REGISTRIES AND META-ANALYSES

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REGISTRIES and OBSERVATIONAL STUDIES

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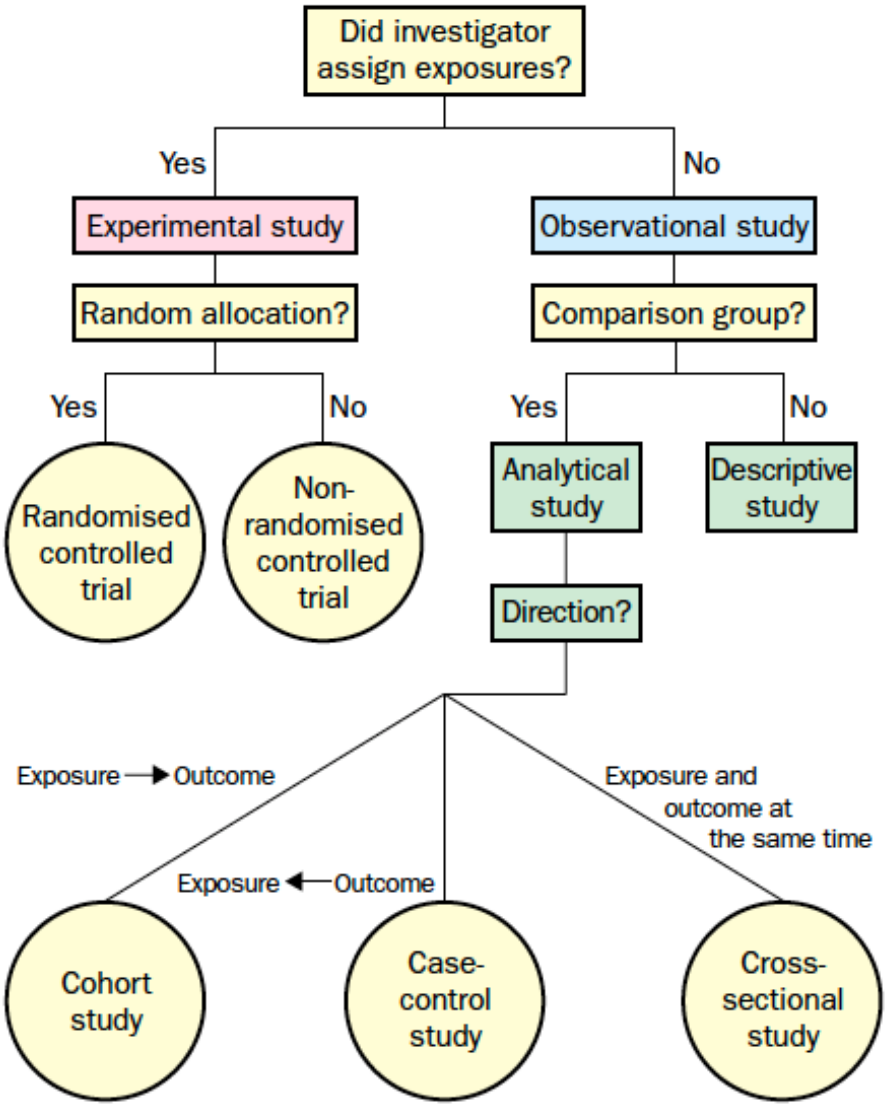
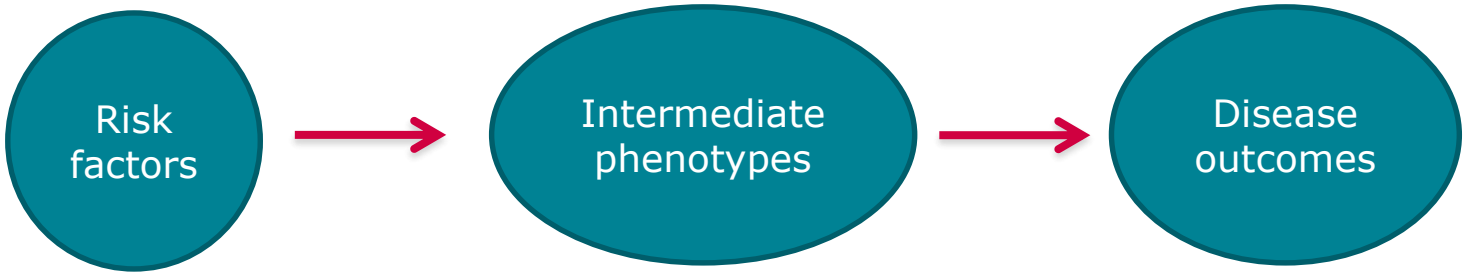
Type of studies



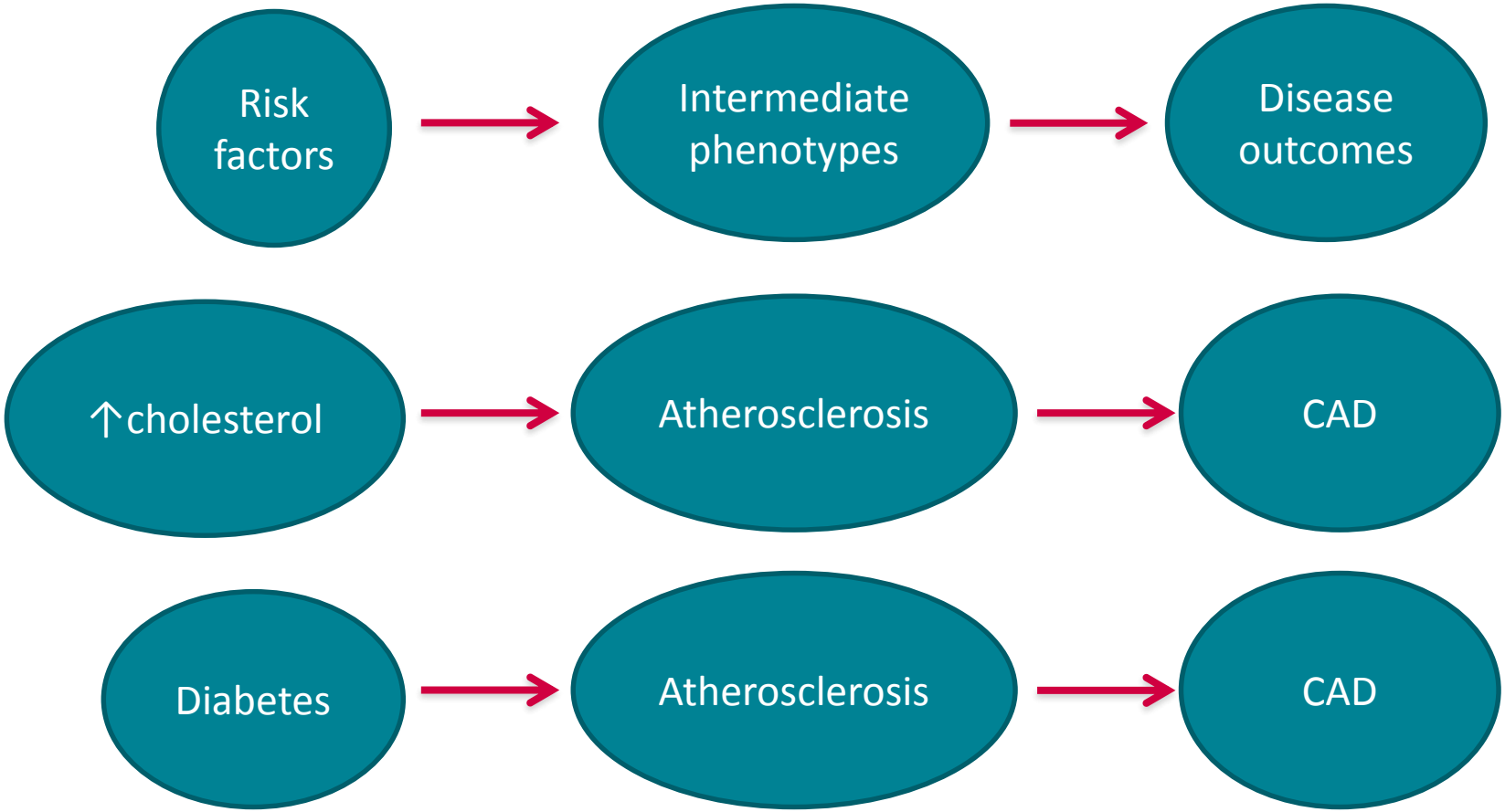
- **Descriptive studies**
  - describe **frequency, natural history** and **determinants of a condition**
- **Analytic studies**
  - Describe **association** between **exposure** and **outcome**

Grimes DA. Lancet 2002; 359:57

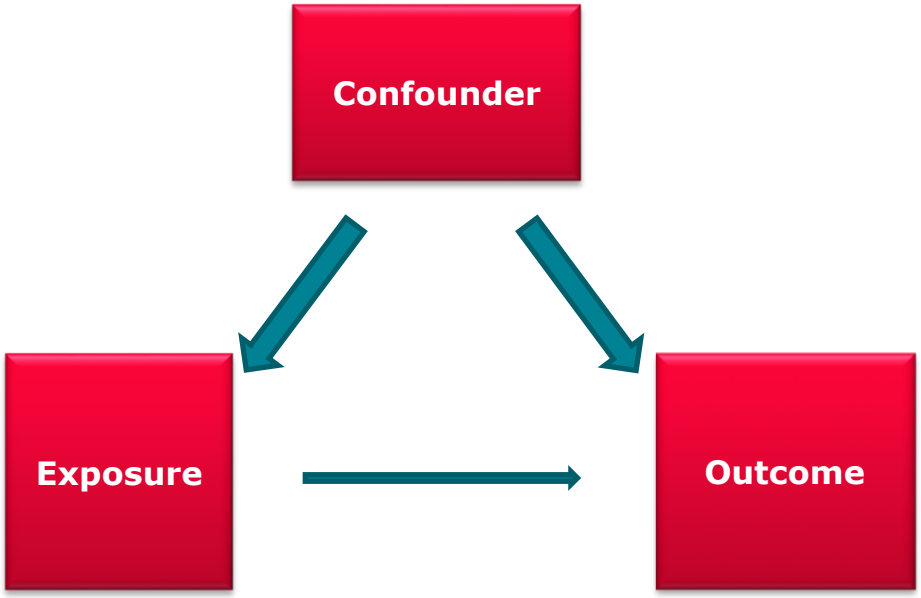
Causal association



Causal association



Confounders



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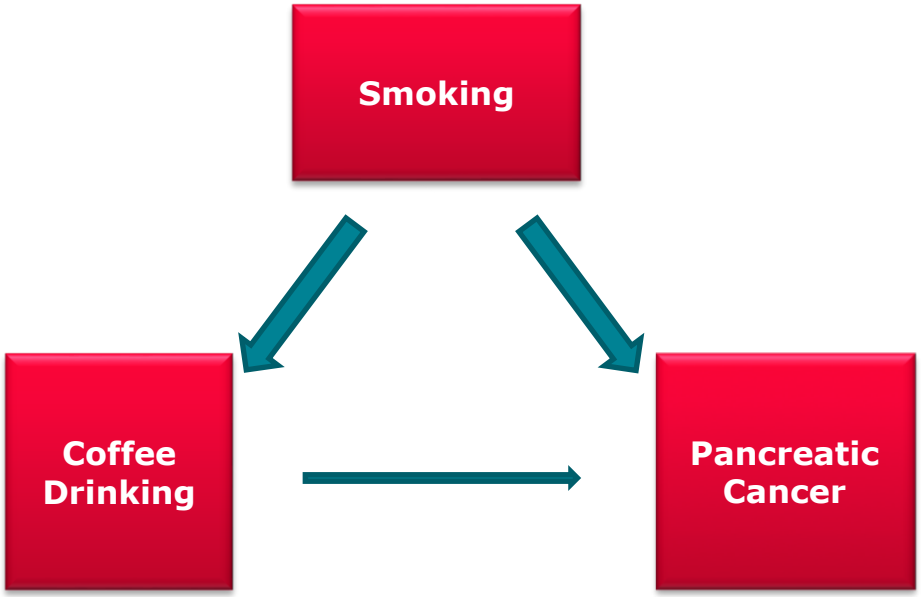

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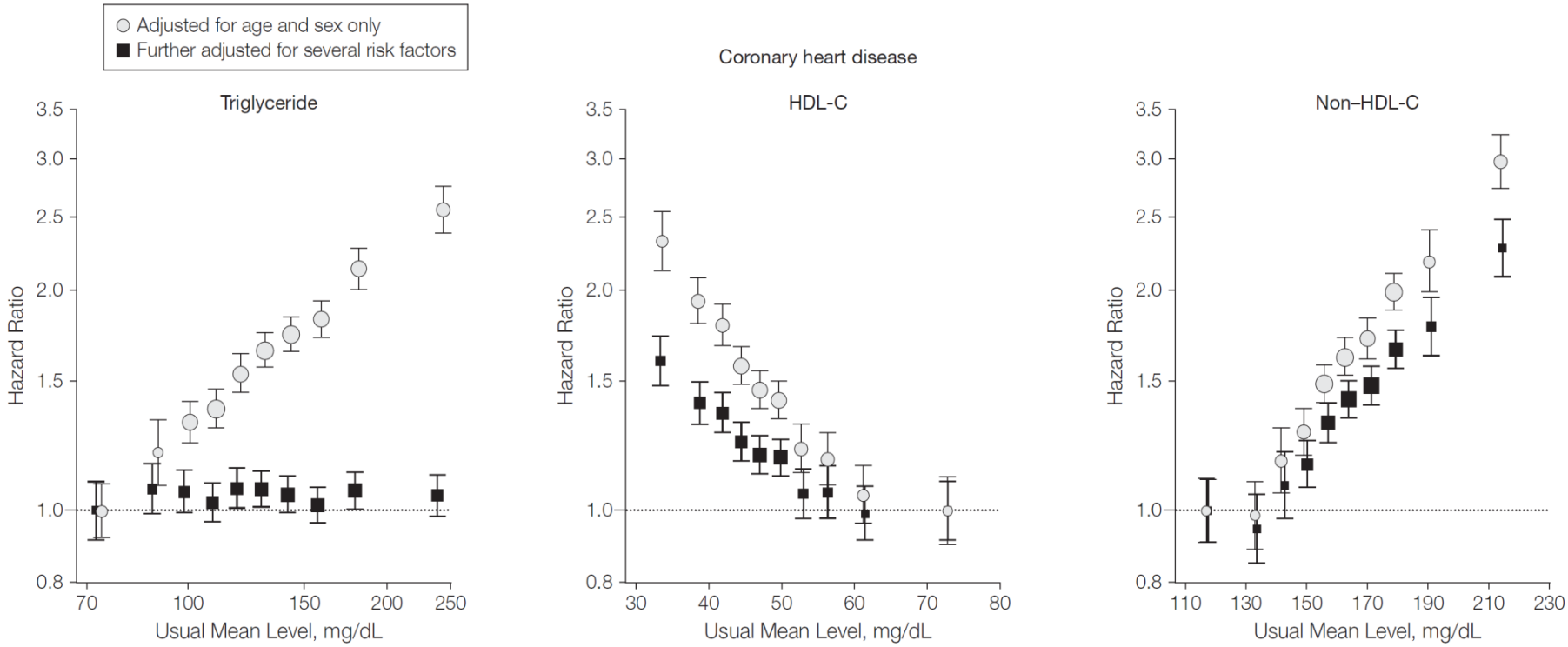

ERFC, *JAMA* 2009

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Criteria to be a Confounder

- The confounding factor must be associated with both the exposure and the outcome.
- The confounding factor must be distributed unequally among the study groups.
- A confounder cannot be an intermediary step in the causal pathway from the exposure to the outcome of interest.

Adjusted analyses

- Multivariable models
- Matching

Propensity score

The propensity score is defined as a subject's probability of treatment selection, conditional on observed baseline covariates.

Austin PC. Stat Med. 2015 Dec 10;34(28):3661-79.

Propensity score matching

- **Nearest neighbor matching** - matching to a given treated subject that untreated subject whose propensity score is closest to that of the treated subject.

- **Nearest neighbor matching within a specified caliper distance** - the absolute difference in the propensity scores of matched subjects must be below some prespecified threshold (the caliper distance).

- **Stratification on the propensity score** - stratifying subjects according to their estimated propensity score.

Austin PC. Multivariate Behav Res. 2011 May; 46(3): 399–424.

European Heart Journal (2013) **34**, 1481–1488
doi:10.1093/eurheartj/ehs348

CLINICAL RESEARCH
Arrhythmia/electrophysiology

Increased mortality among patients taking digoxin—analysis from the AFFIRM study

Matthew G. Whitbeck, Richard J. Charnigo, Paul Khairy, Khaled Ziada, Alison L. Bailey, Milagros M. Zegarra, Jignesh Shah, Gustavo Morales, Tracy Macaulay, Vincent L. Sorrell, Charles L. Campbell, John Gurley, Paul Anaya, Hafez Nasr, Rong Bai, Luigi Di Biase, David C. Booth, Guillaume Jondeau, Andrea Natale, Denis Roy, Susan Smyth, David J. Moliterno, and Claude S. Elayi*

Division of Cardiovascular Medicine, Gill Heart Institute University of Kentucky, 326 C.T. Weth

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See pages 1465 and 1468 for the editorial comments on this article (doi:1

European Heart Journal (2013) **34**, 1489–1497
doi:10.1093/eurheartj/eht120

CLINICAL RESEARCH
Arrhythmia/electrophysiology

Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from *post hoc* propensity-matched analysis of the AFFIRM trial

Mihai Gheorghiade[1], Gregg C. Fonarow[2], Dirk J. van Veldhuisen[3], John G.F. Cleland[4], Javed Butler[5], Andrew E. Epstein[6], Kanan Patel[7], Inmaculada B. Aban[7], Wilbert S. Aronow[8], Stefan D. Anker[9], and Ali Ahmed[7,10]*

[1]Northwestern University, Chicago, IL, USA; [2]University of California, Los Angeles, CA, USA; [3]University Medical Centre, Groningen, The Netherlands; [4]Hull York Medical School, Kingston-Upon-Hull, UK; [5]Emory University, Atlanta, GA, USA; [6]University of Pennsylvania, Philadelphia, PA, USA; [7]University of Alabama at Birmingham, 1720 2nd Avenue South, CH-19, Suite 219, Birmingham 35294-2041 AL, USA; [8]New York Medical College, Valhalla, NY, USA; [9]Center for Clinical and Basic Research, IRCCS San Raffaele, Rome, Italy; and [10]Veterans Affairs Medical Center, Birmingham, AL, USA

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See pages 1465 and 1468 for the editorial comments on this article (doi:10.1093/eurheartj/eht087 and doi:10.1093/eurheartj/ehs483)

AFFIRM study – Whitbeck et al.

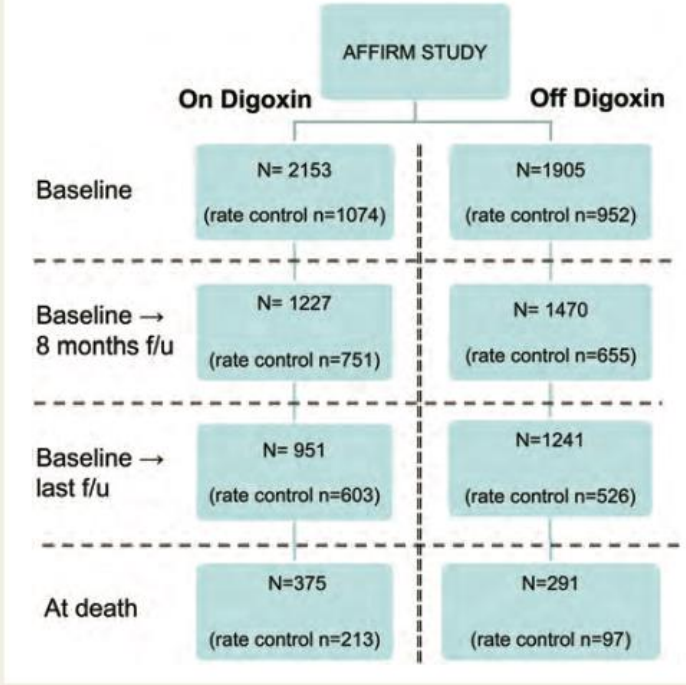

Figure 1 Number of patients on digoxin vs. not on digoxin at critical times of the study.

Whitbeck et al. European Heart Journal (2013) 34, 1481–1488

AFFIRM study – Whitbeck et al.

Table I Covariates used to generate propensity scores in patients with and without digoxin therapy within 6 months of randomization

Covariate	Digoxin (n = 2153)	No digoxin (n = 1905)	P-value
History of coronary artery disease	837 (39%)	712 (37%)	0.33
History of angina pectoris	564 (26%)	481 (25%)	0.49
Prior myocardial infarction	392 (18%)	311 (16%)	0.11
History of hypertension	1486 (69%)	1390 (73%)	<0.001
History of cardiomyopathy	259 (12%)	82 (4%)	<0.0001
History of valvular heart disease	318 (15%)	186 (10%)	<0.0001
History of congenital heart disease	14 (<1%)	7 (<1%)	0.27
Symptomatic bradycardia/AV block	156 (7%)	127 (7%)	0.49
Prior stroke or TIA	272 (13%)	269 (14%)	0.16
History of peripheral vascular disease	163 (8%)	118 (6%)	0.09
History of hepatic or renal disease	130 (6%)	101 (5%)	0.34
History of pulmonary disease	370 (17%)	221 (12%)	<0.001
Permanent pacemaker	130 (6%)	120 (6%)	0.74
Prior interventional procedure	171 (8%)	183 (10%)	0.06
Oestrogen/progesterone within 6 months of randomization	224 (10%)	152 (8%)	<0.01
Lipid-lowering therapy within 6 months of randomization	434 (20%)	479 (25%)	<0.001
Symptoms during AF within 6 months of randomization	1969 (91%)	1635 (86%)	<0.0001
Cardioversion since qualifying episode of AF	900 (42%)	782 (41%)	0.63
Failure of antiarrhythmic drug prior to randomization	431 (20%)	281 (15%)	<0.0001
Hospitalization for qualifying arrhythmia	1021 (47%)	872 (46%)	0.29
Recurrent episodes of AF prior to randomization	682 (32%)	709 (37%)	<0.001
Amiodarone as initial therapy	399 (19%)	338 (18%)	0.54
Beta-blocker as initial therapy	552 (26%)	644 (34%)	<0.0001
Diltiazem as initial therapy	419 (19%)	364 (19%)	0.78
Sotalol as initial therapy	299 (14%)	314 (16%)	0.02
Verapamil as initial therapy	126 (6%)	119 (6%)	0.59
Class I drug as initial therapy	298 (14%)	226 (12%)	0.06

Hx, history; TIA, transient ischaemic attack; ACE, angiotensin converting enzyme; PND, paroxysmal nocturnal dyspnoea.
Atrial fibrillation symptoms included chest pain, diaphoresis, dizziness/light-headedness, dyspnoea, oedema, fast heart rate, fatigue, orthopnea, palpitations, panic, PND, syncope, and other.

Whitbeck et al. European Heart Journal (2013) 34, 1481–1488

AFFIRM study – Whitbeck et al.

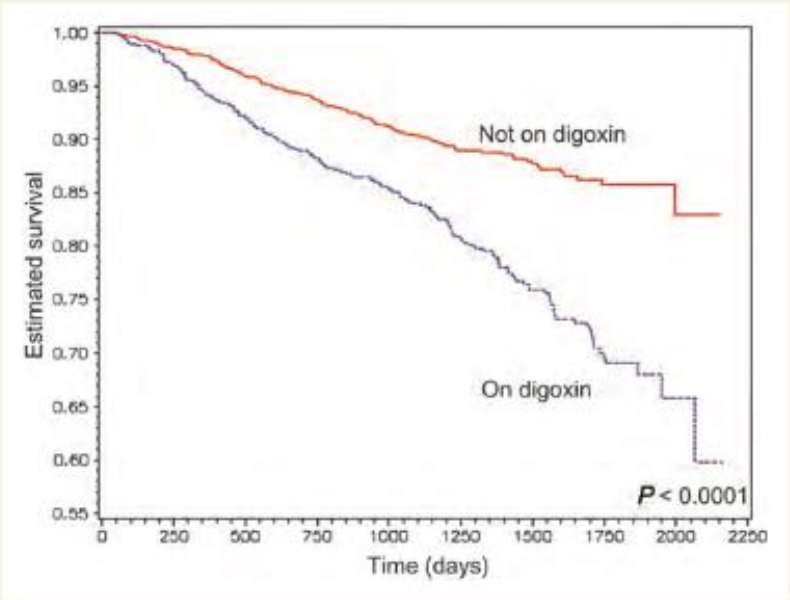

Figure 2 Kaplan–Meier curves for all-cause mortality based on digoxin use during the study. Shown are Kaplan–Meier curves for all-cause mortality in patients always or never on digoxin during the study. *P*-value for this comparison is <0.0001 by the likelihood ratio test.

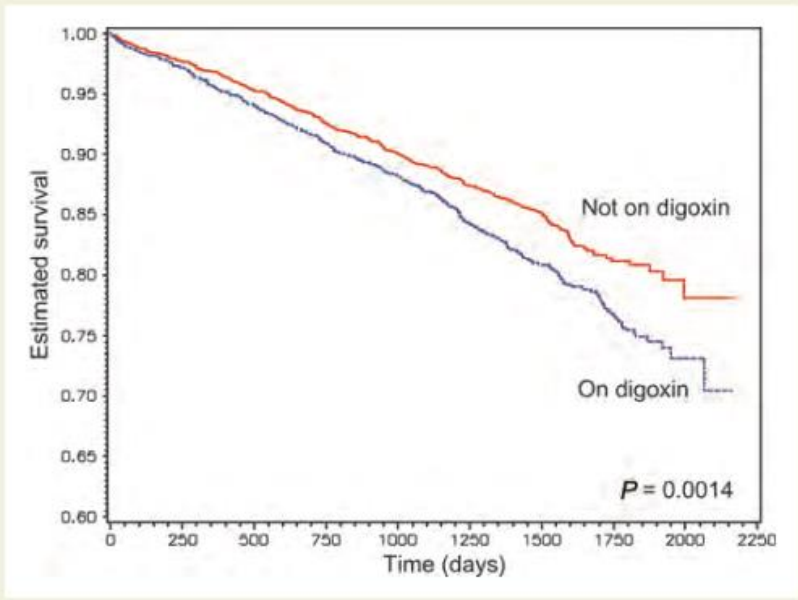

Figure 3 Kaplan–Meier curves for all-cause mortality based on digoxin use at baseline. Kaplan–Meier curves depict all-cause mortality in patients receiving or not receiving digoxin within the six months preceding randomization. *P*-value for this comparison is 0.0014 by the likelihood ratio test.

Whitbeck et al. European Heart Journal (2013) 34, 1481–1488

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AFFIRM study – Gheorghiade et al.

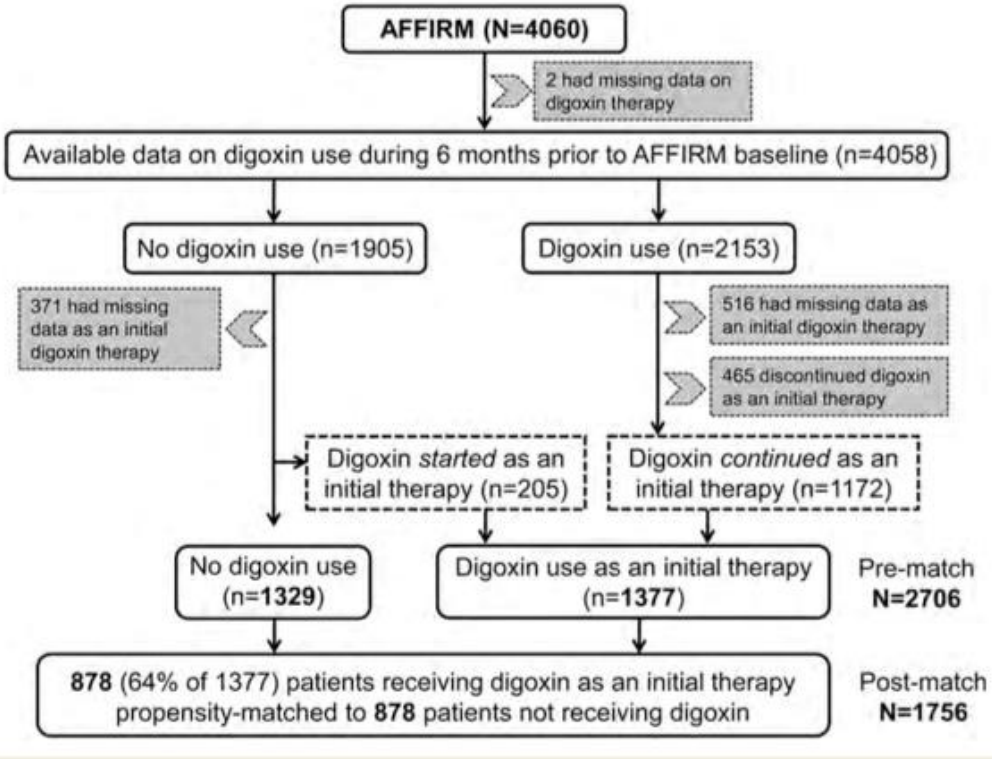

Figure 1 Flow chart displaying assembly of study cohorts.

Gheorghiade et al. European Heart Journal (2013) 34, 1489–1497

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AFFIRM study – Gheorghiade et al.

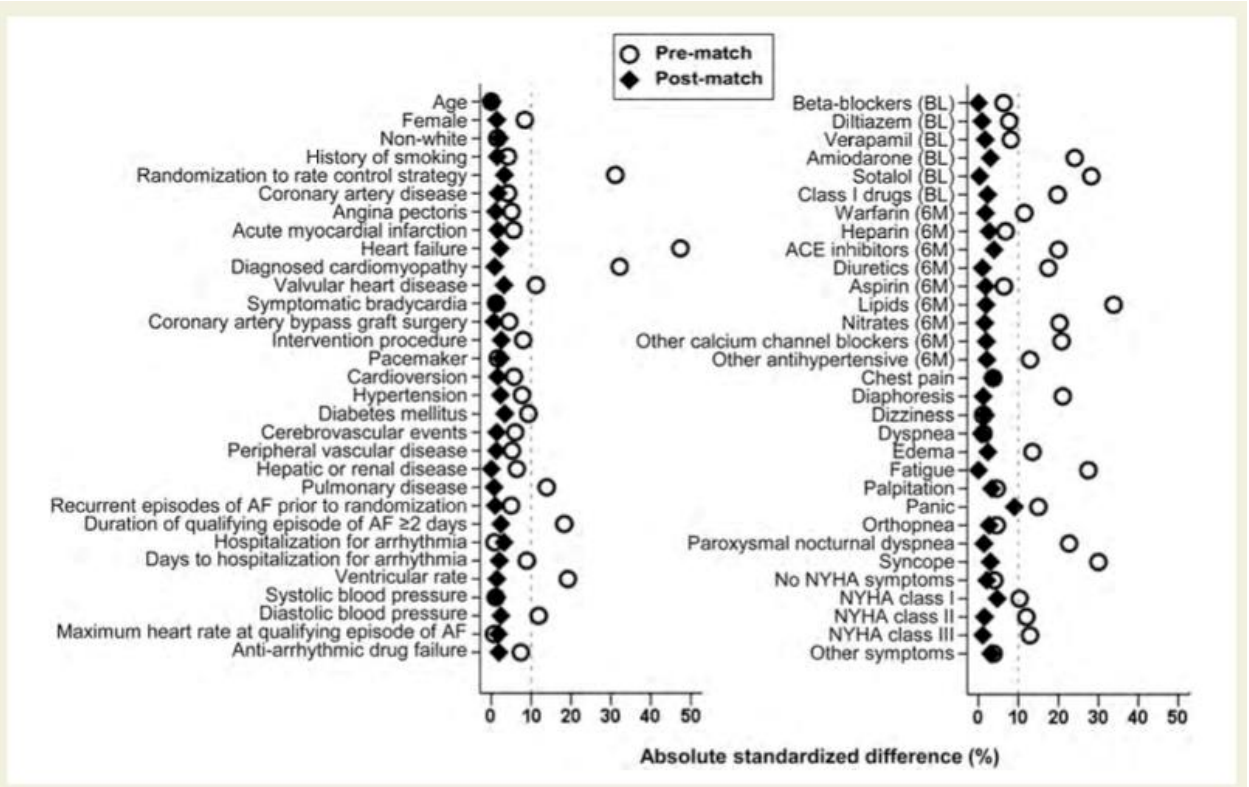

Figure 2 Love plot displaying absolute standardized differences for 59 baseline characteristics between patients with atrial fibrillation receiving and not receiving digoxin as initial baseline therapy in AFFIRM, before and after propensity score matching (NYHA = New York Heart Association; BL = Therapy at baseline or at randomization to rate vs. rhythm control strategies; 6M = Therapy during 6 months prior to randomization to rate vs. rhythm control strategies).

Gheorghiade et al. European Heart Journal (2013) 34, 1489–1497

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Table I Baseline characteristics by the use of digoxin as initial therapy in patients with atrial fibrillation during randomization (to rate vs. rhythm control strategy) in AFFIRM, before and after propensity-matching

Variables Mean ± SD or *n* (%)	Before propensity-matching			After propensity-matching		
	Digoxin use		*P*-value	Digoxin use		*P*-value
	No (*n* = 1329)	Yes (*n* = 1377)		No (*n* = 878)	Yes (*n* = 878)	
Age (years)	70 ± 8	70 ± 8	0.998	70 ± 8	70 ± 8	0.970
Age 65 years or older	1007 (76)	1053 (77)	0.670	679 (77)	690 (79)	0.560
Female	485 (37)	559 (41)	0.028	349 (40)	343 (39)	0.803
Non-whites	151 (11)	163 (12)	0.699	104 (12)	98 (11)	0.713
History of smoking	147 (11)	171 (12)	0.273	99 (11)	95 (11)	0.813
Randomization to rate control strategy	717 (54)	949 (69)	<0.001	356 (41)	342 (39)	0.506
Past medical history						
Coronary artery disease	478 (36)	523 (38)	0.278	324 (37)	317 (36)	0.761
Angina pectoris	317 (24)	359 (26)	0.183	216 (25)	212 (24)	0.866
Acute myocardial infarction	204 (15)	240 (17)	0.144	141 (16)	136 (16)	0.792
Heart failure	161 (12)	428 (31)	<0.001	147 (17)	140 (16)	0.664
Valvular heart disease	136 (10)	191 (14)	0.004	96 (11)	105 (12)	0.538
Symptomatic bradycardia	84 (6)	91 (7)	0.761	57 (7)	54 (6)	0.847
Coronary artery bypass graft	157 (12)	183 (13)	0.247	111 (13)	109 (12)	0.942
Interventional procedure	126 (10)	100 (7)	0.037	76 (9)	70 (8)	0.661
Pacemaker implantation	79 (6)	87 (6)	0.685	52 (6)	57 (7)	0.699
Cardioversion	526 (40)	507 (37)	0.140	324 (37)	331 (38)	0.762
Hypertension	979 (74)	967 (70)	0.047	640 (73)	631 (72)	0.675
Diabetes mellitus	241 (18)	301 (22)	0.015	168 (19)	180 (21)	0.513
Cerebrovascular events	186 (14)	165 (12)	0.119	114 (13)	110 (13)	0.831
Peripheral vascular disease	82 (6)	103 (8)	0.177	64 (7)	61 (7)	0.856
Hepatic or renal disease	68 (5)	91 (7)	0.099	50 (6)	50 (6)	1.000
Pulmonary disease	159 (12)	232 (17)	<0.001	123 (14)	125 (14)	0.946
Diagnosed cardiomyopathy	14 (1)	103 (8)	<0.001	14 (2)	15 (2)	1.000
Recurrent episodes of AF prior to randomization	502 (38)	487 (35)	0.194	303 (35)	307 (35)	0.880
Duration of qualifying episode of AF ≥2 days	867 (65)	1014 (74)	<0.001	592 (67)	602 (69)	0.635
Hospitalization for arrhythmia	566 (43)	592 (43)	0.832	352 (40)	366 (42)	0.524
Days to hospitalization for arrhythmia	2.0 ± 3.3	2.3 ± 3.6	0.020	2.0 ± 3.4	2.1 ± 3.4	0.661
Symptoms during atrial fibrillation in the last 6 months						
Chest pain	290 (22)	337 (25)	0.102	194 (22)	194 (22)	1.000
Diaphoresis	231 (17)	281 (20)	0.045	163 (19)	160 (18)	0.902
Dizziness	408 (31)	475 (35)	0.035	286 (33)	279 (32)	0.756
Dyspnoea	626 (47)	813 (59)	<0.001	445 (51)	458 (52)	0.555
Leg swelling	178 (13)	335 (24)	<0.001	143 (16)	144 (16)	1.000
Fatigue	651 (49)	810 (59)	<0.001	473 (54)	463 (53)	0.667
Palpitation	603 (45)	704 (51)	0.003	416 (47)	424 (48)	0.734
Panic	123 (9)	156 (11)	0.076	80 (9)	87 (10)	0.626
Orthopnoea	133 (10)	231 (17)	<0.001	106 (12)	95 (11)	0.447
Paroxysmal nocturnal dyspnea	57 (4)	118 (9)	<0.001	46 (5)	44 (5)	0.911
Syncope	41 (3)	59 (4)	0.098	32 (4)	35 (4)	0.801
Other symptoms	130 (10)	120 (9)	0.338	78 (9)	87 (10)	0.510
Current heart failure status by NYHA class symptoms						
Class I	102 (8)	192 (14)		80 (9)	84 (10)	
Class II	56 (4)	130 (9)	<0.001	44 (5)	48 (6)	0.484
Class III	11 (1)	34 (3)		11 (1)	9 (1)	

Continued

AFFIRM study – Gheorghiade et al.

Table 3 Association of digoxin use as initial therapy at baseline with outcomes in a propensity-matched cohort of patients with atrial fibrillation enrolled in the AFFIRM trial

Post-match (n = 1756)	Events (%)		Hazard ratio (95% CI)	P-value
	Digoxin use as initial baseline therapy			
	No (n = 878) (%)	Yes (n = 878) (%)		
All-cause mortality[a]	118 (13)	124 (14)	1.06 (0.83–1.37)	0.640
Cardiovascular	56 (6)	63 (7)	1.13 (0.79–1.63)	0.494
Non-cardiovascular	48 (6)	51 (6)	1.08 (0.73–1.60)	0.709
All-cause hospitalization	516 (59)	495 (56)	0.96 (0.85–1.09)	0.510
Non-fatal arrhythmias[b]	10 (1)	9 (1)	0.90 (0.37–2.23)	0.827

[a]The sum of cause-specific deaths may not equal total deaths as some deaths were unclassified.
[b]Incident non-fatal arrhythmias included torsades de pointes ventricular tachycardia, sustained ventricular tachycardia, and resuscitated cardiac arrest due to ventricular tachycardia, ventricular fibrillation, electromechanical dissociation, bradycardia, or other reasons.

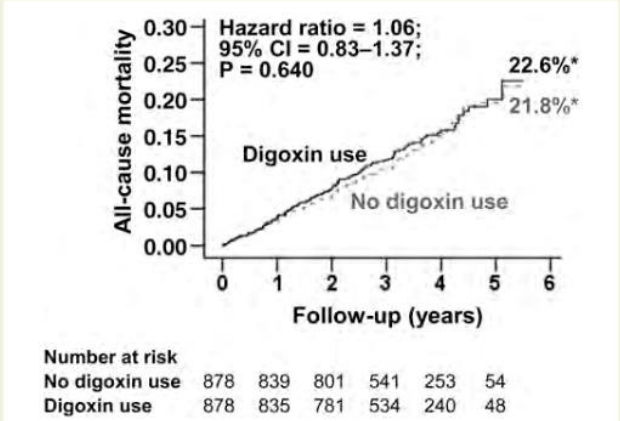

Figure 3 Kaplan–Meier plots for all-cause mortality in propensity-matched AFFIRM patients with atrial fibrillation receiving and not receiving digoxin as initial therapy at baseline. *These percentages derived from Kaplan–Meier analysis are different from raw percentages presented in *Table 3*.

Gheorghiade et al. European Heart Journal (2013) 34, 1489–1497

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Biases

Reverse causation?

Indication bias?

European Heart Journal (2013) **34**, 1465–1467
doi:10.1093/eurheartj/eht087

STATISTICAL VIEWPOINT

When 'digoxin use' is not the same as 'digoxin use': lessons from the AFFIRM trial

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Online publish-ahead-of-print 16 April 2013

Table I Summary of differences between AFFIRM studies in the primary methods used for evaluating the relationship between digoxin use and all-cause mortality

	Whitbeck *et al.*	Gheorghiade *et al.*
Study design	Non-randomized, observational analysis using data from randomized AFFIRM trial	Non-randomized, observational analysis using data from randomized AFFIRM trial
Time point digoxin used assessed	Time-varying covariate, throughout study	Fixed, at baseline only
Cohort	Full cohort ($n = 4058$)	Selected cohort ($n = 1756$)
Propensity method	Adjustment	Matching[a]
Primary HR for digoxin and all-cause mortality association	HR 1.41, 95% CI 1.19–1.67; $P < 0.001$	HR 1.06, 95% CI 0.83–1.37; $P = 0.640$
Main conclusion from authors	Digoxin associated with significant increase in all-cause mortality in patients with AF	No evidence of increased mortality associated with digoxin use as baseline initial therapy in patients with AF

AF, atrial fibrillation; CI, confidence interval; HR, hazard ratio.
[a]Propensity adjustment used for sensitivity analysis.

Conclusions

What conclusions can be drawn from these two analyses?

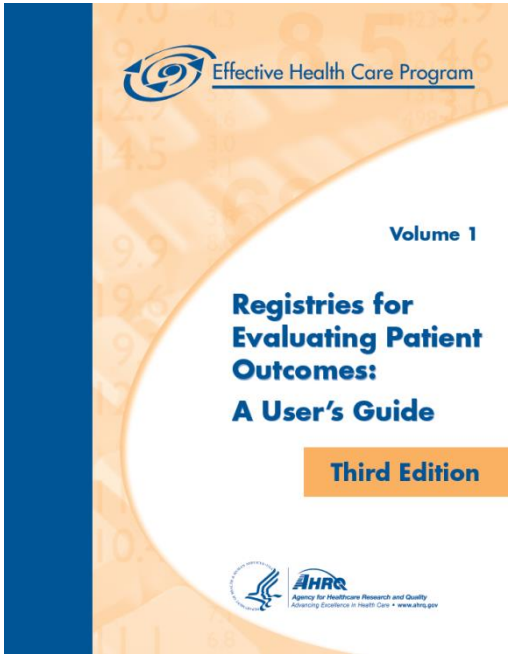
- Given the non-randomized, observational design of both studies, the findings should be considered hypothesis generating

- Even sophisticated statistical methods such as propensity analysis cannot replace randomization

- It to understand the cohorts and the how treatment groups are defined, because sometimes digoxin use is not the same as digoxin use

Murphy. European Heart Journal (2013) 34, 1465

Suggestions:



READ!!!!

Registries for Evaluating Patient Outcomes, 3 edition
A User's Guide

USE!!!!

STROBE Statement – when you write a paper using observational data!!!

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Meta-analyses

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What is a Systematic Review?

“ A review that is conducted according to clearly stated, scientific research methods, and is designed to minimize biases and errors inherent to traditional, narrative reviews.”

Kevin C. Chung, MD, Patricia B. Burns, MPH, H. Myra Kim, ScD, “Clinical Perspective: A Practical Guide to Meta-Analysis.” The Journal of Hand Surgery. Vol. 31A No.10 December 2006. p.1671

Why are Systematic Reviews important?

- To remain up to date on a topic
- Individual studies with conflicting conclusions

Margaliot, Zvi, Kevin C. Chung. “Systematic Reviews: A Primer for Plastic Surgery Research.” PRS Journal. 120/7 (2007) p.1839

Characteristics of Systematic Reviews

Two possible approaches:

- Qualitative synthesis (systematic review)
- Statistical synthesis of data (meta-analysis) if appropriate and possible

Hypothesis

Hypotheses must be conceived a priori.

Four steps

- **Identify studies (appropriate literature search)**
- **Determine eligibility apriori**
  - Inclusion criteria
  - Exclusion criteria
- **Abstract data from the studies**
- **Statistical analysis (if possible)**

Literature Search

- **Literature search strategy has to be defined apriori**
- **List of popular databases to search**
  - Pubmed/Medline
  - Embase
  - Cochrane Review
  - ISI Web of Science
  - SCOPUS

→ Database bias!!!

- **Other potential sources**
  - Trial registries (clinicaltrials.gov)
  - Abstracts from meetings
  - Personal references
  - References from published reviews/meta-analysis/trials
  - Contact experts
  - Web, eg. Google (http://scholar.google.com)

→ Grey litterature

Literature Search – Risk of Bias

- **English-language bias -** papers in languages other than English are more likely to be excluded

- **Citation bias -** studies with significant or positive results vs. those with inconclusive or negative results are more likely to be referenced in other publications, thus are more likely to be identified.

- **Publication Bias –** studies with positive results are more likely to be published

Data Collection

- The variables of interest and, thus, the list of data to be extracted should be decided a priori.
- A data extraction form should be used so that the same data are extracted from each study and by all the reviewers.
- At least two independent readers should perform the literature search and the data extraction in order to be reproducible and accurate
- If two reviewers disagree about including or not a study, disagreement between readers could be solved by agreements or by a third reviewer

Data Collection

- **Study characteristics** (year and journal of publication, number of patients in each arm, treatments performed, duration of follow-up)
- **Demographics** (age, % males or females)
- **Clinical characteristics** (traditional CV risk factors - % hypertensive pts, % diabetic pts, % dyslipidemic pts, % smokers – concomitant treatments, comorbidities, etc)
- **Outcomes** (all-cause death, CV death, MI, stroke, etc)

Quality Assessment

"The validity of a systematic review ultimately depends on the scientific method of the retrieved studies and the reporting of data."

Margaliot, Zvi, Kevin C. Chung. "Systematic Reviews: A Primer for Plastic Surgery Research." PRS Journal. 120/7 (2007) p.1839

Quality Assessment

THE SCORING SYSTEM USED FOR *CLINICAL EVIDENCE* REVIEWS

Type of evidence		
Initial score based on type of evidence	+4	RCTs/ SR of RCTs, +/– other types of evidence
	+2	Observational evidence (e.g., cohort, case-control)
Quality		
Based on	Blinding and allocation process	
	Follow-up and withdrawals	
	Sparse data	
	Other methodological concerns (e.g., incomplete reporting, subjective outcomes)	
Score	0	No problems
	–1	Problem with 1 element
	–2	Problem with 2 elements
	–3	Problem with 3 or more elements
Consistency		
Based on	Degree of consistency of effect between or within studies	
Score	+1	Evidence of dose response across or within studies (or inconsistency across studies is explained by a dose response); also 1 point added if adjustment for confounders would have increased the effect size
	0	All/most studies show similar results
	–1	Lack of agreement between studies (e.g., statistical heterogeneity between RCTs, conflicting results)
Directness		
Based on	The generalisability of population and outcomes from each study to our population of interest	
Score	0	Population and outcomes broadly generalisable
	–1	Problem with 1 element
	–2	Problem with 2 or more elements
Effect size		
Based on	The reported OR/RR/HR for comparison	
Score	0	Not all effect sizes >2 or <0.5 and significant; or if OR/RR/HR not significant
	+1	Effect size >2 or <0.5 for all studies/meta-analyses included in comparison and significant
	+2	Effect size >5 or <0.2 for all studies/meta-analyses included in comparison and significant

The final GRADE score: we use 4 categories of evidence quality based on the overall GRADE scores for each comparison: high (at least 4 points overall), moderate (3 points), low (2 points), and very low (one or less).

GRADE

Grading of Recommendations Assessment, Development and Evaluation

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? BMJ. 2008 May 3;336(7651):995-8.

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Data Synthesis

Data could be summarized quantitatively if study designs are not too different in:

- **outcome definition (composite outcome?);**
- **population sizes**
- **population characteristics**
- **interventions**

HETEROGENEITY

What is meta analysis?

Quantitative approach for systematically combining results of previous research to arrive at conclusions about the body of research.

Petitti, 1994:5

Protocols – PRISMA

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

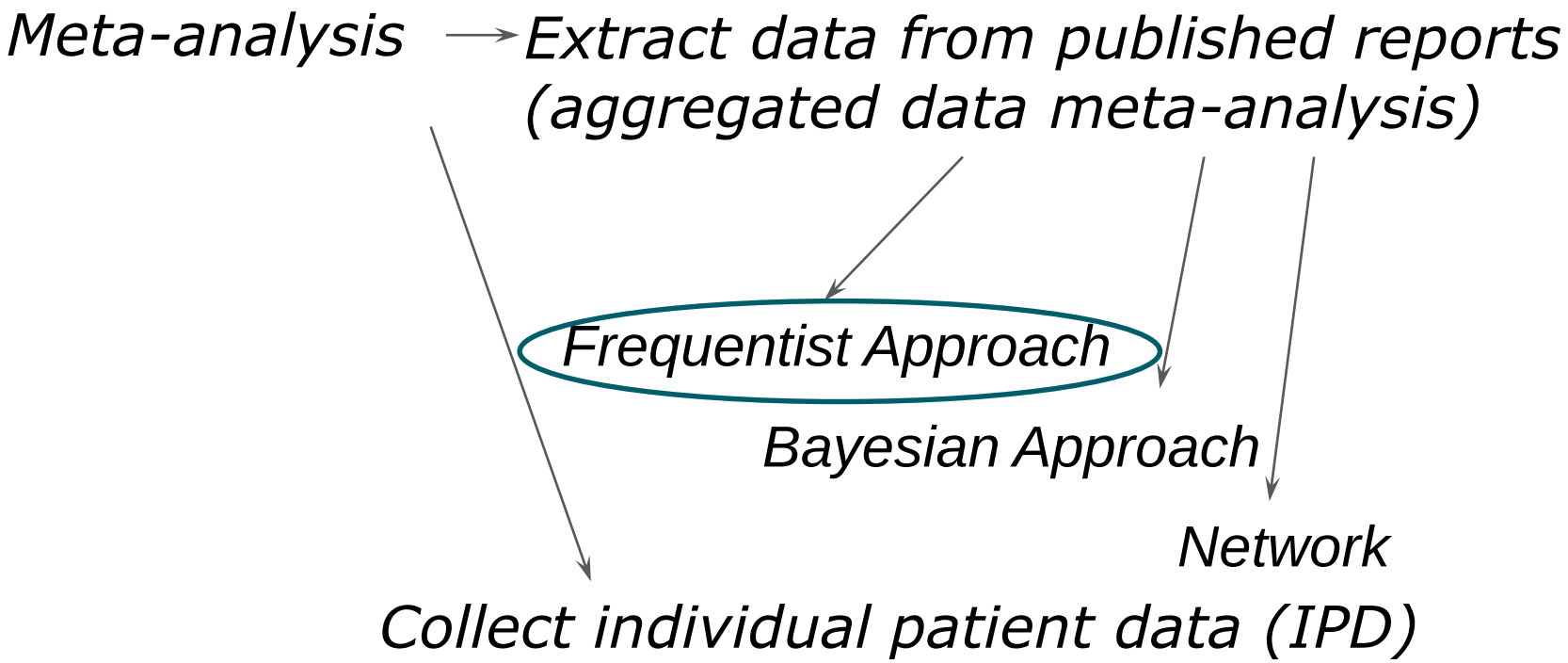
PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Types of Meta-analysis/Terminology



Stwart et al. Cochrane Workshop on Reviews using IPD

Meta-analysis: Statistical Models

- **2 statistical models:**
  - Fixed effects:
    1. Effect of treatment is the same for every study;
    2. Low heterogeneity
  - Random effects:
    1. True effect estimate for each study varies;
    2. High heterogeneity
    3. Provide larger CI

Heterogeneity

- **Clinical heterogeneity: variability in the participants, interventions and outcomes studied**

+

- **Methodological heterogeneity: variability in study design**

Statistical heterogeneity

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

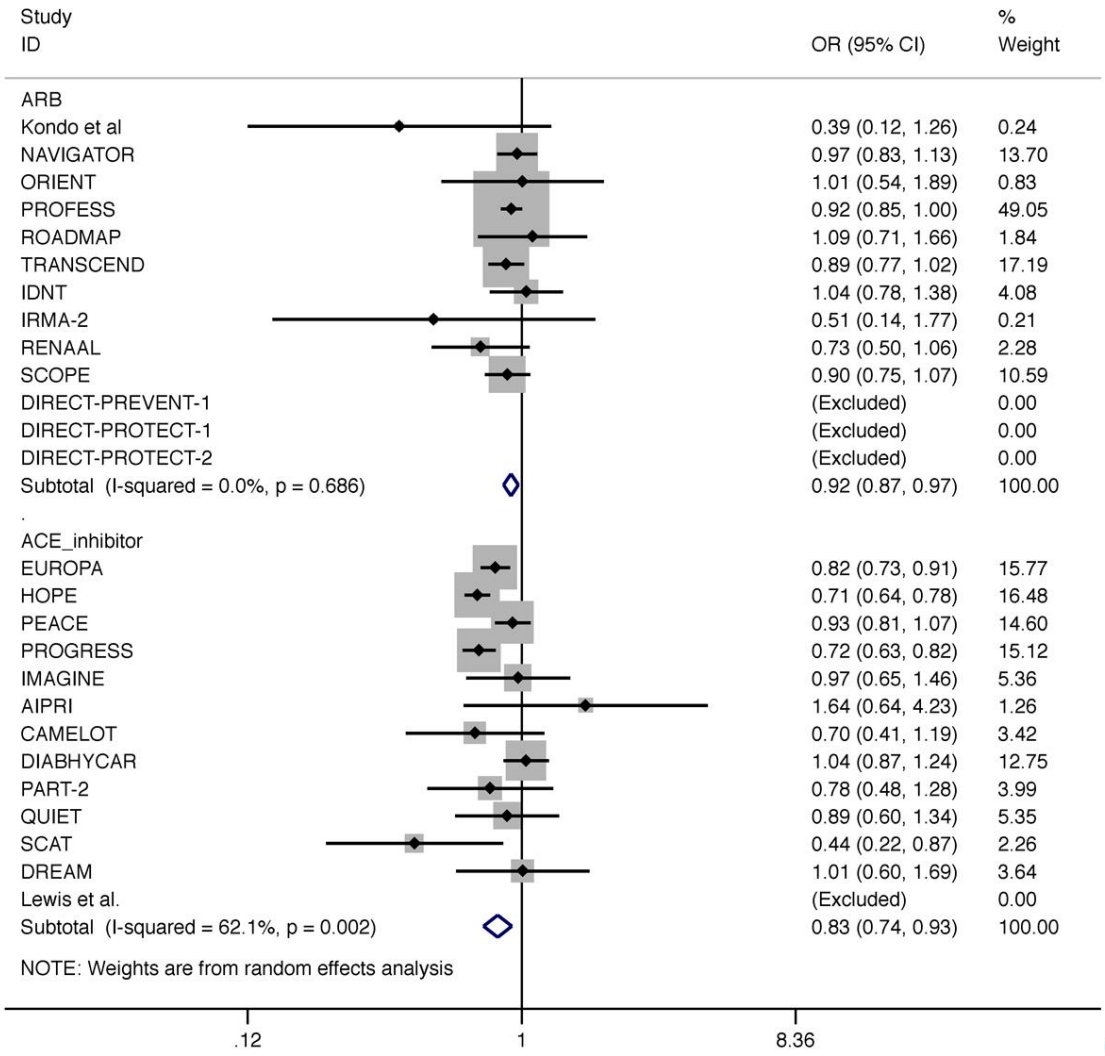
Heterogeneity assessment

- **Do the confidence intervals for the results of individual studies have poor overlap?**
- **Check the Cochrane Q statistic: a p value decided apriori defines the presence of significant heterogeneity.**
- **Check I^2 statistic: describes the percentage of variation across studies that is due to heterogeneity rather than chance.**

1. **0% to 40%: heterogeneity might not be important;**
2. **30% to 60%: may represent moderate heterogeneity;**
3. **50% to 90%: may represent substantial heterogeneity;**
4. **75% to 100%: considerable heterogeneity.**

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Heterogeneity assessment



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Strategies for addressing heterogeneity

- Check again that the data are correct
- Do not do a meta-analysis
- Explore heterogeneity (subgroup analysis, meta-regression)
- Ignore heterogeneity (there is no an intervention effect but a distribution of intervention effects)
- Perform a random-effects meta-analysis (when heterogeneity cannot be explained)
- Change the effect measure (different scales in different studies)
- Exclude studies (outlying studies)

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Sensitivity analysis

- One study removed meta-analysis
- Meta-regression analysis

Meta-Regression Analysis

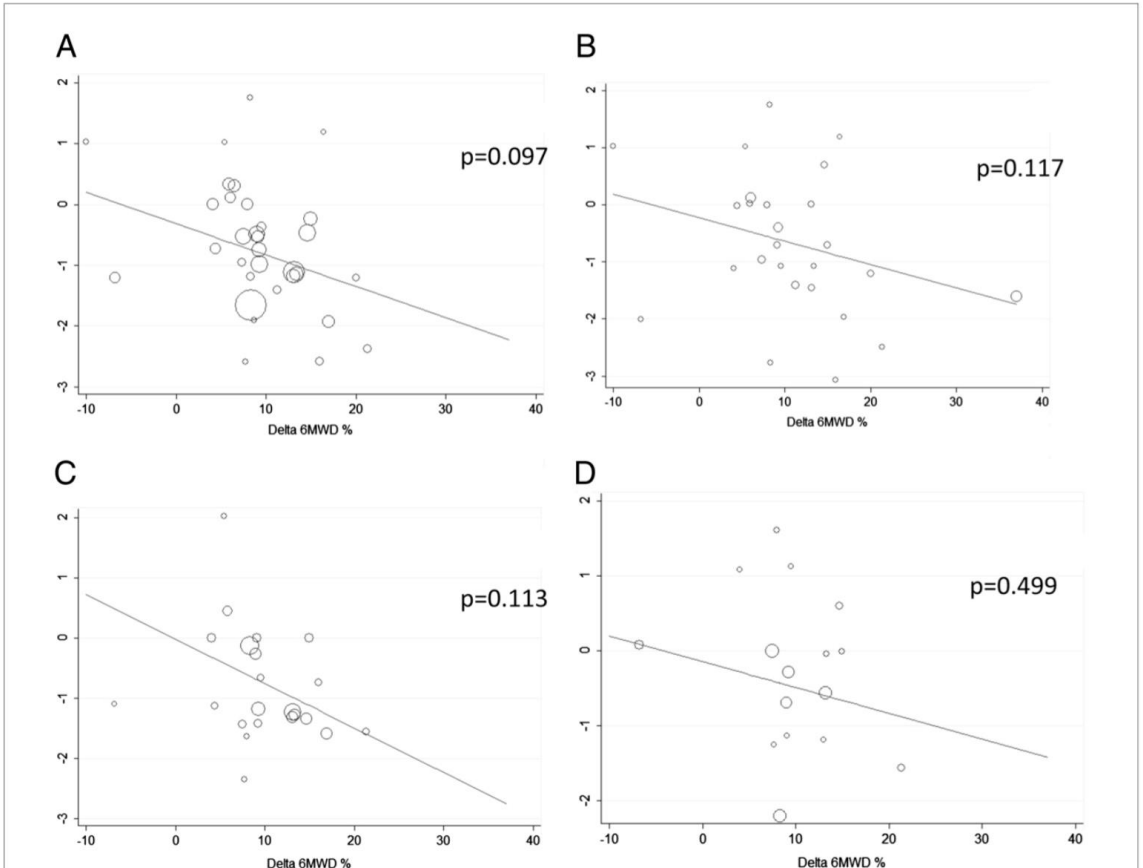
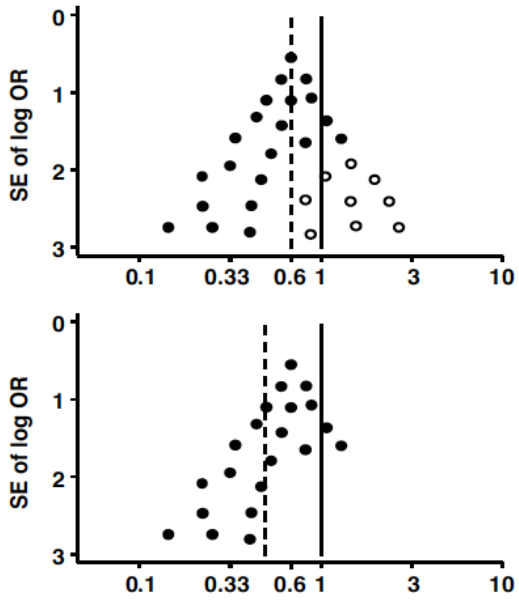


Figure 3 **Meta-Regression Analysis**

Meta-regression between **(A)** Δ6MWD and composite outcome, **(B)** all-cause death, **(C)** hospitalization for pulmonary arterial hypertension (PAH) and/or lung or heart-lung transplantation, **(D)** and initiation of PAH rescue therapy. 6MWD: 6-minute walking distance

Publication Bias



Symmetrical plot in the absence of bias (open circles indicate smaller studies showing no beneficial effects)

Asymmetrical plot in the presence of publication bias (smaller studies showing no beneficial effects are missing)

Jonathan A et al. The Stata Journal 2004; 4:127

Publication Bias

Reference	Basis of test
(Begg 1994)	Rank correlation between standardized intervention effect and its standard error.
(Egger 1997a)	Linear regression of intervention effect estimate against its standard error, weighted by the inverse of the variance of the intervention effect estimate.
(Tang 2000)	Linear regression of intervention effect estimate on 1 /ÖN$_{tot}$, with weights N$_{tot}$.
(Macaskill 2001)*	Linear regression of intervention effect estimate on N$_{tot}$, with weights S×F/N$_{tot}$.
(Deeks 2005)*	Linear regression of log odds ratio on 1/ÖESS with weights ESS, where effective sample size ESS = 4N$_E$ ×N$_C$ / N$_{tot}$.
(Harbord 2006)*	Modified version of the test proposed by Egger et al., based on the 'score' (O–E) and 'score variance' (V) of the log odds ratio.
(Peters 2006)*	Linear regression of intervention effect estimate on 1/N$_{tot}$, with weights S×F/N$_{tot}$.
(Schwarzer 2007)*	Rank correlation test, using mean and variance of the non-central hypergeometric distribution.
(Rücker 2008)	Test based on arcsine transformation of observed risks, with explicit modelling of between-study heterogeneity.

* Test formulated in terms of odds ratios, but may be applicable to other measures of intervention effect.

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Thank you

Are you <40 years?

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