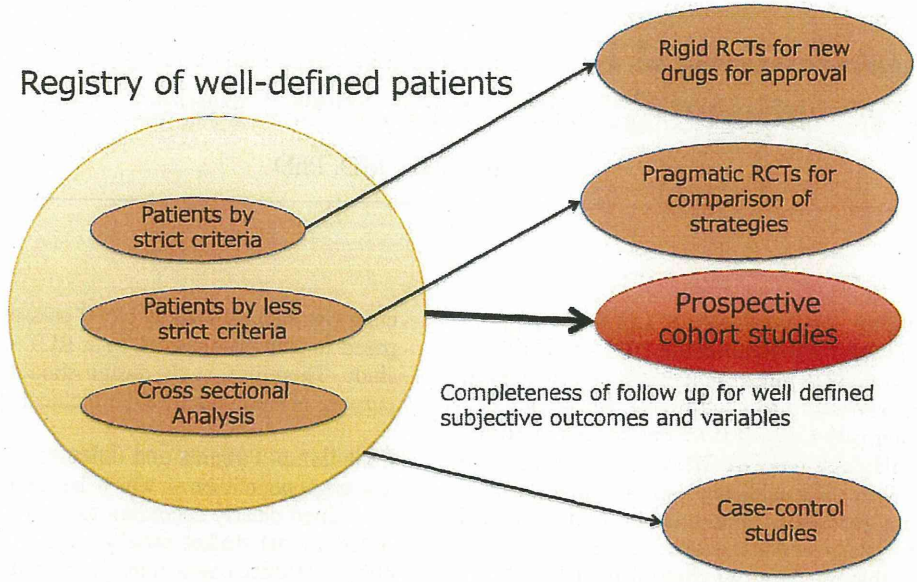


Figure. Well-constructed registrations of patients can be used as platforms for several types of clinical research.

cular diseases are focused on in observational studies, outcomes may be death, nonfatal myocardial infarction and nonfatal stroke, whereas double-blind RCTs are allowed to assess less objective and milder endpoints such as worsening of heart failure or angina. Outcomes in observational studies should also be easier to diagnose than in RCTs. Most diagnostic criteria in clinical trials appear to be unfriendly and cannot be translated for use in large observational studies like as inclusion and exclusion criteria. Improvement of feasibility, usually at lower cost than in pharmaceutical trials, at the expense of the precision of diagnosis may be acceptable traded off. A debate still lives on in terms of accuracy of case-specific mortality even in clinical trials.[7,8] Because fewer researchers contribute to observational studies than clinical trials and reporting cases with selected information carries unavoidable and unadjustable biases, intensive laboring to determine the cause of death in many cases, which may be more complicated than those in RCTs, may be impractical.

Variables

Because the aim of observational studies may principally be seeking a possible association of target variables with outcomes and confounding is a key threat to the validity of results, logical selection and definition of target variables (independent variables to be tested) and variables confounding results (confounders or adjusters) in accordance with the purpose of the study is necessary.

Registration of Patients and Collection of Their Information

Once the patient group is well defined, patients must be consecutively registered. Either intentional or unintentional exclusion of eligible patients causes a selection bias. Missing patients are usually not missing at random. Logically excluded patients from the registry should also be recorded and reported precisely with the reason of exclusion for validity of the summarized data and sensitivity analysis. An advantage of observational studies is inclusion of a population representative of clinical practice, so exclusion of patients may reduce this advantage. Recently developed data storage systems may help consecutive registration of patients through automatic data extraction systems. Care is needed, however, because coded diagnosis is not necessarily correct and therefore adequate validation of extraction system is absolutely required.

Registration of 3,000 patients receiving newly approved drugs as typical post-marketing surveillance in Japan has little value in terms of assessment of safety and efficacy because of intentional selection of patients, lack of comparators, and sometimes forced switching from drugs competing new drugs without any sensible clinical reasons. Such studies should not be regarded as proper observational studies but just seeding trials only for promotion of new drugs.

Relevant variables and outcomes also should be collected with similar caution. Reliability of results from prospective cohort studies may depend on completeness of follow-up. As mentioned before, missing variables and outcomes, which are not usually missing at random, may cause biases. Researchers, hopefully with biostatisticians and research coordinators, are advised to discuss which and how many variables and outcomes should be collected. Standard operating procedures for data collection and data management at participating sites and central data centers should be established. Although intensive monitoring of data, such as source document verification, done in the same way as pharmaceutical trials is difficult in observational cohort studies, central quality control of collected data at data centers by a biostatistician may improve the accuracy of results.

Registries of Patients as Platforms for Any Clinical Research (Figure)

Appropriately constructed registries of patients can be platforms for any clinical research. Prospective or even retrospective collection of well-defined outcomes and variables may allow researchers to conduct sensible cohort studies, case-control studies and cross-sectional studies based on one registry. Prop-

er data management and central statistical monitoring of registries by biostatisticians may improve the quality of data at lower cost. From this point of view, registries of patients can also be platforms for RCTs. In fact, the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial investigators recently successfully conducted a large, clinical question-based RCT at very low cost based on the platform of a well-constructed registry of patients.[9] Unlike pharmaceutical trials, researchers in academic trials are haunted by concerns about cost, enrolment of patients and quality control. Registry-based RCTs as well as observational studies may help researchers overcome such obstacles.

Disclosures

None.

References

1. Ely JW, Osheroff JA, Ebell MH, Bergus GR, Levy BT, Chambliss ML, et al. Analysis of questions asked by family doctors regarding patient care. *BMJ* 1999; **319:** 358–361.
2. Minakata K, Bando K, Tanaka S, Takanashi S, Konishi H, Miyamoto Y, et al. Preoperative chronic kidney dysfunction as a strong predictor for postoperative infection and mortality after coronary artery bypass grafting. *Circ J* 2014; **78:** 2225–2231.
3. Daida H, Miyauchi K, Ogawa H, Yokoi H, Matsumoto M, Kitakaze M, et al; PACIFIC investigators. Management and two-year long-term clinical outcome of acute coronary syndrome in Japan: Prevention of atherothrombotic incidents following ischemic coronary attack (PACIFIC) registry. *Circ J* 2013; **77:** 934–943.
4. Japanese Circulation Society Resuscitation Science Study Group. Chest-compression-only bystander cardiopulmonary resuscitation in the 30:2 compression-to-ventilation ratio era: Nationwide observational study. *Circ J* 2013; **77:** 2742–2750.
5. Ezekowitz MD, Connolly S, Parekh A, Reilly PA, Varrone J, Wang S, et al. Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. *Am Heart J* 2009; **157:** 805–810.
6. The U.S. Food and Drug Administration (FDA). A Protocol for Assessment of Dabigatran and Selected Safety Outcomes. http://mini-sentinel.org/assessments/medical_events/details.aspx?ID=219 (accessed July 25, 2014).
7. Gottlieb SS. Dead is dead: Artificial definitions are no substitute. *Lancet* 1997; **349:** 662–663.
8. Hauptman PJ. Does it matter why and how patients with heart failure die?: A debate that lives on. *Circ Heart Fail* 2008; **1:** 89–90.
9. Fröbert O, Lagerqvist B, Olivecrona GK, Omerovic E, Gudnason T, Maeng M, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med* 2013; **369:** 1587–1597.

発表資料 2

REGISTRY OF CAD PATIENTS WITH DIABETES

PRAGMATIC PLATFORM FOR SENSIBLE CLINICAL RESEARCH

世界の潮流を見据えた日本型臨床研究のあり方を探る

琉球大学大学院医学研究科　臨床薬理学
琉球大学医学部附属病院　臨床研究支援センター
植田真一郎

日本循環器学会 COI 開示

筆頭発表者名：　植田真一郎

演題発表に関連し、開示すべきCOI関係にある企業などとして、

講演料：日本ベーリンガーインゲルハイム、アステラス、田邊三菱、MSD、ファイザー、バイエル薬品工業
研究費：バイエル薬品工業、興和創薬、MSD、ブリストルマイヤーズ、アステラス、武田薬品工業、ファイザー

治験と臨床的疑問の解決に向けた研究の違い

新薬、未承認薬の薬効評価シーズ育成「治験」	診療の現場での臨床的疑問、ニーズに基づいた治験以外の臨床研究
・厳密なデザイン、RCT、二重盲検による承認申請を前提とした薬効評価 ・薬剤そのものの比較 ・厳しい選択除外基準 ・申請のための規制(GCP運用通知、ICH-GCPガイダンス) ・製薬会社、CRO、SMO、ARO? ・比較的潤沢な資金	・「薬効」よりも「有用性」や「安全性」 ・現実的なデザイン、RCTやコホート、しばしば非盲検 ・治療方針の比較、予後と変数の関連 ・緩やかな基準 ・倫理指針 ・医師、医療従事者、疫学者、臨床疫学者、臨床薬理、ARO? ・比較的乏しい資金

Obstacles in "academic" clinical research

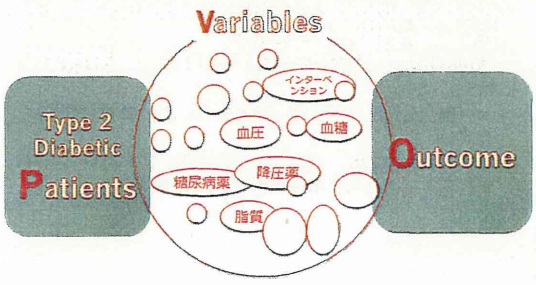
研究計画の作成
- 臨床的疑問から研究仮説の作成はしばしば困難
- Big questionになりがち
- 現実的なスタディデザイン　実現性と内的妥当性のはざま
- 臨床研究＝承認申請を目的とした臨床試験という誤解

試験実施上の問題
- 新倫理指針での「モニタリング」や「監査」の負担
- 患者登録、追跡

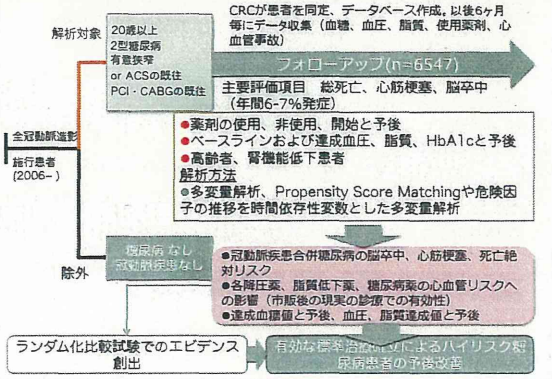
基盤、人材育成、教育に関するもの
- 研究費
- 人材育成の場
- 継続的な臨床研究人材の雇用
- アカデミア≠Pharma

リサーチクエッションにおけるフラストレーション

ハイリスク糖尿病患者への介入は多くのvariationが存在し、新薬の臨床試験をはじめとする単独のランダム化比較試験だけではなかなか解決しない



2型糖尿病を合併した冠動脈疾患のレジストリー

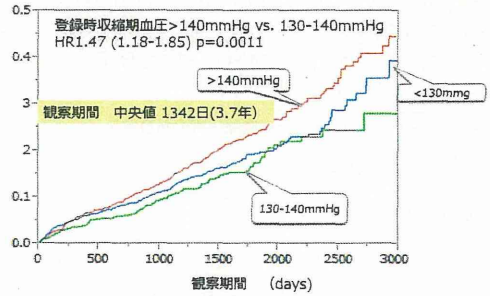


研究の進捗

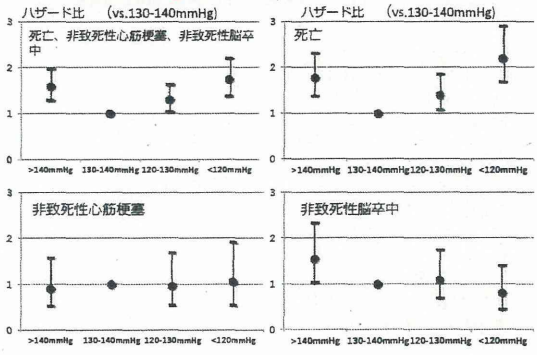
- 22施設
- 昨年度末まで症例数6547
- 死亡、非致死性心筋梗塞、非致死性脳卒中1140例発症

症例数		非致死性心筋梗塞		非致死性脳卒中		死亡	
		件数	%/年	件数	%/年	件数	%/年
沖縄県内12施設	4066	114	1.02%	211	1.93%	520	4.60%
県外11施設	2481	60	0.88%	66	0.97%	169	2.44%
合計	6547	174	1.12%	277	1.81%	689	4.38%

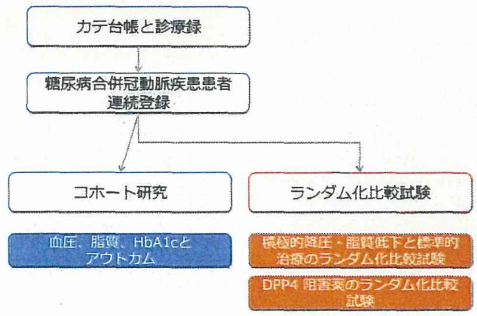
登録時収縮期血圧とアウトカム（死亡、非致死性心筋梗塞、非致死性脳卒中）



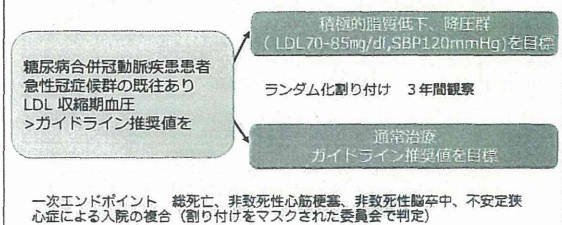
経過中の平均収縮期血圧とアウトカムの関連 130-140mmHgをreference



RCT on Registry



ランダム化比較試験
糖尿病合併ハイリスク冠動脈疾患患者における積極的脂質低下・降圧療法

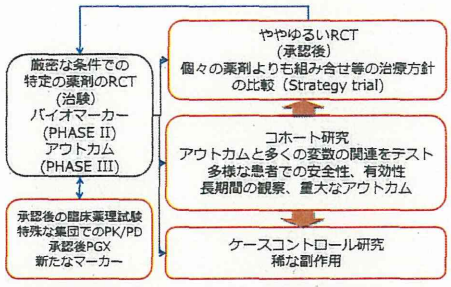


一次エンドポイント　総死亡、非致死性心筋梗塞、非致死性脳卒中、不安定狭心症による入院の複合（割り付けをマスクされた委員会で判定）

糖尿病合併CAD患者レジストリーを基盤とした研究の利点

- 大規模コホートの構築が比較的容易で検出力も得易い
- ハイリスク患者を登録しており、いわゆるハードエンドポイントでの解析が可能となる
- コホートの段階である程度のデータ管理、品質管理が可能
- ベースにしたランダム化比較試験の実施、患者登録をしやすい
- さまざまな臨床的疑問についての解析、多くの探索的解析が可能であり人材育成の場としても有用

目的に応じた理想的な臨床研究の枠組み



目的に応じたRCTとコホート研究

	薬効評価型研究	結果	有用性、安全性の評価のためのコホート	結果
B遮断薬	Heart Attack Trial (1981)	心筋梗塞患者の生命予後改善	急性期病院でのレジストリ研究	COPD, 心不全患者、高齢者での生命予後改善
メトフォルミン	UKPDS	肥満糖尿病患者での死亡率、心血管合併症リスク低下	REACH registry	心不全患者、腎機能低下患者での生命予後改善
ダビガトラン	RELY	脳梗塞リスク低下	FDAセンチネルプロジェクト Medicareコホート	Medicare コホートではRELYと一致
スピロノラクトン	RALES	重症心不全生命予後改善	心不全レジストリ研究	高カリウム血症による死亡↑

Obstacles in "academic" clinical research

研究計画の作成
- 臨床的疑問から研究仮説の作成はしばしば困難
- Big questionになりがち
- 現実的なスタディデザイン　実現性と内的妥当性のはざま
- 臨床研究＝承認申請を目的とした臨床試験という誤解

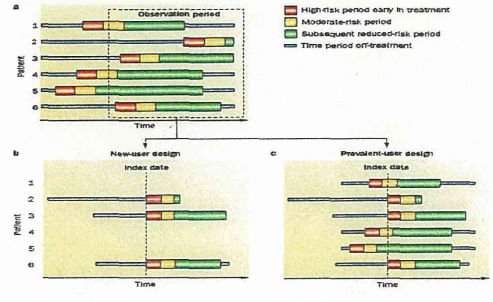
試験実施上の問題
- 新倫理指針での「モニタリング」や「監査」の負担
- 患者登録、追跡

基盤、人材育成、教育に関するもの
- 研究費
- 人材育成の場
- 継続的な臨床研究人材の雇用
- アカデミア≠Pharma

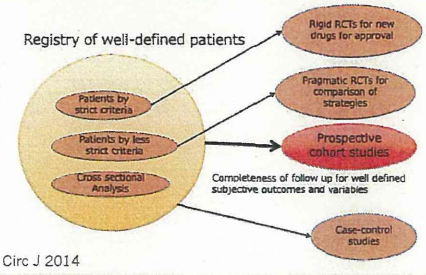
克服すべき問題点

- 患者の定義
- 連続性
- アウトカム評価
- 変数の適切な収集と交絡因子のハンドリング
- 時間依存性変数と予後の関連

薬剤の比較はnew user cohort ／active comparatorの方が容易



No Cohort, No RCT, No Development, No Research Training



Ueda S, Circ J 2014

Figure. Well-constructed registrations of patients can be used as platforms for several types of clinical research.

Conclusion

- 診療の現場からの疑問に基づいた臨床研究は 新薬の承認申請をめざした治験とはちがったデザイン、基盤、質の管理、人材育成を必要とする。
- ２型糖尿病を合併した冠動脈疾患患者のコホートは糖尿病、冠動脈疾患の診療上の疑問解決の基盤として有用である。
- 患者レジストリは克服すべき問題は多々あるもののそれ自体大規模なコホート研究となる。
- 治験も含めたランダム化比較試験実施の基盤、臨床研究トレーニングの基盤となり得る。
- データ収集の段階から品質管理を行うことで新倫理指針への対応も可能である。