APPLYING EVIDENCE TO THE CARE OF A PATIENT WITH HEART FAILURE AND COPD: HOW TO FIND AND USE A SYSTEMATIC REVIEW

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The traditional approach to practicing evidence-based medicine (EBM) begins with a clinical encounter that identifies the need for more information. This encounter then launches the stepwise process of *assessing* the patient/clinical problem, *asking* the right clinical question, *acquiring* and *appraising* the evidence, and *applying* the evidence and *assessing* its impact. In an ideal world, we would work through each step in the EBM process to find the best available evidence to answer our clinical question. However, we often lack the knowledge, skills, or time to take this approach in our daily practice, which presents one of the most significant barriers to practicing EBM.

One solution to help overcome this barrier is the development and widespread dissemination of high-quality, user-friendly, and validated evidence-based resources that can provide fast and reliable answers at the point-of-care. Over the past 10 years, substantial progress has been made on this front, with better resources constantly being developed, but it will be a long time before any of these resources can meet most of our needs. Meanwhile, one way to deal with the challenge of practicing EBM in the current clinical environment is to apply the "4S" (*Systems, Synopses, Syntheses, Studies*) pyramid for selecting evidence resources, which provides an efficient tiered strategy for finding the current best evidence to answer our clinical questions [1].

When searching for answers to clinical questions, we ideally would start at the top of the pyramid—*systems* of evidence. An example of an evidence system is an electronic medical record with evidence-based computerized clinical decision support. Unfortunately, most institutions currently do not have such a sophisticated clinical information system in place. Therefore, we must often skip to the next layer in the resource pyramid—*synopses* of evidence, such as the brief structured summaries (abstracts) found in *ACP Journal Club*. If no synopsis is available to answer our clinical question, we are compelled to search within the third layer of the pyramid—*syntheses* of evidence. These resources include systematic reviews and meta-analyses and are the focus of this article.

Systematic reviews are review articles that have been prepared using a "systematic approach to minimizing biases and random errors, which is documented in a materials and methods section" [2]. These articles usually are developed to comprehensively answer a specific clinical question. Systematic reviews should adhere to standard methodologic principles, including use of a preplanned strategy to conduct a comprehensive search for all relevant studies in the subject area, application of evidence-based principles to appraise the validity of each study, and synthesis of the data to answer a specific clinical question. Systematic reviews can be qualitative or quantitative. A qualitative systematic review summarizes the results of the primary studies but does not combine the results of each study into a single pooled estimate of effect. A quantitative systematic review, or *meta-analysis*, takes things a step further by employing statistical techniques to mathematically combine the results of the different studies into a single pooled estimate of effect. Thus, all meta-analyses are systematic reviews but not all systematic reviews are meta-analyses.

In contrast to systematic reviews, a narrative review provides a more subjective summary of the literature. Traditionally written by an expert in the field, narrative reviews generally offer a broad overview of a topic, including information on disease pathophysiology, diagnosis, and therapeutic interventions, rather than answer a particular clinical question or address a specific issue in depth. Although

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narrative reviews can provide a good summary of the literature, recommendations are usually based on the author's opinion. Because opinions can be influenced by many factors and often vary among clinicians (even those who are "experts"), recommendations in a narrative review are dependent on who is writing the review rather than what has been demonstrated by the current best evidence on important patient-centered health outcomes. Narrative reviews do not apply the same standardized, rigorous approach to searching, appraising, and synthesizing the literature that is necessary for conducting a proper systematic review and that helps to ensure the validity of the results and recommendations, nor do they include explicit descriptions of their methods. They are thus more prone to bias.

Systematic reviews are a useful tool to help us keep up-to-date with the vast amounts of medical information published in the literature, especially when the individual studies are small or yield conflicting results. By combining the results of multiple studies, they increase power and create more precise estimates of treatment effects. They can also provide more generalizable information because they combine multiple studies that involve different study populations, providers, and treatment settings. Perhaps the most practical benefit of systematic reviews is that they are an efficient, time-saving source of information. A well-conducted systematic review can provide "one stop shopping" for the latest evidence on a particular topic.

This article uses a case of a patient with congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) to discuss how to find and use a systematic review as part of an evidence-based strategy to answer a patient-specific question—in this case, the question of whether or not to initiate β-blocker therapy. For illustrative purposes, we have assumed that no resource was available from higher in the 4S pyramid that could have answered our clinical question.

Assessing the Clinical Problem

Mr. Miles is a 62-year-old man with COPD who was recently admitted to the hospital after a 1-week history of worsening dyspnea on exertion, 2-pillow orthopnea, and lower extremity edema. Physical examination revealed volume overload, and a chest radiograph revealed mild to moderate pulmonary edema. An evaluation for the cause of heart failure revealed no evidence of coronary artery disease or valvular heart disease. An echocardiogram revealed left ventricular systolic dysfunction with an ejection fraction of 32%. While hospitalized, Mr. Miles was started on a diuretic and an angiotensin-converting enzyme inhibitor but not a β blocker because of the acute nature of his heart failure symptoms. He responded well to treatment and was discharged home with instructions for follow-up by his primary care physician.

You are a second-year resident who will be seeing Mr. Miles today at the university's primary care clinic. You review his record and decide that he might benefit from being prescribed a β blocker, but you wonder if it will worsen his COPD symptoms. During the examination, Mr. Miles reports that he has done well since discharge. He notes no further swelling, and his dyspnea on exertion is back to its baseline of occurring only on moderate exertion with activities like mowing the yard or walking more than 3 blocks. On further questioning, he reports 1 to 2 COPD exacerbations per year requiring visits to the emergency department, with occasional hospitalization. On physical examination, Mr. Miles shows no signs of volume overload but has mild, diffuse wheezing bilaterally on forced expiration.

You present Mr. Miles to your clinic attending, Dr. Bertman, who asks if there are any other interventions that should be offered to Mr. Miles. You report that β blockers have been shown to reduce mortality from CHF but are contraindicated in patients with COPD. Dr. Bertman asks for your evidence supporting this contraindication. You report that you have no specific evidence other than what you were told in your pharmacology course during medical school, which was taught by a recognized leader in the field.

You and Dr. Bertman briefly discuss β blockers and cardiovascular disease. You both agree that these agents have been proven to reduce mortality in patients with acute myocardial infarction and in patients with chronic CHF. You then discuss patients in whom β blockers might be relatively contraindicated, including those with COPD/asthma, reduced left ventricular ejection fractions, overt heart failure, or diabetes. Dr. Bertman concurs that nonselective β blockade can precipitate bronchospasm in those who are predisposed but adds that cardioselective β blockers appear to be safe, as do β blockers with combined α-adrenergic blockade. He suggests that these agents can be administered safely with close monitoring of the patient.

Dr. Bertman adds that he recently saw an abstract of a systematic review of the respiratory effects of

β blockers in patients with COPD, although he cannot recall where he saw it. Recognizing a learning opportunity, Dr. Bertman gives you an "educational prescription" [3] and suggests that you have Mr. Miles return in 1 week, after you've filled your prescription, to discuss the potential risks and benefits of added β-blocker therapy.

As previously noted, the EBM process is set in motion when a clinical encounter generates a need for more information that will guide our management decisions about a specific patient. In this case, we face the common scenario of an older patient with coexisting cardiovascular and pulmonary conditions—CHF and COPD. Although Mr. Miles appears to be doing okay with his current treatment regimen, every clinical encounter provides us with an opportunity to assess whether we can improve the quality of health care we are delivering. At this visit, an important new issue has been raised: can we optimize Mr. Miles' cardiovascular care and reduce his risk of future cardiovascular events without adversely affecting the management of his COPD?

This case highlights the range of issues that should be considered when assessing a clinical problem, including our learning needs (how accurate, complete, and up-to-date is our knowledge?), the state of the medical literature (is there compelling new evidence that challenges earlier paradigms of medical practice?), and patient preferences, values, and needs (what does our patient value most and how can we optimize his quality of life?).

Asking a Focused Clinical Question

You return to the exam room to discuss with Mr. Miles the role of β blockers in CHF and their side effects, including the possibility of inducing bronchospasm. Mr. Miles is interested in the potential health benefits of the drugs but expresses a clear concern that they might worsen his COPD, and he wants to know the chances of this occurring. You admit that you are unsure and that you need to gather more information. You add that you would like to research the question and provide Mr. Miles with a clearer sense of the potential risks and benefits of β-blocker therapy in his particular case. Mr. Miles agrees to return to the clinic for a follow-up visit in 1 week. In the meantime, you will review the data so the 2 of you can make a more informed shared decision regarding adding β-blocker therapy at his next visit.

You finish clinic early that day and head to the library to fill your educational prescription, which is to determine the risk of β blockade in patients with COPD.

Once we identify a knowledge gap that is worth filling, the next step is to develop a focused clinical question, the recommended method for which is to use the PICO format (patient/problem, intervention or diagnostic test of interest, comparison intervention, outcome). The PICO components for this case may be defined as:

P = elderly patients with CHF and COPD
I = β blockers in addition to standard CHF therapy
C = standard CHF therapy alone
O = increased dyspnea or hospitalizations for COPD exacerbation

Using this framework, our question regarding Mr. Miles would be:

In **elderly patients with CHF and COPD**, does the **addition of β blockers to standard CHF therapy**, compared with **standard CHF therapy alone**, lead to **increased dyspnea or hospitalizations for COPD exacerbation**?

Developing a focused clinical question can help make our search for evidence more efficient and, when more than one systematic review exists on a topic, can help guide us to the review that best answers our question. For example, sometimes more than one systematic review will be published on a seemingly similar topic, but on closer inspection, the patient population or outcome measures may differ. In our scenario, we want to find a systematic review that addresses the effect of β blockade on risk for increased dyspnea or hospitalizations for COPD exacerbation. If we find 2 systematic reviews addressing the use of β blockers in COPD, one that uses peak flow measurements as the outcome of interest and another that uses patients' documentation of respiratory symptoms as the outcome, we might be more interested in the latter review because it more directly addresses our question. By asking a focused and explicit question, we increase the probability of finding a review that provides a better answer to address our patient's specific needs.

Acquiring the Current Best Evidence

At the library, you decide to start by looking for the systematic review Dr. Bertman mentioned. Being unsure how best to search for these articles, you consult

Table 1. Online Resources for Locating Systematic Reviews

Resource	Description	Publisher/Sponsor
Cochrane Database of Systematic Reviews (www.cochrane.org)	Extensive collection of systematic reviews on therapy and prevention; free access to abstracts; subscription required for full-text access	Cochrane Collaboration
Ovid (www.ovid.com/site/index.jsp)	Search engine/tools for accessing databases, journals, and books; multiple products available by subscription only	Wolters Kluwer Health
PubMed Clinical Queries (www.pubmed.gov)	Search tool for finding citations for systematic reviews/meta-analyses, reviews of clinical trials, consensus development conferences, and guidelines; free access to abstracts	National Library of Medicine and National Institutes of Health
DARE (www.york.ac.uk/inst/crd/darefaq.htm)	Collection of summaries of systematic reviews that meet strict quality criteria; free	Centre for Reviews and Dissemination, University of York

DARE = Database of Abstracts of Reviews of Effectiveness.

the medical librarian, who suggests a few online databases that contain systematic reviews. You join her at a computer workstation, where she demonstrates these resources and reviews search strategies that can be used to identify systematic reviews.

Where and How to Find a Systematic Review

Table 1 summarizes the main online resources currently available to help locate systematic reviews.

Cochrane Database of Systematic Reviews. The Cochrane Library is a set of databases maintained by the Cochrane Collaboration and should be considered the first-line resource for searching for a systematic review. The Library's primary database, the Database of Systematic Reviews (available at www.cochrane.org), currently contains more than 2600 completed systematic reviews prepared by members of the Collaboration plus approximately 1200 protocols for reviews that are in progress but not yet completed. This database is updated quarterly.

Each Cochrane review addresses an explicit clinical question, although at present only questions related to therapy and prevention are included in the database. Each review brings together the relevant research findings on a topic, synthesizes the evidence, and presents the synthesis in the form of an abstract followed by a description of the search strategy and rationale for conclusions drawn from the data. In addition, each review uses explicit methods to minimize bias and is peer reviewed. Although the Library contains a large number of completed reviews, the content areas covered are still somewhat limited considering all the questions that are generated in clinical practice. Nonetheless, Cochrane reviews have been shown to be of higher methodologic quality than other systematic reviews [4]. One of the main drawbacks is that access to full-text documents in the Cochrane Library is by subscription only. However, many medical libraries have institutional licenses, and free access to abstracts is available.

Database of Abstracts of Reviews of Effectiveness (DARE). Another database included in the Cochrane Library, DARE is a public domain, full-text database containing critical assessments of systematic reviews from a variety of medical journals. DARE is produced by the expert reviewers at the National Health Services' Centre for Reviews and Dissemination at the University of York in the United Kingdom (available at www.york.ac.uk/inst/crd/darefaq.htm). DARE covers topics such as diagnosis, prevention, rehabilitation, screening, and treatment. It is updated monthly. Like Cochrane, DARE contains high-quality reviews but can be limited in the scope of topics covered. Because DARE is one of the databases maintained in the Cochrane Library, a search of the Cochrane Library for systematic reviews will retrieve records from both DARE and the Cochrane Database of Systematic Reviews. Other routes for accessing DARE are through the TRIP (Turning Evidence into Practice) database (www.tripdatabase.com) and SUMSearch (http://sumsearch.uthscsa.edu).

MEDLINE. If the Cochrane Database of Systematic Reviews and DARE do not include a useful systematic review to address our clinical question, the next step is to search MEDLINE, which contains references to more than 13,000 systematic reviews,

Table 2. Search Strategies for Retrieving Systematic Reviews from MEDLINE via Ovid

Strategy Type	Ovid Search Strategy	Sensitivity (%)	Specificity (%)
High sensitivity	Review.pt OR meta-analysis.mp,pt OR tu.xs	98	69
High specificity	Search strategy.tw.	59	99.9
Optimal balance	Review.pt OR meta-analysis:.tw. OR Cochrane.tw.	93	92

NOTE: To apply, include the clinical topic terms of your search on one line, type in one of the Ovid search strategies from above on a second line, then combine the searches by putting "1 AND 2" on the third line. "pt" signifies publication type; "tu.xs" signifies exploded subheading; "tw" signifies text word. These terms tell MEDLINE where to look for articles. For example, "pt" tells MEDLINE to look for articles that are classified as a review article and to ignore other publication types such as controlled trials. (Adapted from Straus SE, Richardson WS, Glaziou P, Haynes RB. Evidence-based medicine: how to practice and teach EBM. 3rd ed. Edinburgh: Churchill Livingstone; 2005:41–2. Copyright 2005, with permission of Elsevier.)

including the reviews from the Cochrane Library. **Table 2** lists strategies that can be used to search MEDLINE for systematic reviews via Ovid. These strategies are also available in Ovid under the Clinical Queries limit type. The sensitive search strategy will retrieve a relatively complete set of systematic reviews relevant to a clinical question but will also contain many citations that have little or nothing to do with the question, requiring us to sift through superfluous citations to find the good ones. In contrast, the specific search strategy will be more targeted and retrieve fewer citations overall, including potentially useful reviews, but will minimize the need for us to sift through the pile to find the relevant articles. The trade-off is that a specific search may be more efficient but may also miss some of the important articles that relate to our question. Ovid also offers a limit feature, Evidence Based Medicine Reviews, which allows simultaneous searching for original articles in MEDLINE, synopses in *ACP Journal Club* and *Evidence Based Medicine*, and systematic reviews from the Cochrane Library and DARE, thus providing an efficient way to search for evidence that is available on a topic.

If access to MEDLINE via Ovid is not an option, MEDLINE may be searched for free via PubMed (available at www.pubmed.gov). Here, we would want to use the Clinical Queries option, available as a link on the left side of the PubMed menu, to limit our search to systematic reviews.

Appraising Evidence for Validity and Importance

Armed with search strategies suggested by the librarian, you begin your search at the Cochrane Library, which you now know is the best place to look for a systematic review addressing a therapy question. Entering the terms "beta-blockers and COPD" into the search field yields 2 results, 1 of which appears to be a promising systematic review entitled "Cardioselective beta-blockers for chronic obstructive pulmonary disease" [5]. Skimming the abstract, you note that the objective of the review is to "assess the effect of cardioselective beta-blockers on respiratory function of patients with COPD." Since this review appears to answer your question about Mr. Miles, you print a full-text copy so you can appraise the article later.

A few days later, you find time to devote to completing your educational prescription. You begin by reading the full text of the Cochrane systematic review by Salpeter and colleagues [5]. Then, with your copy of the Users' Guides to the Medical Literature [6] at hand, you proceed with critically appraising the article using criteria for a systematic review.

Systematic reviews, like other scientific investigations, are prone to bias and must be critically appraised before they can be applied to patient care decisions. The *Users' Guides to the Medical Literature* [6] outlines specific criteria for assessing the validity and importance of results reported in a review article (**Table 3**). As we review each of these appraisal criteria, we will consider how the systematic review prepared by Salpeter and colleagues [5] measures up.

Criteria for Appraising Validity

- **Did the review address a sensible clinical question?**

Systematic reviews should ideally address very specific clinical questions. Thus, the first step of conducting a systematic review is to define the clinical question that will be answered. The investigators must clearly define the patient population, intervention or exposure of interest, and outcomes. From this point, the investigators will develop inclusion and exclusion criteria to select an unbiased sample of

Table 3. Users' Guides Criteria for Appraising and Applying the Results of a Systematic Review

Are the results valid?
Did the review address a sensible clinical question?
Was the search for relevant studies detailed and exhaustive?
Were the primary studies of high methodologic quality?
Were assessments of studies reproducible?
What are the results?
Were the results similar from study to study?
What are the overall results of the review?
How precise are the results?
How can I apply the results to patient care?
How can I best interpret the results to apply them to my patient?
Were all clinically important outcomes considered?
Are the benefits worth the costs and potential risks for my patient?

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studies to include in the review. It is important to consider whether or not the authors have tried to combine studies with very different patient populations, interventions, or outcomes. Doing so can lead to misleading or nonsensical results.

The objective of the review by Salpeter et al [5] was to evaluate the effect of cardioselective β blockers on respiratory function in patients with COPD. The patient population studied had COPD as defined by the American Thoracic Society's criteria [7] or a baseline forced expiratory volume in 1 second (FEV_1) of less than 80% predicted. Both intravenous and oral cardioselective β blockers, given either as a single dose or for an extended period of time, were studied. The outcomes of interest were explicitly defined as changes in FEV_1 and COPD symptoms. Ideally, we would prefer a systematic review that included studies that assessed important patient-centered health outcomes such as mortality, hospitalizations, and effects on quality of life. However, we can at least be encouraged that the review by Salpeter and colleagues addressed an important COPD-related symptom (dyspnea, an intermediate subjective outcome) and an objectively measured change in lung function (FEV_1, an intermediate physiologic outcome). In general, clinical decisions should be based, whenever possible, on evidence that a service or intervention improves important patient-centered health outcomes. Unfortunately, this is one of the limitations of systematic reviews; the investigators must work with the outcomes that are included in the original studies.

- **Was the search for relevant studies detailed and exhaustive?**

To ensure that all important studies relevant to the clinical question are included in the review, the investigators must perform an exhaustive search for studies both published and unpublished. A multifaceted search should be undertaken that is limited not only to searches of relevant electronic databases such as MEDLINE and EMBASE (the European version of MEDLINE) but one that also includes hand searches of references from retrieved articles and other review articles, searches of meeting abstracts and conference proceedings, contact with experts and researchers for additional data, contact with funding agencies, and searches of trial registries. Searching these other resources is important so that unpublished studies can be identified and included in the review. Otherwise, there is a risk of *publication bias.* Publication bias is a well-known phenomenon that occurs when studies with positive findings are preferentially published compared to studies that demonstrate negative findings or no effects. Publication bias is also referred to as the "file drawer problem" because of the potential for certain studies to be filed away, never to be seen or heard from again [8]. If positive studies are preferentially published compared to negative studies, it can lead to overestimation of the beneficial effects of a service or intervention in a systematic review.

In general, we can trust Cochrane reviews to be based on a comprehensive literature search because all Cochrane investigators use a standardized, validated, comprehensive search strategy to identify research data. Indeed, Salpeter and colleagues [5] used a standard Cochrane search protocol and searched several electronic databases including MEDLINE, EMBASE, CINAHL (a database covering nursing and allied health literature), and the Cochrane Central Register of Controlled Trails. In addition, the investigators hand-searched respiratory journals, meeting abstracts, and references from retrieved articles. Furthermore, they did not restrict the articles in their systematic review to those published in the English language.

- **Were the primary studies of high methodologic quality?**

It is important that studies included in a systematic review are methodologically sound. To reassure us of this, we will want to know that the included articles were scrutinized for validity using criteria similar to those outlined in the *Users' Guides* [6]. In a systematic review, the investigators should determine the validity of each included study to ensure that questionable data do not unduly influence the results. Furthermore, the investigators should describe the quality of the evidence in their review. This is important because differences in study results may otherwise be related more to differences in study methodology than true differences in efficacy between interventions. For example, observational studies of postmenopausal hormone replacement therapy tend to overestimate the effects of estrogen and progesterone on the primary prevention of cardiovascular disease compared with randomized trials [9,10]. Similarly, studies using historical controls overestimate the benefits of new treatments when compared with randomized controlled trials, because control groups in historical control studies tend to have poorer outcomes than control groups selected through randomization, thus biasing the results in favor of the new treatments [11].

Turning our attention to the review by Salpeter and colleagues [5], we learn that the investigators evaluated the quality of each of the included studies. Further, they noted that most were small crossover trials, many without placebo controls. In many of the studies included in the systematic review, the randomization process (the most important validity element of a therapy study) was not clearly defined, and many were single-blind studies.

- **Were assessments of studies reproducible?**

Investigators must decide which articles to include in a review, the validity of those articles, and which data to extract from them. These steps involve a certain amount of judgment on the part of each investigator that can be affected by bias. Bias results from any process that introduces reproducible systematic errors and leads to results that differ from the truth. To help guard against errors along each of these steps, multiple investigators should perform each of these steps independently, and any differences should be resolved by consensus. Furthermore, the level of agreement between investigators should be reported (eg, using Kappa statistics).

In the review by Salpeter et al [5], 2 investigators independently evaluated studies for inclusion and independently extracted data from the selected studies. Differences were resolved by consensus, and the interrater agreement for study inclusion was good, at 94%.

Upon completing your appraisal of the systematic review by Salpeter and colleagues [5], you feel confident that a thorough search strategy was used. Although you would have preferred that the review had included studies that assessed important patient-centered health outcomes, you are glad that it addressed an important COPD-related symptom and an objectively measured change in lung function. The quality of the individual trials disappoints you somewhat and does not provide as much confidence as you would prefer in terms of the quality of the evidence. However, you recognize that better quality data are unlikely to be available or forthcoming in the near future, so you accept it as a limitation of the type of evidence that is available on this particular topic.

Overall, you feel the methods used in the review are appropriate and that the investigators did a reasonably good job of trying to minimize bias. Satisfied with the study methodology, you proceed to consider the results of the review.

Criteria for Appraising Results

- **Were the results similar from study to study?**

Patients, interventions, outcome measures, and study protocols usually differ from study to study. As a result, treatment effects will vary from study to study. Whenever possible, investigators performing a systematic review will often try to statistically combine results of multiple studies into a summary estimate of effect (ie, perform a meta-analysis). It makes most sense to combine studies that have similar qualitative effects (ie, the direction of the effect is the same, either beneficial or harmful) but that differ quantitatively (ie, the magnitude of the benefit or harm differs). We should be concerned if investigators combined studies that showed significant benefit with other studies that showed significant harm or with studies that specifically excluded benefits or harms.

Heterogeneity is a term used to describe differences between studies included in a systematic review [12]. If studies are too dissimilar, it may be inappropriate to combine them, analogous to "combining apples with oranges." Heterogeneity can be clinical (eg, important differences between study participants, baseline disease

severity, interventions, outcome measures, or duration of follow up), methodologic (eg, important differences in the design and/or conduct of the study), or statistical (eg, important differences in the quantitative results or reported effects). A detailed explanation of these concepts is beyond the scope of this article. However, from a clinical and methodologic perspective, a simple way to assess for heterogeneity is to use our judgment to decide whether it makes sense to combine the studies. For example, does it make sense to combine studies that used a randomized controlled trial design with studies that used a case-control study design or to combine a study that involved elderly males with diabetes with a study that involved middle-aged men and women who may or may not have had diabetes? From a statistical perspective, a simple way to determine heterogeneity is to look at the confidence intervals (CIs)of the individual studies to see if they overlap one another. If they overlap, this indicates that the studies are qualitatively similar and probably reasonable to combine. More formally, investigators can apply statistical tests of heterogeneity to determine whether differences between studies are due to something other than chance. If the studies are found to be heterogeneous, the investigators should explore and explain the causes of the heterogeneity, and they should determine what influence, if any, the study differences had on the overall study results. Furthermore, investigators may be able to account for these differences using statistical techniques. If significant statistical heterogeneity is not found, it is reasonable to combine the results of the studies in a meta-analysis.

Reviewing the studies included in the review by Salpeter et al [5], we note that all the CIs overlap each other. Furthermore, formal tests of heterogeneity were performed and revealed no significant heterogeneity.

- **What are the overall results of the review? How precise are the results?**

Results of systematic reviews are presented differently than results of individual studies. When individual studies cannot be combined statistically because of significant heterogeneity, investigators can still present tables or graphs summarizing the results of the individual studies. When meta-analysis is appropriate, results of individual studies are usually weighted according to the inverse of their *variance*, a statistical measure of variability or spread of the data. In other words, the smaller the variance or variability of the study results, the more weight (and thus more importance) it receives in the meta-analysis. Variance is affected by several factors, but most important are the sample size of the population studied and the magnitude of the effect. Studies that include a larger number of patients and that demonstrate a larger *effect size* will have smaller variances, thus garnering greater weight in the meta-analysis. (Note that *effect size* is a measure of the magnitude of the treatment effect and usually is reported as a standardized difference between the mean outcome effect in one group compared to the mean outcome effect in another group. It reflects by how many standard deviations the 2 groups differ.)

Results of meta-analyses of studies with discrete outcomes (eg, recurrence of cancer versus nonrecurrence, dead versus alive) are usually presented as odds ratios or relative risks. Studies with continuous outcomes (eg, FEV_1, serum cholesterol) are usually presented as mean differences, weighted mean differences, or standardized mean differences.

Systematic reviews usually present their results graphically (**Figure 1**, **Figure 2**); these diagrams are sometimes referred to as *forest plots* [13]. Individual studies are listed down the left side, usually in chronologic order. The result of each study is represented as a box, with the 95% CI or precision of that result represented by the horizontal lines extending outward from the box. The size of the box is proportional to the weight given to that study in the meta-analysis. The diamond at the bottom of the figure represents the pooled or summary estimate of effect of all the trials combined. The center of the diamond is the pooled summary estimate, whereas the ends of the diamond represent the 95% CI. Graphic depictions of trial results are useful to determine trends in the data and to grossly detect heterogeneity as discussed above.

Examining the results of the Salpeter review shows us that there were 5 studies evaluating the effects of long-term use of cardioselective β blockers on FEV_1 (Figure 1) and 8 studies evaluating the effects on respiratory symptoms (Figure 2). Overall, there appears to be a slight reduction in FEV_1 in those patients who received β blockers compared with controls, but this difference did not reach statistical significance (weighted mean difference, –2.39% [95% CI –5.69 to 0.91]). This small reduction in FEV_1 was also clinically insignificant, as there was no change at all in respiratory symptoms (risk difference, 0% [95% CI –0.05 to 0.05]).

Applying Evidence to Patient Care

You feel that combining the results of these studies is reasonable. Encouraged by the clinically and

Study	Treatment N	Treatment Mean (SD)	Control N	Control Mean (SD)	Weighted Mean Difference (Fixed) [95% CI]	Weight (%)	Weighted Mean Difference (Fixed) [95% CI]
Dorow 1986a	34	0.60 (21.00)	34	–1.90 (10.40)		17.5	2.50 [–5.38, 10.38]
Fenster 1983	6	–12.60 (8.90)	6	–6.60 (4.80)		16.6	–6.00 [–14.09, 2.09]
Fogari 1990	20	–4.30 (8.90)	10	–3.70 (10.40)		19.2	–0.60 [–8.13, 6.93]
Ranchod 1982	15	–5.40 (8.90)	15	–1.20 (4.80)		41.6	–4.20 [–9.32, 0.92]
van der Woude 2005	15	–6.51 (19.35)	15	–7.05 (21.42)		5.1	–0.54 [–14.07, 15.15]
Total (95% CI)	90		80			100	–2.39 [–5.69, 0.91]

Test for heterogeneity: chi-square = 3.10; df = 4; P = 0.54

Test for overall effect: z score = 1.42; P = 0.02

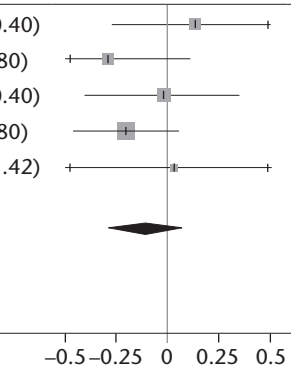

Figure 1. Excerpt of a forest plot included in the systematic review by Salpeter et al, showing results of studies comparing FEV_1 effects of long-term cardioselective β blocker use versus placebo. CI = confidence interval; df = degrees of freedom; FEV_1 = forced expiratory volume in 1 second; SD = standard deviation. (Adapted from Salpeter S, Omiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005;[4]:CD003566. Copyright Cochrane Library, reproduced with permission.)

Study	Treatment n/N	Control n/N	Risk Difference (Fixed) [95% CI]	Weight (%)	Risk Difference (Fixed) [95% CI]
Butland 1983	0/10	0/10		9.1	0.00 [–0.17, 0.17]
Fenster 1983	1/6	0/6		5.4	0.17 [–0.19, 0.53]
Fogari 1990	0/20	0/10		12.1	0.00 [–0.14, 0.14]
Lammers 1985a	0/8	0/8		7.3	0.00 [–0.21, 0.21]
Ranchod 1982	0/11	0/11		10.0	0.00 [–0.16, 0.16]
Tivenius 1976	0/12	0/12		10.9	0.00 [–0.15, 0.15]
Wunderlich 1980	0/35	1/35		31.7	–0.03 [–0.10, 0.05]
van der Woude 2005	0/15	0/15		13.6	0.00 [–0.12, 0.12]
Total (95% CI)	117	107		100	0.00 [–0.05, 0.05]

Total events: I (treatment); I (control)

Test for heterogeneity: chi-square = 1.38; df = 7; P = 0.99

Test for overall effect: z score = 0.00; P = 1

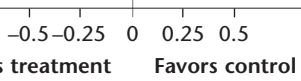

Figure 2. Excerpt of a forest plot included in the systematic review by Salpeter et al, showing results of studies comparing respiratory symptom effects of long-term cardioselective β blocker use versus placebo. CI = confidence interval; df = degrees of freedom; SD = standard deviation. (Adapted from Salpeter S, Omiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005;[4]:CD003566. Copyright Cochrane Library, reproduced with permission.)

statistically insignificant reductions in FEV_1 caused by the β blockers studied and the fact that this reduction did not lead to worsening respiratory symptoms, you plan to prescribe a cardioselective β blocker to Mr. Miles when he returns to clinic. However, 3 issues are still bothering you.

First, you want to make sure patients in the studies had a similar severity of COPD as Mr. Miles. If the studies included only asymptomatic or minimally symptomatic patients, you would still be concerned about the possibility that β blockers could exacerbate COPD in patients with more severe disease.

Your second concern is whether or not patients in the studies had CHF in addition to COPD. You feel this is an important comorbidity that could potentially influence the degree of dyspnea symptoms. In addition, you wonder whether CHF could affect airway physiology and thus potentially affect FEV_1 measurements.

Finally, you want to know if the β blockers you are considering prescribing, metoprolol and carvediolol, were studied. Although different drugs in the same class may have similar therapeutic effects, you know there can also be individual differences between them (including differences in adverse effects), so evidence that the drug you are prescribing has been studied would be reassuring.

Determining Applicability of Results

A systematic review is not helpful if we cannot apply the study results to our patient. It is therefore important to assess whether there are any compelling reasons why the results of the review would not apply to the patient at hand. The goal is not to find excuses for dismissing the study results, but rather to assess whether there are legitimate reasons to be concerned about the applicability of the study results to an individual patient. Some general questions to ask when using systematic reviews (and other types of studies) to guide our clinical decision-making include:

- Were patients in the studies similar to the patient at hand in terms of sex, age, race, diseases, disease severity, and comorbidities?
- Is the intervention or service available to the patient, and, if so, how easy or difficult is it to access?
- Is the patient willing and able to comply with treatment?
- Is the patient willing and able to afford the costs of treatment?

Let's see whether we can apply the results of the systematic review to Mr. Miles.

Mr. Miles is 62 years old, which is similar in age to patients in the individual studies (median age 53.8 years, range 26 to 75 years). In addition to COPD, Mr. Miles has CHF. All patients in the studies that were included in the review had COPD. However, there is no mention that patients with heart failure were included, which could affect the applicability of the results to Mr. Miles. On the other hand, the investigators did note that many patients in the studies had heart disease and hypertension, and there was no mention that patients with CHF were excluded. In addition, information on COPD severity among study patients is provided, which reassures us that patients with a broad range of COPD severity were included. Finally, although carvedilol was not used in any of the studies, metoprolol was among the several different β blockers studied, none of which decreased FEV_1 or worsened pulmonary symptoms.

Although you are somewhat concerned that there is no explicit mention in the review that patients with heart failure were included in the studies, you are reassured by the fact that all patients in the studies had COPD. Your concern about potential adverse effects of β blockers on patients with COPD is why you hesitated prescribing one of these agents to Mr. Miles in the first place. You are disappointed that carvedilol was not used in any of the studies, because you know this β blocker was shown to reduce mortality in patients with CHF. In doing some further research, however, you find that in a head-to-head study, metoprolol and carvedilol improved symptoms, exercise tolerance, and quality of life to a similar degree in patients with CHF [14]. Armed with this information, you are now ready to share with Dr. Bertman the results of your educational prescription and to meet with Mr. Miles to present your findings.

At the follow-up visit with Mr. Miles, you do your best to explain in plain terms the findings of the review by Salpeter and colleagues [5]. You conclude that you are now comfortable prescribing a "cardioselective" type of β blocker to Mr. Miles for the purpose of helping to reduce his cardiovascular risk. Mr. Miles is reassured by the findings from the article and is agreeable to starting a β blocker. You have decided to prescribe metoprolol because it was one of the β blockers included in the review and also happens to cost less than carvedilol. Given the fact that Mr. Miles is on a limited fixed income and does not have prescription drug coverage, this is welcome news to him.

Conclusion

Table 4 summarizes the EBM approach as it applies to the decision whether to add a β blocker to Mr. Miles' heart failure regimen. This case illustrates the various resources that can be searched to locate systematic reviews. The Cochrane Library should be considered the first-line resource when questions of therapeutic or preventive measures arise, but it is somewhat limited in the scope of reviews that it contains. However, readers can be assured that Cochrane

Table 4. Summary of the Evidence-Based Medicine Approach to Deciding Whether to Add a β Blocker to Mr. Miles' CHF Treatment Regimen

Assess	Mr. Miles has CHF and COPD. From the perspective of optimal management of his CHF, Mr. Miles would benefit from the addition of a β blocker to his medication regimen. However, he is concerned about its potential adverse effects on his COPD.
Ask	In elderly patients with CHF and COPD, does the addition of β blockers to standard CHF therapy, compared with standard CHF therapy alone, lead to increased dyspnea or hospitalizations for COPD exacerbation?
Acquire	Cochrane Database of Systematic Reviews: 1 systematic review, updated in 2005, concluding that cardioselective β blockers do not produce adverse respiratory effects in patients with COPD.
Appraise	The systematic review meets the validity criteria. The search was comprehensive, and the investigators used appropriate meta-analytic techniques to minimize potential bias. The methodologic quality of the individual studies is somewhat limited. Two investigators independently extracted data from the studies with good inter-rater agreement. Long-term use of β blockers resulted in no significant reduction in FEV_1 or worsening of respiratory symptoms.
Apply	Study patients were similar in age to Mr. Miles, but it is unclear whether any of the study patients had CHF in addition to COPD, although some did have "heart disease." Therefore, a β blocker should provide benefits for Mr. Miles' CHF without worsening his COPD. As a result, you feel it is reasonable to prescribe a β blocker with clinical monitoring for positive and negative effects on important health outcomes.

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.

reviews are performed using high-quality standards and can be trusted to be methodologically sound. MEDLINE can also be searched for a broader array of systematic reviews via Ovid using validated search strategies (Table 1) or via PubMed using the Clinical Queries option. In our case example, we were able to locate the same systematic review using each of the resources outlined. Using criteria outlined in Table 3, we were able to determine that the review that was found was methodologically sound and able to answer our question.

From a practical perspective, some readers may not feel they have the knowledge, skills, or time to critically appraise a systematic review. In such cases, you can feel confident that Cochrane reviews are conducted using well-defined, commonly accepted, standardized methodology; therefore, you could consider skipping the critical appraisal step for Cochrane reviews. However, for most other reviews and as a general rule, being able to appraise the quality of a systematic review, like any other article, is a useful skill and one you should strive to acquire.

This case illustrates how to develop a clinical question, search for and appraise a systematic review, and apply the findings to an individual patient. Because systematic reviews combine and summarize the results of multiple studies, they are very useful for answering clinical questions and allow more efficient use of our limited time. Furthermore, systematic reviews can improve the generalizability of the results to a broader range of patients, providers, and settings than might be possible from a single study.

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How to cite this article:
Shaneyfelt T, Ortiz E. Applying evidence to the care of a patient with heart failure and COPD: how to find and use a systematic review. Semin Med Pract 2006;9:29–40. Available at www.turner-white.com.

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