Retrieving and appraising systematic reviews

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Outline

- Information overload
- Evidence based medicine
- Narrative vs. systematic reviews
- Retrieving systematic reviews
- QUality Of Reporting Of Meta analyses (QUOROM) statement
- Overview of QUOROM principles
- Examples

Information Overload

- 1980 Biomedical literature expanding 6-7 % annually, *doubling* every 10-12 years
- 1998 > 25,000 biomedical journals
  General medicine - 19 articles / day
  - 6,935 articles / year
- New Drugs eg. Hypertension
  - 1972 Original JNC Guidelines - 20 drugs
  - 1998 JNC VI Guidelines - 79 drugs

BMJ 1995;310:1085-86
Arch Intern Med 1997;157:2413-46

Evidence-based drug therapy

"Integrating the best evidence, the individual characteristics of the patient, and individual expertise, into a decision-making process which leads to optimal drug therapy"

BMJ 1996;312:71-72

Pharmaceutical Care and EBM

Pharmaceutical Care
- Review of systems
- Drug related problems
- Goals of therapy
- Evaluate alternatives
- Treatment plan
- Monitoring plan
- Evaluate outcomes

Evidence-Based Medicine
- Clinical question
- Search for evidence
- Evaluate evidence
- Apply evidence
- Evaluate outcome

Systematic Review Explosion

- First pooling of studies in 1904
- "Meta analysis" term coined in 1976 by Glass
- Increasing numbers of meta analyses of RCTs
  - 1970s 16
  - 1980s 279
  - 1996 > 500
- Linear explosion of health-related meta analyses reported in the literature

Eval Health Prof 2001;24:327-335.

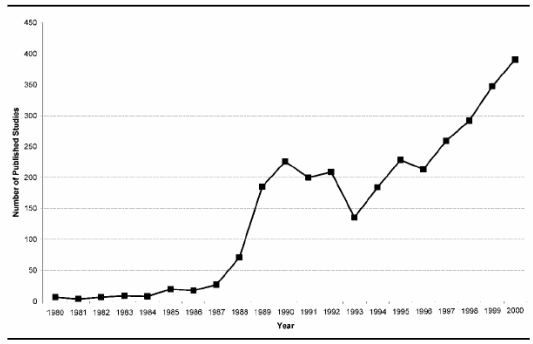

Figure 1: Health-Related Meta-Analyses Published From 1980 to 2000

Eval Health Prof 2001;24:327-335.

Definitions

Narrative review (Traditional)

- Reviews on therapy conducted by experts in the field using informal methods to collect and interpret data

Systematic review (EBM)

- Reviews of primary research with an explicit, comprehensive search strategy to identify all relevant studies that are then appraised and synthesized according to a predetermined, rigorous and reproducible methodology
- *Meta analyses* are quantitative reviews that statistically combine studies to produce a single estimate of effect

Narrative vs. Systematic Reviews

Feature	Narrative	Systematic
Question	Broad in scope	Focused clinical question
Sources/search	Not usually specified, potentially biased	Comprehensive sources, explicit search strategy
Selection	Not usually specified, potentially biased	Criterion-based selection, uniformly applied
Appraisal	Variable	Rigorous critical appraisal
Synthesis	Often a qualitative summary	Quantitative summary*
Inferences	Opinion, sometimes evidence-based	Evidence-based

**Meta analysis is a quantitative summary that includes a statistical analysis*

CHEST 1992;101:1645-1655.

Narrative vs. Systematic Reviews

Criterion	1996 Narrative Reviews (%)	1996 Meta-analyses (%)
Focused Question	34	95
Search described	28	95
Explicit selection criteria	14	68
Independent quality assessment	11	74
Sources of heterogeneity assessed	14	75
Quantitative synthesis of data	21	100

Ann Intern Med 1999;131:947-951.

Retrieving systematic reviews

- Electronic and bibliographic databases
  - MEDLINE, EMBASE, Cumulated Index to Nursing and Allied Health Literature (CINAHL), Health Services Technology Assessment and Research (HealthSTAR), Science Citation Index Expanded (SCI-EXPANDED), Cochrane Database of Systematic Reviews (CDSR), Health Technology Assessment Database (HTA), Database of Abstracts of Reviews of Effectiveness (DARE), LILACS Database (English), BioMed Central (BMC) database, Turning Research Into Practice (TRIP) database

Retrieving systematic reviews

- Abstracting journals/pre-appraised literature
  - ACP Journal Club, Clinical Evidence, Evidence-Based Medicine
- Health Care Agencies
  - Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
- Full text evidence reports and EB guidelines
  - Health Sciences/Technology Assessment Text (HSTAT)

Utility of Systematic Reviews

- Enable efficient integration of large amounts of valid information
- Resolve therapeutic controversies from conflicting studies
- Improve statistical power by pooling of smaller studies
- Provide better estimate of precision in effect size or risk
- Determine generalizability of findings and consistency of results by comparing results of difference studies

THE COCHRANE COLLABORATION®

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Utility of Systematic Reviews

- Identify reasons for inconsistency across studies and generate hypotheses about subgroup effects
- Reduce delay from research discoveries to implementation of useful therapies
- Enable valid conclusions to be drawn that can be applied by researchers, clinicians, health policy makers and legislators
- Preferred by clinicians over narrative reviews

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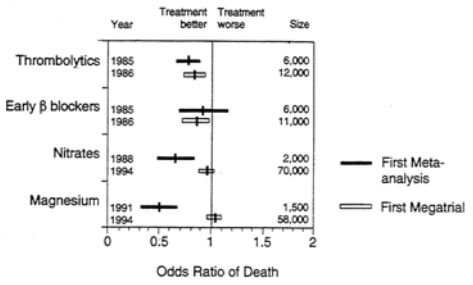
Discordance - Meta analyses and large RCTs



Ann Intern Med 1995;123:873-8777.

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Discordance - Meta analyses and large RCTs

- Agreement exists in 82-90% of cases
- Early meta analyses of small studies did not predict subsequent results from large RCTs 35% of the time in one study
  - Limitations of pooling small RCTs
  - Publication bias
  - Language bias
  - Heterogeneity

JAMA 1996;276:1332-1338.
N Engl J Med 1997;337:536-542.

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Role of Systematic Reviews

- Controversial
- Methodological rigor is paramount
- Hypothesis generating vs. hypothesis testing?
- To generate hypotheses for future RCTs
- To obtain a typical and unbiased estimate of treatment effect and to explore interactions among subgroups

Control Clin Trials 1997;18:568-579.
JAMA 1995;274:1800-1804.

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Quality of Systematic Reviews

- Designation as a "systematic review" does not ensure study was conducted or reported well
- Surveys from 1987 to 1992 showed only 28% of meta analyses addressed 6 essential content areas
- Reviews published in "high impact" journals are not of higher methodological rigor
- Reviews in subspecialty literature may not be better
- Cochrane reviews may be more complete than those in print journals, however, 29% still had major flaws

N Engl J Med 1987;316:450-455.
JAMA 1998;280:278-280.
Ann Emerg Med 2001;38:518-526.
BMJ 2001;323:829-823.

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Overview of Quality Assessment

Overview Quality Assessment Questionnaire
- 10 item criteria to assess scientific quality of overview

Users Guides to the Medical Literature
- Are the results of the study valid?
- What are the results?
- Will the results help me in caring for my patient?

Potsdam consultation on meta analysis
- 14 item guideline on conduct and interpretation of meta analyses

J Clin Epidemiol 1991;44:1271-1278.
JAMA 1994;272:1367-1371.
J Clin Epidemiol 1995;48:167-171.

QUality Of Reporting Of Meta Analyses (QUOROM)

- Conference of 30 clinical epidemiologists, clinicians, statisticians, editors, researchers
- Identified items that should be included in a checklist of standards to improve the quality of reporting of meta analyses
- Inclusion of checklist items guided by research evidence wherever possible
- 8 of 18 items in checklist proven to contribute to bias in meta analyses

Lancet 1999;354:1896-1890.

QUOROM Checklist

Title
Abstract
- Objectives, data sources, review methods, results, conclusion

Introduction
Methods
- Searching, selection, validity assessment, data abstraction, study characteristics, quantitative data synthesis

Results
- Trial flow, study characteristics, quantitative data synthesis

Discussion

Lancet 1999;354:1896-1890.

QUOROM "Top 8 List"

- Structured abstract
- Search techniques
- Publication status
- Language of publication
- Covert duplicate publication
- Assessment of quality of studies
- Blinded abstraction/assessment
- Potential sources of bias cautiously explored
  - Publication, heterogeneity

Lancet 1999;354:1896-1890.

Searching

- Comprehensive search should include:
  - Computerized bibliographic databases
  - Clinical trial registries
  - Health care agencies
  - Proceedings of conferences and meetings
  - Summaries of dissertations
  - Reference lists of articles
  - Hand searching
  - Contacts with experts in the field
  - Pharmaceutical industry
  - Others?

Searching

Restrictions based on publication status:

- Failing to include unpublished or "grey" literature risks introduction of publication bias
- Conflicting data as to quality of unpublished vs. published studies
- Limiting inclusion to only published trials overestimated treatment effect by 12%
- Unpublished data may be incomplete and not subject to peer-review
- Controversial, must test for publication bias

Lancet 1999;354:1896-1890.

Searching

Restrictions based on language:

- 1/3 meta analyses have language restriction
- No evidence to support difference in study quality based on language
- Some countries are more likely to publish studies with positive results
- Restriction to English language overestimated the treatment effects by 2%
- Restrictions may be based on logisitics

Lancet 1999;354:1896-1890.

Selection

- Explicit inclusion and exclusion criteria for inclusion of studies to answer focused question
  - Population
  - Intervention
  - Outcomes
  - Study design
- *Attempting* to include homogeneous data set and strengthen internal validity
- Beware of covert duplicate publication
  - 17% of RCT data may be duplicated
  - Leads to 23% overestimation of treatment

Quality Assessment

- Extent to which systematic error is minimized (internal validity – "tight" systematic review)
- Extent to which results of trials provide a correct basis for generalization to other circumstances (external validity – "applicability")
- Blinded assessment of trial quality should be performed on trials in a systematic review
- Checklists (qualitative)
- Scales (quantitative)

BMJ 2001;323:42-46. *J Clin Epi 2001;54:651-654.*

Quality Assessment

- 90% of methodologists feel quality assessment of RCTs included in meta analysis is very or somewhat important
- A recent report found only 52% of published meta analyses assessed study quality
- Mean quality scores of RCTs included in meta analyses has been about 50% (39-83%)
- Debate exists as to the relative merits and risks of quality assessment of RCTs to be included in meta analyses

Health Tech Assess 1999;3:1-106. *BMJ 2001;323:42-46.*

Quality Assessment

Pros

- "Garbage in = garbage out"
- Trials with weaker methodologies both overestimate and underestimate effect

Cons

- Assessment tools are complex, time-consuming, may be disease-specific
- Lack of rigorous, validated scales
  - Not based on items proven to reduce bias
  - Subject to inter-rater reliability
  - Lack of agreement between scales (23-74%) may affect results depending on scale used

Control Clin Trials 1995;16:62-73. *J Clin Epi 2001;651-654.*

Quality Assessment

Bottom Line Options

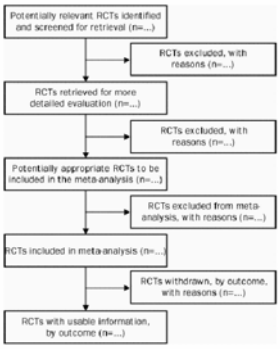
- Include only trials meeting a quality threshold
- Use quality score as a weight in estimating the overall effect size (be careful)
- Plot graphs to see if quality affects results, and perform sensitivity analyses by excluding them
- Use key components of design important to your clinical question!
  - Concealment of treatment allocation
  - Proper randomization
  - Appropriate blinding
  - Account for those lost to follow-up

Int J Technol Assess Health Care 1996;12:195-208 .

Data abstraction

- Quality assessment and data abstraction under masked conditions to reduce bias
- Independent assessment and abstraction by multiple reviewers in duplicate
- Inter-rater agreement should be reported
- Resolve discrepancies by consensus

Trial Flow Diagram



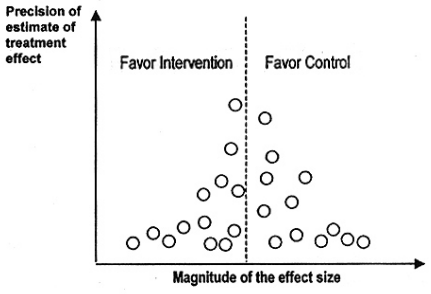
Lancet 1999;354:1896-1890.

Publication Bias

- Positive studies more likely to be published, important threat to validity
- 50% of meta analyses may have missed studies, but it affects results < 10% of the time
- Look for evidence of publication bias:
  - Inspect funnel plot (< 7% compliance)
- Determine robustness of meta analysis
  - Calculate "Fail-safe N" using "File drawer"
- Prospective trial registries may minimize PB

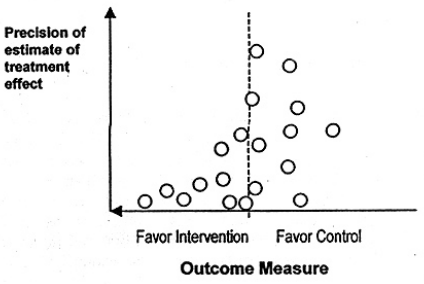
BMJ 2000;320:1574-1577. *BMJ 2001;323:101-105.*

Publication Bias (-)



Mayo Clin Proc 2000;75:1284-1288.

Publication Bias (+)



Mayo Clin Proc 2000;75:1284-1288.

Heterogeneity

- Focused question and strict inclusion and exclusion criteria to attempt homogeneity
- Studies are heterogeneous when there is greater variation between their results than is compatible with the play of chance
- Heterogeneity is "noise" that may partially explain the results of the overall analysis and threaten the internal validity of the meta analysis

BMJ 1994;309:1351-1355. *Stat Med 2001;20:3625-3633.*

Heterogeneity

- Two types of meta analytic models:
  - Fixed effects model vs. Random effects model
- Random effects model assumes some underlying heterogeneity, more *conservative*
- Statistical tests to look for heterogeneity should be performed in all meta analyses
- Recent studies show heterogeneity testing done in only 72% of published meta analyses

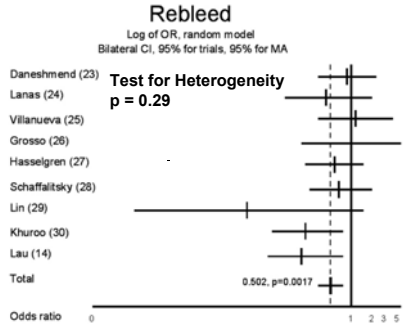
BMJ 1994;309:1351-1355. *Stat Med 2001;20:3625-3633.*

Heterogeneity

- Statistical tests for heterogeneity are underpowered, so cut-off should be 0.10
- If p < 0.10, null hypothesis is rejected, and the studies are heterogeneous
- Only 40% of recently published meta analyses use 0.10 cut-off
- Graphical testing for heterogeneity should be performed even if statistical tests fail to show heterogeneity
  - Forest plot
  - Galbraith plot, L'abbe plot, etc.

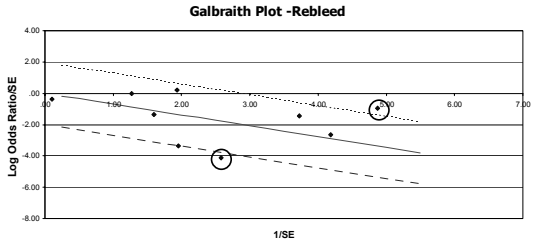
BMJ 1994;309:1351-1355. *Stat Med 2001;20:3625-3633.*

Forest plot



Ann Pharmacother 2001;35:1528-1534.

Galbraith plot



Ann Pharmacother 2001;35:1528-1534.

Heterogeneity

- Before you test for statistical heterogeneity, state *a priori* what clinical factors may be the cause
- Clinical heterogeneity is due to differences in the *characteristics* of the included studies, and may be one contributor to statistical heterogeneity
- If graphical evidence for heterogeneity exists (outliers), re-run the analysis excluding the outliers to see if the results are still the same (robust)

BMJ 1994;309:1351-1355. *Stat Med 2001;20:3625-3633.*

Sensitivity Analysis

- Multiple analyses to answer "How *sensitive* are the results to *how* the meta analysis was done?"
- Analyses run based on study factors
  - Model (fixed or random), study design (blinded vs. unblinded, lower quality), etc.
- Confident in meta analysis if overall results are the same (robust) and benefits are consistent across factors analyzed
- Hypothesis-generating only, risks are akin to post-hoc subgroup analyses of RCTs

Subgroup Analyses

- Similar to subgroups analyses in RCTs
- Analyses run based on patient factors, should be defined up front, “a priori”
- Post-hoc subgroup testing is not ideal and is subject to bias
- Meta analyses may have more power to examine potential differential effects in subgroups
- Role should always be “hypothesis-generating”

Summary Results

- Quantitative results can be expressed as:
  - Effect sizes (0.2 small, 0.5 mod, 0.8 large)
  - Odds ratio (OR)
  - Relative risk (RR) or relative risk reduction (RRR)
  - Absolute risk (ARR)
- How data is presented affects clinicians *perceptions* of benefit of therapy
- Summary measure should be converted to NNT or NNH with 95% CI to help determine clinical significance of intervention

Converting ORs to NNTs

When OR < 1

Patient Expected Event Rate (PEER)	For Odds Ratios LESS than 1						
	0.9	0.8	0.7	0.6	0.5	0.4	0.3
0.05	209	104	69	52	41	34	29
0.10	110	54	36	27	21	18	15
0.20	61	30	20	14	11	10	8
0.30	46	22	14	10	8	7	5
0.40	40	19	12	9	7	6	4
0.50	38	18	11	8	6	5	4
0.70	44	20	13	9	6	5	4
0.90	101	46	27	18	12	9	4

When OR > 1

Patient Expected Event Rate (PEER)	For Odds Ratios GREATER than 1						
	1.1	1.25	1.5	1.75	2	2.25	2.5
0.05	212	86	44	30	23	18	16
0.10	113	46	24	16	13	10	9
0.20	64	27	14	10	8	7	6
0.30	50	21	11	8	7	6	5
0.40	44	19	10	8	6	5	5
0.50	42	18	10	8	6	5	4
0.70	51	23	13	10	9	8	7
0.90	121	55	33	25	22	19	18

http://www.cebm.utoronto.ca/practise/ca/therapysr/important.htm

Discussion

- Summarize key findings
- Compared to methodologists, authors more likely to rate conclusions as “positive” or “insufficient/inconclusive evidence”, and less likely to rate conclusions as “no effect”
- Interpret results in context of ALL of the available evidence
- Describe potential limitations and biases
- Suggest future novel or confirmatory studies

Int J Technol Assess Health Care 2001;17:457-466 .

Applying the Evidence

- Is our patient so different from those in the study that its results cannot apply?
- Is the treatment feasible in our setting?
- What are our patient’s potential benefits and harms from the therapy
- What are our patient’s values and preferences for both the outcome we are trying to prevent and the side-effects we may cause?

JAMA 1994;272:1367-1371.
Evidence-Based Medicine 2000. Sackett DJ.

Case #1

Atrial fibrillation

You are the ED pharmacist in Paradise BC.

A 63 yo man comes in complaining of “my heart pounding”, “mild dizziness”, and “nausea”. The episode started 8 hours ago, but didn’t go away so he came in to the ED. He is diagnosed with rapid AF of 165 bpm. His rate is controlled to 95 with IV diltiazem, he is hemodynamically stable, but he is still having some symptoms so the EP wants to pharmacologically convert him to NSR. His only PMH is HT x 8 years, and he is taking HCTZ 12.5 mg/d.

MINIREVIEW

Conversion of Recent-Onset Atrial Fibrillation with Intravenous Amiodarone: A Meta-Analysis of Randomized Controlled Trials

Daniel E. Hilleman, Pharm.D., and Sarah A. Spinler, Pharm.D.

Study Objective. To evaluate efficacy and safety of intravenous amiodarone for conversion of recent-onset atrial fibrillation.

Data Sources. MEDLINE search of published, randomized, controlled trials assessing the efficacy and safety of intravenous amiodarone in recent-onset (< 7 days) atrial fibrillation, supplemented with searches of reference lists of identified articles and bibliographies of secondary and tertiary review articles.

Study Selection. The identified trials were eligible for meta-analysis if they met the following criteria: patients had recent-onset atrial fibrillation; patients were randomized to intravenous amiodarone, placebo, or another antiarrhythmic agent; no other antiarrhythmic agent except digoxin was administered simultaneously with intravenous amiodarone or other active treatments; the number and percentage of conversions to sinus rhythm after treatment began were reported; and the number and type of adverse drug reactions occurring after treatment began were reported.

Pharmacotherapy 2002;22:66-74.

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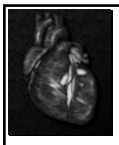
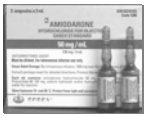


Case #1



The EP read a recent meta analysis on IV amiodarone for pharmacological conversion of recent-onset AF, and he says it should be the agent of choice for acute conversion. After reviewing the meta analysis, what would you say?

Patient	Intervention	Comparator	Outcome
In a patient with recent-onset AF…	…would administering IV amiodarone…	…compared to no antiarrhythmic therapy…	…acutely convert AF to NSR

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Case #2

DVT prophylaxis

You are the Ortho pharmacist in Stinkyville ON.

A 73 yo man comes in for an elective total hip replacement. His OR 7 days ago was uneventful, and he has been receiving enoxaparin 40 mg SC daily for VTE prophylaxis with no ADRs. His past medical history includes osteoarthritis, type II diabetes, hypertension, and reduce visual acuity. His medications include HCTZ 12.5 mg/d, enalapril 5 mg/d, and glyburide 5 mg bid.

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ARTICLES

Articles

Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials

John W Eikelboom, Daniel J Quinlan, James D Douketis

Summary

Background The optimum duration of prophylaxis against venous thromboembolism after total hip or knee replacement is uncertain. Our primary objective was to establish the efficacy of extended-duration prophylaxis on symptomatic venous thromboembolic events.

Methods We identified randomised trials comparing extended-duration prophylaxis using heparin or warfarin with placebo or untreated control in patients undergoing elective total hip or knee replacement by searching electronic databases (MEDLINE, EMBASE), references from retrieved articles, and abstracts from conference proceedings, and by contact with pharmaceutical companies and investigators. Two reviewers independently extracted data on study design, symptomatic and symptomless venographic venous thromboembolism, death, and bleeding outcomes. Results from individual trials were combined with the Mantel-Haenszel method.

Introduction

The optimum duration of prophylaxis against venous thromboembolism after total hip or knee replacement surgery remains uncertain.[1] It is common practice to administer prophylaxis until discharge from hospital, usually 7 to 14 days after surgery. However, in patients receiving in-hospital prophylaxis, the frequency of venographic deep vein thrombosis is still 15–30% at the time of hospital discharge, and an additional 10–25% of patients develop symptomless new deep vein thrombosis during the next 3 to 4 weeks.[2-5] Randomised trials have shown that extending prophylaxis beyond the time of hospital discharge substantially reduces the risk of developing new symptomless thrombi at 30 to 45 days,[6-9] which has led these investigators to recommend that longer duration prophylaxis should be used in all patients undergoing hip replacement.

More recently, however, two prospective studies conducted in patients without known proximal deep vein thrombosis at the time of discharge from hospital

Lancet 2001;358:9-15.

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Case #2

The orthopedics attending wants to send all of his patients home on self-administered enoxaparin 40 mg SC daily to complete a total 6 week course of prophylaxis, and says there is a recent meta analysis to support this. After reviewing the meta analysis, how would you respond?

Patient	Intervention	Comparator	Outcome
In a patient post elective total hip replacement…	…would administering enoxaparin 40mg SC daily for 6 weeks…	…compared to no DVT prophylaxis…	…prevent symptomatic DVT?

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Perspective

"…far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise."

Tukey J. Ann Math Stat 1962;33:1-67.

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Useful Electronic Resources for Locating and Retrieving Systematic Reviews

Search Engines	**URL**	
Google	http://www.google.com/	
Copernic	http://www.copernic.com/	
Metacrawler	http://www.metacrawler.com/	
Websites	**URL**	**Databases**
National Library of Medicine (PubMED)	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi	MEDLINE
ISI Web of Science	http://woscanada.isihost.com/	Science Citation Index Expanded (SCI-EXPANDED)
Cochrane Collaboration	http://www.update-software.com/cochrane/	Cochrane Database of Systematic Reviews (CDSR) Cochrane Review Methodology Database (CRMD) Cochrane Controlled Trials Register (CCTR)
National Health Services Centre for Reviews & Dissemination (NHS CRD)	http://nhscrd.york.ac.uk/welcome.html	Health Technology Assessment Database (HTA) Database of Abstracts of Reviews of Effectiveness (DARE)
Virtual Health Library (VHL)	http://www.bireme.br/bvs/I/ihome.htm	LILACS Database
BioMED Central	http://www.biomedcentral.com/default.asp	BioMed Central Database
Turning Research into Practice	http://www.tripdatabase.com	Turning Research Into Practice (TRIP) Database
Canadian Coordinating Office for Health Technology Assessment (CCOHTA)	http://www.ccohta.ca/	Database of EB reviews of emerging technologies
Other sites to identify reviews	**URL**	**Comment**
ScHARR Netting the Evidence	http://www.sheffield.ac.uk/~scharr/ir/netting/	Links to multiple online databases for EBM articles
Centre for Evidence Based Medicine (CEBM)	http://cebm.jr2.ox.ac.uk/	EBM resources
Bandolier	http://www.jr2.ox.ac.uk/bandolier/	Evaluations of articles dealing with EBM practice
American College of Physicians Journal Club (ACP Journal Club)	http://www.acpjc.org/	Abstracting journal/pre-appraised literature
Clinical Evidence	http://www.clinicalevidence.org	Abstracting journal/pre-appraised literature
Evidence-Based Medicine	http://ebm.bmjjournals.com/	Abstracting journal/pre-appraised literature
Effective Health Care	http://www.york.ac.uk/inst/crd/ehcb.htm	Peer-reviewed bulletin on systematic reviews

UBC Library	**Search Engines**	**Databases**
http://www.library.ubc.ca/	OVID	MEDLINE, EMBASE, Cumulated Index to Nursing and Allied Health Literature (CINAHL), Health Services Technology Assessment and Research (HealthSTAR), *Cochrane Database of Systematic Reviews (CDSR), *Cochrane Controlled Trials Register (CCTR), *Database of Abstracts of Reviews of Effectiveness (DARE), *ACP Journal Club, Clinical Evidence,
	ISI Web of Science	Science Citation Index Expanded (SCI-EXPANDED)

*All included under “EBM Reviews”

R. Slavik, PharmD Aug/02