2018-02-10
분자폐암연구회, 동계 임상연구 워크숍
백범김구기념관 컨벤션홀

아산 임상연구자 교육 프로그램 소개

ACREP

Asan Clinical Research Education/Training Program

임영석

Young-Suk Lim, MD, PhD

Asan Medical Center
University of Ulsan College of Medicine
Seoul, Korea

ASAN Medical Center

UNIVERSITY OF ULSAN COLLEGE OF MEDICINE

Introduction

- Clinical Epidemiology
- Clinical Research Training Program in Mayo Clinic
- Asan Clinical Research Education/Training Program (ACREP)
- Designing Clinical Research
  - Randomized Controlled Trial (RCT)
  - (Prospective) Cohort Study
  - Case-Control Study
  - Historical Cohort Study
- Historical Cohort Study Design

Clinical Research ≠ Clinical Medicine

Clinical Research =

Clinical Medicine + Epidemiology

= Clinical Epidemiology

Clinical Researcher =

Clinician + Epidemiologist

= Clinical Epidemiologist

Clinician: Consumer

Clinical Epidemiologist: Producer

of Research Information (Evidence)

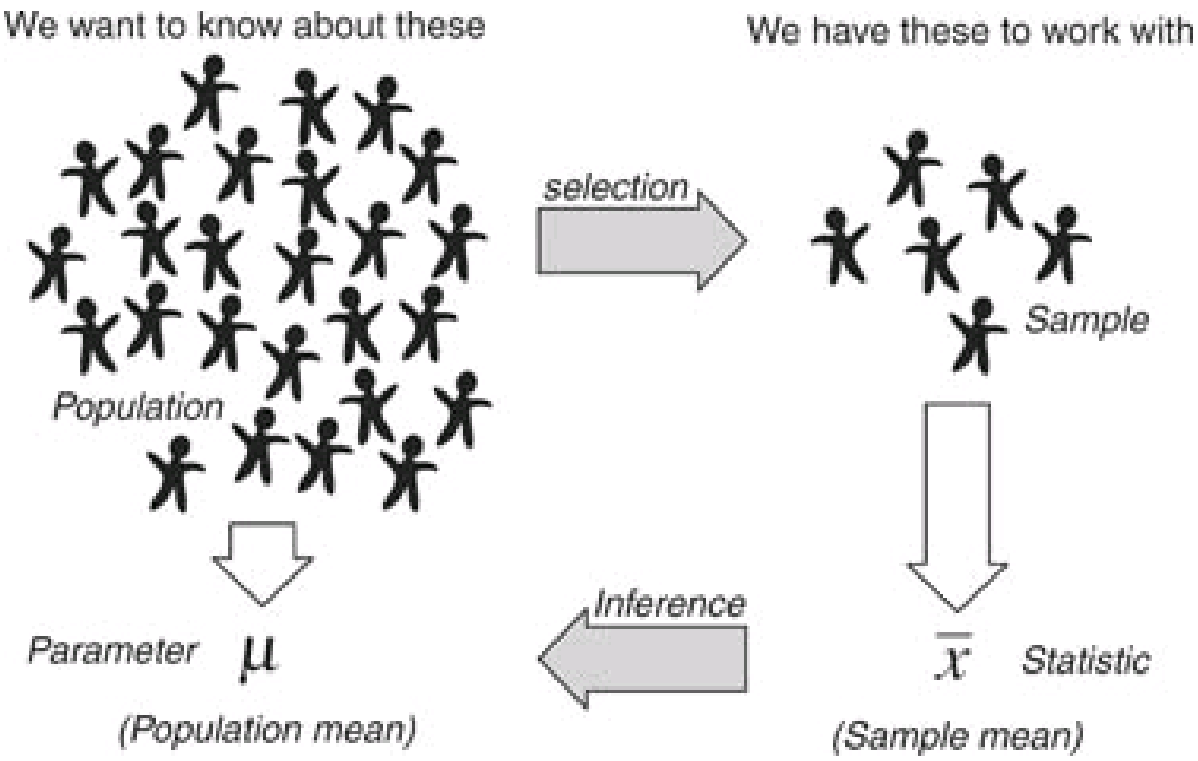
Hierarchy of Clinical Studies
- Evidence Levels -

Strongest Evidence

Weakest Evidence

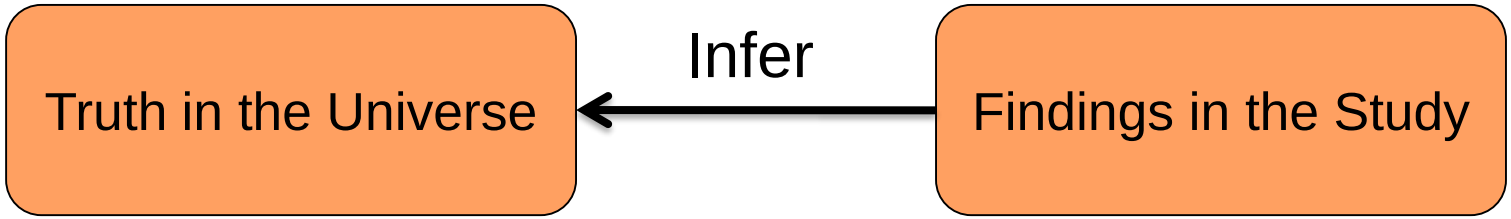
Fundamental Concept of Clinical Research
- Population vs. Sample -

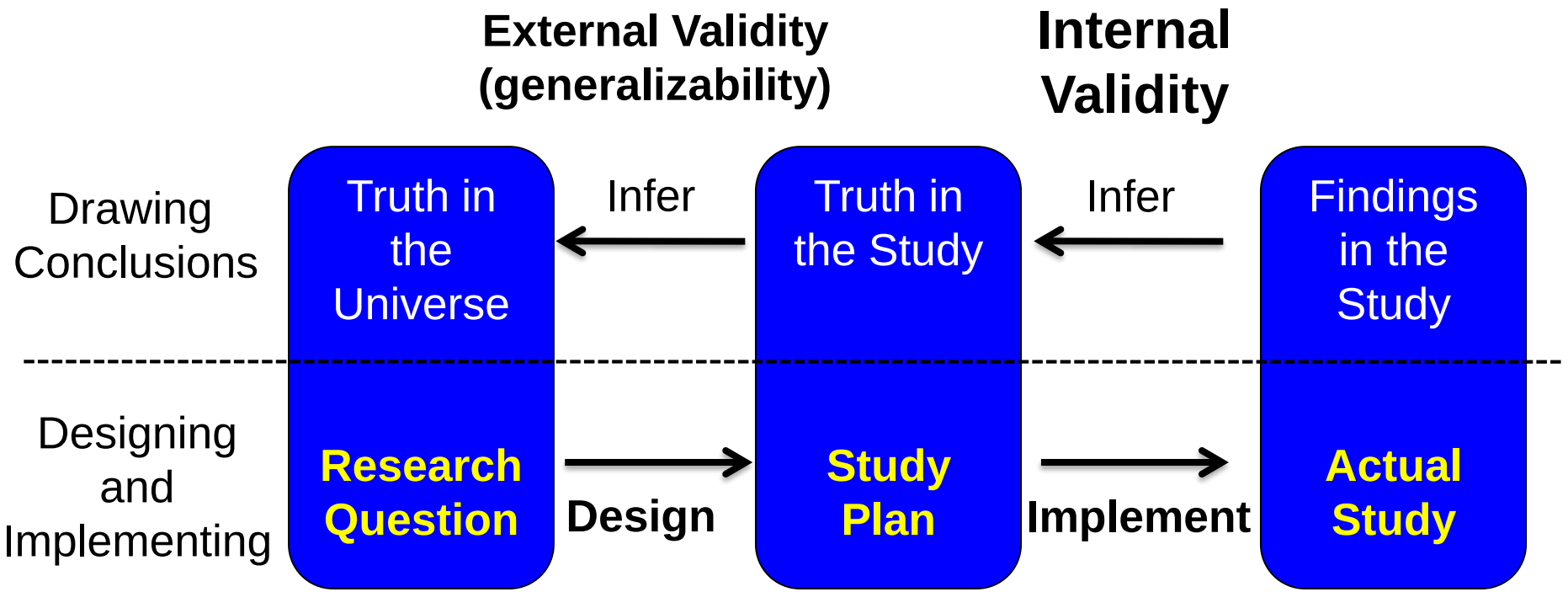
- The **uncertainty** about something in the **population** that the investigator wants to resolve by making **measurements** on his **study subjects (sample)**.



Hulley SB, Cummings SR, et al. Designing clinical research, 2nd ed. Lippincott Williams & Wilkins: Philadelphia, PA, 2001.

Physiology of Clinical Research





Caution in Assessing Causality
- Association vs. Cause -

Explanation

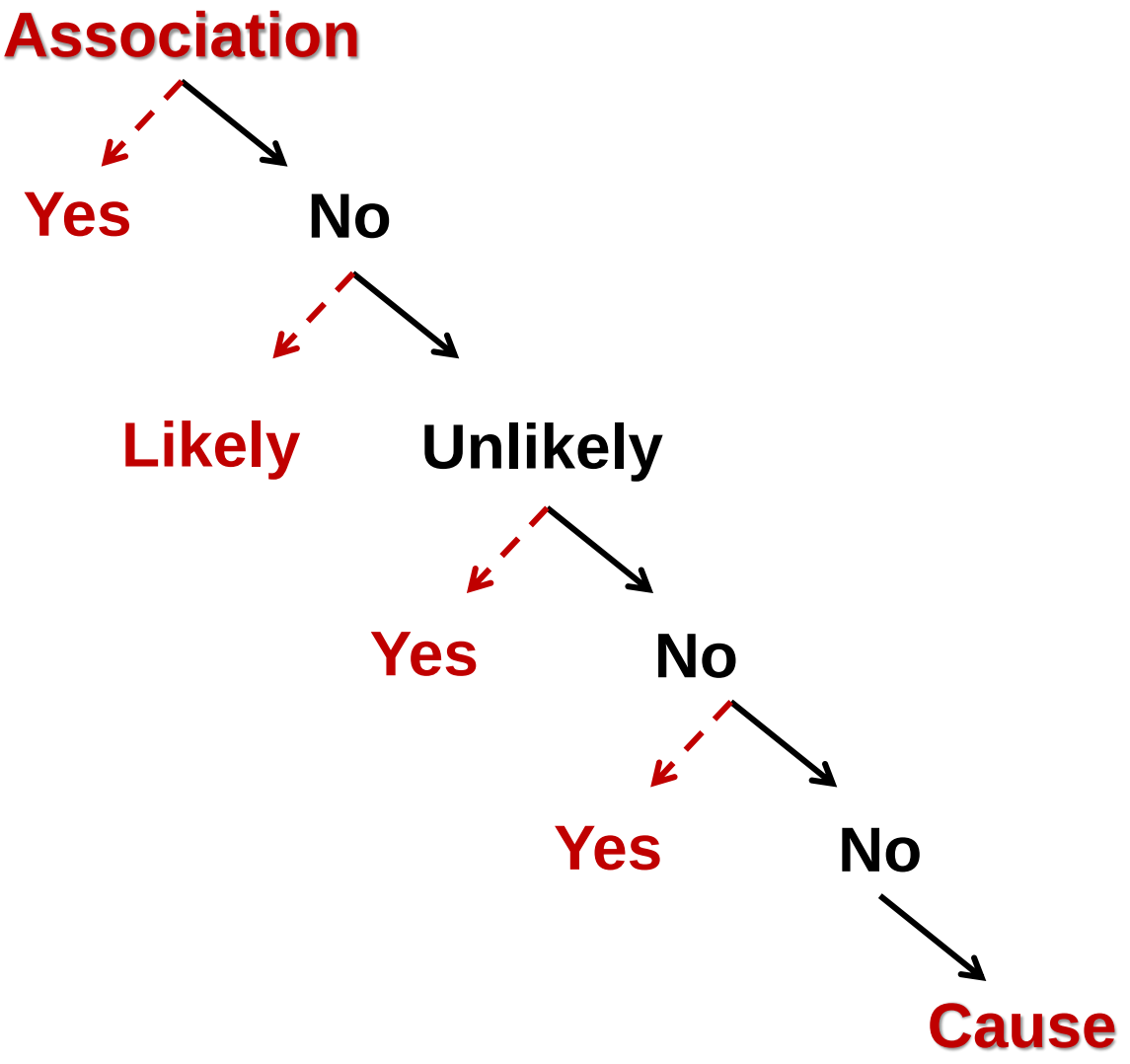
Bias in selection or measurement

Chance

Confounding

Effect → Cause

Cause



Fletcher RH and Fletcher SW. Clinical Epidemiology, 4th ed. Lippincott Williams & Wilkins: Philadelphia, PA, 2005.

Advantages & Drawbacks of Observational Studies

- **Main advantage: Feasibility**
  - Participants
  - Research fund
  - Time
- **Drawback: Possibility of misleading conclusions**
  - Random error (Chance)
  - Systematic error (Bias)
  - Confounding
  - Effect-cause

Chance (Random Error) vs. Bias (Systematic Error)

- **Chance**
  - A random departure from the truth
  - The average of measurements influenced by chance alone would reflect the true average value.
  - Either direction
  - Solution: increase the sample size

- **Bias**
  - A systematic departure from the truth (error) due to design or measurement characteristics.
  - The average of biased measurements would not reflect the true average value.
  - One direction
  - Solution: better design

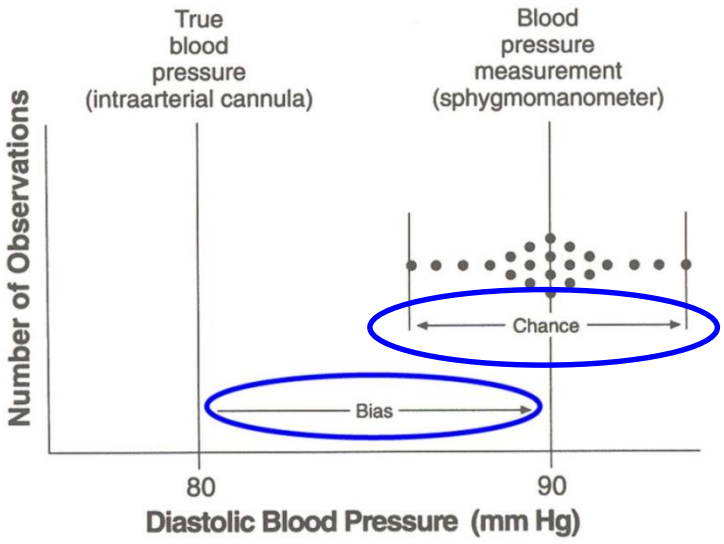
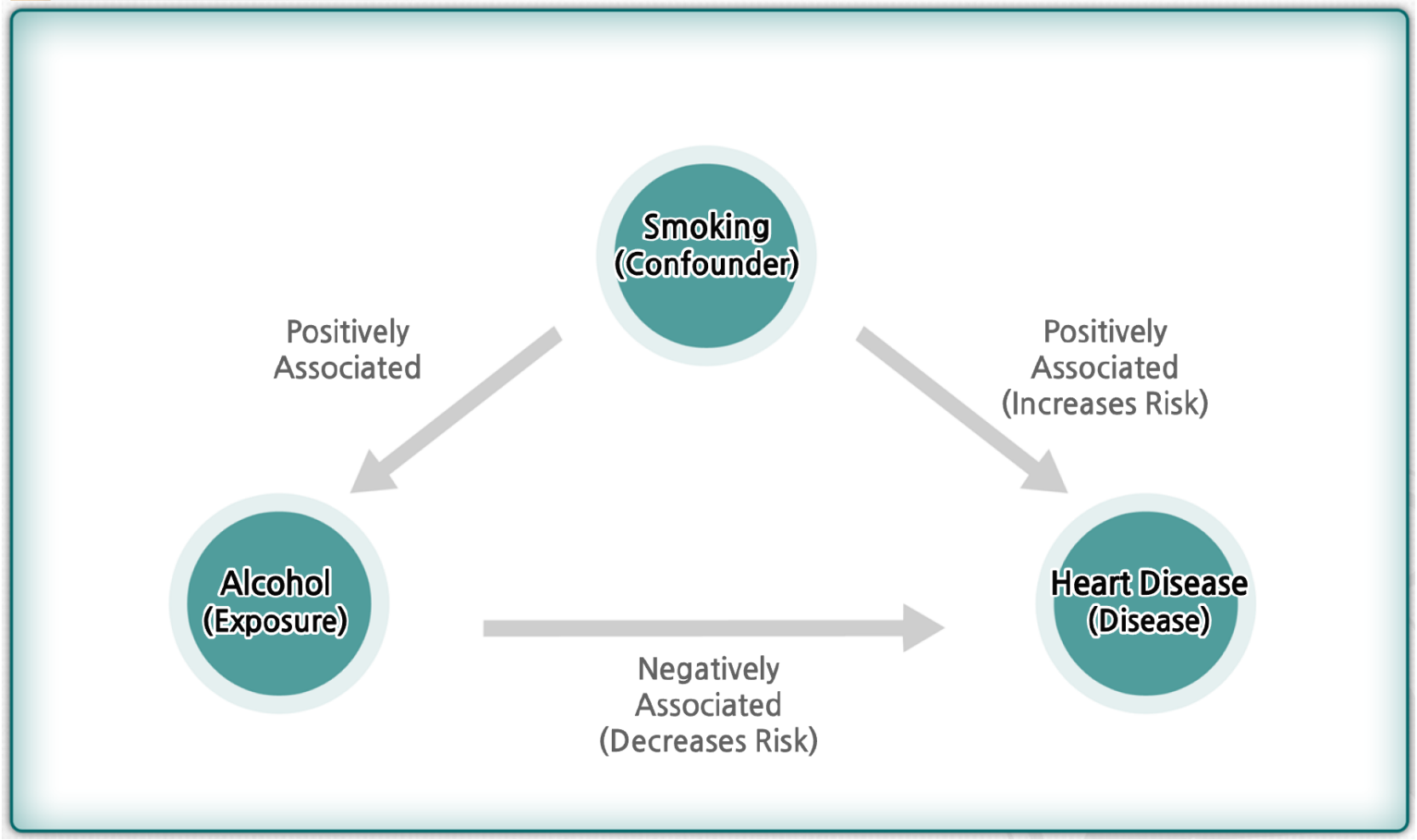


Figure 1.2. Relationship between bias and chance: Blood pressure measurements by intraarterial cannula and sphygmomanometer.

Fletcher RH and Fletcher SW. Clinical Epidemiology, 4th ed. Lippincott Williams & Wilkins: Philadelphia, PA, 2005.

Confounder


Smoking
(Confounder)
Positively
Associated
Positively
Associated
(Increases Risk)
Alcohol
(Exposure)
Heart Disease
(Disease)
Negatively
Associated
(Decreases Risk)

Preventing Non-Causal Associations in Observational Studies

- Chance, Bias, Effect-cause, Confounding
- In general, the further one departs from the randomized trials, the less the research design protects against possible biases and the weaker the evidence is for a cause-and-effect relationship.
- Judge the validity of an observational study by considering how a randomized controlled trial of the same question would have been conducted.
- To deal with extraneous differences between the groups so as to mimic as closely as possible in RCT.

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Clinical Research Training Program









"educating a new generation of clinical investigators to bring discovery into practice"

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Mayo Clinic Center for Translational Science Activities (CTSA)

- **CTSA Research Resources**
- **CTSA Community Engagement**
- **CTSA Service Center**
- **CTSA Education Resources – Dr. Sherine Gabriel, Director**

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Mayo Clinic
Center for Translational Science Activities (CTSA)

- **CTSA Education Resources**
  - **Predoctoral Programs**
  - **Postdoctoral Programs**
    - **Certificate Program (CRTP)**
    - **Master's Degree (CRTP)**
    - **K12 Career Development Program**
  - **CRC & Continuing Education Programs**

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Mayo Clinic's CRTP

Goals:

- To train independent investigators prepared to carry out outstanding extramurally-funded patient based research

- To enhance clinical research skills for Mayo faculty as a whole

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Scholar Enrollment

	2000	2001	2002	2003	2004	2005	2006	2007	Total
Admit	7	19	44	37	45	47	58	18	276
Comp		2	11	15	17	22	25	2	99
W/D		1	3	2	2	3	2	0	12
Current									148

Program Fee implemented in 2005
$7000 (MS) $3500 (Cert)

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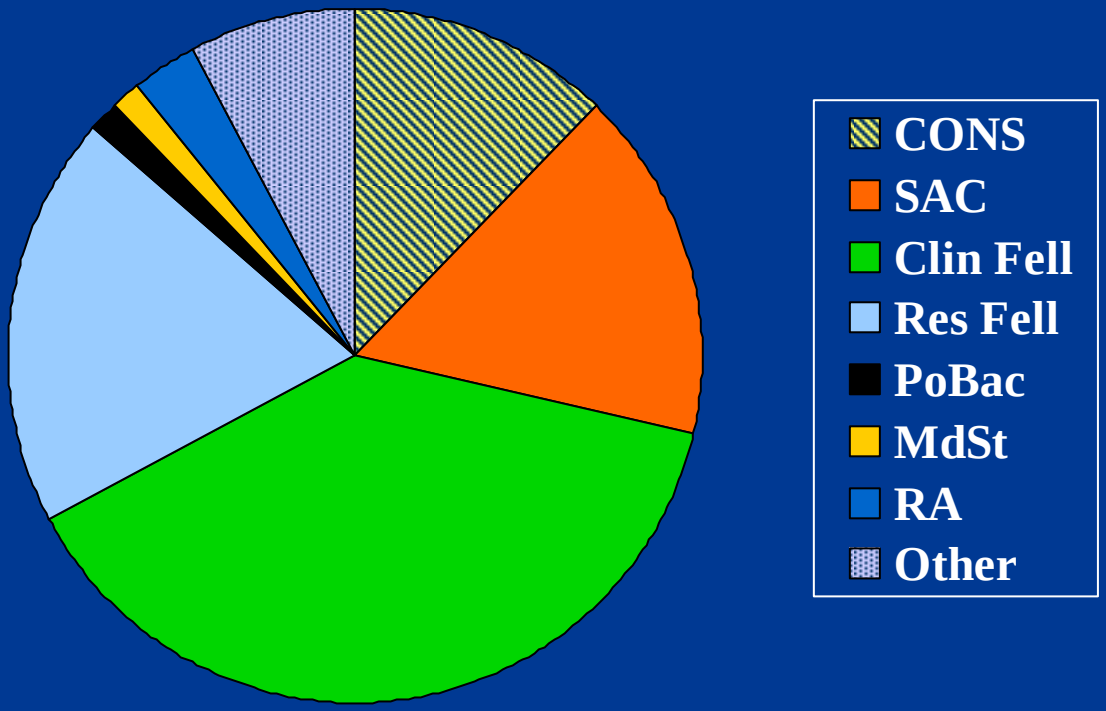
CRTP Scholars by Appointment Type



16% Jr. Faculty
84% Trainees

(n=148)
36% Clinical Fellows
18% Research Fellows

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CRTP Competencies

- *Critically evaluate the medical literature*
- *Articulate the ethical & legal responsibilities*
- *Develop feasible and testable hypotheses*
- *Design and conduct a clinical research project*
- *Write grant proposal*
- *Publish research results*

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CRTP Competencies

- *Orally present research results*
- *Articulate and apply appropriate study designs*
- *Utilize appropriate biostatistical methods*
- *Understand the peer-review process*

See complete listing on pages 3 and 4 in CRTP Scholar/Mentor Manual

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CRTP Outcomes

- *Career Development Awards (K Awards)*
- *Intra- or Extramural Funding*
- *Publications, Presentations*
- *Academic Rank*

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What is CRTP?

- **Certificate Program - CPOR**
  - 12 credits - 3.0 GPA
  - Mentored research project resulting in a manuscript
  - Can be completed in one year or more
- **Post-Doctoral Master's Degree - MGS**
  - 24 credits - 3.0 GPA
  - Comprehensive written exam
  - Mentored research project resulting in a thesis
  - Final oral exam (thesis defense)
  - Can be completed in 2-7 years

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Required Courses for the Master's Degree - 17 credits

- **Biostatistical Methods I & II**
- ***Statistics in Clinical Research (Certificate only)***
- **Critical Appraisal of Statistical Methods in the Medical Literature**
- **Clinical Epidemiology I & II**
- **Advanced Applied Epidemiological Methods**
- **Intro to Clinical Research**
- **Clinical Research Protocol Development**
- **Responsible Conduct of Research**
- **Clinical Trials: Design and Conduct**
- **Regulatory Issues in Clinical Research**

Required Courses for the Certificate Program: 8 credits

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Certificate Completion

- **12 didactic credits (including 8 required)**
- **Grade point average of 3.0 (check transcript)**
- **Workshop - Publication**
- **Manuscript**
- **Current CV**
- **Mentor's summary statement**

MAYO CLINIC College of Medicine

Master's Degree Completion

- 24 didactic credits (including 17 required)
- Grade point average of 3.0
- Two Workshops-Grant Writing/Publication
- Comprehensive Written Examination
- Thesis
- Final Oral Examination
- Current CV

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"The research we do today will determine the type of medical and surgical practice we carry on at the Clinic tomorrow."

-William J. Mayo, M.D.

연구 교육부 주관 ACREP W/S

제1회, 2011-07-09

임상연구 기획과 설계
WORKSHOP
(임상연구 계획서 작성법)

임상연구지원센터에서는 우수 임상연구 연구자 양성을 목적으로 공개 워크샵을 아래와 같이 개최합니다.

이번 워크샵에서는 일방적 강의보다는 실제 사례를 들면서 핵심적인 내용을 아주 쉽게 전달할 계획입니다.
임상연구 경험이 풍부한 임상과 교수와 의학통계 분야에 해박한 의학통계학과 교수가 다수 강사로 참여합니다.

- 일 시 : 2010년 7월 9일(토) 9:00~16:50
- 장 소 : 동관 6층 소강당
- 대 상 : 임상연구 연구자
  (교수, 임상교수, 임상강사, 전공의)
- 접 수 : 6월 1일(수) ~ 6월 24일(금) 선착순 120명 限
- 방 법 : 원내 메일
  (담당 : 연구행정TFT 이유미 / ☎ 2213)
- 자세한 프로그램 내용과 신청양식은 AMCnet 게시판 참조 바랍니다.

Time	Lecture Title	Instructor
9:00	축사	진료부원장
9:05	인사말	문대혁 (핵의학과)
9:10	Introduction of ACREP W/S	오연목 (호흡기내과)
9:15	Writing clinical research protocol	권순억 (신경과)
9:35	Choosing a good clinical research question	임영석 (소화기내과)
10:05	*Break*	
10:20	Introduction to clinical epidemiology	오연목 (호흡기내과)
10:40	Descriptive and Analytic epidemiology, Type of data	김화정 (의학통계학과)
11:00	Bias, Confounder, Effect modifier	이무송 (의학통계학과)
11:20	Intention-to-treat vs. Per-protocol analysis	이무송 (의학통계학과)
11:40	*Lunch*	
12:40	Cohort study, Prognostic/Survival study design	임영석 (소화기내과)
13:10	Clinical trial design	박덕우 (심장내과)
13:30	Cross-sectional study, Case-control study design	권순억 (신경과)
13:50	Overview of clinical study design	임영석 (소화기내과)
14:10	*Break*	
14:25	Risks, Ratios, Prevalence, Incidence / Odds ratio, Relative risk, Hazard ratio	김화정 (의학통계학과)
14:45	Sensitivity, Specificity, Predictive values	한승봉 (의학통계학과)
15:05	Confidence interval and Hypothesis testing	윤성철 (의학통계학과)
15:25	*Break*	
15:40	Data management	오연목 (호흡기내과)
16:00	To get papers accepted in journals	박덕우 (심장내과)
16:20	Q&A	ALL
16:50	Closing remarks	오연목 (호흡기내과)
16:55	Close	

제9회, 2017-05-26

2017 아산 임상연구자 교육 프로그램
ACREP
AMC Clinical Research Education·Training Program

영향력 있는 임상시험의 비법
How Can We Run a High-impact Clinical Trial?

일시
2017년 5월 26일(금) 08:55 – 17:25

장소
동관 6층 소강당

대상
원내 임상연구자 및 임상연구 수행자

신청방법 AsanNet 게시판 및 임상의학연구소 홈페이지 접수
*참가비 무료 / 사전등록자에 한하여 책자 및 수료증 제공 / 중식은 제공되지 않습니다.

사전등록기간 2017년 4월 10일(월) ~ 5월 19일(금) / 사전등록인원에 따라 조기 마감 될 수 있음

PROGRAM

시간	주제	연자
08:55~09:00	Opening Remark	울산의대 서울아산병원 영상의학과 **박성호**
09:00~09:30	좋은 임상연구란 무엇인가?	울산의대 서울아산병원 소화기내과 **임영석**
09:30~10:00	Clinical Trial / Study 디자인 및 수행에 대한 Overview : 임상연구자의 관점	울산의대 서울아산병원 심장내과 **안정민**
10:00~10:45	Clinical Trial / Study 디자인 및 분석을 위한 기본 방법론적 요소	울산의대 서울아산병원 의학통계학과 **김화정**
10:45~11:00	Break	
11:00~11:30	Clinical Trial에서의 DSMC, Study Monitoring 및 Interim Analysis	울산의대 서울아산병원 의학통계학과 **이정복**
11:30~12:00	성공적인 다기관 연구수행 : Expert Tips	울산의대 서울아산병원 신경과 **권순억**
12:00~13:00	Lunch	
	임상연구비 획득 방법	
13:00~13:20	NECA NHCR 연구비를 획득한 연구자의 경험 / Tips	연세의료원 세브란스병원 심장내과 **정보영**
13:20~13:50	NECA 임상연구비 소개 및 획득 방법	한국보건의료연구원(NECA) **김수경**
13:50~14:20	NECA 보건의료빅데이터 활용을 통한 연구성과 창출 방법	한국보건의료연구원(NECA) **고민정**
14:20~14:35	Break	
14:35~15:05	Industry 연구비 획득 방법	울산의대 서울아산병원 종양내과 **이대호**
15:05~15:20	원내 임상연구비 획득 방법	울산의대 서울아산병원 의학통계학과 **이정복** 울산의대 서울아산병원 영상의학과 **박성호**
15:20~15:50	임상연구 관련 Regulatory Issue Update	보건복지부 **정통령**
15:50~16:20	임상연구비에 대한 이해 및 연구비 Planning을 잘 하는 방법	울산의대 서울아산병원 ARO **김신애**
	Latest Trends in Clinical Trial	
16:20~16:50	Registry-Based Pragmatic Trial	울산의대 서울아산병원 심장내과 **박덕우**
16:50~17:20	Screening / Surveillance Strategy Trial	울산의대 서울아산병원 영상의학과 **박성호**
17:20~17:25	Closing Remark	울산의대 서울아산병원 영상의학과 **박성호**

• NECA : 한국보건의료연구원(National Evidence-based Healthcare Collaborating Agency)

문의 서울아산병원 연구지원팀 **이선기** 사원
02-3010-2517 sunki@amc.seoul.kr

주최 서울아산병원 Asan Medical Center 임상의학연구소 Clinical Research Center

참가자 분포 및 만족도

제1회 W/S (2011-07-09)

임상과장	2
교수	11
부교수	12
조교수	27
임상부교수	2
임상조교수	16
촉탁의	3
임상전임강사	7
임상강사	42
전공의	13
연구조교수	1
전담연구원	1
합계	137

제2회 W/S (2012-01-13 ~ 14)

			percent(%)
워크숍 만족도	1	매우만족	33.3
	2	만족	60.0
	3	보통	6.7
	4	부족함	0
	5	매우부족함	0
선호 프로그램	1	기본코스만 2일	30.0
	2	기본코스+심화코스	50.0
	3	samll group discussion	13.3

총 180명 참가

2016 ACREP Protocol Writing Workshop

- 일자: 2016/10/7(금) ~ 10/8(토)
- 장소: 양평 현대 OOOOO
- 참석인원: 총 15 명 (Mentor: 6 명 / Mentee: 7 명)
- Peer review of clinical research protocol

5. Mentee 평가 (연구계획서 및 참여점수)

No.	성 명	연구계획서 평가점수 (워크숍 전)	연구계획서 평가점수 (워크숍 후)	최종점수	종합 순위	Group	특기사항
1		3.00	4.92	14.86	1	1조	도약/기획과제 후보 가능
2		3.25	4.78	14.57	2	1조	
3		3.00	4.41	13.83	3	2조	
4		2.00	4.14	13.29	4	1조	
5		3.00	4.41	13.17	5	2조	
6		2.67	4.41	13.17	5	2조	
7		2.50	3.92	12.86	7	1조	
8		2.33	4.00	12.33	8	2조	원내 과제로 부적절

6. 설문조사 결과: 7 명 응답

1) 전반적인 만족도 (5 점 척도 기준)

구 분	점수(평균)
본 교육에 대해 전반적으로 만족한다.	5.00
본 교육의 내용이 도움이 되었다.	4.86
본 교육은 업무 수행을 향상시킬 수 있는 충분한 정보와 스킬을 제공하였다.	4.57
본 교육은 본인의 기대 수준을 만족 시켰다.	4.57
본 교육에 대한 홍보가 충분하였다.	3.71
본 교육의 강사 구성에 대해 만족한다.	4.86
본 교육 장소 및 기타시설에 대해 만족한다.	4.57
본 교육을 동료들에게 추천할 것이다.	4.57
본 교육의 시기와 진행시간에 만족한다.	4.00

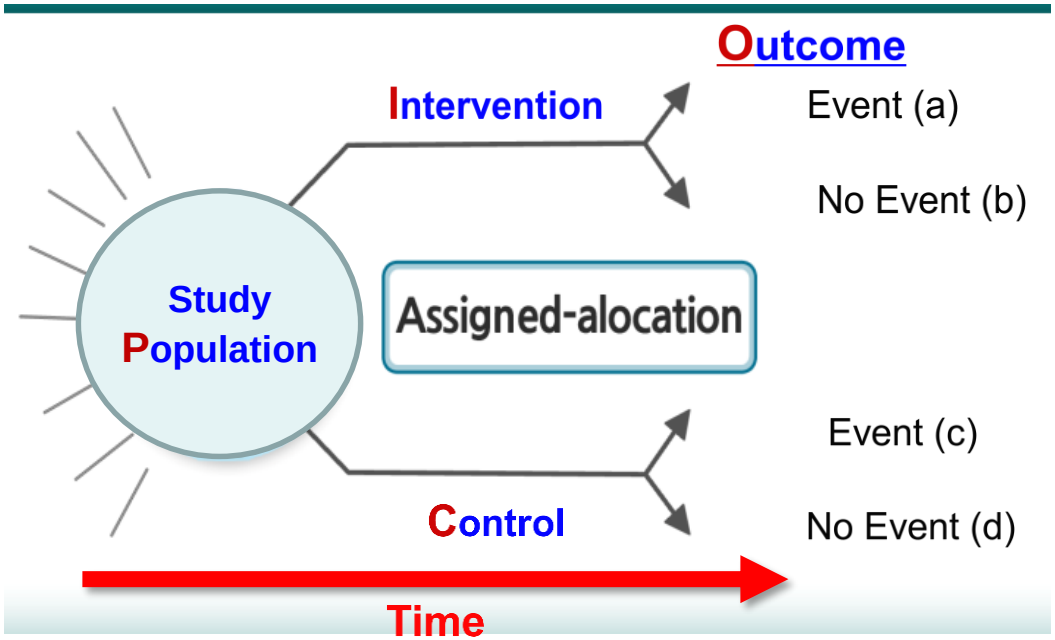
2) 향후 교육에 대한 전반적 의견 및 건의사항

(1) 자유 의견

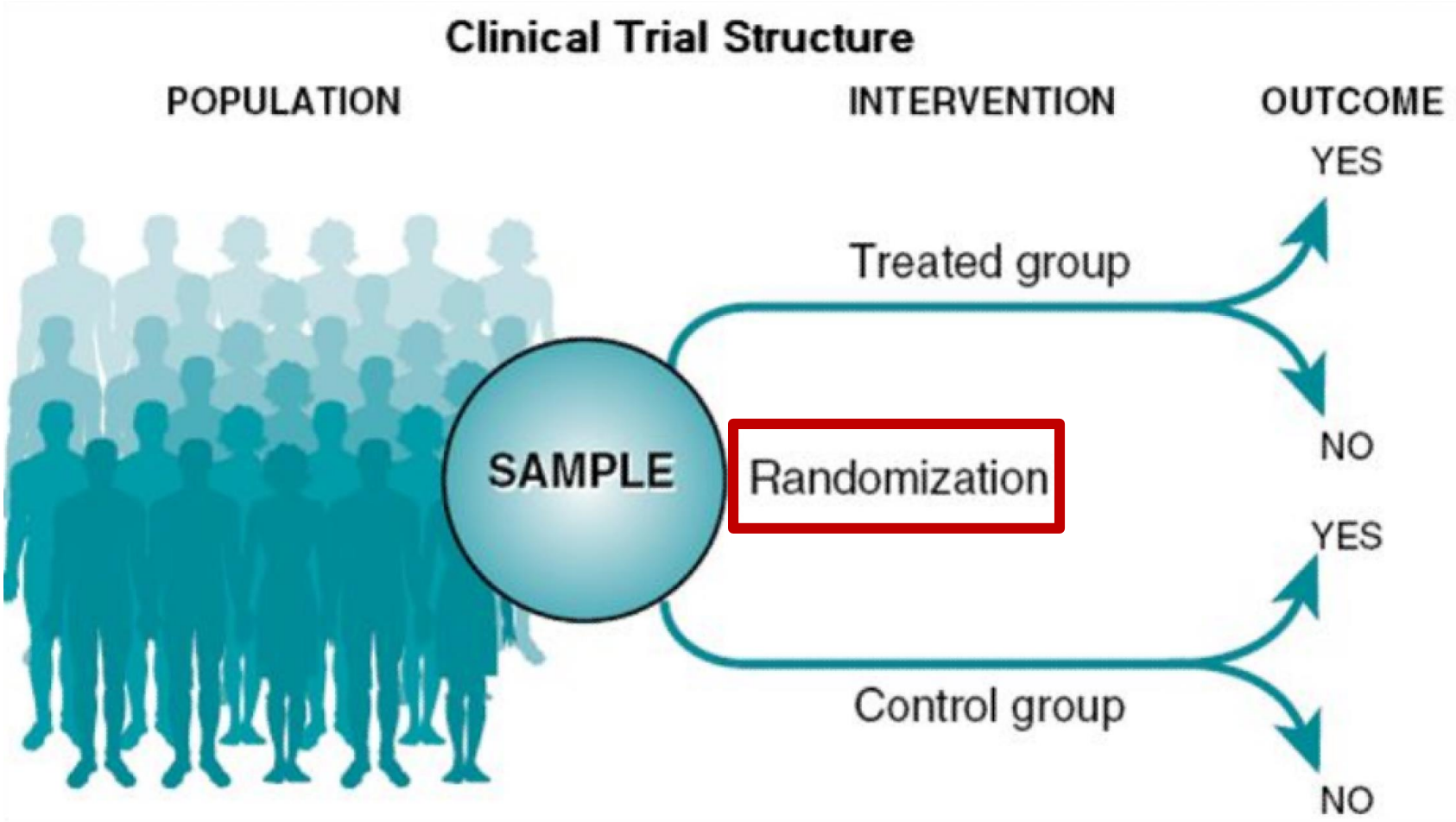
- Mentor&Mentee Workshop 형태에 대해 매우 만족함

Anatomy of Clinical Research
- PICO -

- **P**atient / Population / Problem (**among** _____)
- **I**ntervention / Exposure (**does** _____)
- **C**omparison (**versus** _____)
- **O**utcome (**affect** _____)



Randomized Controlled Trial : Gold Standard of Clinical Studies



Feasibility

- **Research Fund**
- **Number of subjects**
  - Appropriate population & number of subjects
- **Investigator**
  - Adequate technical skills, experience, & equipment
- **Scope**
  - Manageable in scope
  - Problems often arise when an investigator attempts to accomplish too much.
  - Narrow the scope of the study and focus only on the most important goals.

Research Question from Clinic

- Background:
  - 간세포암(HCC) 수술 후 약 50%의 환자들이 3년내에 재발 (important unmet need!)
  - 간세포암 환자들의 약 70%는 만성 B형간염 관련

- 왜 재발할까?

  = 재발의 위험요인은 무엇인가?

  = 재발을 어떻게 줄일 수 있을까?

Hypothesis and Research Question

- 간세포암 수술 이후 활동성 B형간염이 지속되면 간암의 재발이 높을 것이다.
- Does early (< 3 month after resection) oral daily use of anti-hepatitis B viral agents (lamivudine or entecavir; **I**) in patients who undergo first curative surgical resection for early stage (stage 0 or 1) hepatocellular carcinoma with hepatitis B viremia (HBV DNA > 2000 IU/mL; **P**) reduce the rate of HCC recurrence and patients' death (**O**) compared with no treatment (**C**)?

이 질문이 좋은 연구로서 가치가 있는가?

- **Literature Review**
  - Literature (Pubmed…)
  - Ongoing studies (Clinicaltrials.gov…)

- **FINER test**
  1. Feasible
  2. Important and Interesting
  3. Novel
  4. Ethical
  5. Relevant

Study Design
- Prospective RCT -

- **PICO model**

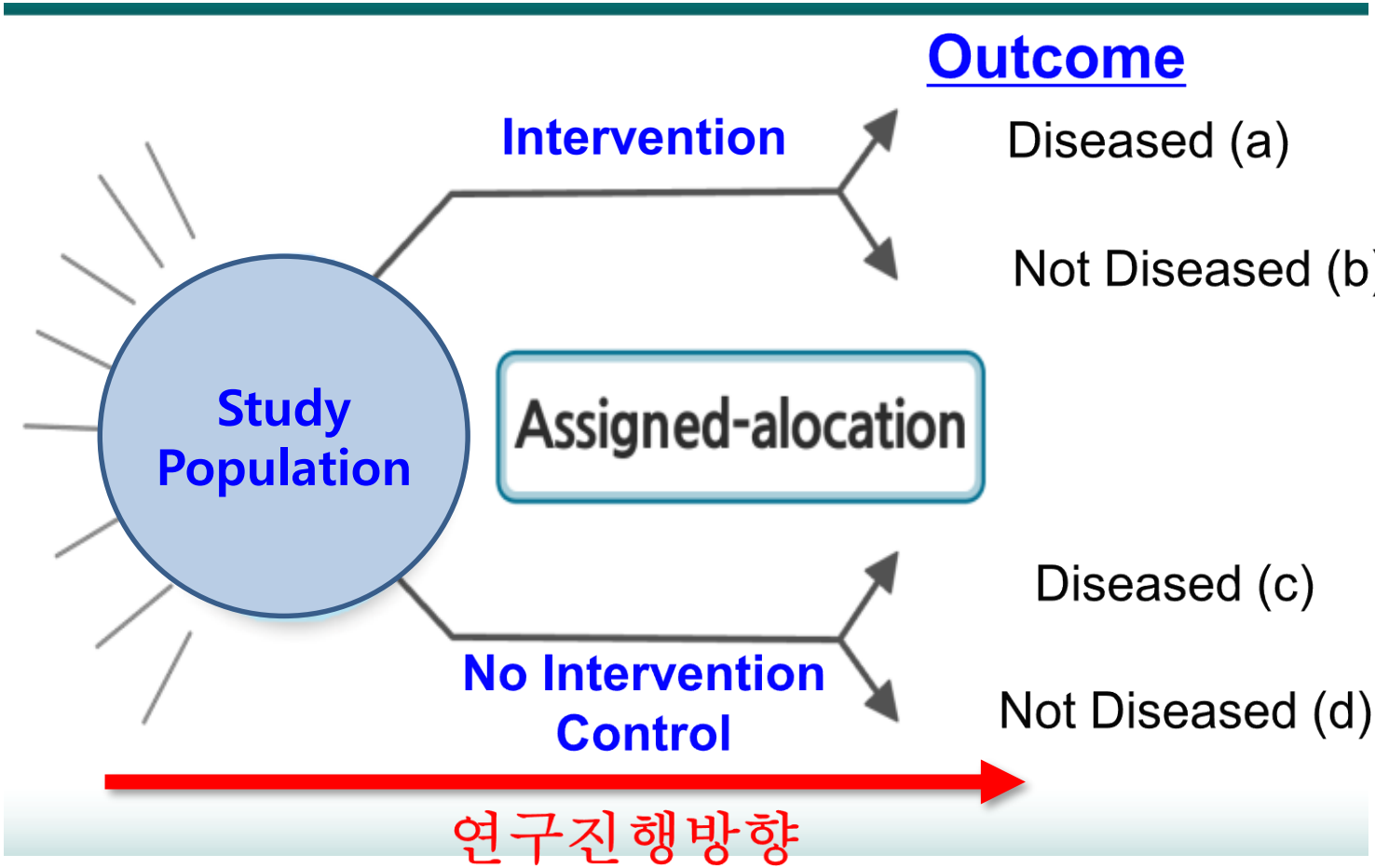
1. Patients
  - HCC의 첫치료로서 수술적 절제술을 받는 환자들

2. Intervention (무작위 배정)
  - Antiviral treatment (ex, Entecavir)

3. Comparison (무작위 배정)
  - No antiviral treatment

4. Outcome of Interest
  - HCC recur (by F/U imaging)

Study Design
- Prospective RCT -

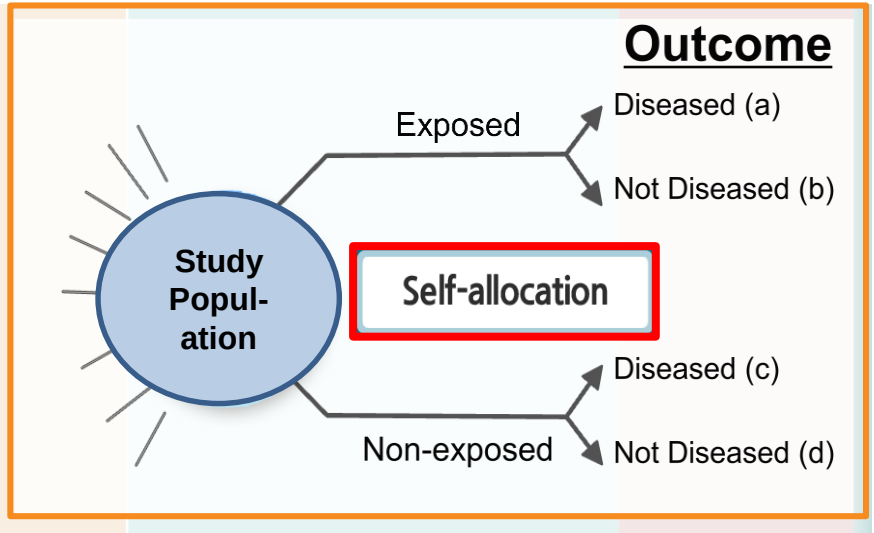


Study Design
- Prospective RCT -

- **Feasible?**
  - Sample size >> n=200
  - Fund; 수억
  - Study duration (3-5년 이상)
- **Ethical?**
  - 의학적으로 효용이 이미 어느 정도는 밝혀져 있고, 보험적용 기준이 되는 환자들을 대조군에 배정?

Study Design
- Prospective Cohort study -

- 2016/7/1 부터 HCC 수술을 하는 모든 환자들을 모집한 후 정기적으로 방문하게 하여 CT검사를 시행
- 방문 간격:
  - 첫 1년간: 3개월 간격
  - 2년째 이후: 6개월 간격
- 방문시 검사
  - CT, AFP, LFT, PT
- Intervention
  - Antiviral treatment (Entecavir)
  - 진료 차원에서 사용되는 환자와 그렇지 않은 환자들의 재발률을 비교
- 문제점: bias (두 그룹간 환자들의 특성이 다를 가능성이 높다.)



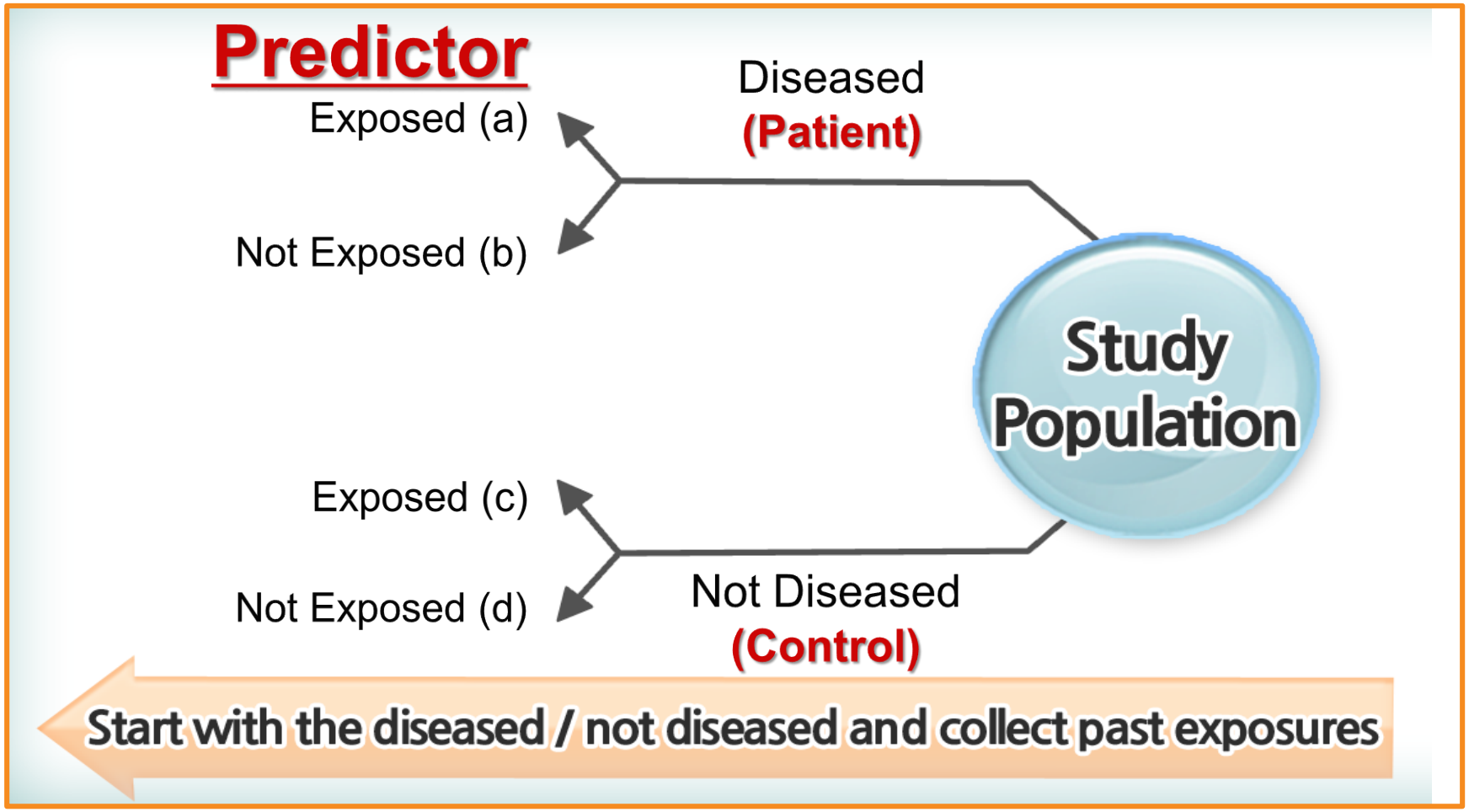
Study Design
- Prospective Cohort study -

- 얼마나 많은 환자들을, 얼마나 오랫동안 추적관찰?
  - **충분한 event (outcome, 간암재발)이 나타나도록**

  = 재발 위험요인에 대한 **다변량 분석이 가능하도록**

  = 10 event당 1개의 변수씩 분석에 투입가능!
- HCC 수술한 100명의 환자를 3년간 관찰한다면
  - 50%의 예상 재발률
  - 5개의 변수를 다변량분석(logistic regression analysis or Cox PH model)에 투입 가능.
- 역시 최소 3년 이상의 시간이 소요됨.

Study Design
- Case-Control study -

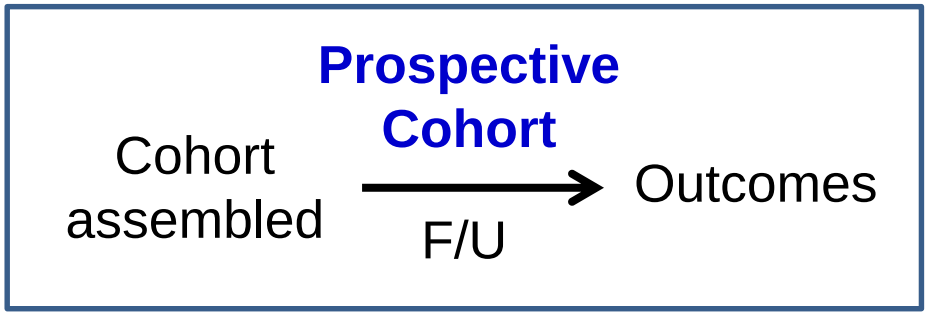


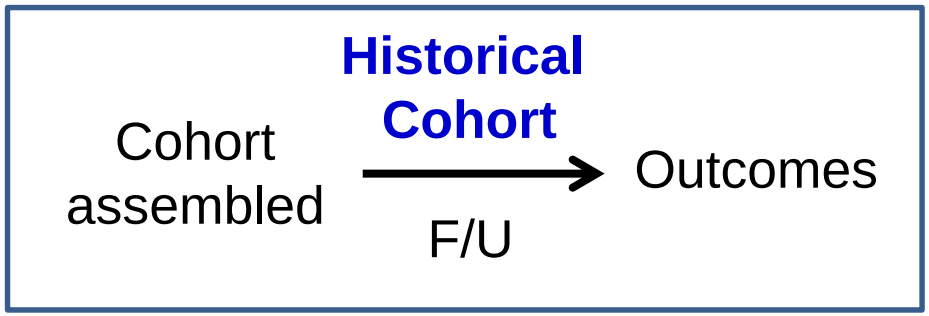
연구진행방향

Study Design
- Case-Control study -

- 환자군(Case)
  - 2011/1/1-2012/12/31 사이에 HCC 수술 후 재발한 환자들을 조사하여 명단을 확보
- 대조군(Control)
  - 2011/1/1-2012/12/31 사이에 HCC 수술 후 재발하지 않은 환자들을 조사하여 명단을 확보
  - 3년 무재발 환자? 5년 무재발 환자?
- 환자군:대조군 비율 = 1:1 – 1:4
- 수술직전의 환자 기록/검사결과 조사, 비교 분석 (항바이러스제 사용자 비율에 유의한 차이가 있는가?)

Cohort Studies
Prospective vs Historical





The logic of these two types of cohort studies are identical.
: the exposures are known before the outcome is known.

Study Design
- Historical Cohort study -

- **2000/1/1-2010/12/31 사이에** 서울아산병원에서 HCC의 초치료로서 근치적 수술적 절제술을 받은 환자들의 명단을 확보
- 수술전 대부분 extensive staging work up 시행
- 추적관찰 방법은 protocol을 따르므로 대개 동일함.
- 1년에 약 200명, 10년에 2,000명
- 이 환자들의 2015/12/31까지의 재발여부를 관찰한다면
  - 50%의 예상 재발률 = 1,000명
  - 100개의 변수를 다변량분석(logistic regression analysis or Cox PH model)에 투입 가능.

Study Design
- Historical Cohort study -

- 장점: 즉시 분석이 가능
- 단점:
  - **Bias**
    - Selection bias: antiviral 치료군과 비치료군간 환자들의 특성이 다를 가능성이 높다.
    - Measurement bias: 이미 알려진 재발 위험인자를 가진 환자들이 더 자주 검사를 하게 됨.
  - **Missing data**
    - 10% 이상이면 data에 현격한 문제가 발생

Historical Cohort study
- JAMA 2012 -

Association Between Nucleoside Analogues and Risk of Hepatitis B Virus–Related Hepatocellular Carcinoma Recurrence Following Liver Resection

Chun-Ying Wu, MD, PhD, MPH
Yi-Ju Chen, MD, PhD
Hsiu J. Ho, PhD
Yao-Chun Hsu, MD, MS
Ken N. Kuo, MD
Ming-Shiang Wu, MD, PhD
Jaw-Town Lin, MD, PhD

Context Tumor recurrence is a major issue for patients with hepatocellular carcinoma (HCC) following curative liver resection.

Objective To investigate the association between nucleoside analogue use and risk of tumor recurrence in patients with hepatitis B virus (HBV)–related HCC after curative surgery.

Design, Setting, and Participants A nationwide cohort study between October 2003 and September 2010. Data from the Taiwan National Health Insurance Research Database. Among 100 938 newly diagnosed HCC patients, we identified 4569 HBV-related HCC patients who received curative liver resection for HCC between October 2003 and September 2010.

Main Outcome Measures The risk of first tumor recurrence was compared between patients not taking nucleoside analogues (untreated cohort, n=4051) and patients taking nucleoside analogues (treated cohort, n=518). Cumulative incidences and hazard ratios (HRs) were calculated after adjusting for competing mortality.

Results The treated cohort had a higher prevalence of liver cirrhosis when compared with the untreated cohort (48.6% vs 38.7%; $P<.001$), but lower risk of HCC recurrence (n=106 [20.5%] vs n=1765 [43.6%]; $P<.001$), and lower overall death (n=55 [10.6%] vs n=1145 [28.3%]; $P<.001$). After adjusting for competing mortality, the treated cohort had a significantly lower 6-year HCC recurrence rate (45.6%; 95% CI, 36.5%-54.6% vs untreated, 54.6%; 95% CI, 52.5%-56.6%; $P<.001$). Six-year overall mortalities for treated cohorts were 29.0% (95% CI, 20.0%-38.0%) and for untreated 42.4% (95% CI, 40.0%-44.7%; $P<.001$). On modified Cox regression analysis, nucleoside analogue use (HR, 0.67; 95% CI, 0.55-0.81; $P<.001$), statin use (HR, 0.68; 95% CI, 0.53-0.87; $P=.002$), and nonsteroidal anti-inflammatory drugs or aspirin use (HR, 0.80; 95% CI, 0.73-0.88; $P<.001$) were independently associated with a reduced risk of HCC recurrence. Multivariable stratified analyses verified the association in all subgroups of patients, including those who were noncirrhotic (HR, 0.56; 95% CI, 0.42-0.76) and diabetic (HR, 0.52; 95% CI, 0.31-0.89).

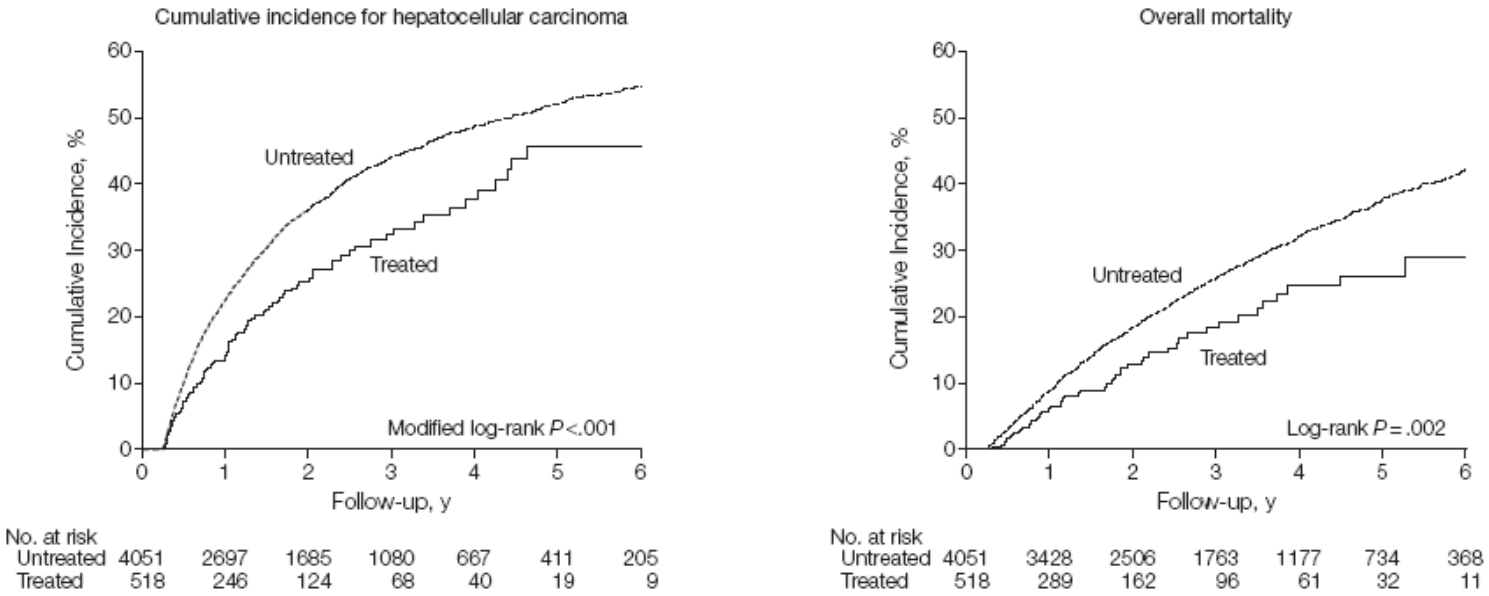
Conclusion Nucleoside analogue use was associated with a lower risk of HCC recurrence among patients with HBV-related HCC after liver resection.

JAMA. 2012;308(18):1906-1913
Published online November 12, 2012. doi:10.1001/2012.jama.11975 www.jama.com

SURGERY IS CONSIDERED THE STANdard curative treatment option for hepatocellular carcinoma (HCC). However, the rate of long-term disease-free survival after liver resection remains unsatisfactory due to persistent high incidences of HCC recurrence.[1] Many factors affect HCC recurrence risk after liver resection, including tumor size and stage, serum α-fetoprotein level, cirrhosis, hepatitis B e antigen (HBeAg) status, and hepatitis B virus (HBV) viral load.[2-4] Among these factors, HBV viral load is the most clinically controllable.

Higher HBV viral load has been reported to be an independent risk factor for HCC recurrence in patients with HBV-related HCC.[5,6] Nucleoside analogues are effective in suppressing HBV replication and in ameliorating HBV-related liver disease.[7,8] They have been

Figure 2. Cumulative Incidences of HCC Recurrence and Overall Mortality Following Liver Resection

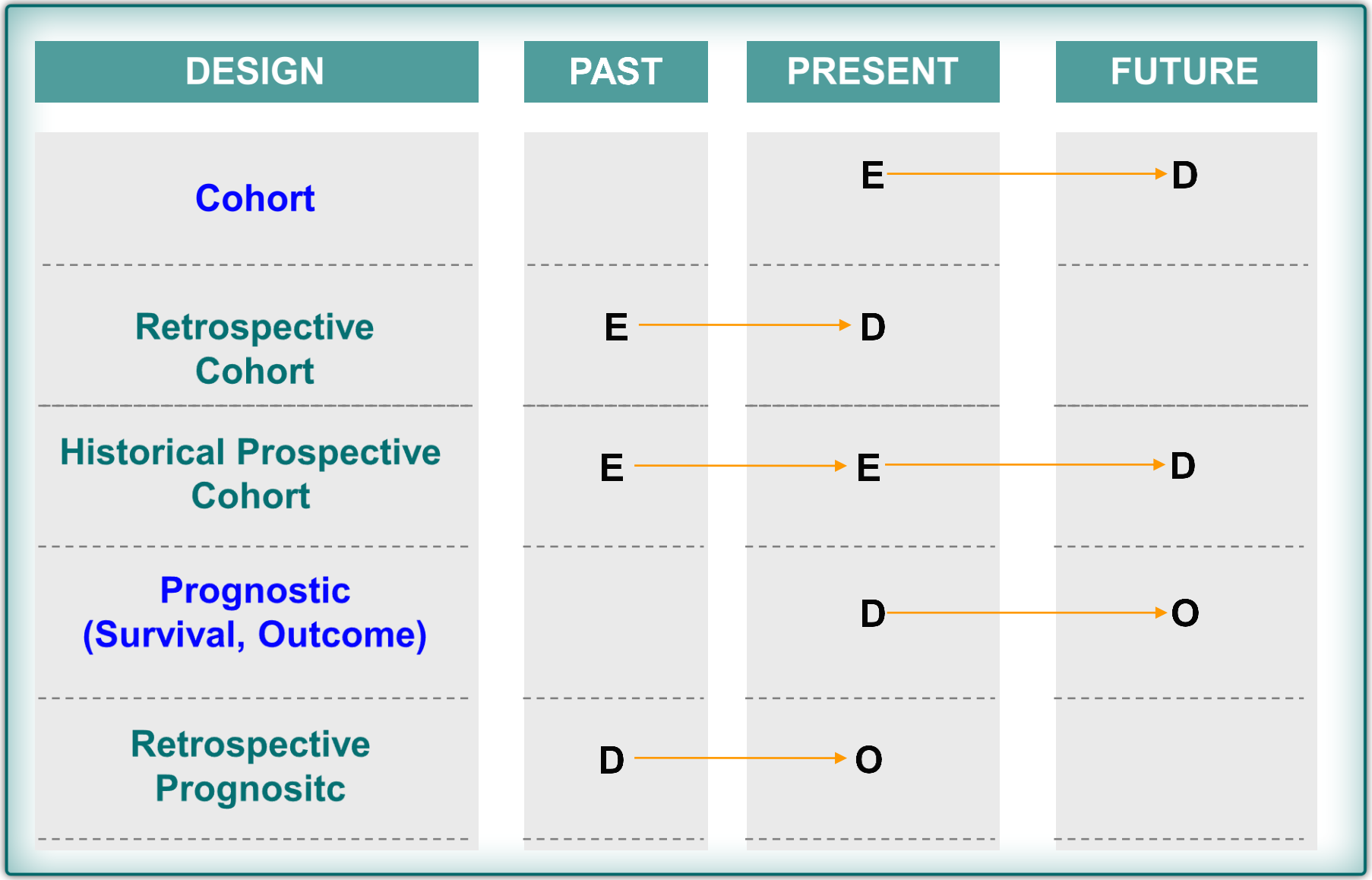


Data were compiled after adjustment for competing mortality. For cumulative incidences of hepatocellular carcinoma (HCC), calculation and comparison in competing risk data ratios were conducted using modified Kaplan-Meier and Gray methods. For overall mortality, Kaplan-Meier method was used. Recurrences (for cumulative incidences of HCC) and deaths (for overall mortality) during the first 3 months were excluded. Treated and untreated categories indicate patients with hepatitis B virus who are receiving nucleoside analogues, and those who are not, respectively.

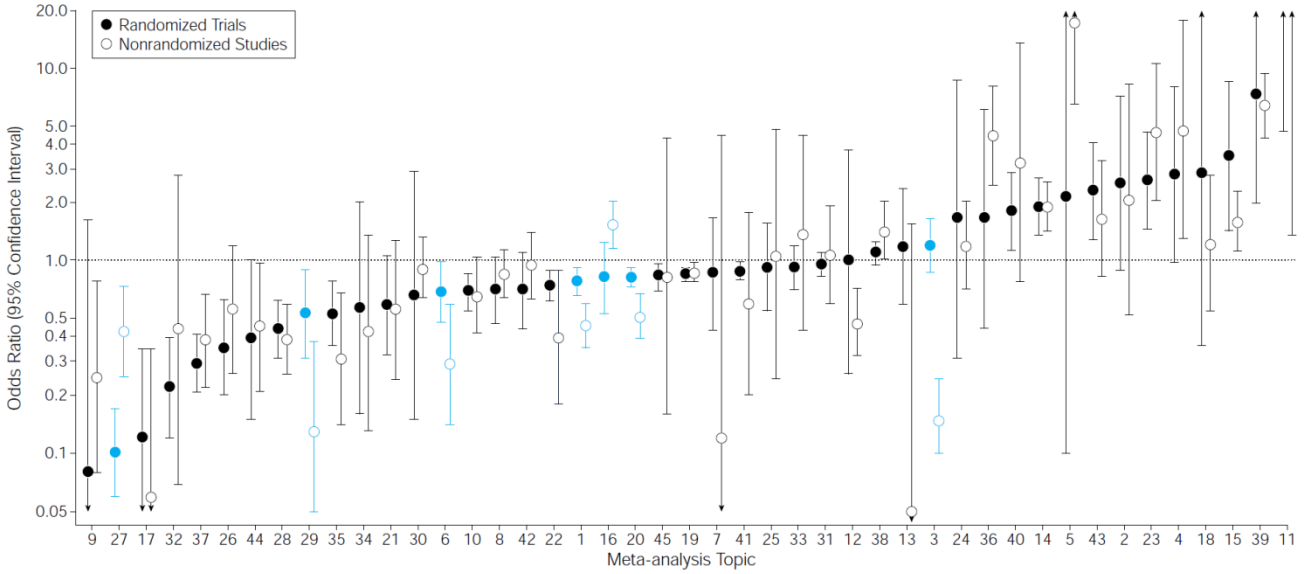
Conclusion

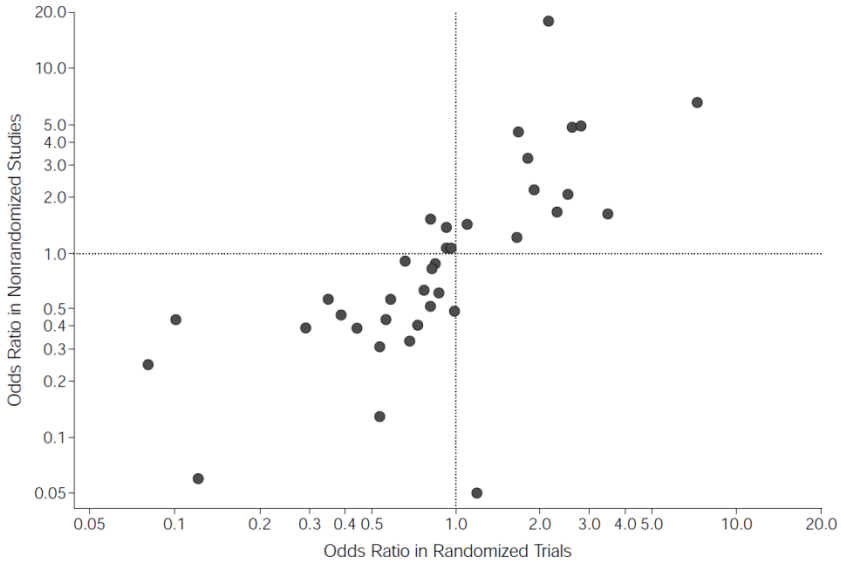
- **Historical Cohort study**
  - 비교적 정확하며 용이하게 추출이 가능한 방대한 환자 자료를 가지고 있는 병원에서 단기간 내에 훌륭한 결과를 낼 수 있는 좋은 Observational study design
  - 좋은 아이디어가 중요
  - 단점의 극복이 중요
    - Bias의 사전 예상, 차단, 보정이 필요.
    - Missing data, Loss of F/U

Cohort Study vs. Prognostic Study



Comparison of Evidence of Treatment Effects in Randomized and Nonrandomized Studies

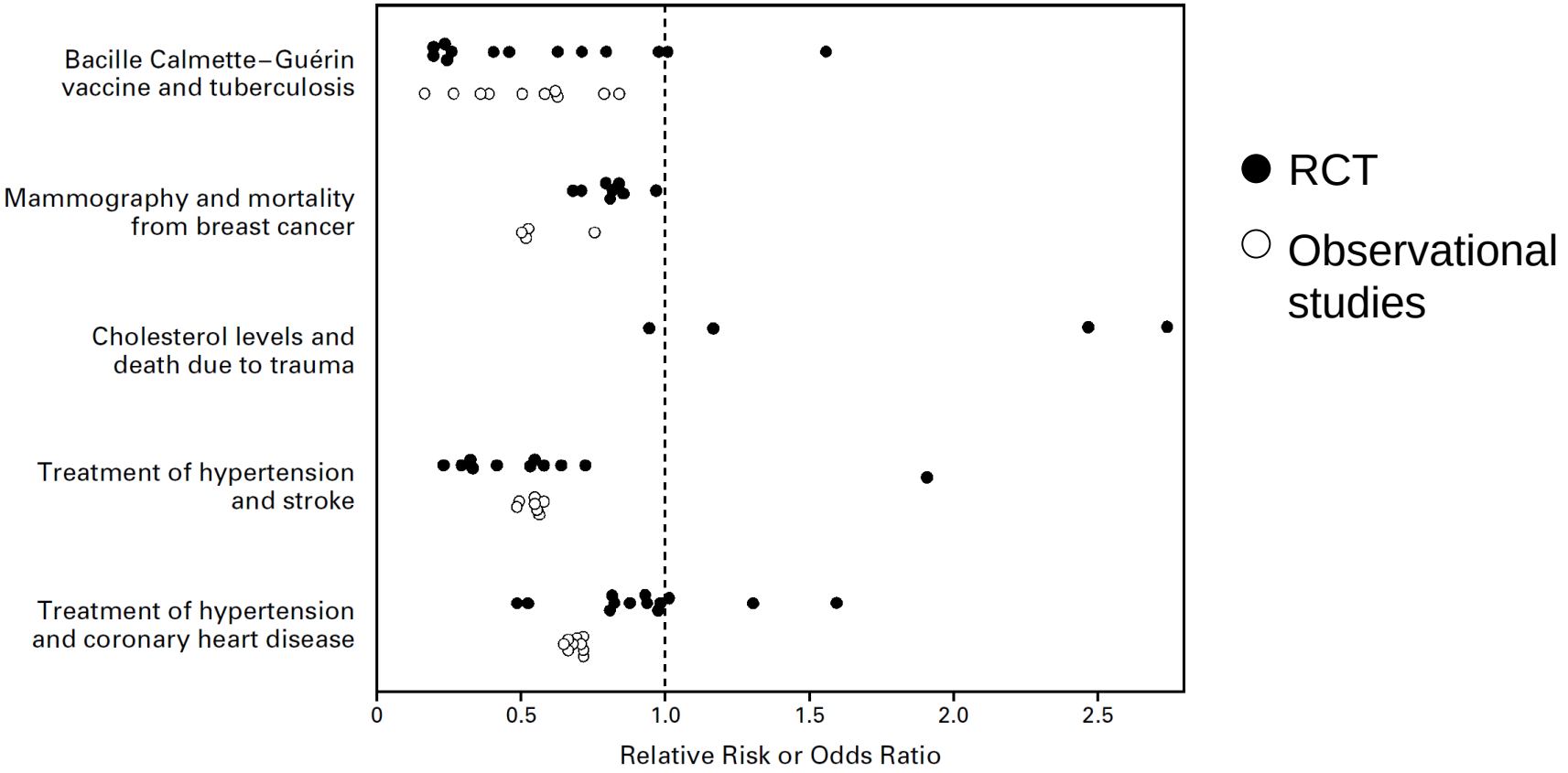




JAMA 2001;286:821.

RANDOMIZED, CONTROLLED TRIALS, OBSERVATIONAL STUDIES, AND THE HIERARCHY OF RESEARCH DESIGNS

JOHN CONCATO, M.D., M.P.H., NIRAV SHAH, M.D., M.P.H., AND RALPH I. HORWITZ, M.D.



Conclusions: The results of well-designed observational studies (with either a cohort or a case–control design) do not systematically overestimate the magnitude of the effects of treatment as compared with those in randomized, controlled trials on the same topic. (N Engl J Med 2000;342:1887-92.)

"Well-Designed Observational Studies"

- Designed with rigorous methods that mimic those of clinical trials
- A specific method used to strengthen observational studies (the "restricted cohort" design) adapts principles of the design of randomized, controlled trials
- Identifies a "zero time" for determining a patient's eligibility and base-line features,
- Uses inclusion and exclusion criteria similar to those of clinical trials,
- Adjusts for differences in base-line susceptibility to the outcome,
- Uses statistical methods (e.g., intention-to-treat analysis) similar to those of randomized, controlled trials.

N Engl J Med 2000;342:1887-92.

Research Question - Example

- Bad:
  - Will treatment of chronic hepatitis B reduce the incidence of liver cancer?

- Better: focused!
  - What is the effect of long-term treatment (>5 years) with a potent oral antiviral agent (entecavir) **(I)** in patients with chronic hepatitis B **(P)** to reduce the incidence of hepatocellular carcinoma **(O)**, compared with no-treatment control **(C)**.

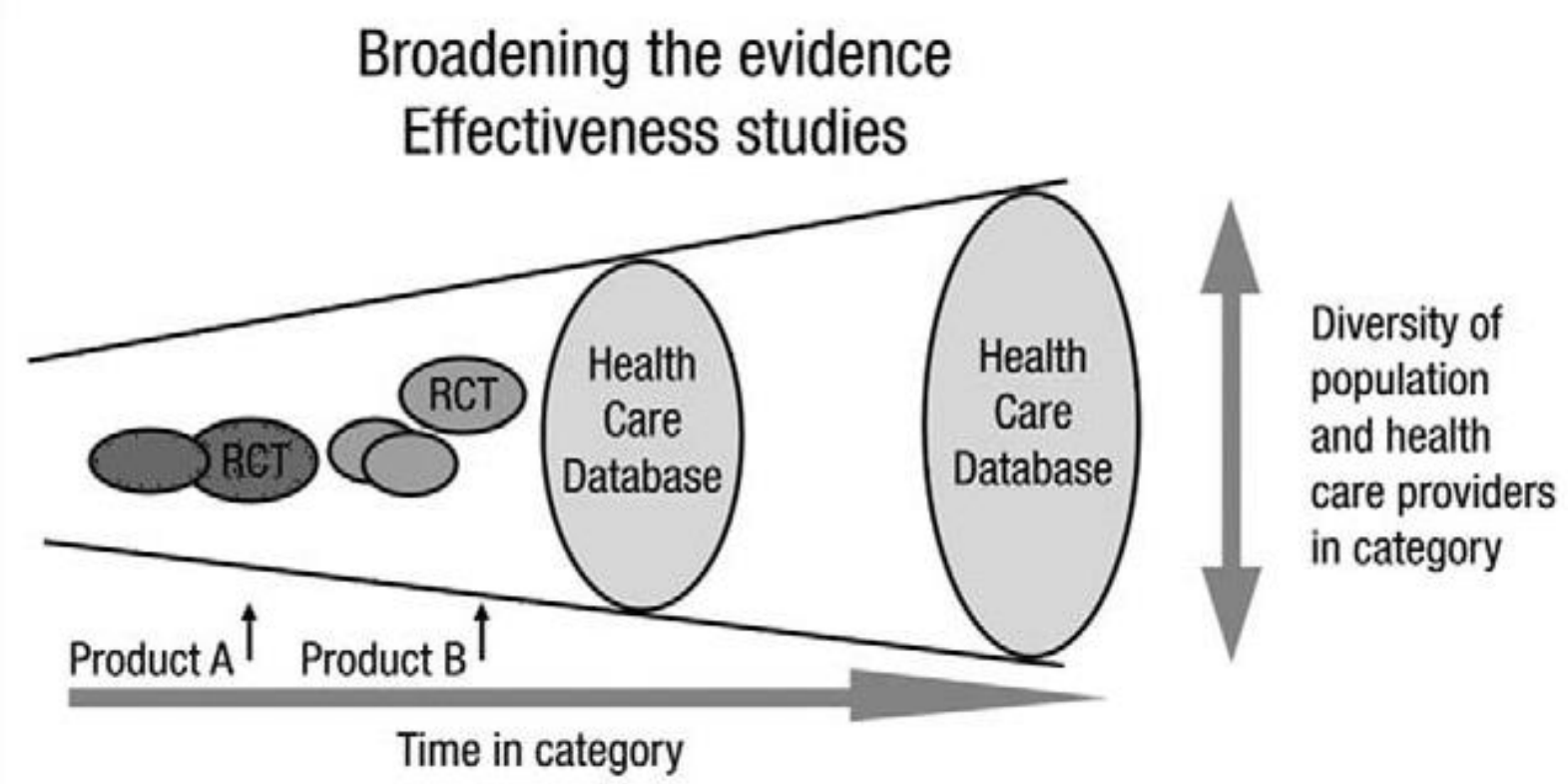
Gastroenterology 2014;147:152–161

Mortality, Liver Transplantation, and Hepatocellular Carcinoma Among Patients With Chronic Hepatitis B Treated With Entecavir vs Lamivudine

Young–Suk Lim,[1] Seungbong Han,[2] Nae–Yun Heo,[3] Ju Hyun Shim,[1] Han Chu Lee,[1] and Dong Jin Suh[1]

[1]Department of Gastroenterology, Liver Center, [2]Department of Clinical Epidemiology and Biostatistics, Asan Medical Center, Seoul, Republic of Korea; [3]Department of Internal Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Republic of Korea

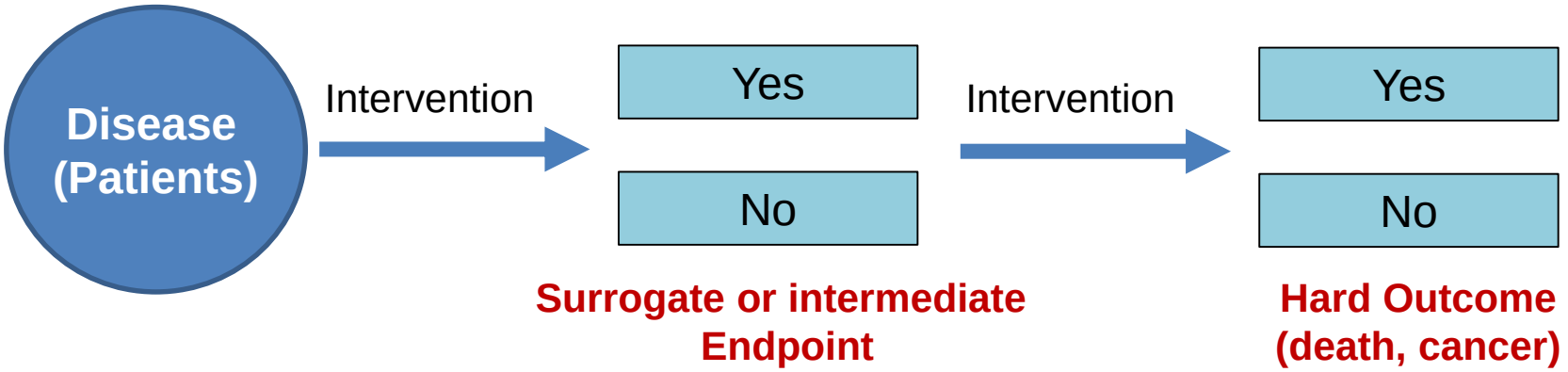
Evolution of Drug Evaluation



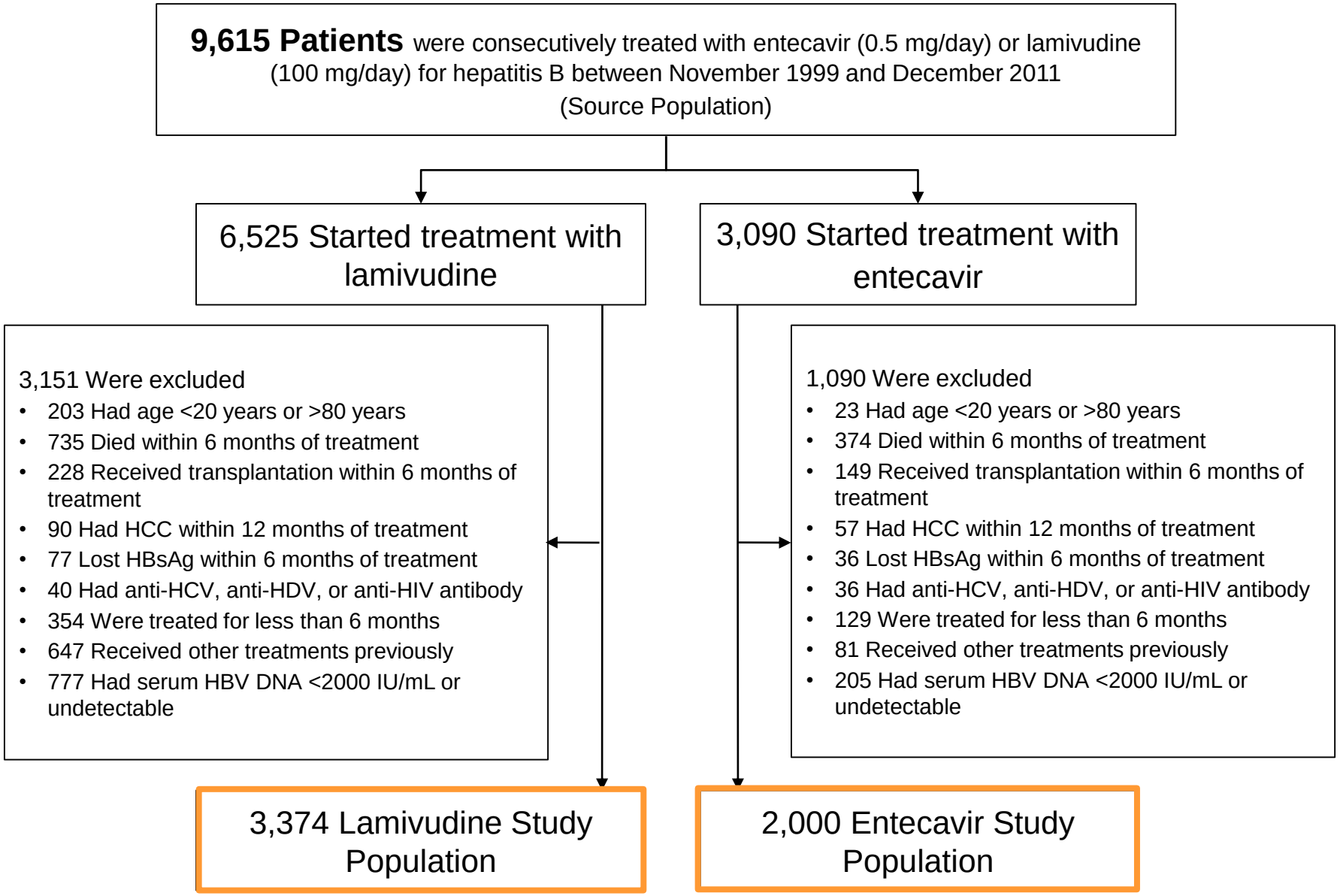
Am J Med 2009;122:114.

Endpoint vs Goal in HBV Tx

- **Endpoint**
  - Virological response
  - High frequency
  - Small number of study patients
  - Short-term observation
- **Goal**
  - Hard outcomes (death, cancer)
  - Low frequency
  - Large number of study patients
  - Long-term observation



Historical Cohort Study with Large Number of Patients



Restriction (Specification)

- **Inclusion criteria**
  - Consecutive adult treatment-naïve CHB patients who were treated with entecavir (0.5 mg/day) or lamivudine (100 mg/day)
  - At Asan Medical Center, an academic tertiary referral hospital in Seoul, Korea, between November 1, 1999 and December 31, 2011
- **Exclusion criteria**
  - Younger than 20 or older than 80
  - Death or transplantation within 6 months of treatment
  - HCC within 12 months of treatment
  - HBsAg seroclearance within 6 months of treatment
  - Anti-HCV, anti-HDV, or anti-HIV antibody
  - Treatment for less than 6 months
  - Previous other treatments
  - Serum HBV DNA <2000 IU/mL or undetectable

Zero Time

- Prognostic cohorts should begin from a point in time, called “zero time”, that is **clearly defined and consistent across patients**.
- This might be time of diagnosis or **at the start of treatment**. This allows the start of observation of each patient to be equal and simplifies interpretation.
- An inception cohort is a cohort of patients that have been followed since the inception of their disease (the date of diagnosis).
- Tx vs No-Tx: Immortal time bias

Blinding

- **Historical Cohort Study**
  - Blind the outcomes (events) at cohort assembly
- **Case-Control Study**
  - Blind the exposure (risk factors) at selecting cases and controls

Extensive Comparison of Baseline Characteristics

Characteristics	Entecavir (n=2000)	Lamivudine (n=3374)	*P*
Age (year)*	47 ± 11	43 ± 11	<0.001
Male	1288 (64.4%)	2386 (70.7%)	<0.001
HBeAg	1168 (58.4%)	2421 (71.8%)	<0.001
HBV DNA (log_{10} IU/mL)*	7.14 ± 1.64	7.49 ± 1.17	<0.001
ALT (IU/mL)†	101 (53-190)	128 (68-244)	0.13
Albumin (g/dL) †	3.8 (3.4-4.1)	3.8 (3.2-4.1)	<0.001
Total bilirubin (mg/dL)†	1.2 (0.9-1.6)	1.1 (0.9-1.6)	0.79
INR†	1.10 (1.00-1.20)	1.10 (1.00-1.30)	<0.001
Platelet (x1000/mm^3)†	142 (96-183)	147 (96-195)	0.03
Cirrhosis	1071 (53.6%)	1621 (48.0%)	<0.001
Duration of overall treatment (year)†	2.6 (1.8-3.9)	6.1 (2.7-9.0)	<0.001
Duration of overall follow-up (year)†	3.1 (2.2-4.3)	8.7 (6.5-11.5)	<0.001

* Mean ± standard deviation † Median (interquartile range)

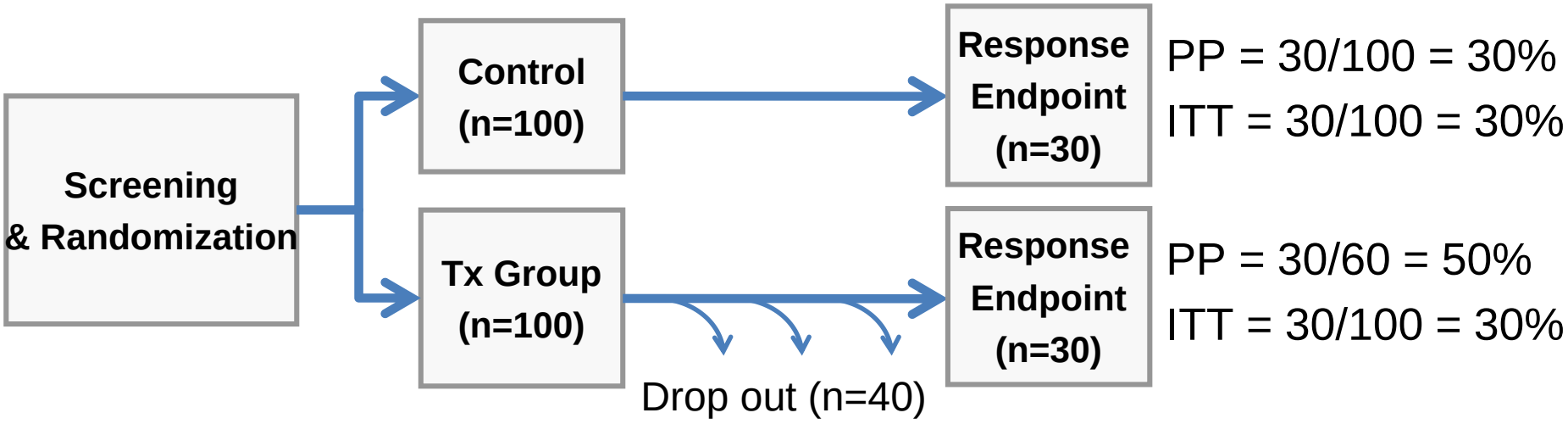
Endpoint Ascertainment

- **Clearly define the endpoints**
  - All-cause mortality or liver transplantation
  - Obtained from electronic medical records
  - Validation
    - National Population Registry of the Korea National Statistical Office
    - Korean National Health Insurance Service database

Follow-Up

- **Follow-up**
  - If follow-up is different btw. treatment groups, then the study results will be biased.
  - At least 10 outcomes are needed for each variable entering multivariable analysis.
  - From the index date (zero time) to death, transplantation, or the last follow-up date (March 31, 2013).
  - Interval: 3-6 months
  - Censored at 6 years
- **Treatment**
  - Continued even after achievement of HBeAg seroconversion

Intention-to-treat (ITT)
vs. Per-protocol (PP) Analysis



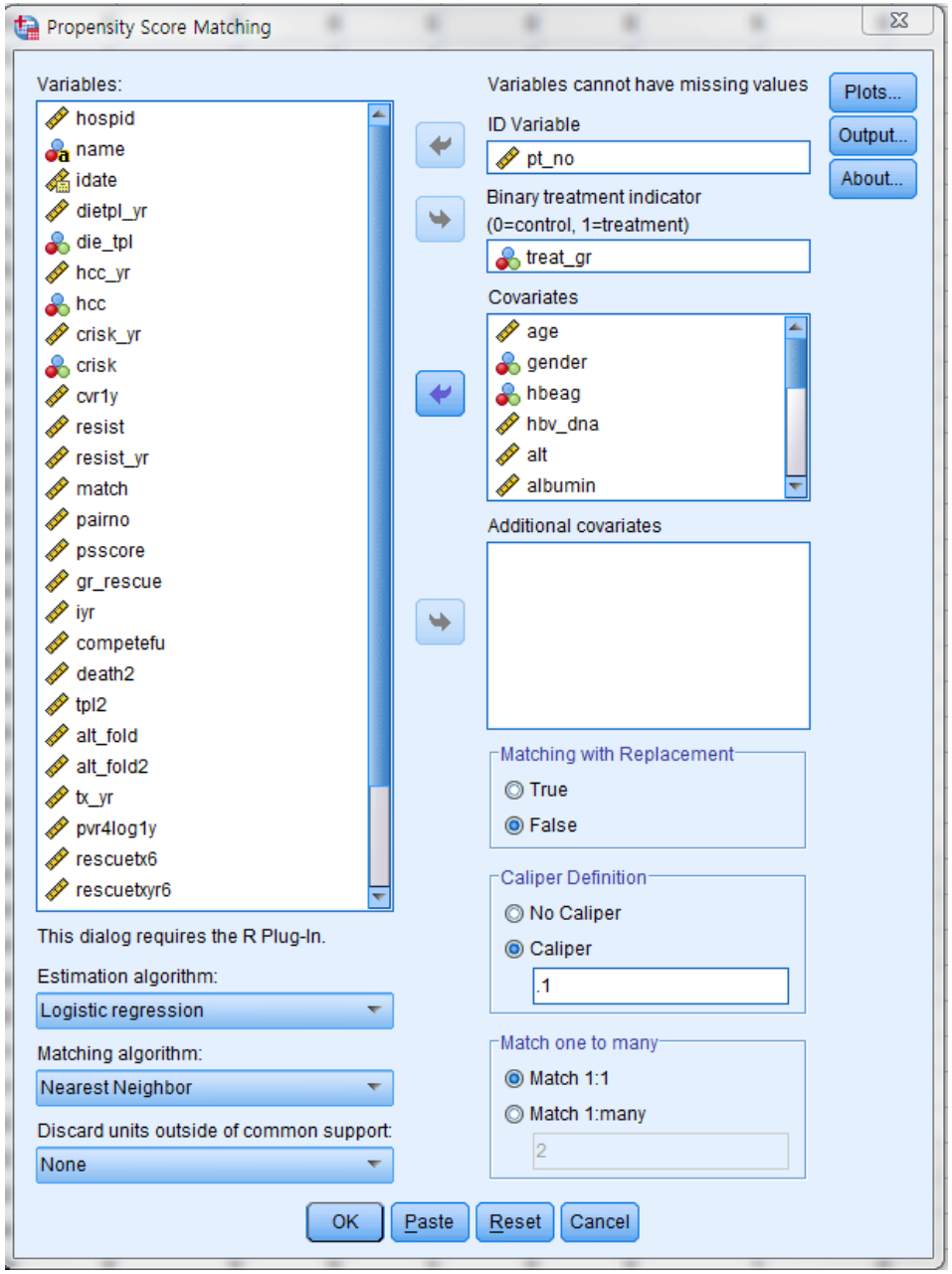
- **ITT analysis**
  - Which treatment option is best at the time de decision must be made?
  - The question corresponds to the one actually faced by clinicians.
- **Explanatory (PP) analysis**
  - Which treatment itself is better?

Multivariable Cox PH Analyses

Variables	Death or Transplantation*			Hepatocellular Carcinoma†		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Treatment with entecavir	**0.49**	**0.38–0.64**	**<0.001**	**1.08**	**0.87–1.34**	**0.48**
Age	1.02	1.00–1.03	0.006	1.06	1.05–1.07	<0.001
Gender (Male)	1.58	1.27–1.96	<0.001	1.81	1.48–2.20	<0.001
Albumin (g/dL)	0.73	0.57–0.93	0.01	0.70	0.61–0.80	<0.001
Platelet ($\times 10^3/\mu L$)	0.989	0.986–0.991	<0.001	0.995	0.993–0.997	<0.001
Diabetes mellitus	2.18	1.59–2.99	<0.001	1.51	1.10–2.08	0.01
Cirrhosis	2.51	1.71–3.68	<0.001	2.59	1.97–3.41	<0.001
Need for rescue therapy	2.14	1.69–2.70	<0.001	1.53	1.23–1.91	<0.001
Overall treatment years‡	0.72	0.69–0.75	<0.001	0.94	0.92–0.97	<0.001

*Total number of patients 5374 number of events 457.
†Total number of patients 5374 number of events 525.
‡Overall duration of treatment with any nucleoside/nucleotide analogue.

Propensity Score-Matching Analyses

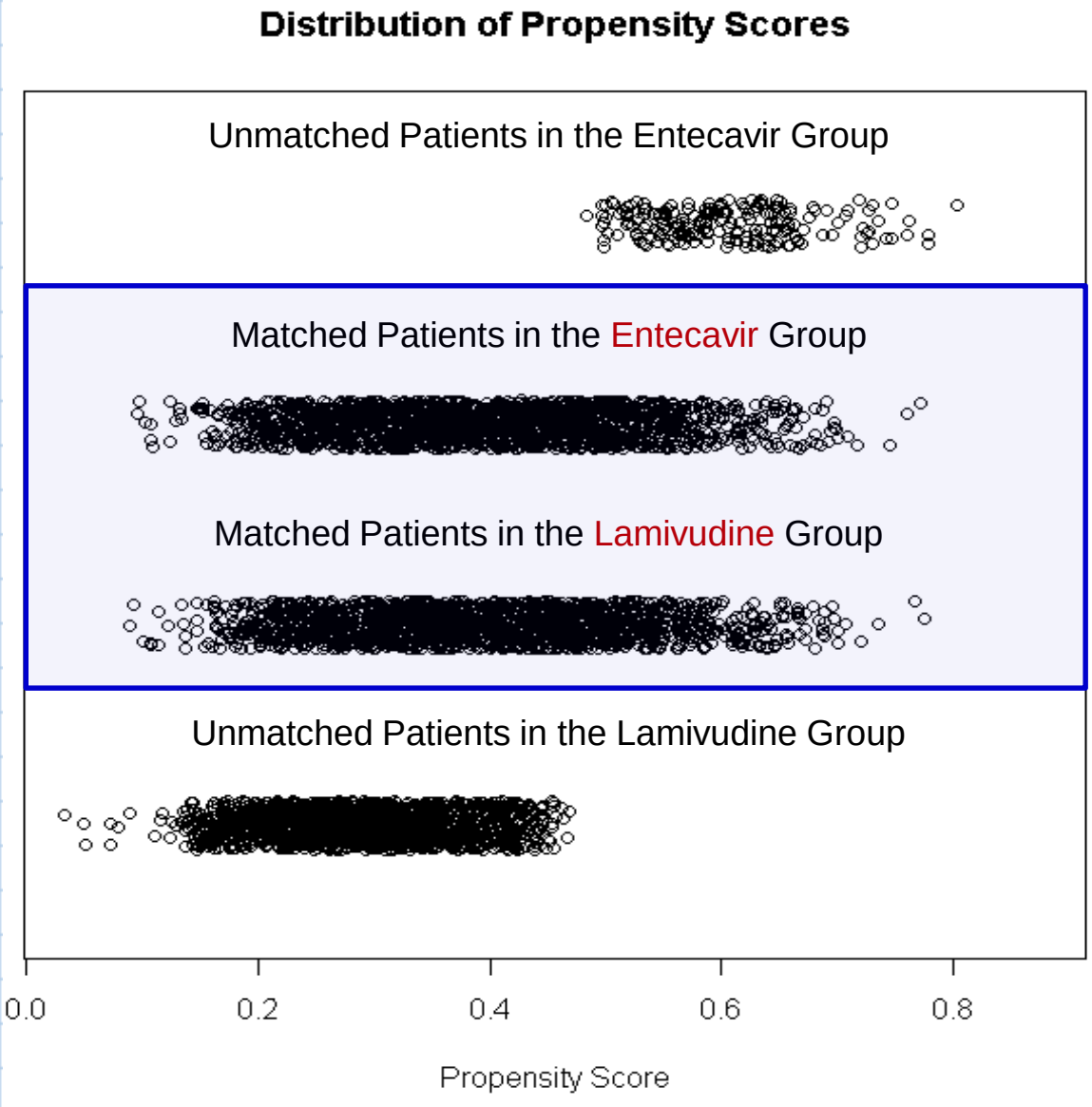


Included variables (15)

- age
- gender
- HBeAg-positivity
- HBV DNA
- ALT
- albumin
- total bilirubin
- creatinine
- INR
- platelet count
- diabetes mellitus
- hypertension
- cirrhosis
- ascites
- CTP scores

Propensity Score Matching

pt_no	ps_score	matching	pair_no
6	.2656	1	1
1559	.2684	1	1
9	.1979	1	2
1863	.1872	1	2
11	.4672	1	3
227	.4590	1	3
18	.6047	1	4
4251	.6096	1	4
19	.5862	1	5
2771	.5763	1	5
20	.4690	1	6
3967	.4649	1	6
31	.4572	1	7
2784	.4486	1	7
34	.2779	1	8
2422	.2683	1	8
38	.4357	1	9
1307	.4366	1	9
39	.2081	1	10
3056	.2119	1	10
42	.4101	1	11
551	.4170	1	11
45	.4717	1	12
2950	.4595	1	12
48	.5662	1	13
2413	.5685	1	13



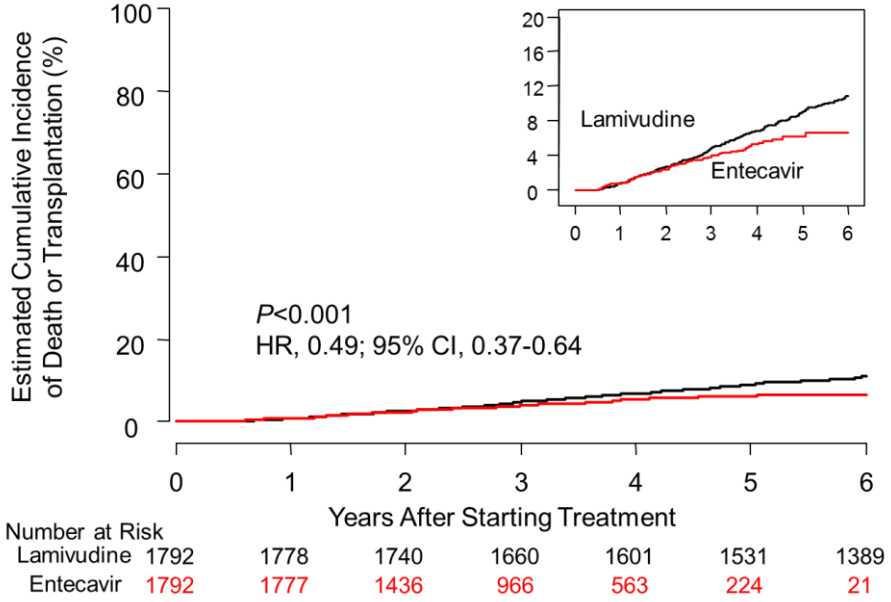
Propensity Score-Matched Overall Cohorts

Characteristics	Entecavir (n=1792)	Lamivudine (n=1792)	*P*
Age (year)*	46.1 ± 10.1	46.1 ± 10.9	0.98
Male	1193 (66.6%)	1179 (65.8%)	0.64
HBeAg	1133 (63.2%)	1107 (61.8%)	0.32
HBV DNA (log_{10} IU/mL)*	7.28 ± 1.55	7.30 ± 1.18	0.57
ALT (IU/mL)†	103 (55-195)	118 (65-223)	0.93
Albumin (g/dL) †	3.8 (3.3-4.1)	3.8 (3.3-4.1)	0.86
Total bilirubin (mg/dL)†	1.2 (0.9-1.6)	1.1 (0.9-1.6)	0.59
INR†	1.10 (1.00-1.20)	1.10 (1.00-1.20)	0.85
Platelet (x1000/mm^3)†	143 (95-184)	140 (96-184)	0.68
Cirrhosis	933 (52.1%)	934 (52.1%)	1.00

* Mean ± standard deviation, † Median (interquartile range)

Propensity Score-Matched Analyses

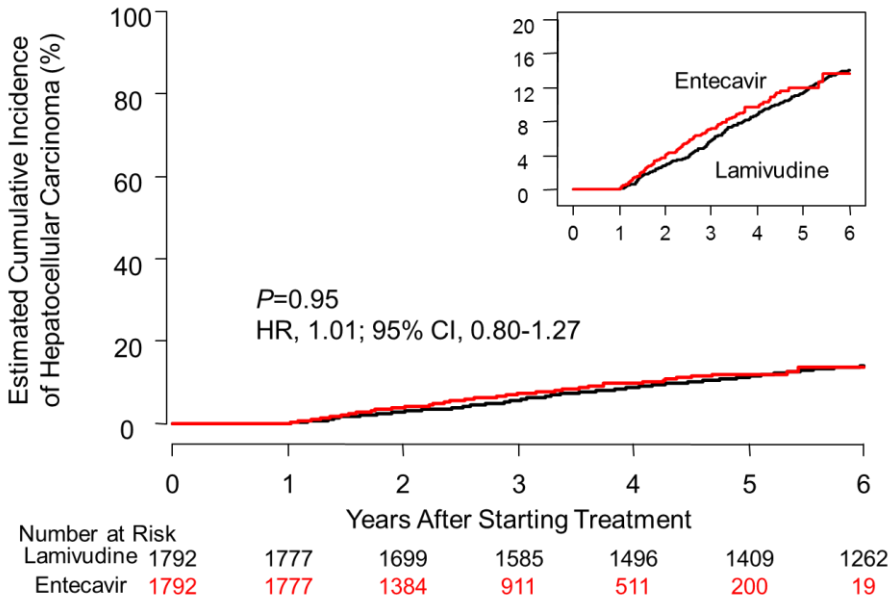
Death/Transplant



Number at Risk

Lamivudine	1792	1778	1740	1660	1601	1531	1389
Entecavir	1792	1777	1436	966	563	224	21

HCC

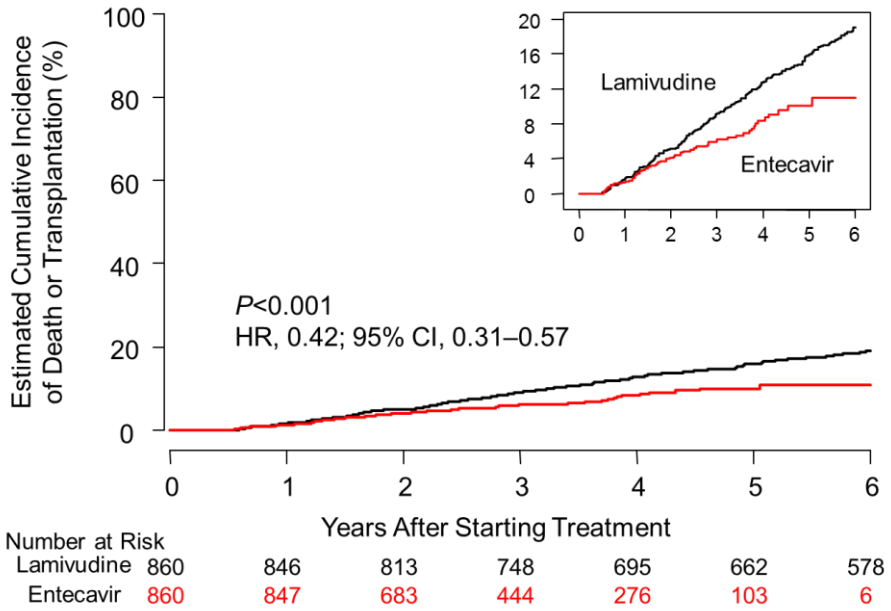


Number at Risk

Lamivudine	1792	1777	1699	1585	1496	1409	1262
Entecavir	1792	1777	1384	911	511	200	19

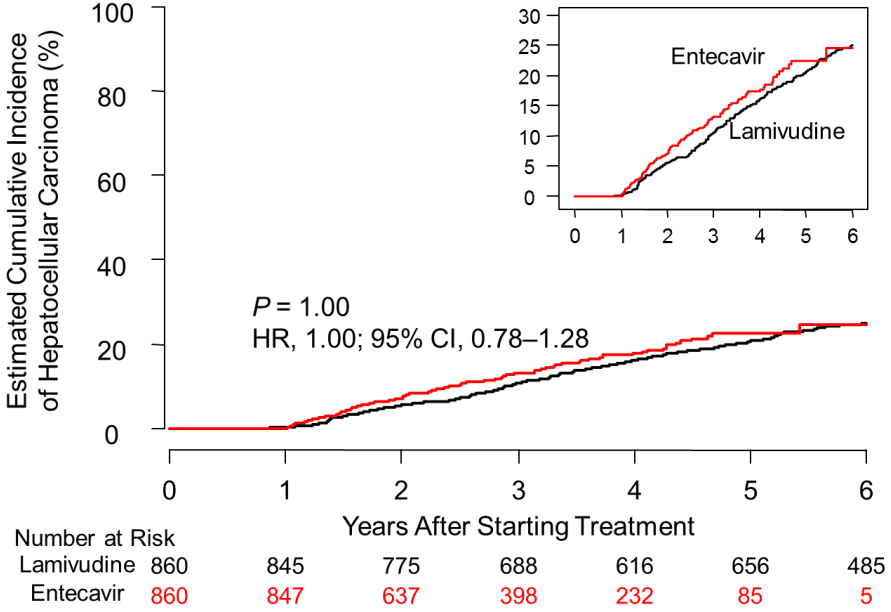
Stratification (Subgroup analysis) - Cirrhosis Sub-cohort -

Death/Transplant



Number at Risk							
Lamivudine	860	846	813	748	695	662	578
Entecavir	860	847	683	444	276	103	6

HCC



Number at Risk							
Lamivudine	860	845	775	688	616	656	485
Entecavir	860	847	637	398	232	85	5

Author's Conclusions

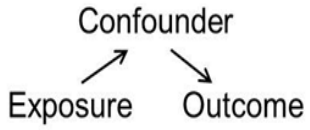
- Entecavir compared with Lamivudine
  - Significantly lower risk of death or transplantation
  - No more reduction of the risk of HCC.
- The findings were consistently observed by unadjusted, multivariable-adjusted, and propensity score-matched analyses.

Lim YS, et al. Gastroenterology. 2014;147:152-161.

Conclusions
- Pitfalls of Observational Studies -

- Bias (Systematic error)
- Confounding (Random error)
- Chance
- Effect-Cause

Association btw. the Intervention and the Outcome in a Sample

Explanation	Type of Association	Causal Model	Prevention at Design Phase	Prevention at Analysis Phase
Chance (Random Error)	Spurious	-	• Increase sample size	• P values • Confidence intervals
Bias (Systematic Error)	Spurious	-	• Carefully consider study subjects, predictor variables, and outcome variables	• Stratification • Adjustment • Propensity scores • Sensitivity analysis
Effect-Cause	Real	Exposure ← Outcome	• Do a longitudinal study with historical sequence	• Consider biologic plausibility
Confounding	Real		• Restriction (strict inclusion & exclusion criteria) • Matching	• Stratification • Adjustment • Propensity scores • Sensitivity analysis
Cause-Effect	Real	Exposure → Outcome		

Conclusions
- Controlling Pitfalls of Observational Studies -

Prevention at Design Phase

- Mimic as closely as possible in RCT
- Use stronger study design
  - Cohort study > Case-control study
- Large sample size
- Restriction
  - Inclusion & exclusion criteria
- Zero time (for prognostic studies)
  - Clearly define!
- Blinding
- Endpoint Ascertainment: Clearly define & Validate!
- Follow-Up
  - Check drop-out rate & equality btw. groups

Conclusions
- Controlling Pitfalls of Observational Studies -

Prevention at Analysis Phase

- Intention-to-treat (ITT) analysis
- Adjustment
  - Multivariable analysis
- Stratification
- Propensity score
- Sensitivity analysis

Thank you for your attention !