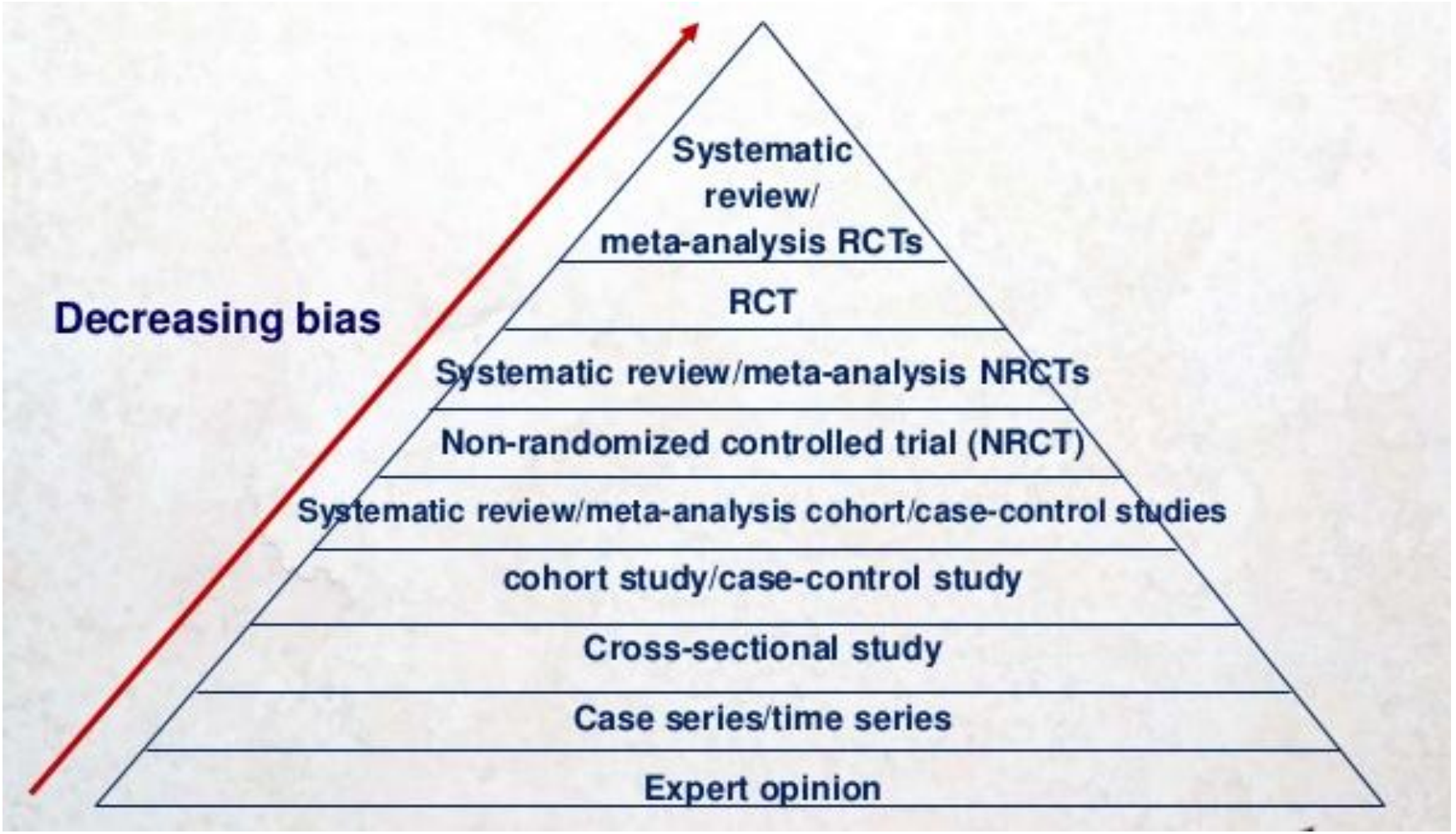
Bias and Artifact of Clinical Study (Essentials for cardiologists)

연세 원주의대
김장영

Hierarchy of evidence in evidence of medicine

Large clinical RCT and met-analysis era…



전통적인 bias in clinical observation

Bias in Clinical Observation	
Selection bias	Occurs when comparisons are made between groups of patients that differ in determinates of outcome other than the one under study.
Measurement bias	Occurs when the methods of measurement are dissimilar among groups of patients
Confounding	Occurs when two factors are associated (travel together) and the effect of one is confused with or distorted by the effect of the other

Biases and Artifacts in Clinical Trial era

- Lack of statistical power (제가 생각하기에는 대부분)
  - clinical vs. statistical significant
- Bias randomization (CAPPP) – not centralized
- Heart Failure artefact (ALLHAT) – diuretics mask symptoms
- Lost to follow-up, unblinding, discontinuation (MRC)
- Regression to the mean – vs. Wilder's principle
- Hawthorne effects (RDN), patient compliance – therapeutic drug monitoring
- Soft endpoints in open trials, data problems and retraction
- Subgroup analysis

당뇨 때 아스피린을 일차예방으로 사용하시는지요 ?

사례1

Aspirin in diabetes (ADA 2015)

ANTIPLATELET AGENTS

Recommendations

- Consider aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with type 1 or type 2 diabetes at increased cardiovascular risk (10-year risk >10%). This includes most men aged >50 years or women aged >60 years who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria). **C**
- Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk <5%, such as in men aged <50 years and women aged <60 years with no major additional CVD risk factors), since the potential adverse effects from bleeding likely offset the potential benefits. **C**

Risk Reduction

Aspirin has been shown to be effective in reducing cardiovascular morbidity and mortality in high-risk patients with previous MI or stroke (secondary prevention). Its net benefit in primary prevention among patients with no previous cardiovascular events is more controversial, both for patients with and without a history of diabetes (57,58). Two randomized controlled trials of aspirin specifically in patients with diabetes failed to show a significant reduction in CVD end points, raising questions about the efficacy of aspirin for primary prevention in people with diabetes (59,60).

59. Ogawa H, Nakayama M, Morimoto T, et al.; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008;300:2134–2141

60. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008;337:a1840

Low-Dose Aspirin for Primary Prevention of Atherosclerotic Events in Patients With Type 2 Diabetes

A Randomized Controlled Trial

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Masafumi Nakayama, MD, PhD
Takeshi Morimoto, MD, PhD
Shiro Uemura, MD, PhD
Masao Kanauchi, MD, PhD
Naofumi Doi, MD, PhD
Hideaki Jinnouchi, MD, PhD
Seigo Sugiyama, MD, PhD
Yoshihiko Saito, MD, PhD
for the Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators

Context Previous trials have investigated the effects of low-dose aspirin on primary prevention of cardiovascular events, but not in patients with type 2 diabetes.

Objective To examine the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in patients with type 2 diabetes.

Design, Setting, and Participants Multicenter, prospective, randomized, open-label, blinded, end-point trial conducted from December 2002 through April 2008 at 163 institutions throughout Japan, which enrolled 2539 patients with type 2 diabetes without a history of atherosclerotic disease and had a median follow-up of 4.37 years.

Interventions Patients were assigned to the low-dose aspirin group (81 or 100 mg per day) or the nonaspirin group.

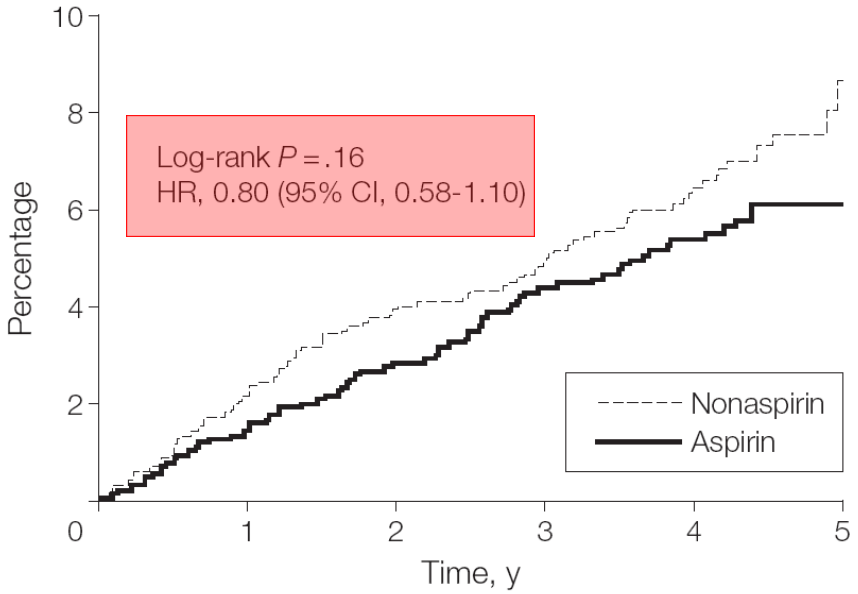
Main Outcome Measures Primary end points were atherosclerotic events, including fatal or nonfatal ischemic heart disease, fatal or nonfatal stroke, and peripheral arterial disease. Secondary end points included each primary end point and combinations of primary end points as well as death from any cause.

Results A total of 154 atherosclerotic events occurred: 68 in the aspirin group (13.6 per 1000 person-years) and 86 in the nonaspirin group (17.0 per 1000 person-years) (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.58-1.10; log-rank test, $P=.16$). The combined end point of fatal coronary events and fatal cerebrovascular events occurred in 1 patient (stroke) in the aspirin group and 10 patients (5 fatal myocardial infarctions and 5 fatal strokes) in the nonaspirin group (HR, 0.10; 95% CI, 0.01-0.79; $P=.0037$). A total of 34 patients in the aspirin group and 38 patients in the nonaspirin group died from any cause (HR, 0.90; 95% CI, 0.57-1.14; log-rank test, $P=.67$). The composite of hemorrhagic stroke and significant gastrointestinal bleeding was not significantly different between the aspirin and nonaspirin groups.

Conclusion In this study of patients with type 2 diabetes, low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.

Trial Registration clinicaltrials.gov Identifier: NCT00110448

DIABETES MELLITUS IS A POWERful risk factor for cardiovascular events. The Framingham Heart Study reported that diabetes was associated with odds ratios for coronary heart disease of 1.5 and 1.8 for men and women, respectively, and relative risks for stroke of 1.4 and 1.7 for men and women, respectively.[1-5] Individuals with diabetes have a 2- to 4-fold increased risk of developing cardiovascular events than those without diabetes.[6]



No. at risk						
Nonaspirin	1277	1220	1165	1117	813	135
Aspirin	1262	1210	1159	1095	806	140

	Aspirin Group		Nonaspirin Group			
	No. (%)	No. per 1000 Person-Years	No. (%)	No. per 1000 Person-Years	Hazard Ratio (95% CI)	*P* Value
Primary end point: all atherosclerotic events	68 (5.4)	13.6	86 (6.7)	17.0	0.80 (0.58-1.10)	.16
Coronary and cerebrovascular mortality	1 (0.08)	0.2	10 (0.8)	2.0	0.10 (0.01-0.79)	.0037
CHD events (fatal + nonfatal)	28 (2.2)	5.6	35 (2.7)	6.9	0.81 (0.49-1.33)	.40
Fatal MI	0	0	5 (0.4)	1.0		
Nonfatal MI	12 (1.0)	2.4	9 (0.7)	1.8	1.34 (0.57-3.19)	.50
Unstable angina	4 (0.3)	0.8	10 (0.8)	2.0	0.40 (0.13-1.29)	.13
Stable angina	12 (1.0)	2.4	11 (0.9)	2.2	1.10 (0.49-2.50)	.82
Cerebrovascular disease (fatal + nonfatal)	28 (2.2)	5.6	32 (2.5)	6.3	0.84 (0.53-1.32)	.44
Fatal stroke	1 (0.08)	0.2	5 (0.4)	1.0	0.20 (0.024-1.74)	.15
Nonfatal stroke						
Ischemic	22 (1.7)	4.4	24 (1.9)	4.6	0.93 (0.52-1.66)	.80
Hemorrhagic	5 (0.4)	1.0	3 (0.2)	0.6	1.68 (0.40-7.04)	.48
Transient ischemic attack	5 (0.4)	1.0	8 (0.6)	1.6	0.63 (0.21-1.93)	.42
Peripheral artery disease[a]	7 (0.6)	1.4	11 (0.9)	2.2	0.64 (0.25-1.65)	.35

www.nature.com/clinicalpractice/cardio

Diabetes and aspirin: beware of underpowered negative trials

Michael E Farkouh and Valentin Fuster

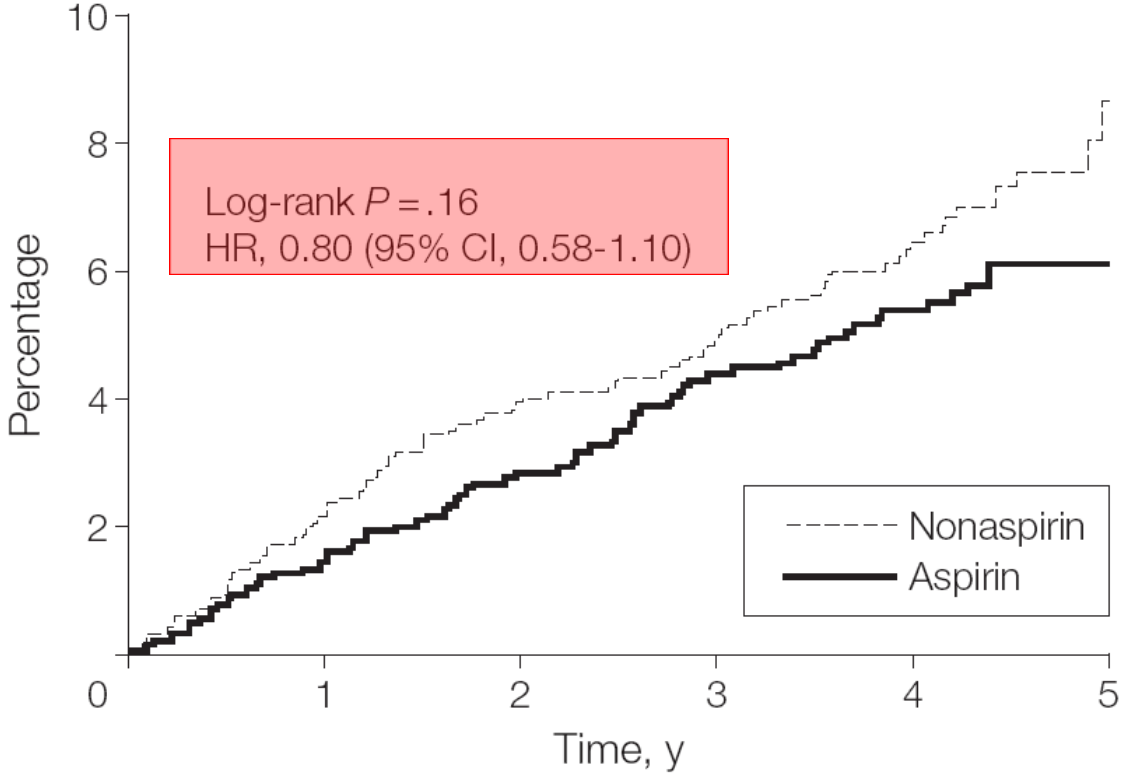
The problem of low power also arises when trialists make unrealistic projections of event rates. In the JPAD trial, the investigators predicted 52 primary cardiovascular events per 1,000 person-years but the actual event rate was only 17 events per 1,000 person-years. This miscalculation occurs frequently in the cardiovascular arena because the rapid advent of new and improved therapies is driving event rates lower over the course of these trials.

When an important public health question is on the line, we should be prepared to use adequately powered trials to attain a reliable answer.

예상 보다 event 적게 발생하면 통계적 power 가 낮아지고
True negative 아닐 가능성이 있다

만약 event rate 가 처음 예측과 같게 아왔다면 결과가 다르게 나오지 않았을까 ..

(예측:52/1000 person-year, 실제 17/1000person-year)



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만약 event rate 가 처음 예측과 왜 다르게..

(예측:52/1000 person-year, 실제 17/1000person-year)

원문

The incidence of cardiovascular death, myocardial infarction, and cerebrovascular events were 7.5, 7.5, and 8.0 events per 1000 Japanese diabetic patients per year, respectively, according to the Hisayama-cho study[22] and Funagata study.[23]

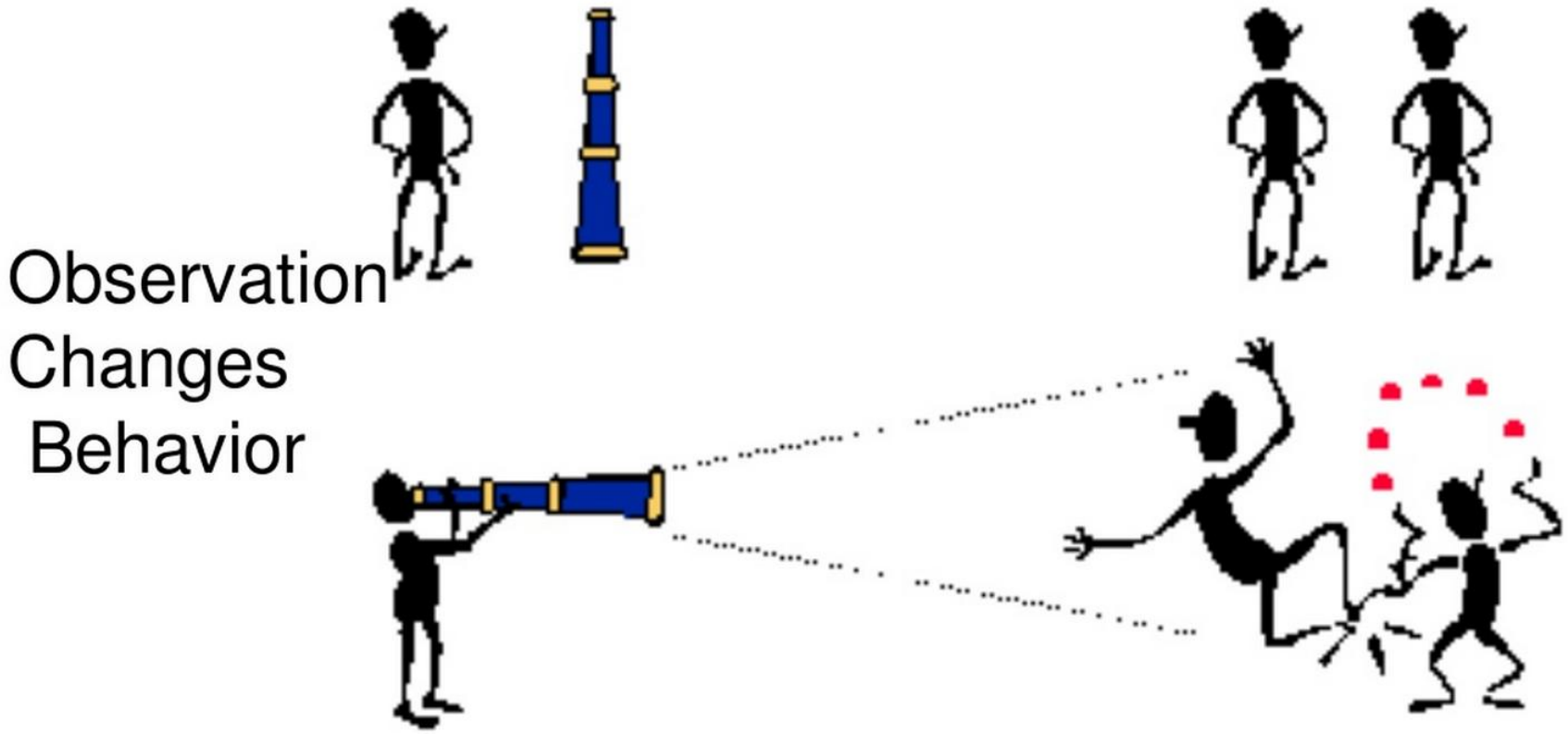
22. Fujishima M, Kiyohara Y, Kato I, et al. Diabetes and cardiovascular disease in a prospective population survey in Japan: the Hisayama Study. *Diabetes*. 1996; 45(suppl 3):S14-S16.

23. Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A. Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose: the Funagata Diabetes Study. *Diabetes Care*. 1999;22(6):920-924.

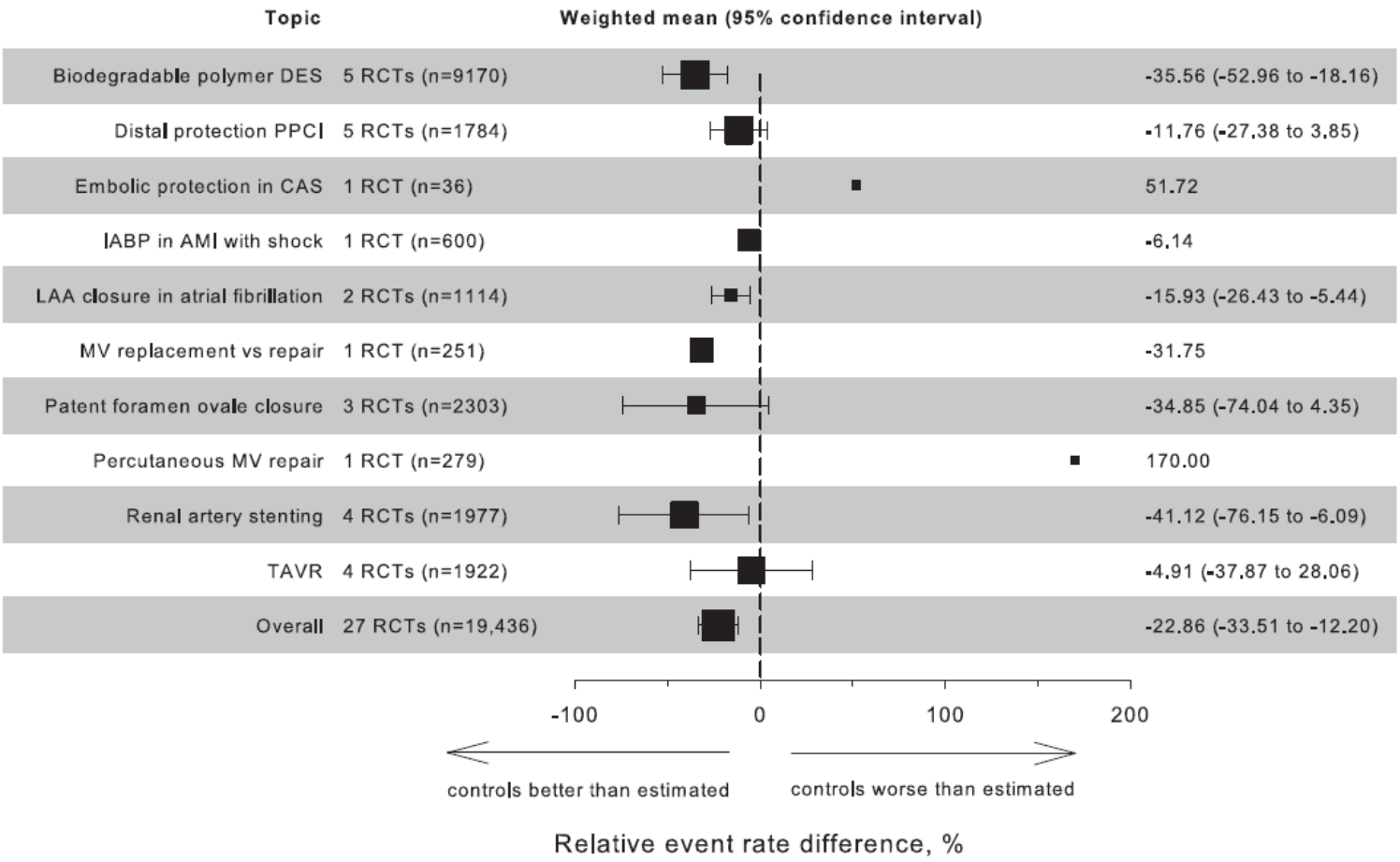
- **Trial design**
  - Progress of overall care prior to trial initiation
  - Lack of prior quality data precluding accurate event rate estimation
- **Differences with reference population***
  - Geographical and patterns of care differences between study population and reference population
- **Trial conduct**
  - Progress of overall care during the trial
  - Greater physician adherence to guideline recommended therapies
- **Patient's reaction to trial participation e the Hawthorne effect**

The Hawthorne Effect:

임상연구에 들어오면 피험자가 평소와 달리 행동하다



현재도 event overestimation 을 하여 underpowered study 생기는가 ?



Am J Cardiol 2015;116:355-363

Summary: statistical power in RCT

- Risk level and endpoint rate
- Number and yrs. of treatment (patient-years)
- No. of treatment arms
- Concomitant treatment
- Delta difference of outcome
- Lost-to-follow up and discontinuation
- Patient adherence
- Alpha and beta value

ACS 에서 anti-thrombotics 사용은 어떻게 하시나요 ?

사례 2

Clinical vs. statistical significant

Statistical vs. Clinical Significant

Intervention	Control (%)	Rx (%)	Summary Risk Ratio (95% CI)	p Value	NNT (95% CI)	Pr (d ≥MCID)	Interpretation of Confidence Intervals
1. ASA vs. placebo (n = 2,856) (10,11)	12.8	5.5	0.43 (0.33–0.56)	<0.01	14 (11–19)	100%	Statistically significant and clinically important (E)
2. ASA + UFH vs. ASA (n = 1,353) (11)	10.4	7.9	0.67 (0.44–1.02)	0.06	44 (∞–18)	87%	Statistically not significant but may be clinically important (B)
3. ASA + UFH + clopidogrel vs. ASA + UFH (n = 12,562) (12)	11.4	9.3	0.82 (0.74–0.92)	<0.01	54 (35–120)	76%	Statistically significant and may be clinically important (D)
4. ASA + UFH + GPI vs. ASA + UFH (n = 27,051) (13)	11.8	10.5	0.91 (0.86–0.99)	0.012	73 (48–157)	4%	Statistically significant but not clinically important (C)
5. ASA + clopidogrel + UFH vs. ASA + clopidogrel + enoxaparin (n = 10,027) (14)	14.5	14.0	0.96 (0.86–1.06)	0.43	184 (∞–52)	1%	Statistically not significant and clinically not important (A)

Summary risk ratios are derived from random-effects meta-analysis except for #3 and #5, which are based on the CURE trial and the SYNERGY trial, respectively. Posterior probabilities (Pr) are derived from Bayesian analysis, and interpretation of confidence intervals (CIs) is based on schema described in Figure 1A.

ASA aspirin; GPI glycoprotein IIb/IIIa inhibitor; MCID minimum clinically important difference of 15% relative risk difference; **NNT number needed to treat;** Rx treatment; UFH unfractionated heparin.

10. BMJ 2002;324:71– 86.
11. J Am Coll Cardiol 2002;40:1366 –74.
12 N Engl J Med 2001;345:494 –502.
13. Lancet 2002;359:189 –98.
14. JAMA 2004;292:45–54..

J Am Coll Cardiol 2010;55:415–27

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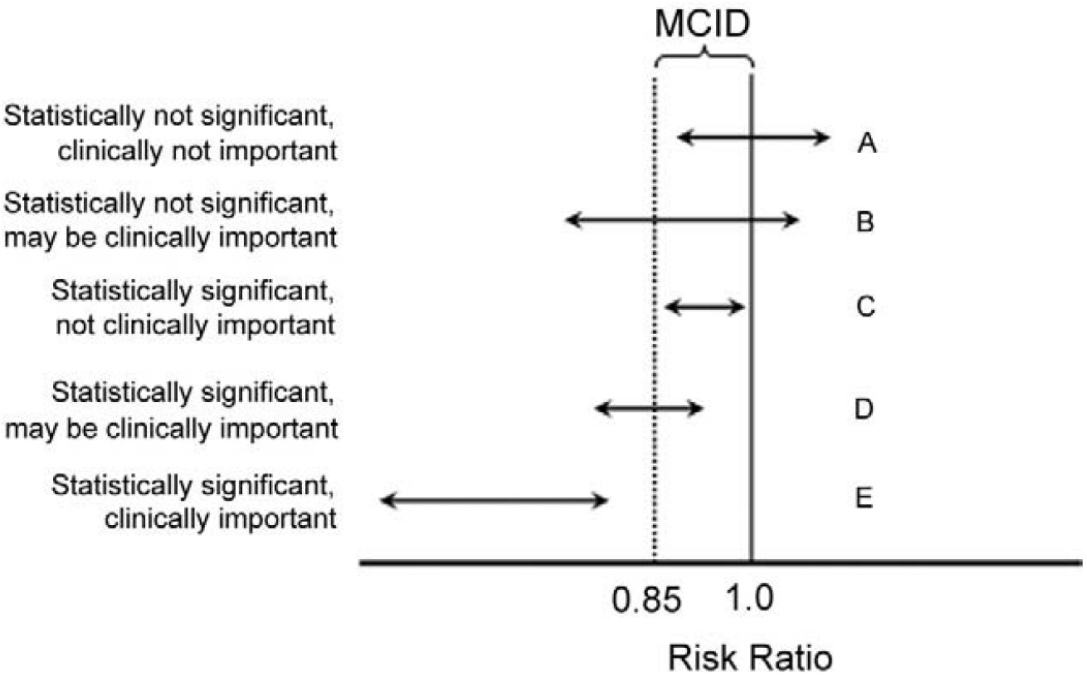


J Am Coll Cardiol 2010;55:415–27

당뇨혈압에서 목표혈압은 140 vs. 130 mmHg 이하가 좋은가요 ?

사례 3

European Heart Journal (2007) 28, 1462–1536
doi:10.1093/eurheartj/ehm236

2007 Guidelines for the management of arterial hypertension

5.2.2 Blood pressure targets in diabetic and very high or high risk patients

In order to maximize cardiovascular protection, in diabetic patients it has been recommended that antihypertensive treatment should be more intense, and a goal blood pressure of < 130/80 mmHg has been proposed. There is very solid evidence of a beneficial effect (reduction in macro and microvascular complications) of a greater versus a smaller blood pressure reduction in type 2 diabetic patients as demonstrated by the HOT and UKPDS trials,[311,427] and confirmed by the ABCD studies.[319,422] A recent meta-analysis of available trials in diabetic patients has calculated a reduced incidence of cardiovascular events (particularly stroke) with more versus less intense treatment, for a between-group difference in systolic and diastolic blood pressure averaging 6.0 and 4.6 mmHg, respectively.[296]

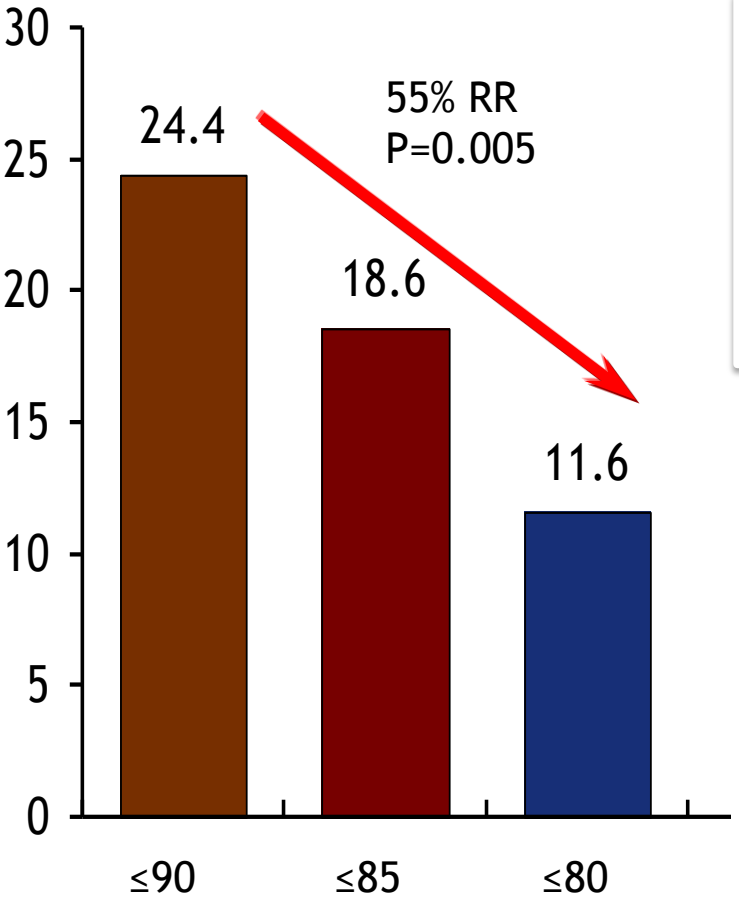
Hansson L,. Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. Lancet 1998;351:1755–1762

UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in Type 2 diabetes. UKPDS38. BMJ 1998;317:703–713.

Estacio RO, et al. Effect of blood pressure control on diabetic microvascular complications in patients with hypertensionand type 2 diabetes. Diabetes Care 2000;23(Suppl 2):B54–B64.

BP Goals of Treatment in High Risk Patients

HOT trial: Effect of target DBP on CV event over 4 yrs in patients with Diabetes



Low event rate : underpowered

Prespecified subgroup analysis ?

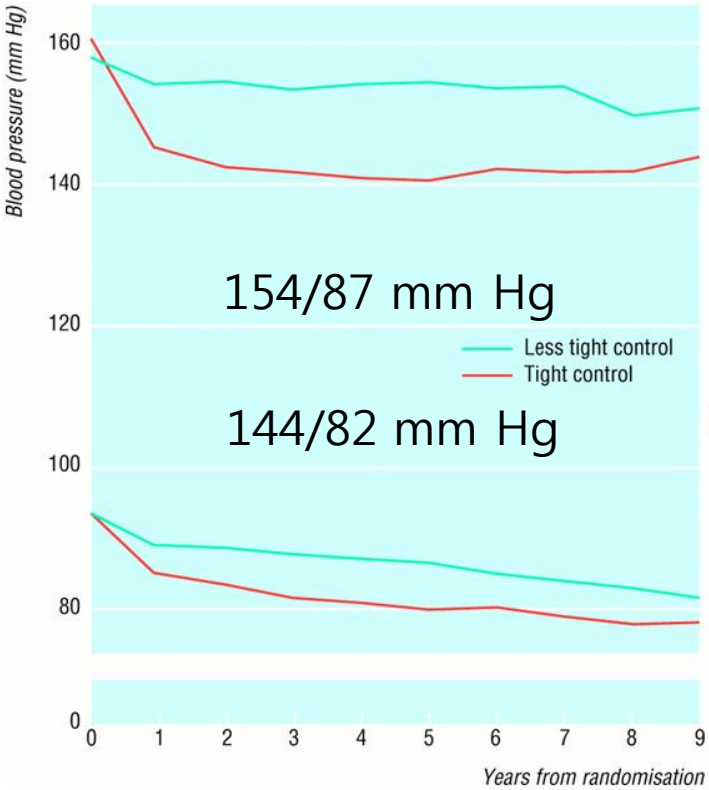
Target diastolic BP < 80 mmHg
: actual 139/81.1 mmHg

	Mean (SD) blood pressure by diastolic blood pressure target group		
	≤90 mm Hg	≤85 mm Hg	≤80 mm Hg
Systolic blood pressure (mm Hg)			
Baseline	169·8 (14·4)	169·5 (14·0)	169·7 (14·1)
Achieved*	143·7 (11·3)	141·4 (11·7)	139·7 (11·7)
Difference	26·2 (13·0)	28·0 (13·2)	29·9 (13·6)
Diastolic blood pressure (mm Hg)			
Baseline	105·4 (3·4)	105·4 (3·4)	105·4 (3·4)
Achieved*	85·2 (5·1)	83·2 (4·8)	81·1 (5·3)
Difference	20·3 (5·6)	22·3 (5·4)	24·3 (5·8)

* All Patient (n=18,790)

Hansson L. et al. Lancet 1998;351:1755-62

UKPDS study



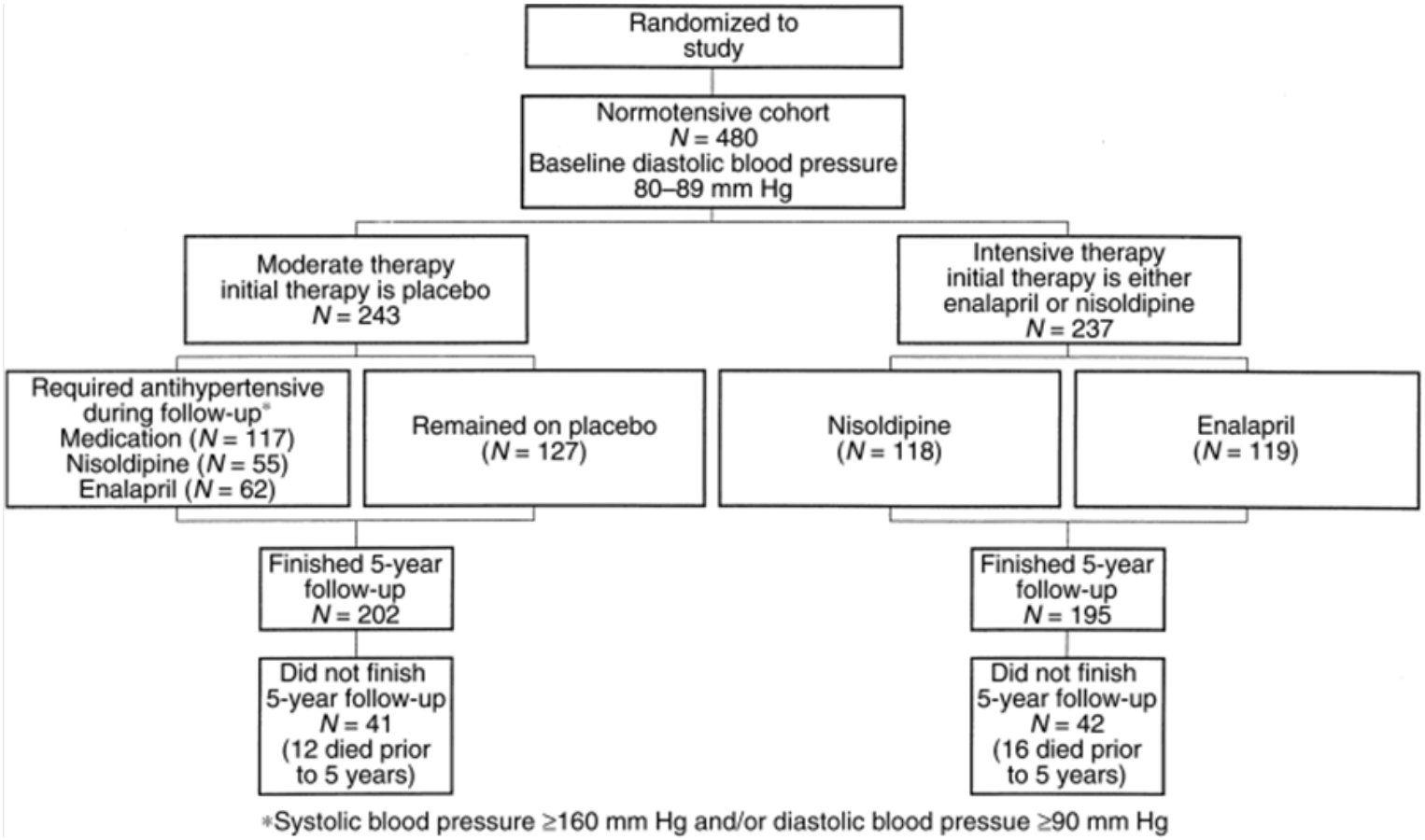
British Medical Journal Publishing Group et al. BMJ 1998;317:703-713

Clinical end point	Patients with aggregate end points: Tight control (n=758)	Patients with aggregate end points: Less tight control (n=390)	Absolute risk (events per 1000 patient years): Tight control	Absolute risk (events per 1000 patient years): Less tight control	P value	Relative risk for tight control (95% CI)
Any diabetes related end point	259	170	50.9	67.4	0.0046	0.76 (0.62 to 0.92)
Deaths related to diabetes	82	62	13.7	20.3	0.019	0.68 (0.49 to 0.94)
All cause mortality	134	83	22.4	27.2	0.17	0.82 (0.63 to 1.08)
Myocardial infarction	107	69	18.6	23.5	0.13	0.79 (0.59 to 1.07)
Stroke	38	34	6.5	11.6	0.013	0.56 (0.35 to 0.89)
Peripheral vascular disease	8	8	1.4	2.7	0.17	0.51 (0.19 to 1.37)
Microvascular disease	68	54	12.0	19.2	0.0092	0.63 (0.44 to 0.89)

Actual controlled BP
: > 130 / 80 mmHg in both group

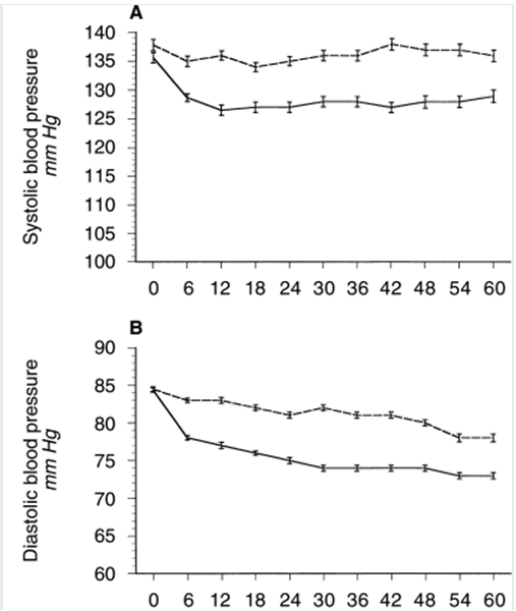
Stroke : prominent outcome

ABCD study



The primary endpoint was the effect of intensive versus moderate blood pressure control on the change in 24-hour creatinine clearance

ABCD study



CV Outcome	Intensive therapy *N* = 237 (%)	Moderate therapy *N* = 243 (%)	OR (95% CI)	*P* value
Myocardial infarction	19 (8.0)	15 (6.2)	0.75 (0.37, 1.52)	0.43
CVA	4 (1.7)	13 (5.4)	3.29 (1.06, 10.25)	0.03
CHF	12 (5.1)	11 (4.5)	0.89 (0.38, 2.06)	0.78
CV death	13 (5.4)	9 (3.7)	0.66 (0.28, 1.58)	0.35
Death	18 (7.6)	20 (8.2)	1.1 (0.56, 2.12)	0.80
	Nisoldipine *N* = 234 (%)	Enalapril *N* = 246 (%)		
Myocardial Infarction	18 (7.7)	16 (6.5)	1.20 (0.60, 2.41)	0.61
CVA	11 (4.7)	6 (2.4)	1.97 (0.72, 5.42)	0.18
CHF	11 (4.7)	12 (4.9)	0.96 (0.42, 2.22)	0.93
CV death	8 (3.4)	14 (5.7)	0.59 (0.24, 1.43)	0.23
Death	19 (8.1)	19 (7.7)	1.1 (0.54, 2.05)	0.87

Relatively small due to primary endpoint (the change in 24-hour creatinine clearance) : underpowered

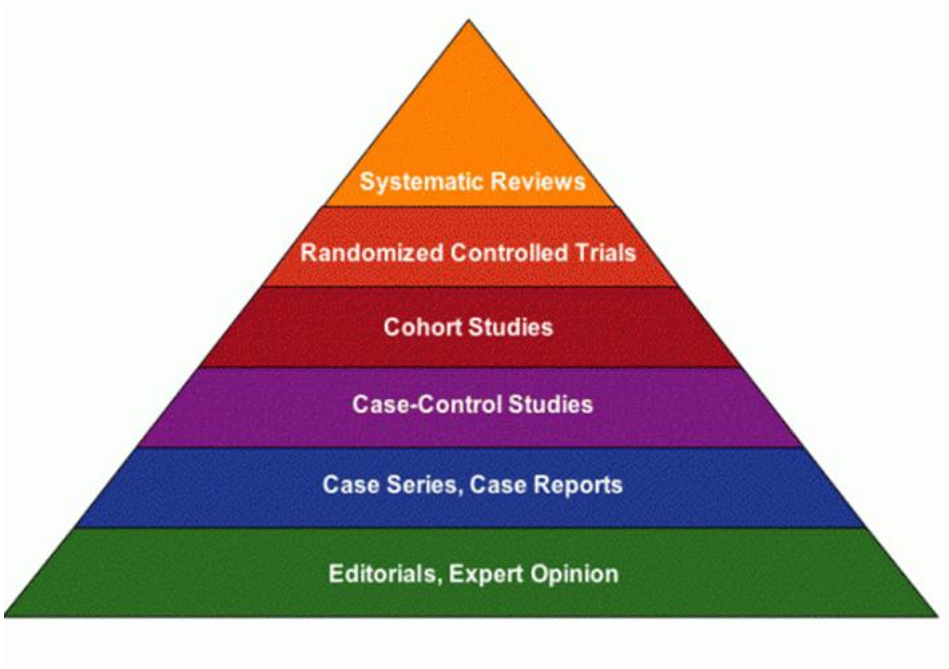
Stroke : prominent outcome

Kidney International (2002) **61**, 1086–1097

당뇨에서 < 130/80mmHg 강압 목표의 문제점

< 130/80 mmHg 이하로 저하와 MACE를 Primary endpoint 를 비교한 high level of evidence 인 Randomized Controlled Trial or systematic review은 없었다.

Subgroup analysis 조심해서



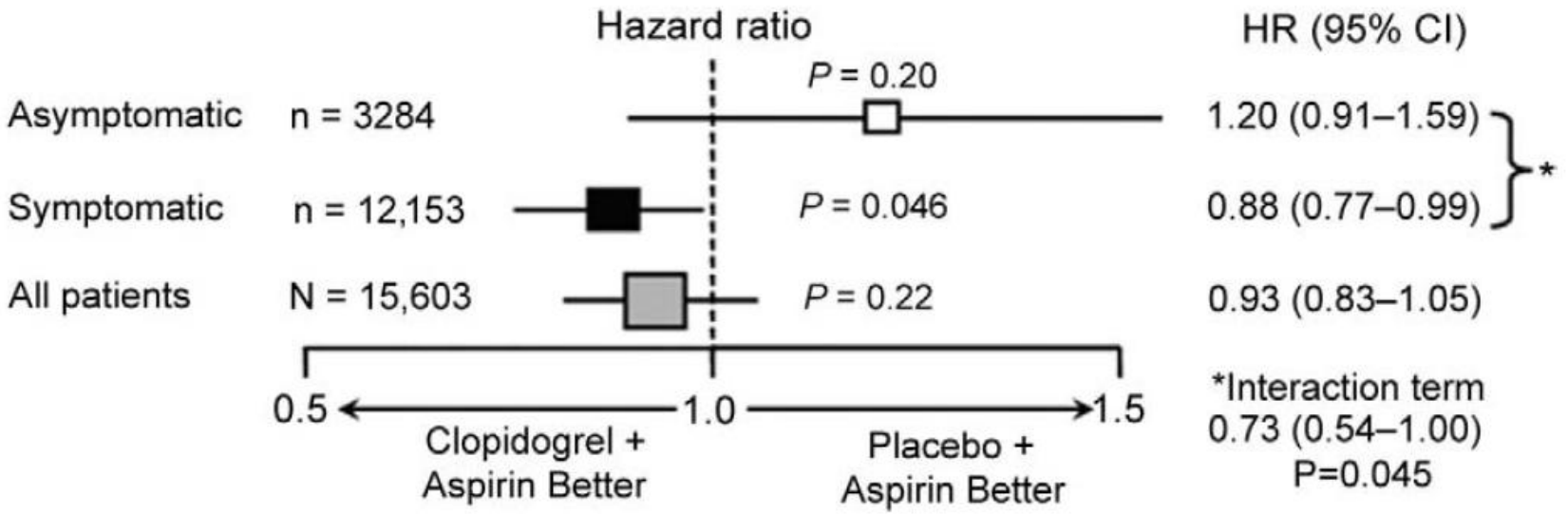
Sub-group analysis

Table 4 **Suggested Guidelines for Subgroup Analysis**

Prospectively define hypothesis.
Limit analyses to biologically plausible subgroups based on prior evidence.
Limit analyses to statistically significant treatment effects in pre-specified overall analysis.
Identify statistically significant interaction of treatment with the subgroup variable.
Perform adjustments for multiple comparisons.
Report results of subgroup analyses as exploratory and requiring independent confirmation.
Avoid overinterpretation of subgroup differences.

J Am Coll Cardiol 2010;55:415–27

Subgroup Analysis for the CHARISMA Trial

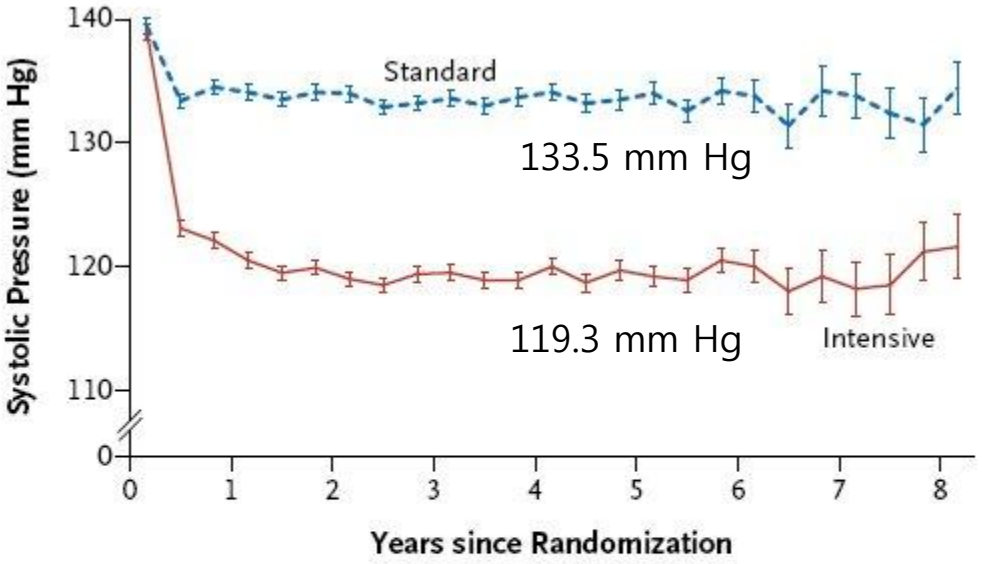


Effects of Intensive BP Control in Type 2 DM

N = 4733 with type 2 DM (high normal BP and hypertension ≥ 130 mmHg)

Intensive therapy < 120 mmHg (SBP)
Standard therapy <140 mmHg (SBP)

Primary composite outcome: nonfatal MI, nonfatal stroke, death from CV cause



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

ACCORD Study Group. N Engl J Med. 2010;362:1575-85.

Effects of Intensive BP Control in Type 2 DM: primary and secondary outcomes

Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

Guidelines for diabetes and hypertension

Recommendations	Class[a]	Level[b]
While initiation of antihypertensive drug treatment in diabetic patients whose SBP is ≥160 mmHg is mandatory, it is strongly recommended to start drug treatment also when SBP is ≥140 mmHg.	I	A
A SBP goal <140 mmHg is recommended in patients with diabetes.	I	A
The DBP target in patients with diabetes is recommended to be <85 mmHg.	I	A
All classes of antihypertensive agents are recommended and can be used in patients with diabetes; RAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria.	I	A
It is recommended that individual drug choice takes comorbidities into account.	I	C
Simultaneous administration of two blockers of the RAS is not recommended and should be avoided in patients with diabetes.	III	B

2013 ESH/ESC hypertension management guidelines

보수적인 결정

Goals

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg. (B)
- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden. (C)
- Patients with diabetes should be treated to a diastolic blood pressure <80 mmHg. (B)

Diabetes Care 2013:36:S11-66

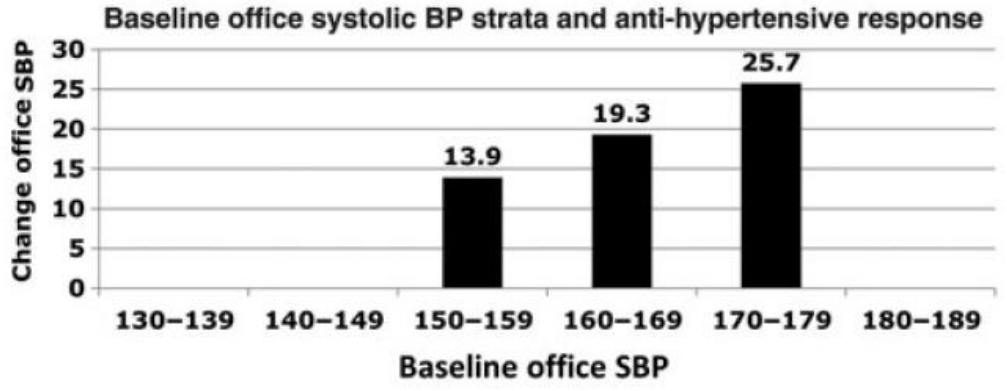
환자를 치료하다 보면 흔히 만나는

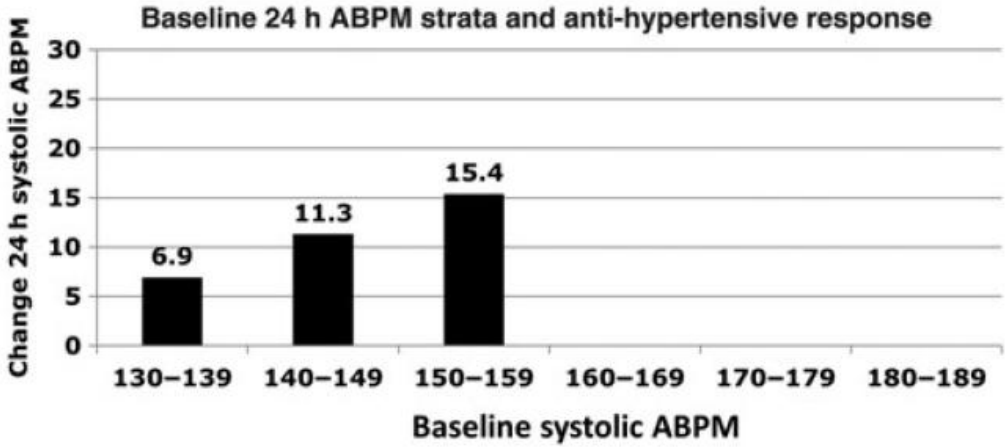
Wilder’s principle

사례4

European Heart Journal (2015) **36**, 576–579
doi:10.1093/eurheartj/ehu467

Wilder's principle: pre-treatment value determines post-treatment response





A similar phenomenon has been observed for the therapeutic response of heart rate, haemoglobin A1c., total cholesterol, LDL and HDL cholesterol, and body mass index after LAP-BAND placement.

Biases and Artifacts in Clinical Trial era

- **Lack of statistical power (MOST TRIALS)**
  - **clinical vs. statistical significant**
- **Bias randomization (CAPPP) – not centralized**
- **Heart Failure artefact (ALLHAT) – diuretics mask symptoms**
- **Lost to follow-up, unblinding, discontinuation (MRC)**
- **Hawthorne effects (RDN), patient compliance – therapeutic drug monitoring**
- **Soft endpoints in open trials, data problems and retraction**
- **Subgroup analysis**
- **Regression to the mean – vs. Wilder's principle**

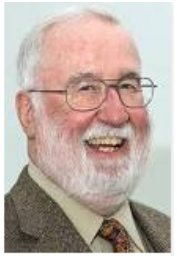
데이빗 새켓

의사

출생: 1934년 11월 17일, 미국 일리노이 주 시카고

사망: 2015년 5월 13일, 캐나다 마크데일

학력: 하버드 대학교



David L. Sackett

The "only formula" of physiological statistics

The formula is ridiculously simple, and looks like this

$$\text{Confidence} = \frac{\text{Signal}}{\text{Noise}} \times \sqrt{\text{Sample size}}$$

Noise: bias and artifact

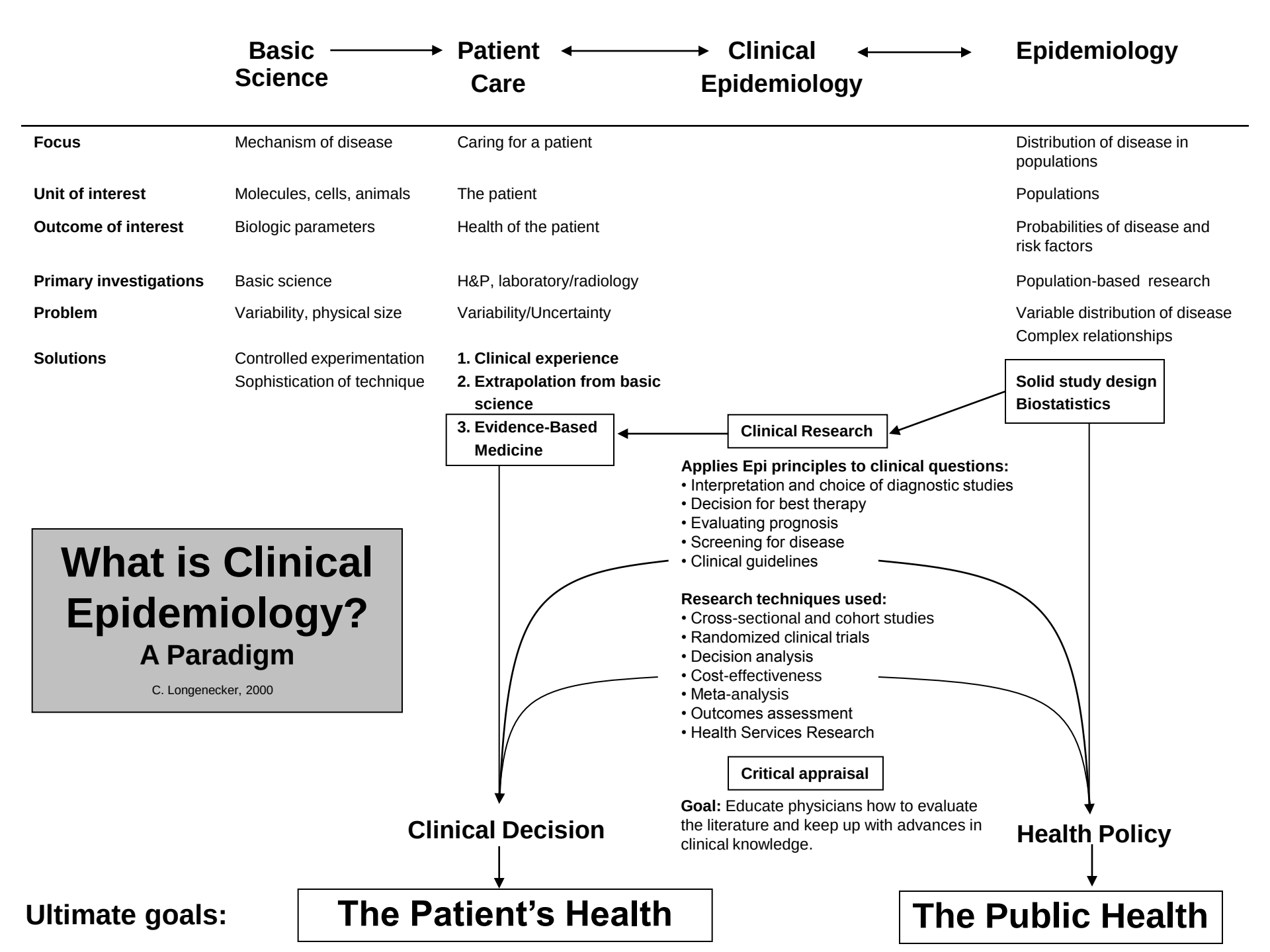
JAMC • 30 OCT. 2001; 165 (9)

감사합니다

Overestimation of event rates

- **Trial design**
  - Progress of overall care prior to trial initiation
  - Lack of prior quality data precluding accurate event rate estimation
  - "Optimism" in study planning, assuming event rates will be high thus requiring fewer trial participants
  - Modifying event rate estimations to "fit" a fixed research budget
- **Differences with reference population***
  - Healthier trial population due to trial eligibility criteria
  - Geographical and patterns of care differences between study population and reference population
  - Genetic differences between study population and reference population
- **Trial conduct**
  - Progress of overall care during the trial
  - Greater physician adherence to guideline recommended therapies
  - Rigorous patient monitoring resulting in early prevention of complications
  - Selective drop-out of patients
  - Premature trial discontinuation (if it affects the ability of primary endpoint evaluation of the included patients)
- **Patient's reaction to trial participation e the Hawthorne effect**
  - Psychological factors (e.g. placebo effect)
  - Behavioral factors (e.g. better medication compliance)

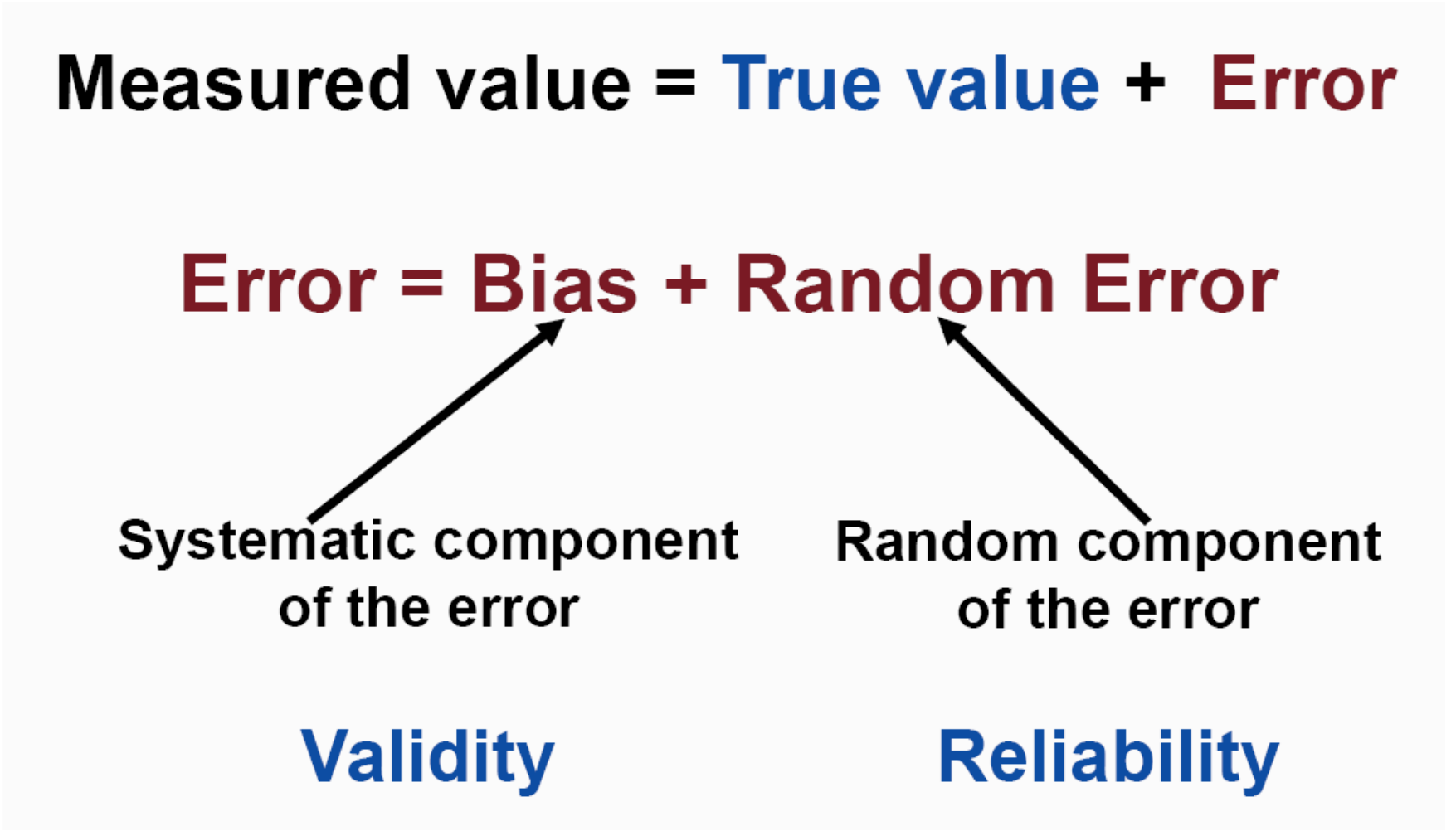
Am J Cardiol 2015;116:355-363


Basic Science
Patient Care
Clinical Epidemiology
Epidemiology
Focus
Mechanism of disease
Caring for a patient
Distribution of disease in populations
Unit of interest
Molecules, cells, animals
The patient
Populations
Outcome of interest
Biologic parameters
Health of the patient
Probabilities of disease and risk factors
Primary investigations
Basic science
H&P, laboratory/radiology
Population-based research
Problem
Variability, physical size
Variability/Uncertainty
Variable distribution of disease
Complex relationships
Solutions
Controlled experimentation
Sophistication of technique
1. Clinical experience
2. Extrapolation from basic science
3. Evidence-Based Medicine
Solid study design
Biostatistics
Clinical Research
Applies Epi principles to clinical questions:
• Interpretation and choice of diagnostic studies
• Decision for best therapy
• Evaluating prognosis
• Screening for disease
• Clinical guidelines
Research techniques used:
• Cross-sectional and cohort studies
• Randomized clinical trials
• Decision analysis
• Cost-effectiveness
• Meta-analysis
• Outcomes assessment
• Health Services Research
Critical appraisal
Goal: Educate physicians how to evaluate the literature and keep up with advances in clinical knowledge.
What is Clinical Epidemiology?
A Paradigm
C. Longenecker, 2000
Clinical Decision
Health Policy
Ultimate goals:
The Patient's Health
The Public Health

Regression to the mean

- 골턴(Galton, F.:1822-1911)은 아들과 아버지 키의 관계에서 아들의 키가 평균으로 돌아가려는 경향이 있음을 찾아 냈다.
- 아버지 키가 클 때, 유전적 영향으로 자식들이 모두 키가 크게 된다면 몇 세대만 내려가더라도 인류는 키가 무척 큰 집안과 키가 무척 작은 집안으로 갈리게 될 것이다.
- 하지만 세대가 거듭되더라도 안정적인 상태를 유지하고 있다. 키 큰 사람의 자손들이 오히려 평균보다 낮은 이들이 많다는 것이다. 이를 '평균으로의 회귀(regression toward the mean)'라고 불렀다.

Noise : source of variation



Most could not exclude the possibility of a treatment effect of at least the size deemed to be clinically relevant by the investigators (i.e., inconclusive).