Evidence-Based Medicine: Effective Use of the Medical Literature

Edward G. Hamaty Jr., D.O. FACCP, FACOI
Using the Medical Literature to Answer Clinical Questions
Evidence Based-Medicine

• First and Foremost, Remember.....

• “the plural of anecdote is **NOT** data!”
Two Main Uses of Medical Literature

• To keep current with the practice of medicine.

• To answer clinical questions.
# How to Avoid EBM 😊
(or understanding the way some docs think)

## Levels of Belief

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Good</strong></td>
<td></td>
</tr>
<tr>
<td>Class 0</td>
<td>Things I believe</td>
</tr>
<tr>
<td>Class 0a</td>
<td>Things I believe despite the available data</td>
</tr>
<tr>
<td>Class 1</td>
<td>Randomized controlled clinical trials that agree with what I believe</td>
</tr>
<tr>
<td>Class 2</td>
<td>Other prospectively collected data</td>
</tr>
<tr>
<td>Class 3</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Class 4</td>
<td>Randomized controlled clinical trials that don’t agree with what I believe</td>
</tr>
<tr>
<td><strong>Bad</strong></td>
<td></td>
</tr>
<tr>
<td>Class 5</td>
<td>What you believe that I don’t</td>
</tr>
</tbody>
</table>

How to Avoid EBM 😊
(or understanding the way some docs think)

1. Don’t pay attention
2. Attack the data
3. Maintain absolute confidence
4. Follow the pack
5. Defer to the expert
6. Bring in the lawyers
7. Blame patients
8. Show how much you’ve changed
9. Pull rank
10. Simply refuse

Does Empiricism = EBM?

- Empiricism
  - Knowledge through the senses, not inherited
  - Experimental or Experiential?
  - Dual etymology

- Evidence-Based Medicine
  - Both! And more.
Introduction

- Asking answerable clinical questions
- Finding the best evidence
- Appraising the evidence
- Making a decision
- Evaluating your performance

Patient
Intervention
Comparison
Outcome
Secondary sources
Primary sources
Is it valid?
Is it important?
Can it help?
How much will it help your particular patient?
Does it meet their values and goals?
Is it cost-effective?
How could you do it better next time?
Definition of Evidence-Based Medicine

- EBM is a conscientious, explicit, and judicious use of the current best evidence in making decisions about the care of individual patients.

- The practice of EBM integrates individual clinical expertise, best external evidence, and patient values and expectations.

  *David Sackett, et al*

Note: The term “Evidence-Based Medicine” is attributed to McMaster University epidemiologists in the early 1990s.
Definition of Evidence-Based Medicine

• Evidence-based medicine is the 'conscientious, explicit and \textit{judicious} use of current best evidence in making decisions about individual patients'.

• This means 'integrating individual clinical expertise with the best available external clinical evidence from systematic research' (Sackett \textit{et al.} 2000).

We can summarize the EBM approach as a five-step model
1. Asking answerable clinical questions.
2. Searching for the evidence.
3. Critically appraising the evidence for its validity and relevance.
4. Making a decision, by integrating the evidence with your clinical expertise and the patient's values.
What’s wrong with the traditional model?

• “Clinical experience . . . has been defined as making the same mistakes with increasing confidence over an impressive number of years.”

• Isaacs and Fitzgerald 1999
WHY EBM?

- We can’t keep up with the literature
- Clinical questions during 3.2/10 encounters
- We often rely on low-quality information
- “Standards” often become myths
- We often practice anecdotaly

“the plural of anecdote is NOT data!”

Empiricism or Bias

Empiricism or Bias?

Ignore it Jeffries. It’s unscientific.
Bias in Research
(when EBM ain’t EBM)

- Confounding
- Selection / Exclusion
- Relative v. Absolute Risks
- Data Dredging
- Disease Oriented Evidence
- Publication
A Better Check on Bias?

Most scientists regarded the new streamlined peer-review process as ‘quite an improvement.’
Asking Answerable Questions

- The four elements of a well-formed clinical question are: (PICO Formulation)
  1. Patient or Problem
  2. Intervention
  3. Comparison intervention (if appropriate)
  4. Outcome(s)

- The terms you identify from this process will form the basis of your search for evidence and the question as your guide in assessing its relevance.
Asking Answerable Questions

• Bear in mind that how specific you are will affect the outcome of your search: general terms (such as 'heart failure') will give you a broad search, while more specific terms (for example, 'congestive heart failure') will narrow the search.

• Also, you should think about alternative ways or aspects of describing your question (for example, New York Heart Association Classification).
<table>
<thead>
<tr>
<th>Element</th>
<th>Tips</th>
<th>Specific example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient or problem</td>
<td>Starting with your patient ask ‘How would I describe a group of patients similar to mine?’</td>
<td>‘In women over 40 with heart failure from dilated cardiomyopathy …’</td>
</tr>
<tr>
<td>Intervention</td>
<td>Ask ‘Which main intervention am I considering?’</td>
<td>‘… would adding anticoagulation with warfarin to standard heart failure therapy…’</td>
</tr>
<tr>
<td>Comparison intervention</td>
<td>Ask ‘What is the main alternative to compare with the intervention?’</td>
<td>‘… when compared with standard therapy alone …’</td>
</tr>
<tr>
<td>Outcome</td>
<td>Ask ‘What can I hope to accomplish?’ or ‘What could this exposure really affect?’</td>
<td>‘… lead to lower mortality or morbidity from thromboembolism.’</td>
</tr>
</tbody>
</table>
Patient or Problem

• First, think about the patient and/or setting you are dealing with.

• Try to identify all of their clinical characteristics that influence the problem, which are relevant to your practice and which would affect the relevance of research you might find.

• It will help your search if you can be as specific as possible at this stage, but you should hear in mind that if you are too narrow in searching you may miss important articles.
Intervention

- Next, think about what you are considering doing.
- In therapy, this may be a drug or counseling; in diagnosis it could be a test or screening program.
- If your question is about harm or etiology, it may be exposure to an environmental agent.
- Again, it pays to be specific when describing the intervention, as you will want to reflect what is possible in your practice.
- If considering drug treatment, for example, dosage and delivery should be included. Again, you can always broaden your search later if your question is too narrow.
Comparison Intervention

• What would you do if you didn't perform the intervention? This might be nothing, or standard care, but you should think at this stage about the alternatives.

• There may be useful evidence which directly compares the two interventions. Even if there isn't, this will remind you that any evidence on the intervention should be interpreted in the context of what your normal practice would be.
There is an important distinction to be made between the outcome that is relevant to your patient or problem and the outcome measures deployed in studies.

You should spend some time working out exactly what outcome is important to you, your patient, and the time-frame that is appropriate. In serious diseases it is often easy to concentrate on the mortality and miss the important aspects of morbidity.

However, outcome measures, and the relevant time to their measurement, may be guided by the studies themselves and not by your original question.

This is particularly true, for example, when looking at pain relief, where the patient's objective may be 'relief of pain' while the studies may define and assess this using a range of different measures.
Questions: PICO

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient or Problem</strong></td>
<td><strong>Intervention</strong> (a cause, prognostic factor, treatment, etc)</td>
<td><strong>Comparison Intervention</strong> (if necessary)</td>
<td><strong>Outcomes</strong></td>
</tr>
<tr>
<td>Starting with your patient, ask “How would I describe a group of patients similar to mine?” Balance precision with brevity.</td>
<td>Ask “Which main intervention am I considering?” Be specific</td>
<td>Ask “What is the main alternative to compare with the intervention?” Again, be specific</td>
<td>Ask “What can I hope to accomplish?”, or “What could this exposure really affect?” Again, be specific</td>
</tr>
<tr>
<td><strong>Tips for Building</strong></td>
<td><strong>Example</strong></td>
<td><strong>...would adding anticoagulation with warfarin to standard heart failure therapy...”</strong></td>
<td><strong>...when compared with standard therapy alone...”</strong></td>
</tr>
<tr>
<td>“In patients with heart failure from dilated cardiomyopathy who are in sinus rhythm...”</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Type of Question

• Once you have created a question, it is helpful to think about what type of question you are asking, as this will affect where you look for the answer and what type of research you can expect to provide the answer.
### Type of Question

<table>
<thead>
<tr>
<th>Type of question</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aetiology:</strong> the causes of disease and their modes of operation.</td>
<td>Case–control or cohort study</td>
</tr>
<tr>
<td><strong>Diagnosis:</strong> signs, symptoms or tests for diagnosing a disorder.</td>
<td>Diagnostic validation study</td>
</tr>
<tr>
<td><strong>Prognosis:</strong> the probable course of disease over time.</td>
<td>Inception cohort study</td>
</tr>
<tr>
<td><strong>Therapy:</strong> selection of effective treatments which meet your patient’s values.</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td><strong>Cost-effectiveness:</strong> is one intervention more cost-effective than another?</td>
<td>Economic evaluation</td>
</tr>
<tr>
<td><strong>Quality of life:</strong> what will be the quality of life of the patient?</td>
<td>Qualitative study</td>
</tr>
</tbody>
</table>
Type of Question

- Deciding which question to ask:
- Which question is most important to the patient's wellbeing? (Have you taken into account the patient's perspective?)
- Which question is most feasible to answer in the time you have available?
- Which question is most likely to benefit your clinical practice?
- Which question is most interesting to you?
Finding the Evidence: How to get the most from your searching

Formulate your PICO question

Try secondary sources

Choose primary database(s)

Combine textwords and thesaurus

Filter for the right type of study

TRIP Database
EBM Online
Cochrane Library

PubMed

a AND b
a OR b
a NOT b
Convert your question to a search strategy
Identify terms that you would want to include in your search:

<table>
<thead>
<tr>
<th>Patient or problem</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, aged 55 Smoker</td>
<td>Low molecular weight heparin</td>
<td>Unfractionated heparin</td>
<td>Recurrence of angina, mortality</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Convert Your Question to a Search Strategy

• Generally, it helps you to construct a search for each concept separately, then combine them.
• Think about what kind of evidence you need to answer your question:
  • 1 Levels of evidence: what type of study would give you the best quality evidence for your question?
  • 2 Secondary sources: is there a quality and relevance-filtered summary of evidence on your question, such as in ACP Journal Club or Clinical Evidence?
  • 3 Systematic reviews: is there a systematic review in the Cochrane Library?
  • 4 Bibliographic databases: in which database would you find relevant studies?
Convert Your Question to a Search Strategy

1 Try these first

<table>
<thead>
<tr>
<th>Database</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIP Database</td>
<td>Use general subject terms (e.g. prostate cancer)</td>
</tr>
<tr>
<td><a href="http://www.tripdatabase.com">http://www.tripdatabase.com</a></td>
<td></td>
</tr>
<tr>
<td>EBM Online</td>
<td>Use advanced search; enter specific key words (e.g. prostatectomy)</td>
</tr>
<tr>
<td><a href="http://ebm.bmjournals.com/">http://ebm.bmjournals.com/</a></td>
<td></td>
</tr>
<tr>
<td>Clinical Evidence</td>
<td>Search or browse</td>
</tr>
<tr>
<td><a href="http://www.clinicalevidence.com">http://www.clinicalevidence.com</a></td>
<td></td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>Search (see p. 13)</td>
</tr>
<tr>
<td><a href="http://www.thecochranelibrary.com">http://www.thecochranelibrary.com</a></td>
<td></td>
</tr>
</tbody>
</table>

These sources will give you the best return on your precious time.
Secondary Sources

- Of course, if someone has already searched for and appraised evidence around your question, it makes sense to use that information if possible.

- **A note about guidelines**

- An authoritative, evidence-based guideline would give you the best starting point for your search.

- However, we have assumed that your questions tend to be the ones that aren't answered by the guidelines.

- Also, it's important to bear in mind that not all guidelines are evidence-based (Grimshaw 1993; Cluzeau 1999).
How to Find Current Best Evidence

The Figure provides a 4S hierarchical structure, with original “studies” at the base, “syntheses” (systematic reviews) of evidence just above the base, followed by “synopses” of studies and syntheses, and, finally, the most evolved evidence-based information “systems” at the top. You should begin your search for best evidence by looking at the highest-level resource available for the problem that prompts your search. The details of how to do this follow.

[Diagram showing the 4S hierarchical structure with levels: Studies, Syntheses, Synopses, Systems, Examples including Computerized decision support system (CDSS), Evidence-based journal abstracts, Cochrane reviews, Original published articles in journals.]

© Elsevier Ltd 2005. Straus et al.: Evidence-based medicine
Levels of Evidence

• The pyramid is an appropriate shape for this graphic, as it represents the quality of research designs by level, as well as the quantity of each study design in the body of published literature. Systematic reviews (higher quality), for instance, are the most time-intensive articles to write and are therefore rarer (lower quantity) than other types of studies.

• More detailed levels of evidence have been developed by the Oxford Centre for Evidence-Based Medicine. They use a numbering scheme ranging from 1a, homogenous systematic reviews of randomized controlled trials, to 5, expert opinion. This system can be especially useful when comparing articles with similar study designs. Equivalent research designs do not always produce results of equal quality.

• Rarely does Evidence-Based Medicine draw on research designs lower in the evidence hierarchy than case series, though occasionally nothing but case reports or even bench research may exist on a topic. When making evidence-based decisions for patient care, it is essential to select the highest level research design available for the specific question of interest.
Levels of Evidence

- Systematic Reviews
- Randomized Controlled Trials
- Cohort Studies
- Case-Control Studies
- Case Series, Case Reports
- Editorials, Expert Opinion
How to Find Current Best Evidence Systems

• Given that we have some way to go before current best evidence is integrated into electronic medical records, some excellent, but less-developed, systems are readily available.

• *Clinical Evidence* from the BMJ Publishing Group is the current pace-setter ([http://www.clinicalevidence.com](http://www.clinicalevidence.com)*, and as a separate title in Ovid†). At present, *Clinical Evidence* includes only evidence for treatment of a relatively limited but expanding range of clinical questions.

• The American College of Physicians (ACP) provides PIER (the Physician’s Information and Education Resource); this is an evidence-based on-line text for ACP members ([http://pier.acponline.org/index.html](http://pier.acponline.org/index.html)), with explicit grading of evidence for internal medicine and primary care.

• *UpToDate*, on CD and the web ([http://www.uptodate.com](http://www.uptodate.com)), is updated quarterly, extensively referenced, and provides MEDLINE abstracts for key evidence. This provides the user at least a sporting chance of dating and appraising the supporting evidence.
How to Find Current Best Evidence-Systems

• *ACP Medicine* (formerly *Scientific American Medicine*) also extensively references its contents, and its Internet version ([http://www.acpmedicine.com/](http://www.acpmedicine.com/)) is augmented with links to MEDLINE citations and abstracts, as well as many other web resources.

• *Harrison’s Principles of Internal Medicine*, available in several formats ([http://www.harrisonsmed.com/](http://www.harrisonsmed.com/)), has been upgrading its currency and provides more references and abstracts on its web version, although the extent of referencing is still very limited, and much of the text is updated only once in 3 years.

• More specialized clinical content is provided in such offerings as *Evidence Based on Call* ([http://www.eboncall.org/content.jsp.htm](http://www.eboncall.org/content.jsp.htm)), *Evidence Based Pediatrics and Child Health* ([http://www.evidbasedpediatrics.com/](http://www.evidbasedpediatrics.com/)), and *Evidence Based Cardiology* ([http://www.evidbasedcardiology.com/](http://www.evidbasedcardiology.com/)).
How to Find Current Best Evidence-Systems

• The systems mentioned here are but a few of those available today.

• If your discipline or clinical question isn’t mentioned try SCHARR (http://www.shef.ac.uk/~scharr/ir/netting/)

• or Google (www.google.com; put “evidence-based” followed by your discipline on Google’s search line).
How to Find Current Best Evidence-Synopses

• When no evidence-based information system exists for a clinical problem, then synopses of individual studies and reviews are the next best source.
• What busy practitioner has time to use evidence-based resources if the evidence is presented in its original form or even as detailed systematic reviews?
• Although these detailed articles and reviews are essential building blocks, they are often too heavy to lift on the run.
• The perfect synopsis of a review or original study would provide only, and exactly, enough information to support a clinical action.
• The declarative title for each abstract that appears in ACP Journal Club and Evidence Based Medicine represents an attempt at this. For example, “Review: low-molecular-weight heparin is effective and safe in the acute coronary syndromes”.
• In some circumstances, this title provides enough information to allow the decision-maker either to proceed, assuming familiarity with the nature of the intervention and its alternatives, or to look further for the details, which, for an ideal synopsis, are immediately at hand. The full abstract for this item is in ACP Journal Club, with an abstract and commentary on one page, accessible in the original print issue or electronically.
• Electronic access is definitely the best way to go for all these resources.
How to Find Current Best Evidence-Synthesis

• If more detail is needed or no synopsis is at hand, then databases of systematic reviews (*syntheses*) are available, notably the Cochrane Library, which is available on a quarterly CD, the Internet ([http://www.cochranelibrary.com/](http://www.cochranelibrary.com/)), and Ovid’s EBMR service.

• These summaries are based on exhaustive searches for evidence, explicit scientific reviews of the studies uncovered in the search, and systematic assembly of the evidence, to provide as clear a signal about the effects of a health care intervention as the accumulated evidence will allow.

• The *Cochrane Reviews* have focused on preventive or therapeutic interventions to date, but the Cochrane Collaboration recently gave its blessing to reviewers interested in summarizing diagnostic test evidence.
How to Find Current Best Evidence-Synthesis

• Stimulated by the success of the Cochrane Collaboration, the number of systematic reviews in the medical literature has grown tremendously in the past few years; if the Cochrane Library doesn’t have a review on the topic you are interested in, it is worthwhile looking in MEDLINE.

• Better still, Ovid’s EBMR provides one-stop shopping for both Cochrane and non-Cochrane systematic reviews. For the example of low molecular weight heparin for acute coronary syndromes, a search on Ovid’s integrated collection of ACP Journal Club, Cochrane Database of Systematic Reviews (CDSR), and DARE, using the terms “acute coronary syndromes” and “low molecular weight heparins”, retrieved seven items, including a recently updated Cochrane Review (synthesis) and three related ACP Journal Club items (synopses).
How to Find Current Best Evidence-Studies

• It takes time to summarize new evidence, and systems, synopses and syntheses necessarily follow the publication of original *studies*, usually by at least 6 months, and sometimes by years. If every other “S” fails (i.e. no systems, synopses, or syntheses exist with clear answers to your question), then it’s time to look for original studies.

• Looking for these in full-text print journals, as we’ve all seen, is generally hopeless, but studies can be retrieved relatively efficiently on the Internet in several ways. If you don’t know which database is best suited to your question, “meta” search engines tuned for health care content can assemble access across a number of web-based services. At least one of these search engines is attentive to issues of quality of evidence: namely, SUMSearch ([http://sumsearch.uthscsa.edu/](http://sumsearch.uthscsa.edu/)).

• Nevertheless, we must appraise the items identified by such a search to determine which fall within the schema presented here. Many of the items will not, especially when convenience of access is favored over quality.
How to Find Current Best Evidence-Studies

• There are also at least two levels of evidence-based databases to search directly: specialized and general.

• If the topic falls within the areas of internal medicine, primary care, nursing or mental health, then ACP Journal Club (www.acpjc.org, formerly Best Evidence), Evidence Based Medicine (http://ebm.bmjournals.com/), Evidence Based Nursing (http://ebn.bmjournals.com/), and Evidence Based Mental Health (http://ebmh.bmjournals.com/), respectively, provide specialized, evidence-based services because the abstracted articles have been appraised for scientific merit and clinical relevance.

• If the search is for a treatment, then the Cochrane Library includes the Cochrane Central Register of Controlled Trials, also available as part of EBMR on Ovid, where it is integrated with ACP Journal Club and DARE. But all these services are subject to the timeline required for evidence summarization, to which is added the Ovid timeline for electronic posting and integration.
How to Find Current Best Evidence-Studies

• For original articles and reviews hot off the press, MEDLINE itself is freely available (http://www.ncbi.nlm.nih.gov/PubMed/), and the Clinical Queries screen (available as a menu item on the main PubMed screen or directly at http://www.ncbi.nlm.nih.gov/entrez/query/static/clinical.html) provides detailed search strategies that home in on clinical content for therapy, diagnosis, prognosis, clinical prediction, etiology, economics, and systematic reviews.

• These search strategies have recently been upgraded and are embedded in the Clinical Queries screen, so that you don’t need to remember them. You can use the “sensitive” search strategy if you want to retrieve every article that might bear on your question.

• Or you can use the “specific” search strategy if you want “a few good references” and don’t have time to sort out the citations that aren’t on target.
How to Find Current Best Evidence Studies

- These search strategies can also be run in proprietary systems that include the MEDLINE database, although they need some translation for the search syntax that is unique to each system. A summary of the best strategies appears in Table 2.1, optimized for Ovid’s search engine.
How to Find Current Best Evidence

The Figure provides a 4S hierarchical structure, with original “studies” at the base, “syntheses” (systematic reviews) of evidence just above the base, followed by “synopses” of studies and syntheses, and, finally, the most evolved evidence-based information “systems” at the top. You should begin your search for best evidence by looking at the highest-level resource available for the problem that prompts your search. The details of how to do this follow.
How to Find Current Best Evidence

- Use this list as you would a ladder, working your way from the top down. Look for best evidence first in Cochrane Database and if you can't find something there, continue down the list, understanding that the farther down you travel, the weaker the evidence you will find.
- Cochrane Database of Systematic Reviews — A collection of structured systematic reviews and protocols (which are systematic reviews in process). Often include meta-analysis in the form of visual "forest plots."
- DynaMed — Evidence-based clinical review summaries. This is an excellent reference and part of the UMDNJ library of Databases!
- DARE (Database of Abstracts of Reviews of Effects) — Abstracts of non-Cochrane systematic reviews.
- ACP Journal Club — Abstracts of articles containing strong evidence from within the primary literature.
- U.S. Preventive Services Task Force — Database of evidence-based recommendations in areas of prevention and screening.
- PubMed Clinical Queries — PubMed/MEDLINE search feature that filters results in order to display only articles backed by good evidence. NOTE: At the PubMed home page, choose Clinical Queries option from the blue, left navigation bar under "PubMed Services."
- National Guideline Clearinghouse — Collection of guidelines from the federal government (Agency for Healthcare Research and Quality (AHRQ)) and professional medical societies.
- Natural Standard — Graded evidence on complementary therapies.
- eMedicine Clinical Knowledge Base — Background narratives, often with emphasis on best-evidence outcomes, covering topics across the medical and surgical spectrum.
- UpToDate — Background narratives, often with emphasis on best-evidence with a special focus on internal medicine, family medicine, pediatrics and obstetrics and gynecology.
POEM’s vs. DOE’s

- **P**- Patient
- **O**- Oriented
- **E** – Evidence
- **M**- Matters

- **D**- Disease
- **O**- Oriented
- **E**- Evidence
<table>
<thead>
<tr>
<th>Example</th>
<th>Disease-Oriented Evidence</th>
<th>Patient-Oriented Evidence that Matters</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic Therapy</td>
<td>Drug X ↓ PVCs on ECG</td>
<td>Drug X increases mortality</td>
<td>POEM study contradicts DOE study</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>Antihypertensive therapy ↓ BP</td>
<td>Antihypertensive therapy ↓ mortality</td>
<td>POEM agrees with DOE</td>
</tr>
<tr>
<td>Prostate Screening</td>
<td>PSA screening detects prostate cancer early</td>
<td>? whether PSA screening ↓ mortality</td>
<td>DOE exists, but the important POEM is unknown</td>
</tr>
</tbody>
</table>
Dr. X, a pulmonary fellow is discussing with me the relative advantages of using Nitric oxide vs prostacycline in the treatment of ARDS.

He knows that the equipment is available and wants to institute therapy in patient who is still hypoxic on the low tidal volume protocol.

I agree to consider it if he can show me the literature to support its use.

I suggest he use the Evidence Based Medicine Data Base of the BMJ. *Clinical Evidence* from the BMJ Publishing Group is the current pace-setter (http://www.clinicalevidence.com*, and as a separate title in Ovid†). At present, *Clinical Evidence* includes only evidence for treatment of a relatively limited but expanding range of clinical questions.
Walking the Walk
Walking the Walk
Walking the Walk

BMJ Clinical Evidence

Acute respiratory distress syndrome
Sat Sharma

You may prefer to read the key points of this review.

Here is a list of clinical questions we have addressed in this review:

- What are the effects of interventions in adults with acute respiratory distress syndrome?

<table>
<thead>
<tr>
<th>What are the effects of interventions in adults with acute respiratory distress syndrome?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beneficial</strong></td>
</tr>
<tr>
<td>Low tidal volume mechanical ventilation</td>
</tr>
<tr>
<td><strong>Likely to be beneficial</strong></td>
</tr>
<tr>
<td>Protective ventilation</td>
</tr>
<tr>
<td><strong>Trade off between benefits and harms</strong></td>
</tr>
<tr>
<td>Prone position</td>
</tr>
<tr>
<td><strong>Unknown effectiveness</strong></td>
</tr>
<tr>
<td>Corticosteroids</td>
</tr>
<tr>
<td><strong>Unlikely to be beneficial</strong></td>
</tr>
<tr>
<td>Nitric oxide</td>
</tr>
</tbody>
</table>

Web publication date: 01 May 2007 (based on August 2006 search)
Effects of interventions in adults with ARDS

Nitric oxide

In this section:
Summary | Benefits | Harms | Comment

Summary
One systematic review and one subsequent RCT found no significant difference between nitric oxide and placebo in mortality, ventilator-free days, or duration of hospital admission. One RCT identified by the reviewer found that nitric oxide improved oxygenation compared with placebo, but the improvement was modest and not sustained.

Benefits
Nitric oxide versus standard treatment (no nitric oxide):

We found one systematic review (5 RCTs, 868 patients, excluding neonates in the first month of life in people with acute hypoxemic respiratory failure). In a meta-analysis of 5 RCTs (adjusted relative risk: 0.92; 95% CI: 0.85 to 0.98), nitric oxide improved oxygenation in the first 24 hours after administration (mean arterial pressure index in the first 24 hours: 14 (120) patients with nitric oxide vs 17 (60) patients with placebo, p = 0.01). There was no significant difference in mortality or duration of mechanical ventilation, and intensive care stay (ventilator-free days) (alive and extubated at 30 days) was 2 (17) patients with nitric oxide vs 2 (20) patients with placebo, p = 0.59; 95% CI: 0.00 to 0.90 (good funnel analysis, no further data reported): people in intensive care at 30 days: 139 (11%) with nitric oxide vs 147 (12%) with placebo: RR 0.94; 95% CI: 0.99 to 1.06; 16.73 patients in hospital at 60 days: 60 (31%) with nitric oxide vs 64 (19%) with placebo (OR 1.42; 95% CI: 0.66 to 3.08). In the same study, 20% of patients had moderate/severe acute lung injury (ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (Po2/Fio2 ratio) > 250) not swayng to resolve and without non-pulmonary organ dysfunction at randomization, acute respiratory distress syndrome, which comprised low dose (1 ppm) nitric oxide with placebo over 28 days. In a subsequent RCT (388 patients) the number of days people were alive and ventilator-free at 28 days; or mortality at 28 days (rate of death of days people were alive and ventilator-free 17.7 days) with nitric oxide 10.6 days vs mortality 10.6 days with placebo: p = 0.07; mortality: 44 (10%) (23%) with nitric oxide vs 39 (10%) (19%) with placebo: p = 0.56.

Harms
The review gave no information on adverse effects. (2) In the subsequent RCT found that, compared with placebo, inhaled nitric oxide increased infections; however, none was (adj.) blind and investigators had been involved in the treatment gas administration: N2O or N2O plus nitric oxide: 41/109 (21%) with nitric oxide vs 41/109 (21%) with placebo; significance assessment not performed. (3) In the same study, a similar number of cardiovascular, gastrointestinal endocrine, hematological, metabolic, nutritional, and nervous system adverse effects were found in nitric oxide and placebo (as a reference, no adverse effects were reported).

Comment
Inhaled nitric oxide may improve oxygenation in people with ARDS. However, this beneficial effect on oxygenation the people given nitric oxide compared with placebo remains modest and is not sustained.

Clinical guide:
Nitric oxide use has not been associated with better survival in RCTs, therefore, its use is not recommended as routine treatment, and must be considered experimental.

References
Walking the Walk

Harms
The review gave no information on adverse effects. [49] The subsequent RCT found that, compared with placebo, inhaled nitric oxide increased infections; however, none was judged by blind investigators to have been related to treatment gas administration (66/192 [34.4%] with inhaled nitric oxide vs 41/193 [21.2%] with placebo; significance assessment not performed). [50] It found a similar number of cardiovascular, gastrointestinal, endocrine, haematological, metabolic, nutritional, and nervous system adverse effects with both inhaled nitric oxide and placebo (absolute figures not reported).

Comment
Inhaled nitric oxide may improve oxygenation in people with ADRS. However, this beneficial effect on oxygenation in the people given nitric oxide compared with placebo remains modest and is not sustained.

Clinical guide:
Nitric oxide use has not been associated with better survival in RCTs; therefore, its use is not recommended as routine treatment, and must be considered experimental.

References

Walking the Walk

• While helpful, site did not address the use of prostacycline, the therapy I was advocating.
• I initiated a search using a different database.
• Using the UMDNJ Library Website, Databases, DynaMed Site, I pulled up ARDS.
Walking the Walk

UMDNJ

University Libraries
Newark • New Brunswick/Piscataway • Stratford • Camden
Health Sciences Library at Stratford
One Medical Center Drive, Stratford, NJ 08084 (866) 866-6800

Catalog

Databases
- Complete List of Databases
- Ovid Databases
  - including: Medline (1996-current)
- PubMed
- VALE/NJGI Databases
- Essential Evidence Plus
- MDConsult
- StatRef

Journals
Toolkits/Internet Resources
Clinical Care Resources
E-Books
Multimedia Collections
Academic Resources
HealthyNJ
Special Collections
Services
Library Information
Educational Technology Minigrants
Walking the Walk

<table>
<thead>
<tr>
<th>Available to the public</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXplain</td>
</tr>
<tr>
<td>Dxtrem is a diagnostic decision support program which allows the user to enter a list of clinical manifestations (historical findings, signs, symptoms, lab test results, etc.) and then generate a list of possible diagnoses. SearchBank provides bibliographic references, abstracts and full text for excerpts and articles from a variety of health publications.</td>
</tr>
</tbody>
</table>

| DynaMed                    |
| A "Just-In-Time" Internet reference integrating evidence based medicine with practical information for clinical practice on more than 1,800 clinical topics. DynaMed for PDA is now available. To obtain a serial number: Email dynamedsupport@epnet.com from your UMDNJ email account (no other email accounts will be accepted) requesting a serial number for your PDA device, or, ask for a serial number from your campus library’s information desk. |

| eMedicine                  |
| eMedicine presents a collection of monographs that cover 68 professional specialties and three consumer areas, complete with full streaming video, audio, and color images suitable for clinical and teaching purposes. It contains a section of Tools, such as Case of the Week. |

| Free version as of 2/1/08 |
| Available to the public - Individual registration required |

| SEE ALSO THE EBM Toolkit |
Acute respiratory distress syndrome (ARDS)

Updated: 2008 Aug 06 04:03 PM

Corticosteroids do not appear beneficial in treatment or prevention of ARDS in adults (BMJ 2008 May 3)

Prone positioning during mechanical ventilation does not improve survival in acute hypoxic respiratory failure (CMAJ 2008 Apr 22)

Multiple risk factors for ARDS development in patients with mechanical ventilation ≥ 48 hours (Chest 2008 Apr)

Related Summaries:

- Respiratory distress syndrome (RDS) of the newborn
- General Information (including ICD-9/10 Codes)
- Causes and Risk Factors
- Complications and Associated Conditions
- History
- Physical
- Diagnosis
- Prognosis
- Treatment
- Prevention and Screening
- References Including Reviews and Guidelines
- Patient Information
- Acknowledgements

Please give us your feedback by clicking on the link below to send an e-mail to DynaMed:

- DynaMedEditor@ebscohost.com
Walking the Walk

Acute respiratory distress syndrome (ARDS)

Medications:
- oxygen (FiO2 < 50%), PEEP if oxygen alone fails
  - maintain O2 at 60-80 mmHg (90% saturation)
  - PEEP usually started at 5 cmH2O + increased by 2-5 cm
  - pulmonary catheter to monitor cardiac output since PEEP decreases venous return + pulmonary vascular resistance
  - PCWP should be kept at 8-12 mmHg
  - review of acute oxygen therapy can be found in [source]
- insufficient evidence to support any pharmacotherapy for adults with acute lung injury or acute respiratory distress syndrome; systematic review of 32 randomized trials with 3,372 patients; no effect on early mortality in pooled results for surfactant (9 trials, 1,441 patients), prostaglandin E1 (7 trials, 697 patients), N-acetylcysteine (5 trials, 239 patients), or early high-dose corticosteroids (2 trials, 1,191 patients); late-phase corticosteroids reduced hospital mortality in 1 trial with 24 patients, pentastine reduced 1-month mortality in 1 trial with 30 patients with metastatic cancer; 9 other interventions did not have significant differences in single trials; systematic review last updated 2004 Aug 23 (Cochran Library 2004 Issue 4:CD004427)
- role of corticosteroids
  - corticosteroids do not appear beneficial in treatment of ARDS in adults [level 2 mid-level evidence]
    - based on systematic review of trials with allocation concealment not stated
    - systematic review of 5 randomized placebo-controlled trials of corticosteroids for treatment of ARDS in 281 patients
    - no trial reported allocation concealment
    - mortality 42% vs. corticosteroids vs. 52.6% with placebo (not significant)
    - no significant differences in rate of new infections
    - Reference - [source]
    - editorial can be found in [source]
  - corticosteroids NOT clearly beneficial for persistent ARDS [level 1 likely reliable evidence]
    - 180 patients with ARDS for 7-28 days, receiving continuous mechanical ventilation and having persistent bilateral infiltrates were randomized to methylprednisolone vs. placebo
    - methylprednisolone dosing intravenously as 2 mg/kg, then 0.5 mg/kg every 6 hours for 14 days, then 0.5 mg/kg every 12 hours for 7 days, then tapered over 4 days; tapering occurred over 2 days if disseminated fungal infection, septic shock, or patient resumed ability to breathe unassisted for 48 hours
    - only significant baseline difference was 40% methylprednisolone vs. 58% placebo group were male
    - comparing methylprednisolone vs. placebo
      - 29.2% vs. 28.6% in-hospital mortality at 60 days (not significant)
      - 31.5% vs. 31.9% mortality at 180 days (not significant)
      - mean 11.2 vs. 6.8 ventilator-free days at 28 days (p < 0.001)
      - median 159 vs. 149 ventilator-free days at 180 days (p = 0.04)
      - mean 8.9 vs. 6.2 ICU-free days at 28 days (p = 0.02)
      - median 152 vs. 150 ICU-free days at 180 days (not significant)
Walking the Walk

Acute respiratory distress syndrome (ARDS)

- 2 trials reporting differences used repeated doses of methylprednisolone 12-24 hours before extubation
  - Reference - Cochrane Database Syst Rev 2009 Apr 16;(2):CD000100

- inhaled nitric oxide does not reduce mortality or ventilator use (level 1 [likely reliable] evidence) and may increase mortality and ventilator use (level 2 [moderate] evidence)
  - based on systematic review
  - systematic review of 12 randomized trials of nitric oxide in 1,237 adults or children (excluding neonates) with acute lung injury or acute respiratory distress syndrome
  - trials had good quality and complete follow-up
  - nitric oxide associated with trend toward increased mortality in meta-analysis of 9 trials with 1,086 patients
    - mortality was 34.5% with nitric oxide vs. 31.8% with control
    - 95% CI for absolute difference approximately -3.5% to +9.5%
  - no significant difference in duration of ventilation in meta-analysis of 3 trials
    - relative difference 16% increase (95% CI 4% to 30%)
    - absolute difference 3.6 additional days (95% CI 0.6 to 6.6 days)
  - no significant difference in ventilation-free days in meta-analysis of 5 trials
    - relative difference 8% decrease (95% CI -16% to 8%)
    - absolute difference 0.6 fewer days (95% CI -1.8 days to +0.7 days)
  - nitric oxide increased incidence of renal dysfunction (19.3% vs. 12.8%, NHN 15) in meta-analysis of 4 trials with 895 patients
  - Reference - BMJ 2007 Apr 14;334(7607):772 full-text, editorial can be found in BMJ 2007 Apr 14;334(7607):767

- insufficient evidence to support use of inhaled nitric oxide for acute hypoxemic respiratory failure in children or adults; no effect on mortality, inhaled nitrogen oxide improved oxygenation transiently in 1 trial; systematic review of 5 trials with 935 patients last updated 2002 Sep 7 (Cochrane Library 2002 Issue 1:CD000278)
- Inhaled nitric oxide not shown to improve outcomes in 6 trials of adults with acute lung injury or ARDS, but trials statistically underpowered (Int J Med 2005 Dec 22;383(13):2283)
- Inhaled nitric oxide 5 ppm does not affect duration of ventilation or mortality (level 1 [likely reliable] evidence), despite short-term improvement in oxygenation, based on randomized trial of 365 patients with moderately severe acute lung injury who did not have sepsis or nonpulmonary organ system dysfunction (JAMA 2004 Jul 21;292(3):327)
- Inhaled nitric oxide in patients with ARDS and without preexisting coagulation disorders leads to non-dose-dependent decrease in platelet aggregation, improves arterial oxygenation and decreases pulmonary artery pressure (Asthma 1995 Jul 24;11:15)
- Inhaled nitric oxide improves ventilation/perfusion relationships and oxygenation in phase II randomized trial of 177 patients with ARDS, but no differences in mortality or adverse events (Crit Care Med 1998 Jun;26(1):11 in QuickScan Reviews in Fam Pract 1998 Aug;23(5):30)

- surfactant not shown to improve survival in adult ARDS patients
- surfactant not shown to increase oxygenation but does increase mortality
Walking the Walk

• If the information you seek is not available in a synopsis database, you can directly search the medical literature.

• Access the UMDNJ Library Website, MedLine Search Engine.
Walking the Walk

Start Page

Change to Multi-Field Search
Walking the Walk
Walking the Walk

Fill in as many search terms as necessary, add more rows if necessary, specify search fields.
Walking the Walk

117 Results

Can narrow search by journal.
Walking the Walk

This can reduce the number of articles to a manageable quantity.
Walking the Walk

Let’s look at a recent review article to see if the information we seek is readily available.
Walking the Walk

Let’s confirm our impression by quickly looking at another review article, this time by a well-known investigator in pulmonary medicine and published in the primary pulmonary medical journal – Chest.

Since this article is available in our library as a full text article, let’s retrieve it for review.
Walking the Walk

Two options for article. We will choose ACCP.
Nonventilatory Treatments for Acute Lung Injury and ARDS

Nonventilatory Treatments for Acute Lung Injury and ARDS

Carolyn S. Calfee, MD and Michael A. Matthay, MD, FCCP

Department of Medicine, Division of Pulmonary and Critical Care Medicine, University of California at San Francisco, San Francisco, CA.

Correspondence to: Carolyn S. Calfee, MD, University of California, San Francisco.
Walking the Walk

Nonventilatory Treatments for Acute Lung Injury and ARDS

Carolyne M. Caffey, MD, and Michael A. Matthay, MD, FCCP

Over the past decade, advances in the ventilatory management of acute lung injury (ALI) and ARDS have improved outcomes; however, until recently the search for other therapies has been less fruitful. Recently, the Acute Respiratory Distress Syndrome Network Fluid and Catheter Treatment Trial reported that a conservative fluid management strategy, compared with a fluid liberal strategy, increased the mean (±SD) number of ventilator-free days in patients with ALI (4.4 ± 2.9 vs 12.1 ± 6.6 days, respectively; p < 0.001). In addition to this beneficial effect on outcomes, the study found that the conservative fluid strategy did not increase the incidence of renal failure or the development of sepsis. Other studies have demonstrated that albumin and hydrocortisone therapy may be beneficial in hypoproteinemic patients with lung injury, though data on outcomes is still lacking. Although several pharmacologic therapies, such as corticosteroids, surfactant, and nitric oxide, have been demonstrated to be ineffective in improving outcomes, several promising new treatments are being investigated in ongoing or upcoming clinical trials. This article reviews those developments and other recent research on the optimal nonventilatory management of patients with ALI.

Key words: acute lung injury; fluid therapy; management; pulmonary edema

Abbreviations: ALI = acute lung injury; CVVH = continuous venovenous hemofiltration; FACCT = Fluid and Catheter Treatment Trial; CHEST = Grantfighter; end-expiratory positive airway pressure; NELMS = National Emergency Research Laboratory and Medical Systems; NO = nitric oxide; PAC = pulmonary artery catheter

Advances in the ventilatory management of acute lung injury (ALI) and ARDS over the past decade have been dramatic. In particular, the use of a low tidal volume (6 mL/kg predicted body weight), plateau pressure-limited strategy has been demonstrated to reduce mortality from 40 to 35%. Further, a large, multicenter, randomized, controlled trial demonstrated the equivalence of higher and lower levels of positive end-expiratory pressure. Over this time period, a number of nonventilatory therapies for ALI/ARDS have been investigated, many of which have not proven to be effective, while others appear more promising. This article will review the most recent and relevant evidence regarding nonventilatory treatments for ALI/ARDS, including advances in fluid management and pharmacotherapy. In addition, we will briefly survey promising new and investigative therapies for ALI/ARDS that are the focus of current and upcoming clinical trials.

FLUID MANAGEMENT

Until recently, the optimal strategy for fluid management in patients with ALI/ARDS was unclear. Pulmonary edema, even when noncardiogenic in origin, increases with a rise in hydrostatic pressures. Experimental studies demonstrated that a modest...
The specific section with a nice Table, including references.

Pharmacotherapy

The search for an effective pharmacologic therapy for ALI/ARDS has continued over the past decade without major success; to date, no pharmacologic agent has been demonstrated to reduce mortality among patients with this condition. Several treatments, however, merit brief discussion due to historical interest as a therapy for ALI, conclusive evidence of lack of benefit, or potentially intriguing analyses of subgroups or secondary outcomes. In addition, we will cover several promising new therapies that are the focus of ongoing or upcoming clinical trials.

Pharmacologic therapies recently investigated as possible treatments for ALI include surfactant, inhaled nitric oxide (NO), corticosteroids, antifungal drugs, and phosphodiesterase inhibitors (Table 3). Exogenous surfactant administration was first administered as a therapy for lung injury in the late 1980s. Several phase I and II trials in humans showed promising trends in outcomes. Inhaled NO has been considered a promising therapy for lung injury due to its ability to provide selective pulmonary vasodilation and improve ventilation-perfusion mismatch. Unfortunately, although several trials have now demonstrated some improvements in oxygenation and pulmonary hemodynamics with the use of NO, the lack of mortality benefit has been just as consistent. Further, while nearly 60% of patients who receive inhaled NO will respond clinically with improved oxygenation, these benefits are typically short-lived, fading after the first 1 to 2 days of administration. Thus, although the use of NO may be considered a rescue therapy in patients who are exceptionally difficult to oxygenate, it has no role in standard therapy for ALI.

Similarly, corticosteroids seemed to be an ideal therapy for lung injury, given their potent antiinflammatory and antibiotic properties. Clinical trials have evaluated the utility of corticosteroids in preventing ALI/ARDS and in treating either early-stage (inflammatory) or late-stage (fibrotic) ALI/ARDS; none have demonstrated a mortality benefit. In addition, the use of corticosteroids has been limited by concerns over their contributions to neuromuscular disorders associated with critical illness, particularly when combined with neuromuscular blocking agents.

Most recently, the NHLBI Acute Respiratory Distress Syndrome Network published the results of a randomized controlled trial of methylprednisolone in ARDS patients of at least 7 days duration. Although therapy with methylprednisolone in-

Table 3—Pharmacotherapies Investigated as Possible Treatment for ALI/ARDS

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Outcomes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surfactant</td>
<td>No significant mortality benefit (adult populations)</td>
<td>28-33</td>
</tr>
<tr>
<td>NO</td>
<td>Improves oxygenation but no mortality benefit</td>
<td>35-40</td>
</tr>
<tr>
<td>Corticosteroids (preventive)</td>
<td>Not effective in preventing ALI/ARDS</td>
<td>42-45</td>
</tr>
<tr>
<td>Corticosteroids (therapeutic)</td>
<td>No mortality benefit; may increase risk in patients with ARDS of ≥14 d duration</td>
<td>40-45,51</td>
</tr>
<tr>
<td>Antifungal agents (e.g., amphotericin)</td>
<td>No mortality benefit in treating established ARDS; may help prevent development of ARDS</td>
<td>70-72</td>
</tr>
<tr>
<td>Phosphodiesterase inhibitors (e.g., isoflurane and pentoxifylline)</td>
<td>No mortality benefit in ALI/ARDS</td>
<td>75</td>
</tr>
</tbody>
</table>

5 more references for more info
Walking the Walk

• Needless to say, we stuck to conventional therapy and then started discussing the use of steroids—and then hit the internet again to see if they showed any benefit.
Walking the Walk

• CLINICAL SCENARIO
• Mrs Smothers, an accountant, is a moderately obese, 56-year-old white woman with type 2 diabetes, first diagnosed 3 years ago. She visits you in a somewhat agitated state. She missed her previous appointment ("tax time"), and has not been at the clinic for over a year. Her 55-year-old sister also had diabetes and recently died of a heart attack. Mrs Smothers found some information on the Internet that will allow her to calculate her own risk of heart attack, but she lacks some of the information needed to do the calculation, including her cholesterol and recent hemoglobin A1c. She wants your help in completing the calculation and your advice about reducing her risk.

• She is currently trying to quit her smoking habit of 25 years. She is on a prescribed regimen of a calorie-restricted diet (with no weight loss in the past year), exercise (she states about 20 minutes of walking once or twice a week, hampered by her osteoarthritis), and metformin 2500mg/day (sometimes missed, especially when she skips meals). Mr Smothers accompanies Mrs Smothers on this visit and interjects that she is also taking vitamin E and beta-carotene to lower her risk for heart disease, based on a health advisory that Mr Smothers read on the Internet. The occasional fasting blood sugars she has taken have been between 7 and 14 mmol/L (126–252mg/dL). She hasn’t had an eye examination in over a year and didn’t get a flu shot. She has no other physical complaints at present, but admits to being depressed since her sister’s death. She specifically denies symptoms of chest pain, stroke, or claudication.

• On examination, Mrs Smothers is 98kg in weight and 172cm in height. Her blood pressure is 148/86mmHg in the left arm with a large adult cuff, repeated. The rest of her examination is unremarkable, including her optic fundi, cardiovascular system, chest, abdomen, skin, feet, and sensation.

• You ask her what risk calculator she found and she shows you the web page that she printed. You tell her that you will check out the web page and enthusiastically endorse tightening up her regimen to bring her into the “green zone” for blood sugar, blood pressure, and cholesterol control. She is not keen to consume additional prescription medication, preferring “natural remedies”, but states that she is open to discussion, especially in view of her sister’s death. She wants to know her risk of heart attack and just how much benefit she can expect from any additional medication you might propose for her. You tell her that you will be pleased to help her get the answers to her questions, but will need to update her lab tests and have her return in 2 weeks. She is not very pleased about having to wait, but accepts your explanation. Heeding a recent dictum from your clinic manager, you order a “lean and mean” minimalist set of lab tests: hemoglobin A1c, lipid profile, creatinine, urinary microalbumin:creatinine ratio, and ECG (electrocardiogram).
Problem: Type 2 diabetes and related cardiovascular risk.

Step 1. Asking answerable questions

Investigations have shown that Mrs Smothers has an $A_1c$ of 8.9%, microproteinuria and hyperlipidemia, with total cholesterol 6.48 mmol/L, LDL 3.4 mmol/L, HDL 0.9 mmol/L, and triglycerides 3.9 mmol/L. With this additional information, we pose the question: In a 56-year-old woman with type 2 diabetes mellitus, microproteinuria, elevated blood pressure, and dyslipidemia, what is the evidence concerning increased risk for cardiovascular complications compared with people with diabetes without these risk factors (and does the risk calculator that Mrs Smothers found provide an evidence-based estimate of risk that fits her circumstances)? In such a patient, does “tight” control of glucose, blood pressure, cholesterol, and proteinuria reduce subsequent morbidity and mortality?

Let’s search about “Does control of BP in Diabetes reduce morbidity and mortality?”
Walking the Walk

BMJ Clinical Evidence

A full list of BMJ Clinical Evidence sections.

- Blood and lymph disorders
- Cardiovascular disorders
- Child health
- Diabetes
- Digestive system disorders
- ENT
- Endocrine and metabolic disorders
- Eye disorders
- HIV and AIDS
- Infectious diseases
- Kidney disorders
- Lifestyle
- Men's health
- Mental health
- Musculoskeletal disorders
- Neurological disorders
- Oncology
- Oral health
- Perioperative care
- Poisoning
- Pregnancy and childbirth
- Respiratory disorders (acute)
- Respiratory disorders (chronic)
- Sexual health
- Skin disorders
- Sleep disorders
- Social and community health
- Supportive and palliative care
- Travel health
- Women's health
- Wounds

Our latest publications
Walking the Walk
Walking the Walk

Systematic reviews
- Diabetic nephropathy
- Dyslipidaemia in diabetes
- Foot ulcers and amputations in diabetes *(updated)*
- Glycaemic control in type 1 diabetes
- Glycaemic control in type 2 diabetes
- Hypertension in diabetes
- Prevention of cardiovascular events in diabetes

Covered elsewhere
- Diabetic retinopathy
- Gout
- Obesity
- Primary hypothyroidism
Prevention of cardiovascular events in diabetes
Ronald Sigal, Janine Malcolm, and Axel Amouyli

You may prefer to read the key points of this review.

We have searched the evidence for systematic and rigorous answers to the clinical questions and situations below, focusing on the outcomes that matter most to patients and clinicians. We have then categorised each treatment or intervention according to its harms and benefits in those situations.

What are the effects of promoting smoking cessation in people with diabetes?
Likely to be beneficial

- Smoking cessation

What are the effects of controlling blood pressure in people with diabetes?
Beneficial

- Antihypertensive treatment (compared with no antihypertensive treatment)
- Lower target blood pressures

Trade off between benefits and harms

- Different antihypertensive drugs
# Walking the Walk

## What are the effects of treating dyslipidaemia in people with diabetes?

<table>
<thead>
<tr>
<th>Beneficial</th>
<th>Statins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely to be beneficial</td>
<td>Aggressive versus moderate lipid lowering with statins</td>
</tr>
<tr>
<td></td>
<td>Fibrates</td>
</tr>
<tr>
<td></td>
<td>Low versus standard statin dose in older people</td>
</tr>
</tbody>
</table>

## What are the effects of antplatelet drugs in people with diabetes?

| Likely to be beneficial | Adding glycoprotein IIb/IIIa inhibitors to heparin in acute coronary syndromes |
| | Clopidogrel |
| Trade off between benefits and harms | Aspirin |
| Unlikely to be beneficial | Adding clopidogrel to heparin in acute coronary syndromes |

## What are the effects of blood glucose control in prevention of cardiovascular disease in people with diabetes?

| Likely to be beneficial | Intensive versus conventional glycaemic control |
| | Metformin versus diet alone as initial treatment in overweight or obese people with type 2 diabetes |
# Walking the Walk

## What are the effects of treating multiple risk factors in prevention of cardiovascular disease in people with diabetes?

<table>
<thead>
<tr>
<th>Beneficial</th>
<th>Intensive multiple risk factor treatment</th>
</tr>
</thead>
</table>

## What are the effects of revascularisation procedures in people with diabetes?

<table>
<thead>
<tr>
<th>Beneficial</th>
<th>Coronary artery bypass graft compared with percutaneous transluminal coronary angioplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely to be beneficial</td>
<td>Percutaneous transluminal coronary angioplasty compared with thrombolysis</td>
</tr>
<tr>
<td>Trade off between benefits and harms</td>
<td>Coronary artery bypass graft compared with percutaneous transluminal coronary angioplasty plus stent</td>
</tr>
</tbody>
</table>

## To be covered in future updates
- Niacin
- Fish oil
- Vitamins C and E
- Diet (including salt reduction)

## Footnote
*No RCT but observational evidence suggests some benefit*

Web publication date: 01 Feb 2006 (based on November 2004 search)
Prevention of cardiovascular events in diabetes

Ronald Sigal, Janine Malcolm, and Amel Arnaout

Interventions  Key points  About this condition  Updates (9)  Guidelines (14)  References  Your responses

You may prefer to read the key points of this review.

We have searched the evidence for systematic and rigorous answers to the clinical questions and situations below, focusing on the outcomes that matter most to patients and clinicians. We have then categorised each treatment or intervention according to its harms and benefits in those situations.

**What are the effects of promoting smoking cessation in people with diabetes?**

<table>
<thead>
<tr>
<th>Likely to be beneficial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
</tr>
</tbody>
</table>

**What are the effects of controlling blood pressure in people with diabetes?**

<table>
<thead>
<tr>
<th>Beneficial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive treatment (compared with no antihypertensive treatment)</td>
</tr>
<tr>
<td>Lower target blood pressures</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Trade off between benefits and harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Different antihypertensive drugs</td>
</tr>
</tbody>
</table>

Updates (new)

We provide up-to-the-minute updates for this review so you always have the latest evidence.

Respond to this review

Remember you have the opportunity to respond to this review if you have any comments, or feel there is anything we have not covered.
Walking the Walk

Top of Chart

Middle of Chart

Prevention of cardiovascular events in diabetes

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Subscribe</th>
<th>EBM resources</th>
<th>About us</th>
<th>Contact us</th>
<th>Contribute</th>
</tr>
</thead>
<tbody>
<tr>
<td>Go back to previous page.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table A: Antihypertensives versus no antihypertensive treatment.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Methods</th>
<th>Participants</th>
<th>Intervention</th>
<th>Mortality</th>
<th>Myocardial Infarction</th>
<th>Stroke</th>
<th>Any cardiovascular event</th>
<th>Adverse effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Systematic review</td>
<td>7572 people with type 2 diabetes and hypertension, aged ≥50 years</td>
<td>Antihypertensives (ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics) vs control</td>
<td>No significant difference in 14,100 person-years of treatment</td>
<td>No significant difference in 15,000 person-years of treatment</td>
<td>No significant difference in 161,000 person-years of treatment</td>
<td>No adverse effects reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>RCT identified by systematic review</td>
<td>500 people with type 2 diabetes, microalbuminuria, and hypertension, mean age 50 years</td>
<td>Ibosartan (angiotensin receptor blocker) vs placebo</td>
<td>No significant difference in non-fatal cardiovascular events: 59/144 (4.1%) with placebo vs 71/130 (5.5%) with ibosartan</td>
<td>No significant difference in non-fatal cardiovascular events: 59/144 (4.1%) with placebo vs 71/130 (5.5%) with ibosartan</td>
<td>No significant difference in non-fatal cardiovascular events: 59/144 (4.1%) with placebo vs 71/130 (5.5%) with ibosartan</td>
<td>No adverse effects reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>RCT</td>
<td>4923 people with type 2 diabetes, aged ≥50 years, with persistent microalbuminuria or proteinuria and serum creatinine &lt; 150 µM</td>
<td>Ramipril (ACE inhibitor) 1.25 mg daily vs placebo</td>
<td>No significant difference in mortality due to cardiovascular events over a mean 47 months: 144/243 (59%) with ramipril vs 122/249 (49%) with placebo</td>
<td>No significant difference in mortality due to cardiovascular events over a mean 47 months: 144/243 (59%) with ramipril vs 122/249 (49%) with placebo</td>
<td>No significant difference in mortality due to cardiovascular events over a mean 47 months: 144/243 (59%) with ramipril vs 122/249 (49%) with placebo</td>
<td>No adverse effects reported</td>
<td>Cough was 6% more frequent with ramipril than with placebo</td>
<td></td>
</tr>
</tbody>
</table>
References


Web publication date: 01 Feb 2006 (based on November 2004 search)

Go back to previous page.
Walking the Walk

• Three minutes and the search is essentially done, except for one detail: you noticed as you were entering the diabetes cardiovascular section in *Clinical Evidence* that the literature search for this section was done in November 2004, whereas the search we’ve just completed above was in 01 February 2006.

• It is good news that the date of last search is posted within each section in *Clinical Evidence*, but it is not so good news that this section has not been revised in so long. While the table you retrieved appears to have more than enough evidence to proceed, it may be worthwhile to check another source.

• Again, we’ll look for a system: *UpToDate*. This is not part of Ovid’s collection. You may be affiliated with an institution that subscribes to it, as ours does; otherwise you will need to acquire a subscription yourself.
Walking the Walk

• A search in *UpToDate* for “diabetes” retrieves a number of titles, and we select “Diabetes mellitus, type 2”. This search retrieves more than a page of subtopics so we click the “Narrow the search results” button beside the search window and select “Treatment”, and then select “Overview of therapy in type 2 diabetes mellitus”. This section summarizes treatments, including aspirin, and medications for lowering blood sugar, blood pressure, cholesterol and triglycerides, and screening for complications such as retinopathy. Further, the chapter summarizes the benefits of “Multifactorial risk factor reduction”, citing a trial published in 2003 by Gaede et al,\(^1\) showing the benefits for patients of therapy that is directed to reducing all risk factors to low levels.

• The Gaede trial looks like just the thing to focus the discussion for Mrs Smothers. The abstract for this study is provided in *UpToDate*, along with its PubMed ID. We “copy” the PubMed ID and “paste” it in the search box for PubMed. The search instantly retrieves the article’s abstract along with links to the full-text article describing the *study* and to its *synopsis* in *ACP Journal Club*. 
Studying a Study and Testing a Test

- Assessing Systemic Reviews
- Assessing Diagnosis Articles
- Assessing Articles on Harm/Etiology
- Assessing Prognosis Articles
- Assessing Qualitative Studies
- Assessing Quantitative Studies
- Assessing Economic Evaluations
- Applying the Evidence