An Overview of the Different Aspects of a Clinical Trial

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ESC Working Group Cardiovascular Pharmacotherapy

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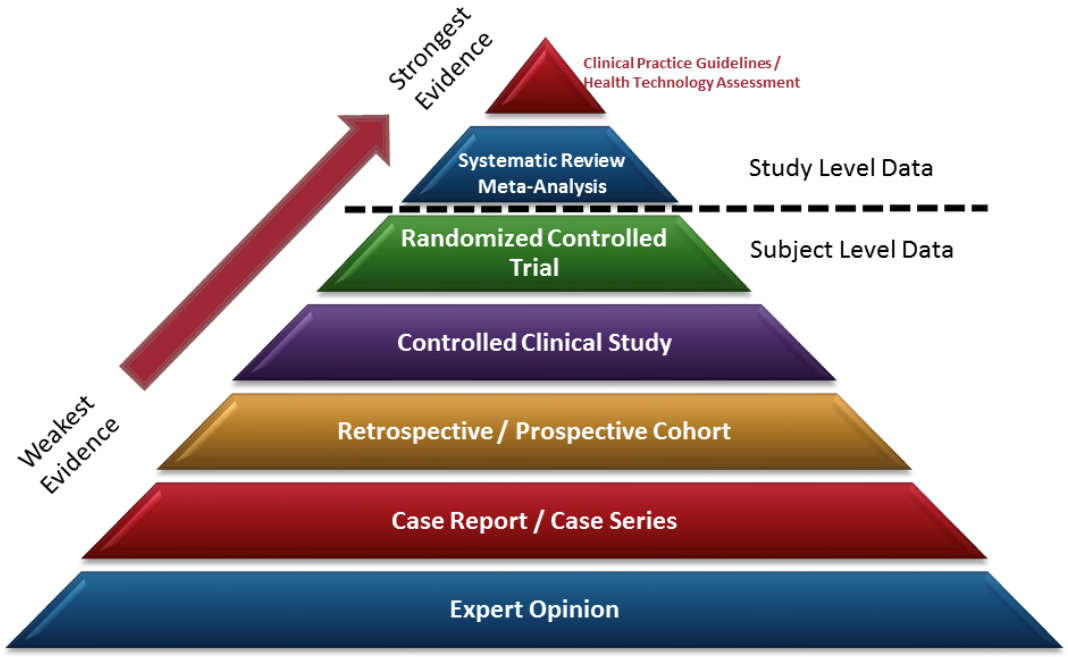
Hierarchy in Science



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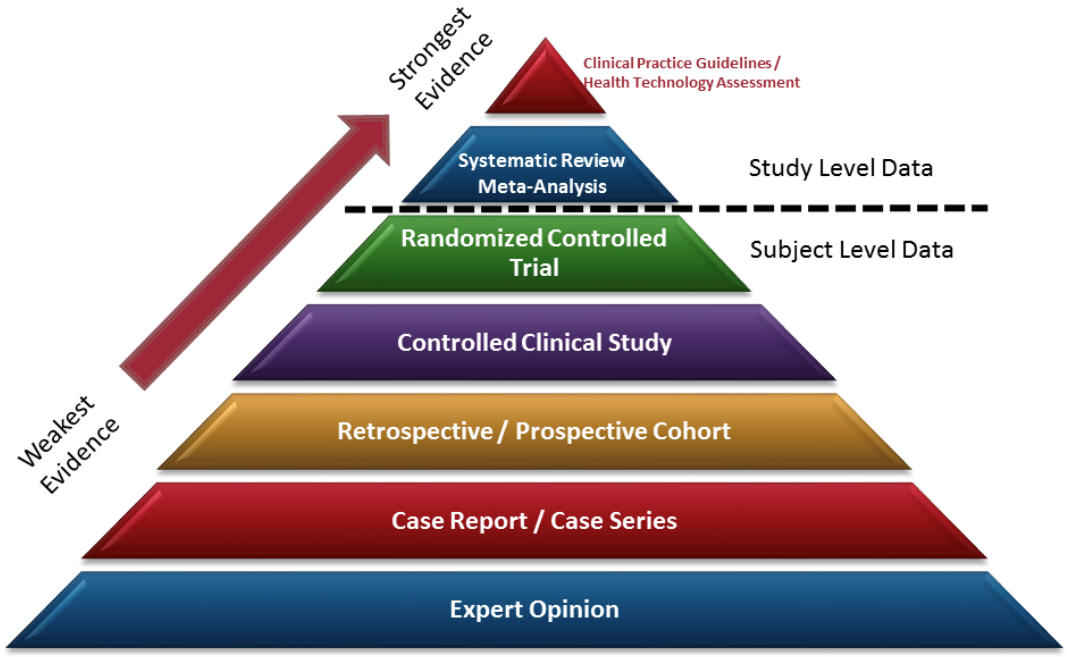
Hierarchy in Science



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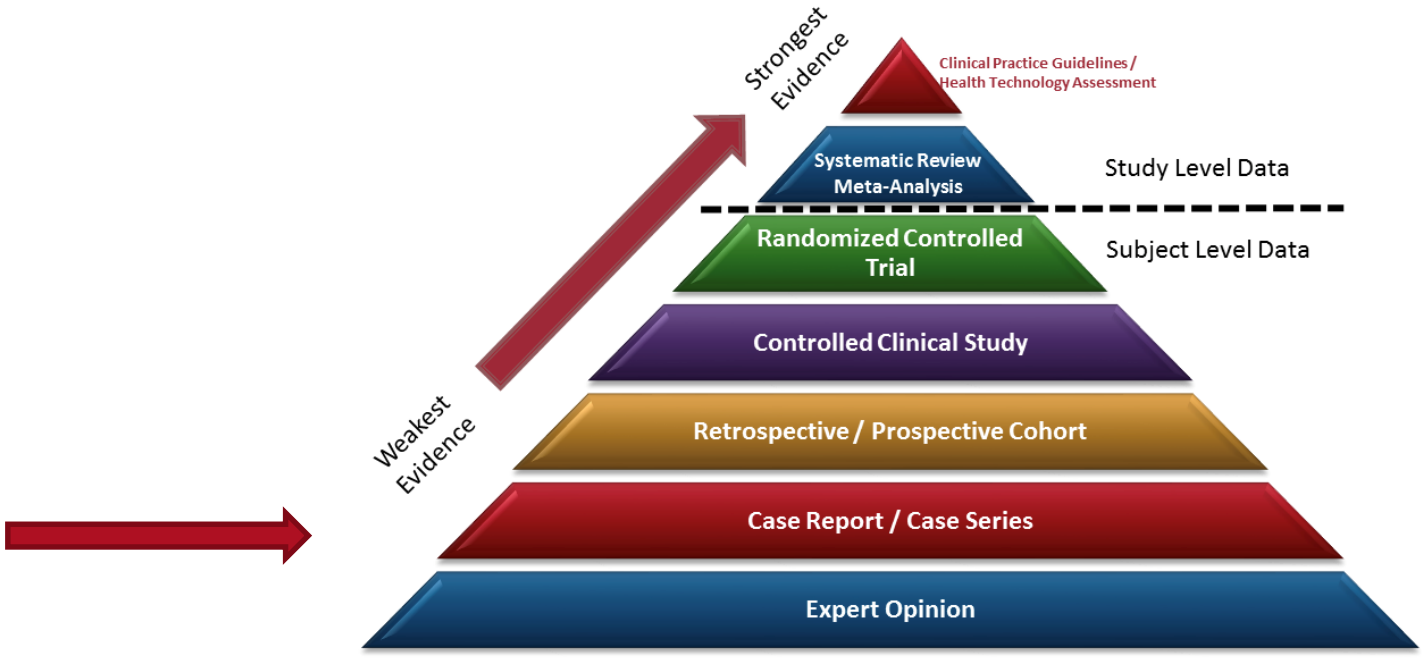

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Case reports

- Identify needs – hypothesis generating
- Identify new drug side effects but also potential novel uses
- Identify rare diseases and rare manifestations of diseases
- Important educational role
- Highlight extremely unusual and novel findings
- No causality – Associations may have other explanations

European Heart Journal Case Reports

JACC Case Reports

BMJ Journals

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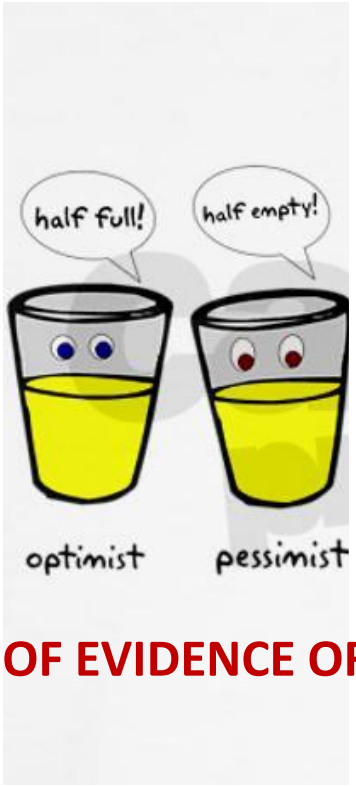
Case reports



THE LOWERST LEVEL OF EVIDENCE OR MAYBE THE FIRST LINE OF EVIDENCE

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Case reports

THE LOWERST LEVEL OF EVIDENCE OR MAYBE THE FIRST LINE OF EVIDENCE

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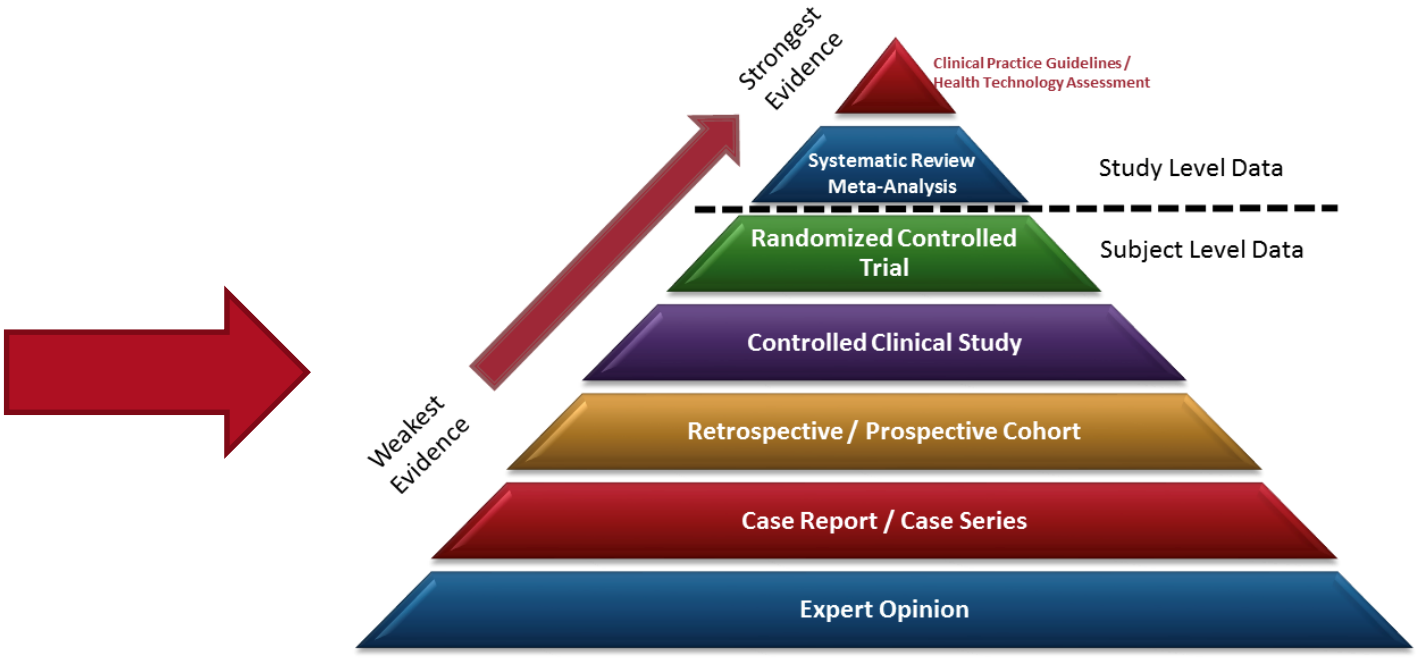
Hierarchy in Science



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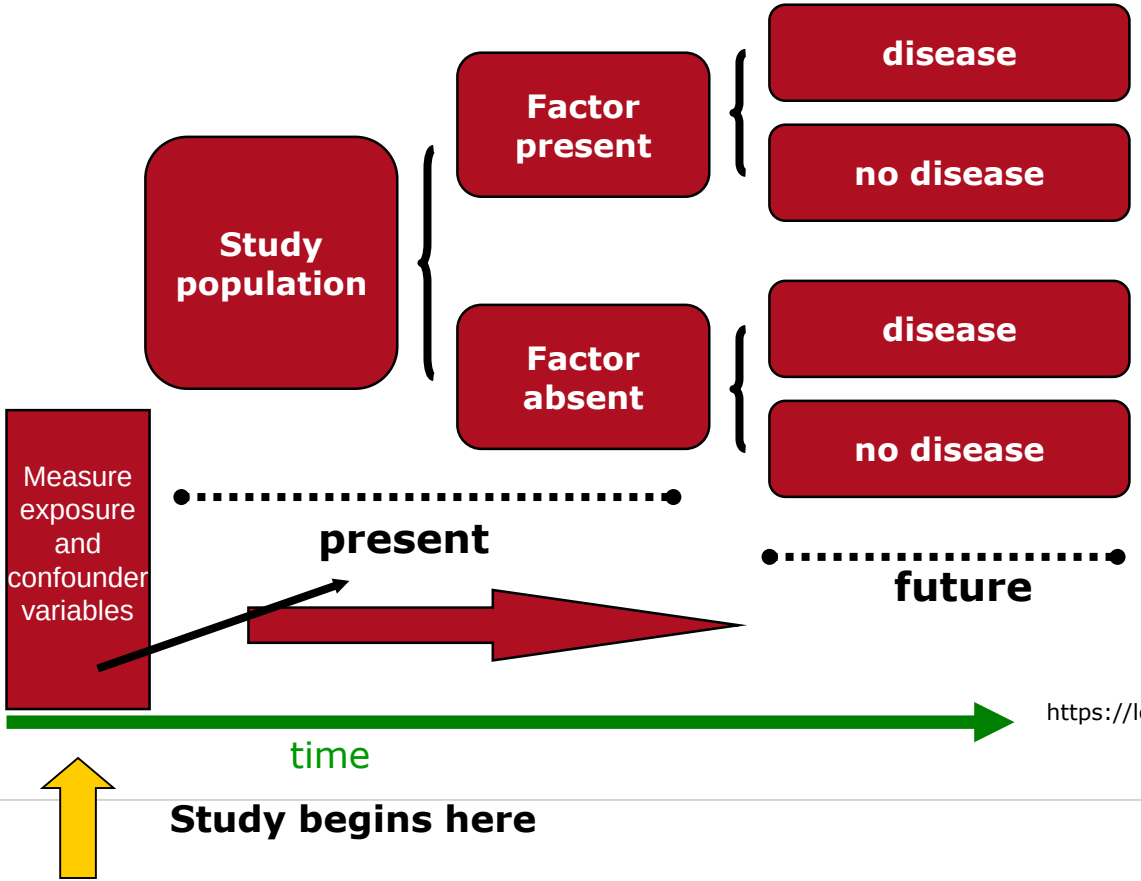
Observational studies

To test the association of a risk factor with an outcome

- **Cohort study**
- **Case-control study**
- **Cross-sectional study**

Cohort studies



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Cohort studies

Merits:

- There is temporal relationship between exposure and outcome
- Investigate several outcomes for each exposure
- It is possible to perform matching limiting confounders role
- Easier and cheaper than a RCT
- Good to measure incidence of an outcome

Limitations:

- Expensive
- Outcome could take time to occur
- Definition of outcome/exposure can change over the time
- No randomization
- Blinding/masking

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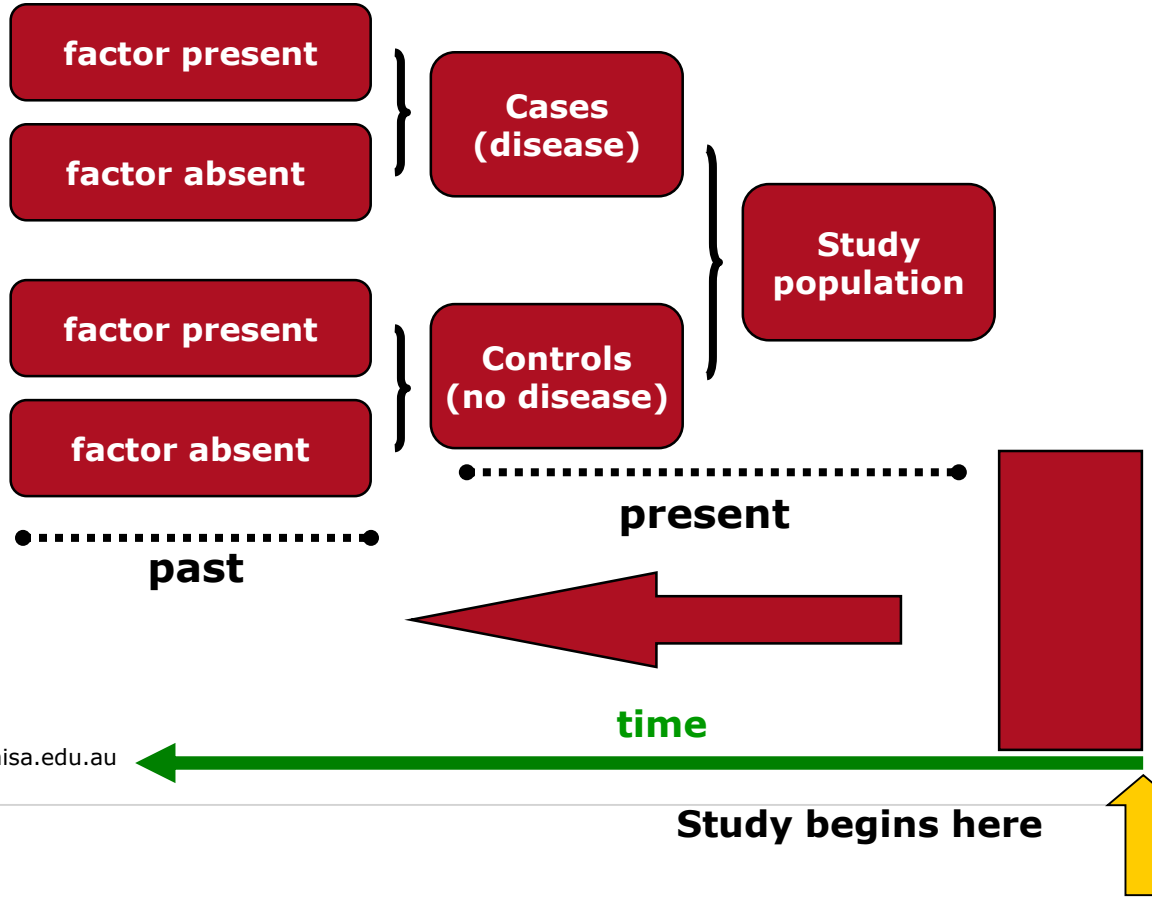
Case-control studies



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Case-control studies

- **Assumption:** non-cases are representative of the source population of cases.

Merits:

- Suitable to investigate rare diseases/outcomes
- Can be not really expensive

Limitations:

- Not suitable for calculating frequency measures
- Not appropriate for rare exposures
- Selection and recall biases

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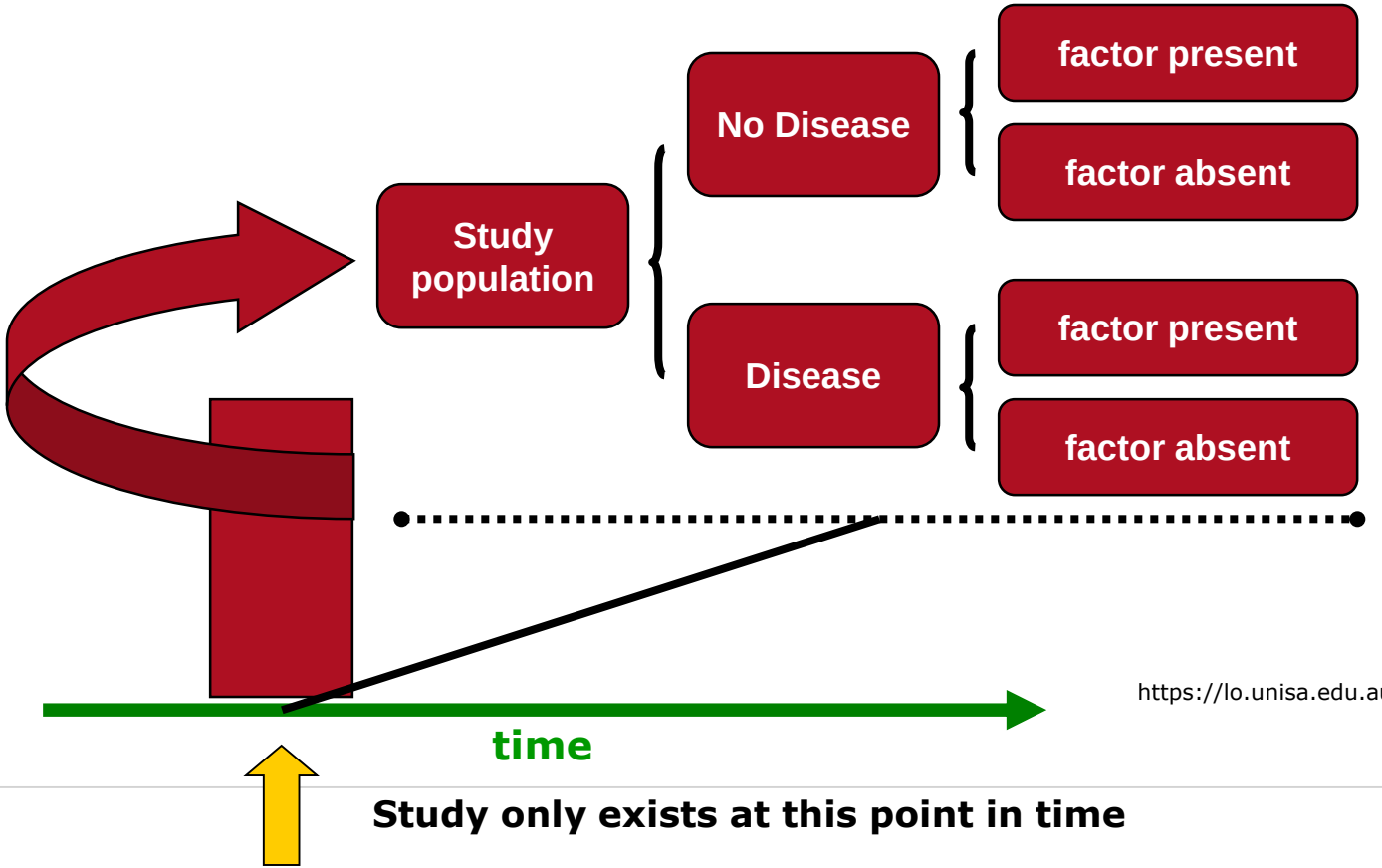
Cross-sectional studies



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Cross-sectional studies

Merits:

- Quick
- Cheap
- Study of several diseases / exposures at the same time
- Assess the prevalence of a disease
- Public health planning

Limitations:

- Temporal ambiguity
- Possible measurement error
- Not suitable for rare conditions
- Survivor bias

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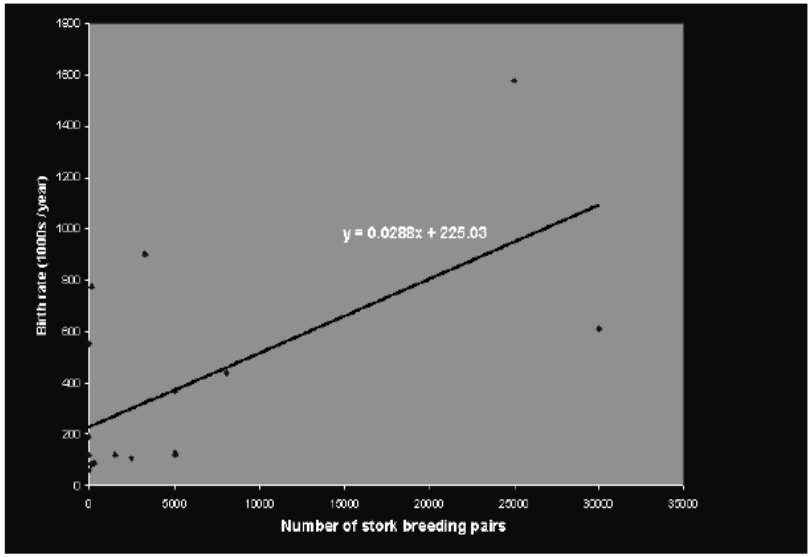
Causality: cause-effect relationship?

Storks deliver babies



Storks Deliver Babies (p . 0.008), Matthews, R, Teaching Statistics. Volume 22, Number 2, Summer 2000

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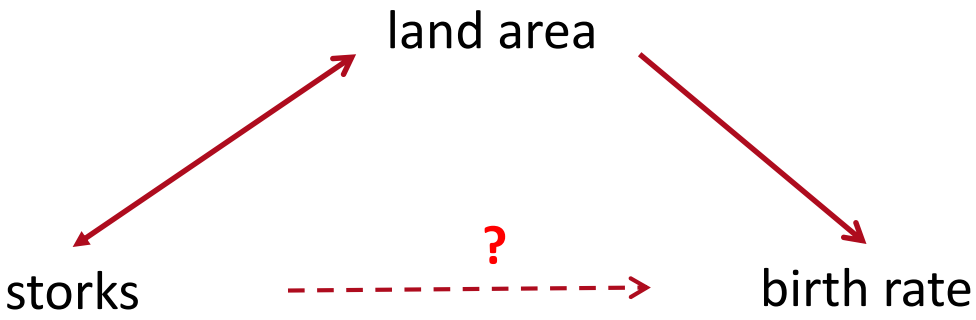
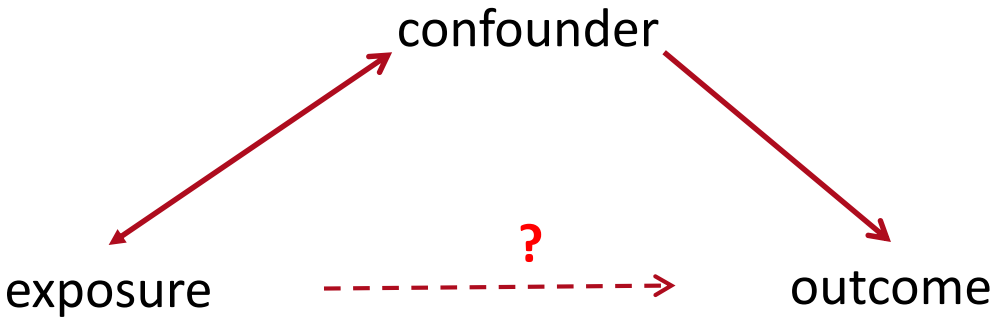
Causality: cause-effect relationship?

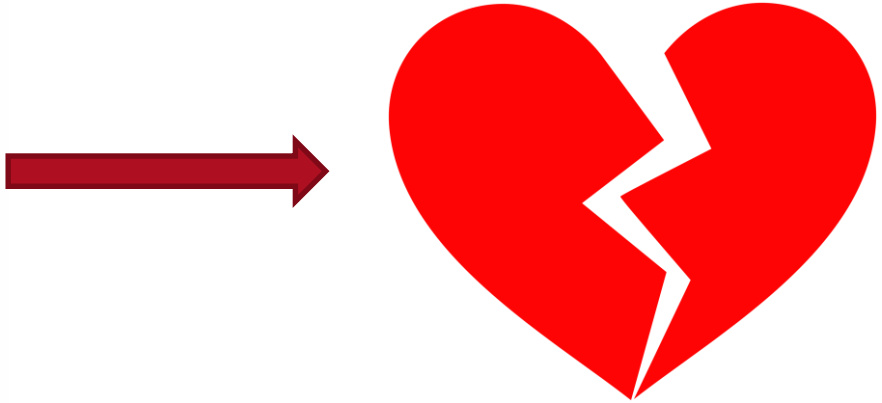


Confounders



positive confounding: the effect seems stronger
negative confounding: the effect seems weaker

Causality: cause-effect relationship?



Rohit S Loomba et al. Circulation.2012; 126: A14459

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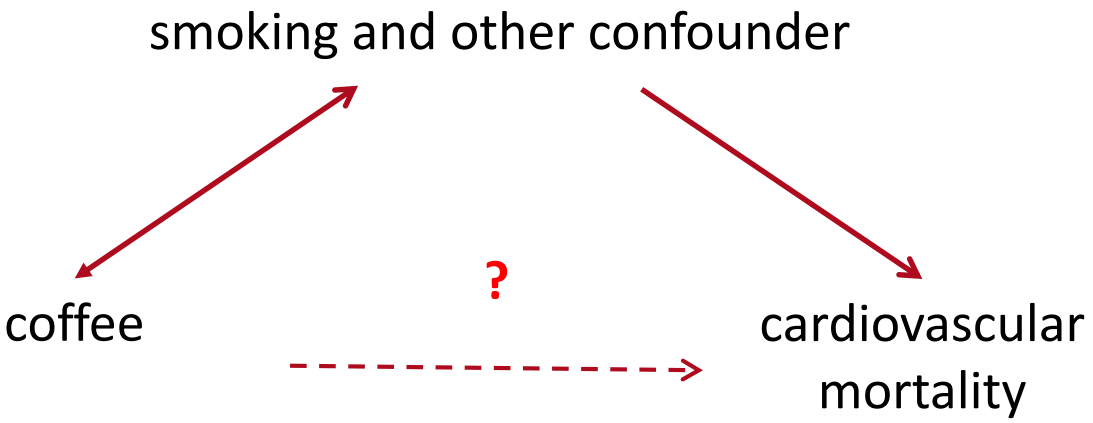
Causality: cause-effect relationship?



Rohit S Loomba et al. Circulation.2012; 126: A14459

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Table 1 Baseline characteristics of patients aged ≥80 years in the overall and matched cohort

	Overall cohort			Matched cohort		
	Beta-blocker non-users	Beta-blocker users	*P*-value	Beta-blocker non-users	Beta-blocker users	Absolute standardized difference[c]
Patients, *n* (%)	922 (14)	5640 (86)		866 (50)	866 (50)	
Age, years, mean (SD)[a,b]	85.4 (4.2)	84.6 (3.6)	<0.001	85.2 (4.0)	85.3 (3.8)	1.1%
Female sex (%)[a,b]	30.5	35.4	0.004	30.9	31.5	1.2%
Location, outpatient (%)[a,b]	36.7	40.2	0.052	37.5	34.9	5.5%
Follow-up location, specialty (%)[a,b]	36.6	47.0	<0.001	38.5	39.2	1.5%
NYHA class (%)[a,b]			<0.001			3.8%
I	5.7	3.5		4.8	4.0	
II	31.9	37.6		33.3	33.4	
III	51.7	51.8		52.0	52.6	
IV	10.7	7.1		9.9	10.0	
EF 30–39% (%)[a,b]	55.3	53.8	0.385	55.5	54.0	3.8%
Clinica						
BMI (kg						
SBP (m						
DBP (m						
MAP (n						
Heart r						
[IQR						
<60						
eGFR (						
medi						
>60						
30–6						
<30						
NT-pro						
medi						
Smokin						
Neve						
Form						
Curr						
Medica						
Atrial fi						
Anaemi						
COPD[a]						
Dilated						
Diabetes[a,b]	21.9	28.9	<0.001	22.6	22.5	0.3%
Hypertension[a,b]	58.8	69.2	<0.001	60.9	62.1	2.6%
Ischaemic heart disease[a,b]	66.8	74.4	<0.001	68.4	70.2	4.0%
Peripheral artery disease[a,b]	16.3	13.3	0.016	16.3	16.2	0.3%
Stroke and/or TIA[a,b]	19.3	20.1	0.604	19.7	19.4	0.9%
Valvular disease[a,b]	40.9	38.5	0.178	41.2	40.9	0.7%
Cancer in the previous 3 years[a,b]	14.1	12.9	0.346	14.0	14.8	2.3%
Dementia	2.4	2.6	0.828	2.4	2.4	0.1%
Procedures (%)						
Coronary revascularization[a,b]	32.8	37.1	0.012	33.6	34.2	1.2%
Devices (CRT or ICD)[a,b]	3.3	5.5	0.008	3.5	2.5	5.4%
Pacemaker (CRT-D, CRT-P or pacemaker)	19.2	19.5	0.137	19.2	20.6	3.7%

ESC European Society of Cardiology
European Journal of Heart Failure (2019)
doi:10.1002/ejhf.1615

RESEARCH ARTICLE

Association between beta-blocker use and mortality/morbidity in older patients with heart failure with reduced ejection fraction. A propensity score-matched analysis from the Swedish Heart Failure Registry

Davide Stolfo[1,2†], Alicia Uijl[1,3,4†], Lina Benson[1], Benedikt Schrage[1,5], Marat Fudim[6], Folkert W. Asselbergs[4,7,8], Stefan Koudstaal[4,7], Gianfranco Sinagra[2], Ulf Dahlström[9], Giuseppe Rosano[10,11], and Gianluigi Savarese[1]*

ADJUSTED FOR KNOWN CONFOUNDERS
BUT NOT
FOR UNKNOWN OR UNMEASURED
CONFOUNDERS

Widowed	38.5	37.8		38.0	38.8	
Education level[a,b]			0.867			3.3%
Compulsory school	57.9	57.4		57.3	58.9	
Secondary school	30.5	31.3		31.2	30.0	
University	11.6	11.3		11.5	11.1	
Income > median[a,b]	42.2	42.8	0.763	42.7	41.6	2.3%

BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillation; CRT-P, cardiac resynchronization therapy with pacemaker; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate (calculated by the Chronic Kidney Disease Epidemiology Collaboration formula); ICD, implantable cardioverter-defibrillator; IQR, interquartile range; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; SD, standard deviation; TIA, transient ischaemic attack; RAS, renin–angiotensin system.
[a]Variables included in multiple imputation together with index year, duration of HF, the composite outcome, and beta-blocker use (yes/no).
[b]Variables included to estimate the propensity score together with index year and duration of HF.
[c]Absolute standardized differences are defined as the difference in means, proportions or ranks divided by the mutual standard deviation.

Interventional studies

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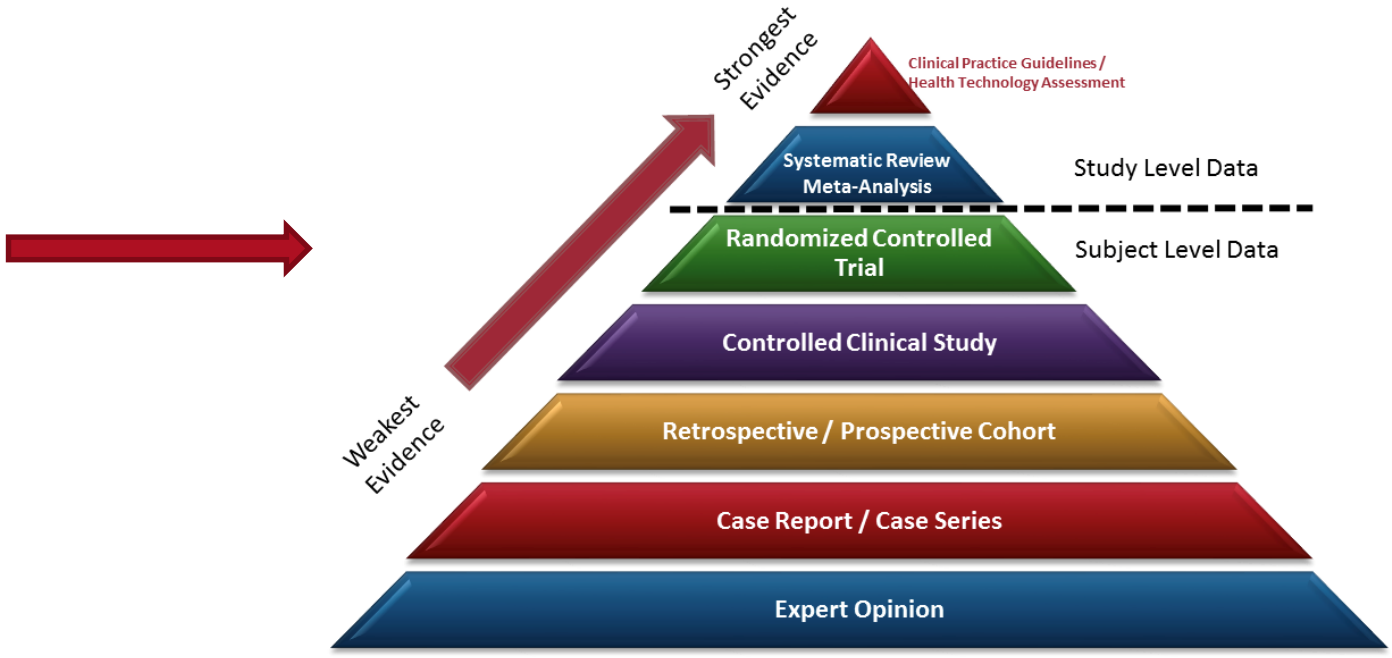
Hierarchy in Science



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Interventional studies: RCTs are the gold standard

Randomization in interventional trial: avoids all confounders

Adjustment for confounders in observational trial: avoids known confounders

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PARAGONHF

19% eligible
in a real-world population

TABLE 1 Eligibility Criteria

Inclusion criteria

1. Written informed consent must be obtained before any assessment is performed
2. ≥50 years of age, male or female
3. LVEF ≥45% by echocardiography during the screening epoch, or within 6 months prior to screening visit (any local LVEF measurement made using echocardiography only)
4. Symptom(s) of HF requiring treatment with diuretic(s) for at least 30 days prior to screening visit
5. Current symptom(s) of HF (NYHA functional class II to IV) at screening visit
6. Structural heart disease evidenced by at least 1 of the following echocardiography findings (any local measurement made during the screening epoch or within the 6 months prior to screening visit):
   a) LA enlargement defined by at least 1 of the following: LA width (diameter) ≥3.8 cm or LA length ≥5.0 cm or LA area ≥20 cm^2 or LA volume ≥55 ml or LA volume index ≥29 ml/m^2
   b) LVH defined by septal thickness or posterior wall thickness ≥1.1 cm
7. Patients with at least 1 of the following:
   a) HF hospitalization (defined as HF listed as the major reason for hospitalization) within 9 months prior to screening visit and NT-proBNP >200 pg/ml for patients not in AF or >600 pg/ml for patients in AF on screening ECG, or
   b) NT-proBNP >300 pg/ml for patients not in AF or >900 pg/ml for patients in AF on the screening visit ECG

Exclusion criteria

1. Any prior echocardiographic measurement of LVEF <40%
2. Acute coronary syndrome (including MI), cardiac surgery, other major cardiovascular surgery, or urgent PCI within the 3 months prior to visit 1 or an elective PCI within 30 days prior to visit 1
3. Any clinical event within the 6 months prior to visit 1 that could have reduced the LVEF (e.g., MI, CABG), unless an echocardiographic measurement was performed after the event confirming the LVEF to be ≥45%
4. Current acute decompensated HF requiring augmented therapy with diuretic agents, vasodilator agents, and/or inotropic drugs
5. Patients who require treatment with 2 or more of the following: an ACEI, an ARB, or a renin inhibitor
6. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
7. Patients with a known history of angioedema
8. Probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e., dyspnea, fatigue), such as significant pulmonary disease (including primary pulmonary hypertension), anemia, or obesity. Specifically, patients with the following are excluded:
   a) Severe pulmonary disease including COPD (i.e., requiring home oxygen, chronic nebulizer therapy, or chronic oral steroid therapy or hospitalized for pulmonary decompensation within 12 months) or
   b) Hemoglobin <10 g/dl, or
   c) Body mass index >40 kg/m^2
9. Patients with any of the following:
   a) Systolic blood pressure (SBP) ≥180 mm Hg at visit 1, or
   b) SBP >150 mm Hg and <180 mm Hg at visit 1 unless the patient is receiving 3 or more antihypertensive drugs. Antihypertensive drugs include but are not limited to a thiazide or other diuretic, mineralocorticoid (MRA), ACEI, ARB, beta blocker, and calcium channel blocker, or
   c) SBP <110 mm Hg at visit 1, or
   d) SBP <100 mm Hg or symptomatic hypotension as determined by the investigator at visit 103 or visit 199/201
10. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer
11. Patients with history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy-induced cardiomyopathy, or viral myocarditis
12. Evidence of right-sided HF in the absence of left-sided structural heart disease
13. Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy
14. Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of HF
15. Presence of hemodynamically significant valvular heart disease in the opinion of the investigator
16. Stroke, transient ischemic attack, carotid surgery, or carotid angioplasty within the 3 months prior to visit 1
17. Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention during the trial
18. Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and AF or atrial flutter with a resting ventricular rate >110 beats per minute
19. Patients with a cardiac resynchronization therapy device
20. Patients with prior major organ transplant or intent to transplant (i.e., on transplant list)
21. Any surgical or medical condition that in the opinion of the investigator may place the patient at higher risk from his/her participation in the study or is likely to prevent the patient from complying with the requirements of the study or completing the study
22. Any surgical or medical condition that might significantly alter the absorption, distribution, metabolism, or excretion of study drugs, including but not limited to any of the following: any history of pancreatic injury, pancreatitis, or evidence of impaired pancreatic function/injury within the past 5 years
23. Evidence of hepatic disease as determined by any 1 of the following: SGOT (AST) or SGPT (ALT) values exceeding 3× the upper limit of normal, bilirubin >1.5 mg/dl at visit 1
24. Patients with 1 of the following:
   a) eGFR <30 ml/min/1.73 m^2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at visit 1, or
   b) eGFR <25 ml/min/1.73 m^2 at visit 103 or visit 199/201, or
   c) eGFR reduction >35% (compared with visit 1) at visit 103 or visit 199/201
25. Presence of known functionally significant bilateral renal artery stenosis
26. Patients with either of the following:
   a) Serum potassium >5.2 mmol/l (mEq/l) at visit 1
   b) Serum potassium >5.4 mmol/l (mEq/l) at visit 103 or visit 199/201
27. History or presence of any other disease with a life expectancy of <3 years
28. History of noncompliance to medical regimens and patients who are considered potentially unreliable
29. History or evidence of drug or alcohol abuse within the past 12 months
30. Persons directly involved in the execution of this protocol
31. History of malignancy of any organ system (other than localized basal or squamous cell carcinoma of the skin or localized prostate cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
32. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin laboratory test
33. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days off study drug

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ALT = alanine aminotransferase; ARB = angiotensin receptor blocker; AST = aspartate aminotransferase; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; LA = left atrial; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase.

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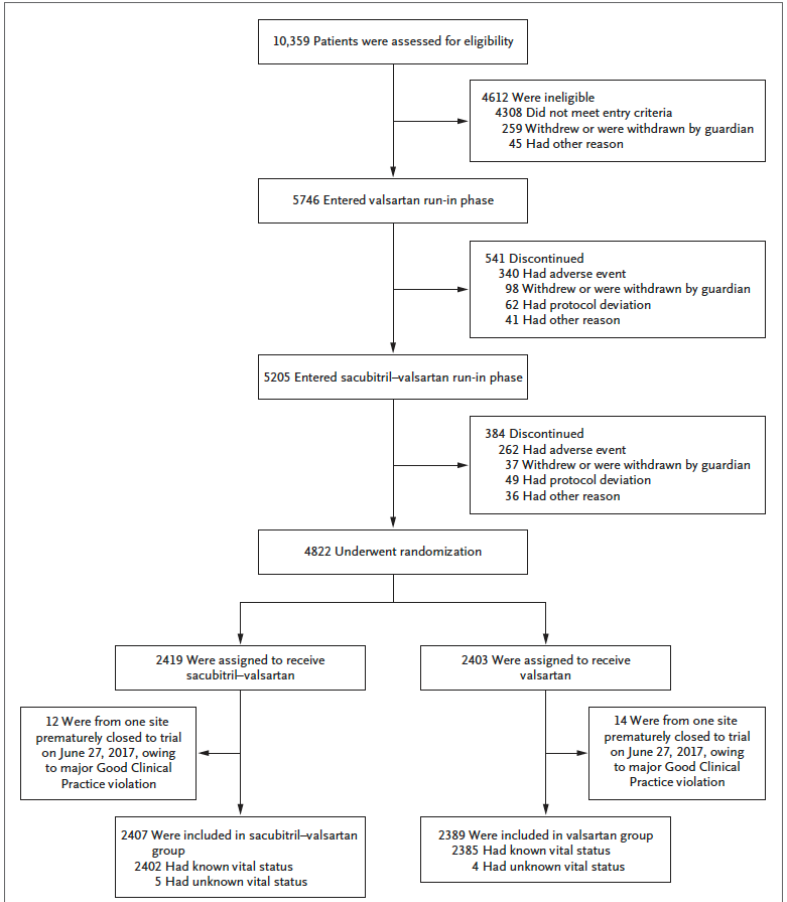

Figure 1. Screening, Randomization, and Follow-up.

The median duration of the valsartan run-in phase was 15 days (interquartile range, 12 to 22). One patient completed the valsartan run-in phase and underwent randomization without entering the sacubitril–valsartan run-in phase. The median duration of the sacubitril–valsartan run-in phase was 19 days (interquartile range, 15 to 23). One patient completed screening and entered the sacubitril–valsartan run-in phase without having entered the valsartan run-in phase.

Interventional studies: RCTs are the gold standard

Is the study population representative of the source population → Can results be translated to the general population of patients?

Strict

- **well defined study population makes the effect more predictable (internal validity)**
- **safer due to exclusion of high-risk patients**
- **difficult to recruit patients, increasing cost, time of recruitment and risk of the failure of the study**

Broad

- **increases external validity**
- **facilitates recruitment of patients**

Already selection of study site (e.g. tertiary centre) restricts patient selection!

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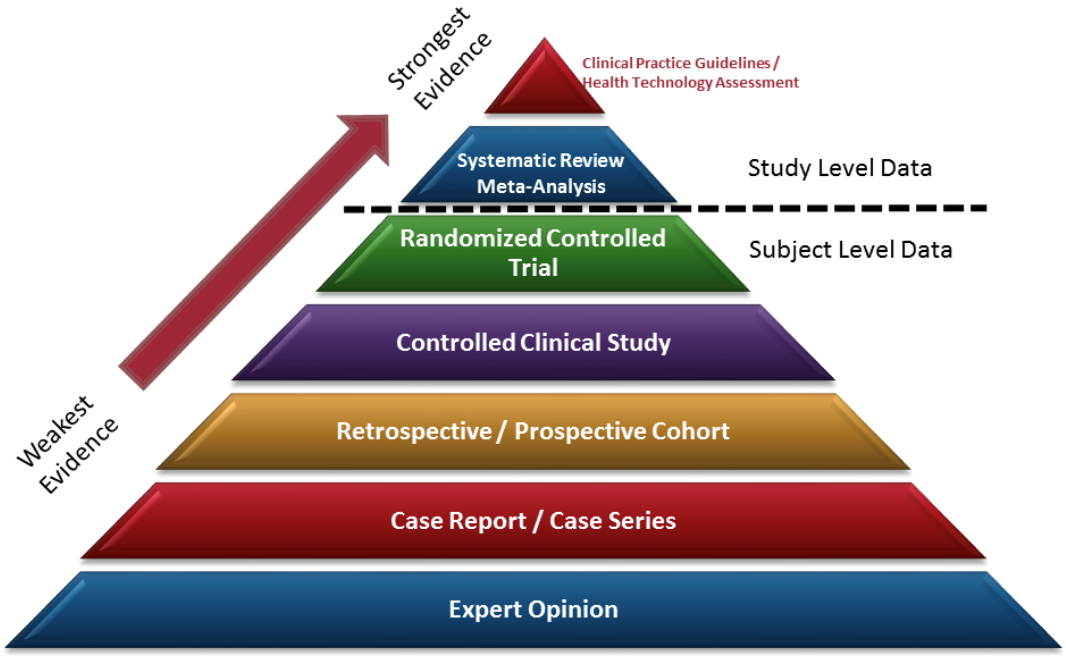
Meta-analyses

A quantitative statistical analysis of several separate but similar experiments or studies in order to test the pooled data for statistical significance.

Why a meta-analysis?

- To increase power
- To improve precision
- To answer questions not posed by individual studies and increase generalizability
- To settle controversies arising from apparently conflicting studies or to generate new hypotheses

Hierarchy in Science



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Registry

- Collects uniform data (clinical, lab, etc)
- Evaluate specified outcomes for a population defined by a particular disease, condition, or exposure

Disease Registry: Includes patients with the disease regardless of drug or device exposure

Product Registry: Includes subjects receiving the drug or device regardless of indication

In principle, no testing of research hypothesis (i.e. cohort study)

Registry: key words

- **Cohort study** – enrolls subjects with something in common (same disease, same treatment, etc.) who are followed up over time.

- **Real-world** - representative of real world patient characteristics (less inclusion and exclusion criteria than in RCTs)

- **Non-interventional**

Garrison LP Jr, et al. Value in Health 2007

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Non-interventional studies

- the **investigational medicinal products** are used in accordance with the terms of the **marketing authorization** and the **normal clinical practice** of the state concerned;
- the assignment of the subject to a particular therapeutic strategy is **NOT decided in advance**;
- the decision to prescribe the investigational medicinal products is not taken together with the decision to include the subject in the clinical study;
- diagnostic or monitoring procedures in addition to normal clinical practice are not applied to the subjects.

REGULATION (EU) No 536/2014

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Registries supports RCTs for:

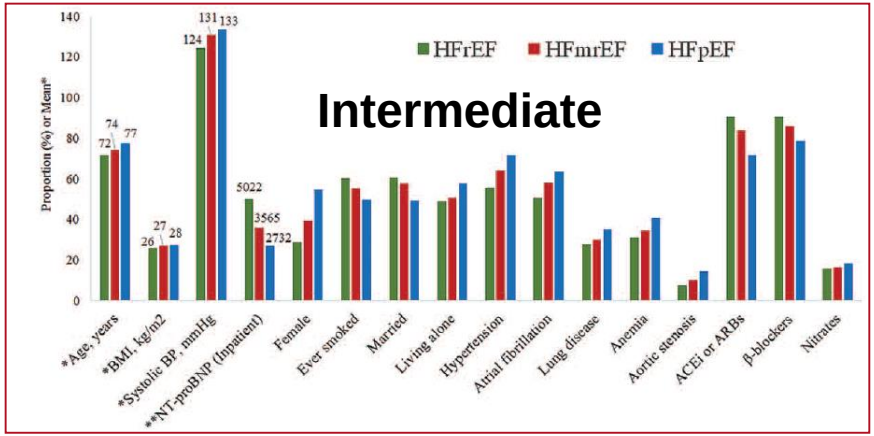
Phenotyping groups of patients to be enrolled in trials

European Journal of Heart Failure (2017) 19, 1624–1634
doi:10.1002/ejhf.945

RESEARCH ARTICLE

A comprehensive population-based characterization of heart failure with mid-range ejection fraction

Angela S. Koh[1,2], Wan Ting Tay[1], Tiew Hwa Katherine Teng[1,3], Ola Vedin[4], Lina Benson[5], Ulf Dahlstrom[6], Gianluigi Savarese[7], Carolyn S.P. Lam[1,2,8]*, and Lars H. Lund[7]*



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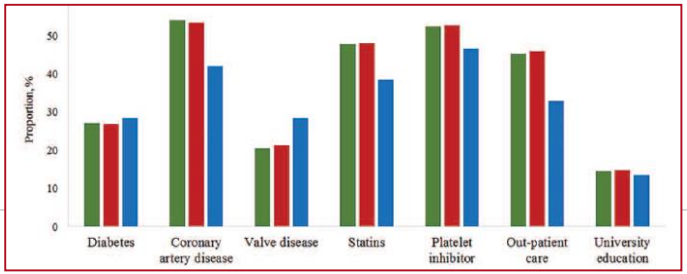
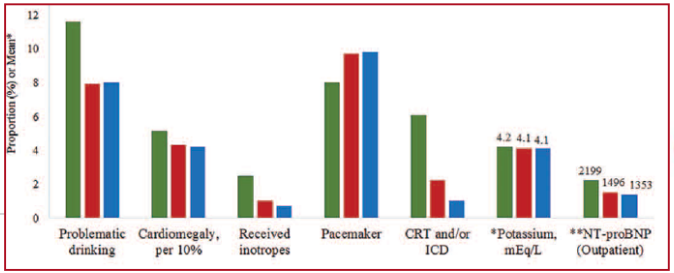
Resembles HFrEF



Resembles HFpEF



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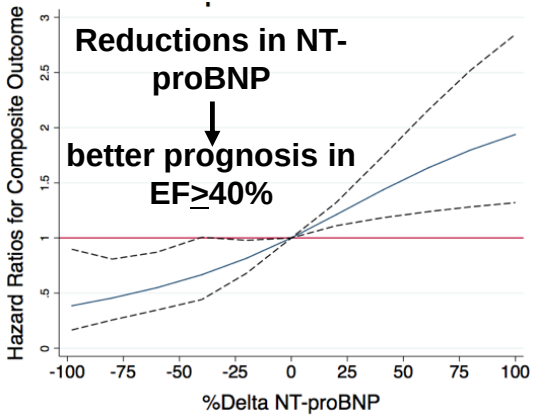
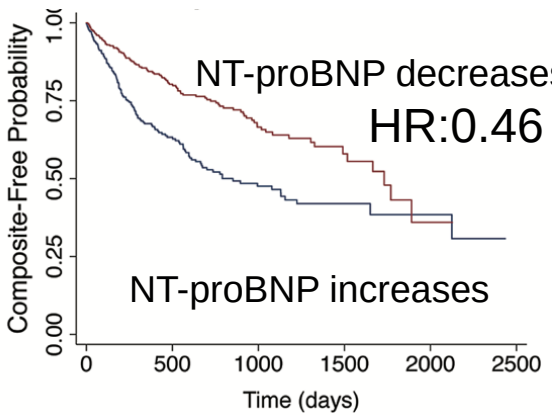
Registries supports RCTs for:

Selecting outcomes and inclusion/exclusion criteria



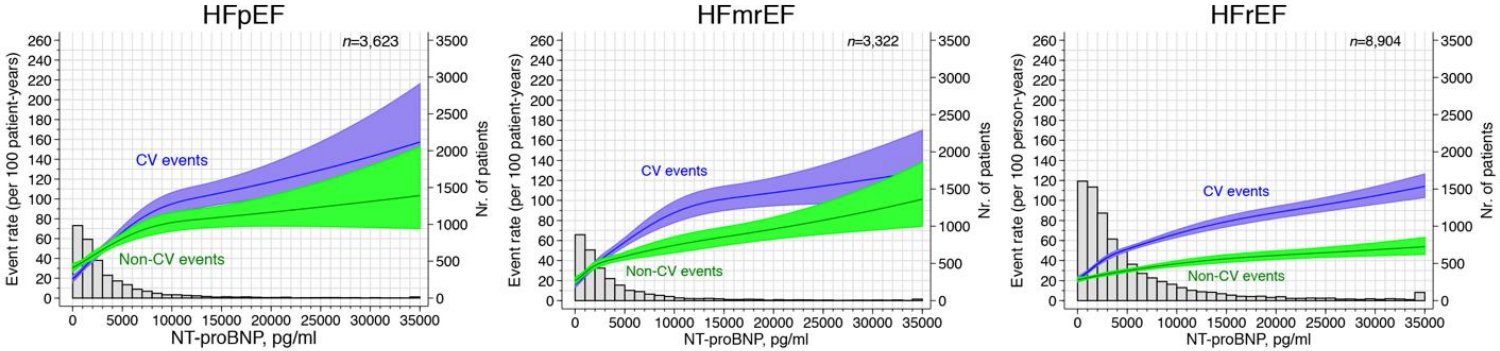


Savarese et al.
Circ HF 2016

RiksSvikt
nationellt hjärtsviktsregister

Relationship between NT-proBNP and CV/non-CV events

Savarese et al. JACC HF 2018



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Registries for:

Exploring subgroups which have been previously neglected

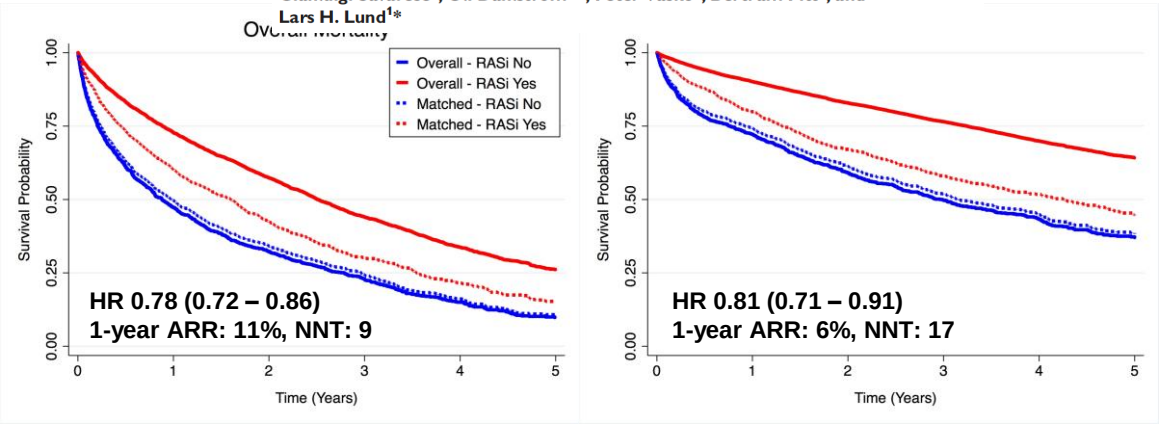
ESC European Society of Cardiology
European Heart Journal (2018) 39, 4257–4265
doi:10.1093/eurheartj/ehy621
FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

Association between renin–angiotensin system inhibitor use and mortality/morbidity in elderly patients with heart failure with reduced ejection fraction: a prospective propensity score-matched cohort study

Gianluigi Savarese[1], Ulf Dahlström[2,3], Peter Vasko[4], Bertram Pitt[5], and Lars H. Lund[1]*

RiksSvikt
nationellt hjärtsviktsregister

Age>80 years
RASi 80%



Age≤80 years
RASi 94%

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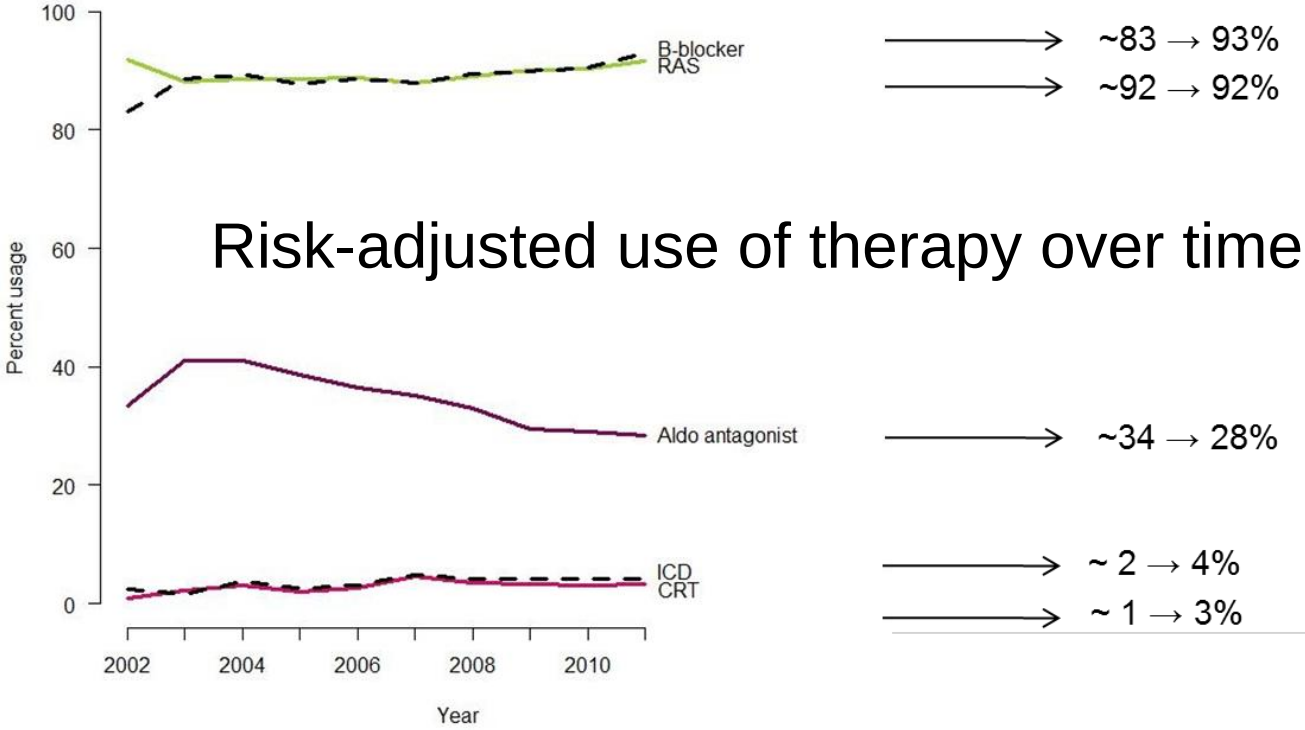
Registries for:

Fostering implementation of treatments in clinical practice

RiksSvikt
nationellt hjärtsviktsregister



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Registries for:

Testing effectiveness

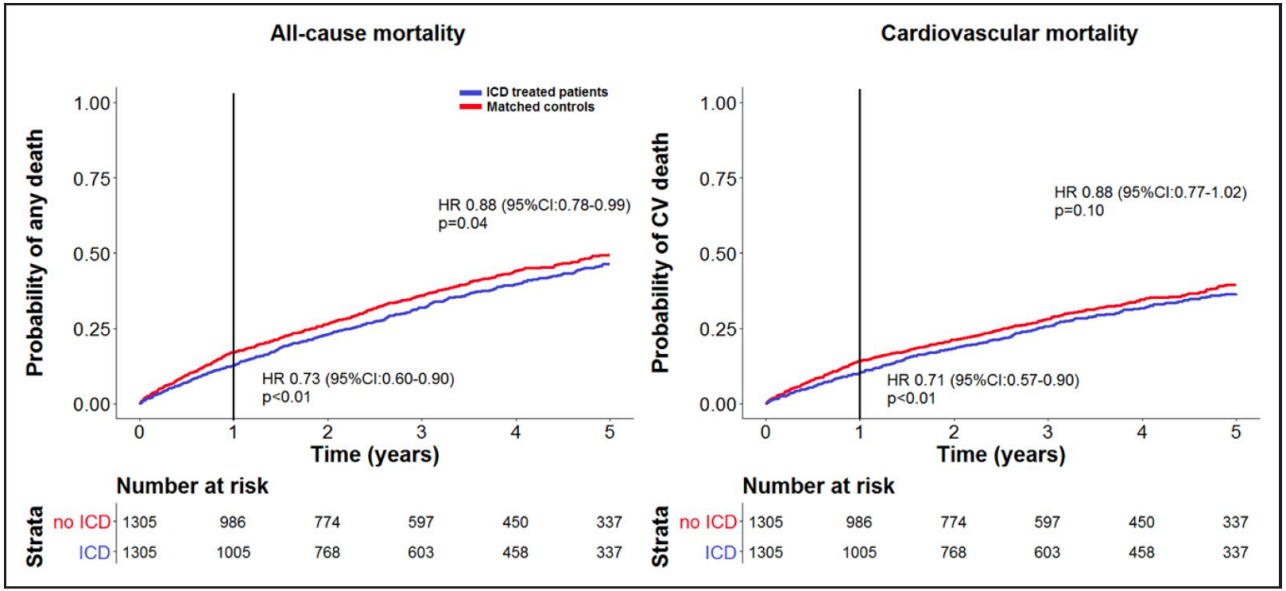
Circulation

ORIGINAL RESEARCH ARTICLE

Association Between Use of Primary-Prevention Implantable Cardioverter-Defibrillators and Mortality in Patients With Heart Failure

A Prospective Propensity Score–Matched Analysis From the Swedish Heart Failure Registry

Benedikt Schrage, MD
Alicia Uijl, MSc
Lina Benson, MSc
Dirk Westermann, MD
Marcus Ståhlberg, MD, PhD
Davide Stolfo, MD
Ulf Dahlström, MD, PhD
Cecilia Linde, MD, PhD
Frieder Braunschweig, MD, PhD
Gianluigi Savarese, MD, PhD



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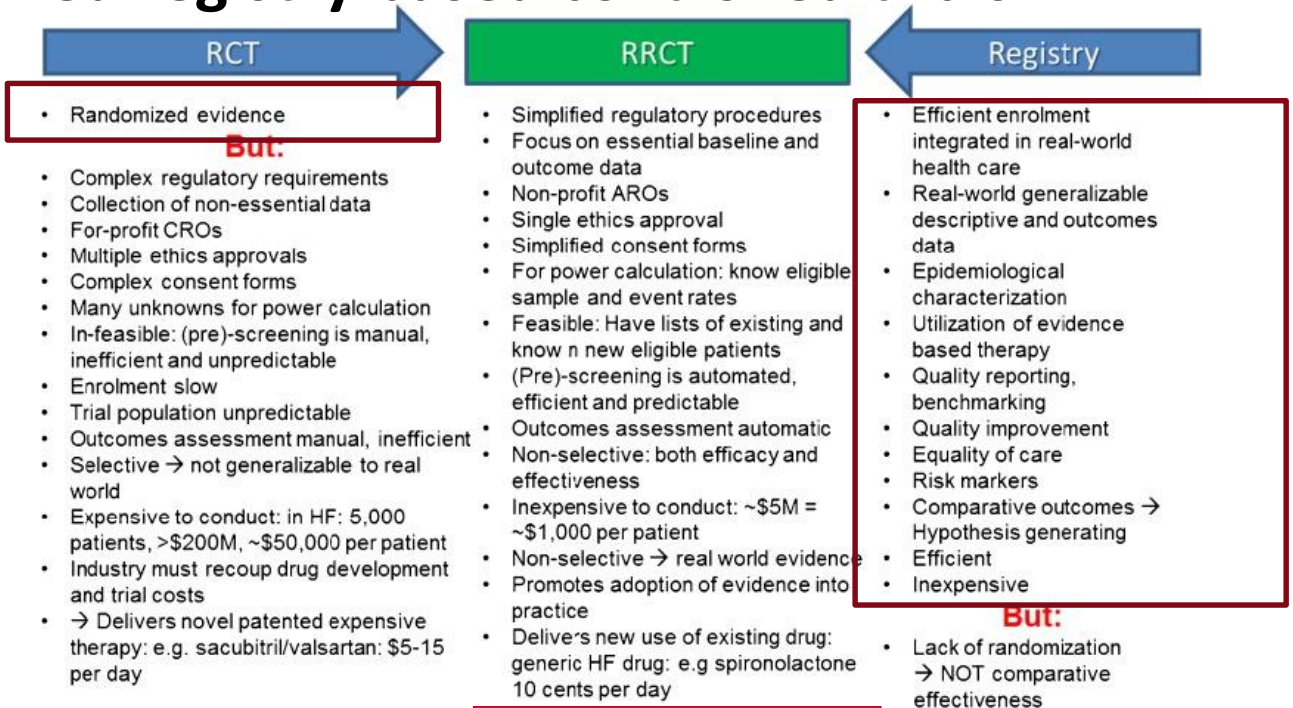
Registries for:

Post-marketing surveillance

- Evaluate short/long-term effectiveness (day-to-day circumstances)
- Measure/monitor short/long-term safety and tolerability
- Measure and/or improve quality of care

Registries for:

Randomized registry based controlled trials



Randomized
Less selective than traditional RCT
Cheaper
Simpler

Lund LH et al. Curr Heart Fail Rep. 2017

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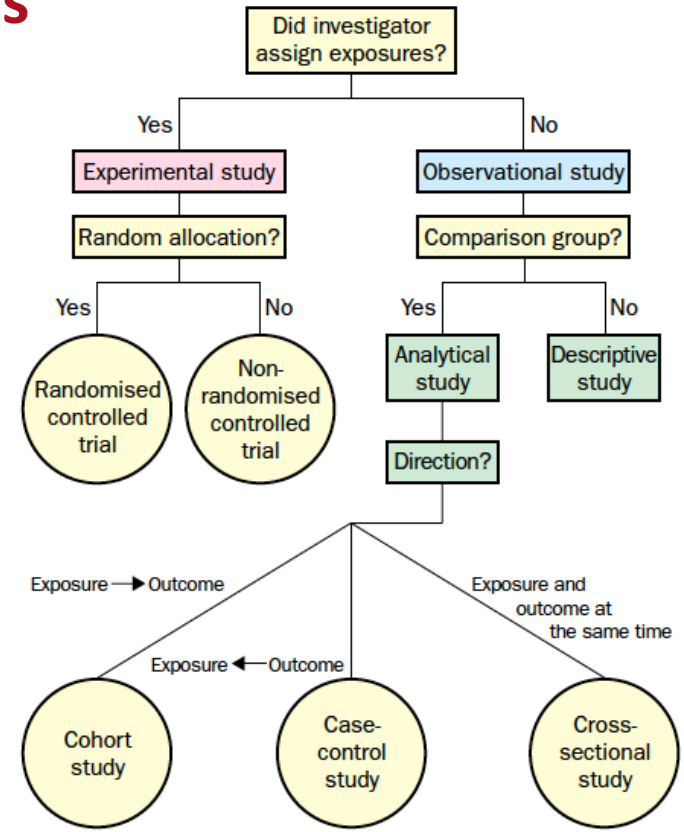
Many study designs



Grimes DA. Lancet 2002; 359:57

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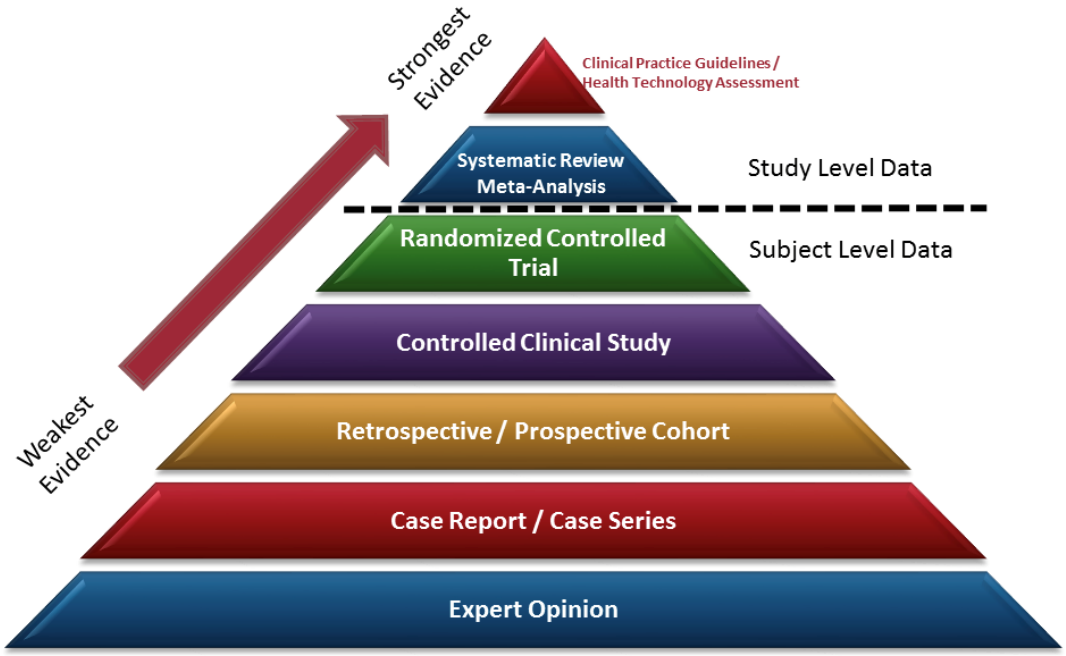
Hierarchy in Science?



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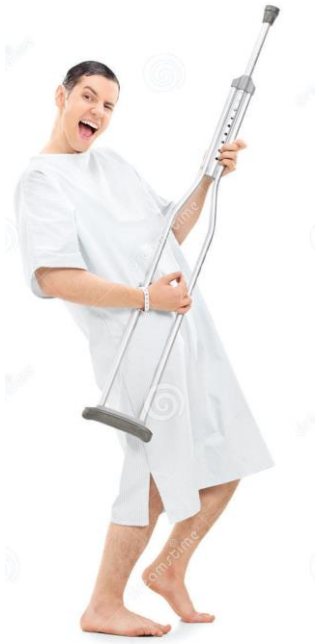
Democracy in Science



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Thank you

Are you <40 years?

Cardiovascular Pharmacotherapists and Trialists of Tomorrow (CPTT)

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A lot of benefits for you!!!