FINDING THE EVIDENCE

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WAYS OF USING THE MEDICAL LITERATURE

This book is about using the medical literature. But not, as we describe in the following section, in the ways medical students most typically use it.

Background and Foreground Questions

There are several reasons that medical students, early in their training, seldom consult the original medical literature. First, they are not usually responsible for managing patients and solving specific patient problems. Even if they attend a school that uses problem-oriented learning as an educational strategy, their interest is primarily in understanding normal human physiology and the pathophysiology associated with a patient’s condition or problem. Once they have grasped these basic concepts, they will turn to the prognosis, available diagnostic tests, and possible management options. Finally, when students are presented with a patient-related problem, their questions are likely to include, for example, what is diabetes, why did this patient present with polyuria, and how might we manage the problem.

By contrast, experienced clinicians responsible for managing a patient’s problem ask very different sorts of questions. They are interested less in the diagnostic approach to a presenting problem and are more interested in how to interpret a specific diagnostic test; less in the general prognosis of a chronic disease and more in a particular patient’s prognosis; less in the management strategies that might be applied to a patient’s problems and more in the risks and benefits of a particular treatment in relation to an alternative management strategy.

Think of the first set of questions, those of the medical student, as background questions; think of the second set as foreground questions. In most situations, you need to understand the background thoroughly before it makes sense to address issues in the foreground.

On her first day on the ward, a medical student will still have a great deal of background knowledge to acquire. However, in deciding how to manage the first patient she sees, she may well need to address a foreground issue. A senior clinician, while well versed in all issues that represent the background of her clinical practice, may nevertheless also occasionally require background information. This is most likely when a new condition or medical syndrome appears (consider the fact that as recently as 20 years ago, experienced clinicians were asking, “What is the acquired immunodeficiency syndrome?”) or when a new diagnostic test (“How does PCR work?”) or treatment modality (“What are COX-2 inhibitors?”) is introduced into the clinical arena. At every stage of training and experience, clinicians’ grasp of the relevant background issues of disease inform their ability to identify and formulate the most pertinent foreground questions for an individual patient.

Figure 1A-1 represents the evolution of the questions we ask as we progress from being novices (who pose almost exclusively background questions) to being experts (who pose almost exclusively foreground questions). This book is devoted to how clinicians can use the medical literature to solve their foreground questions.
Browsing and Problem Solving

Traditionally, clinicians subscribed to a number—sometimes a large number—of target medical journals in which articles relevant to their practice were likely to appear. They would keep up to date by skimming the table of contents and reading articles relevant to their practice. One might label this the browsing mode of using the medical literature.

Traditional approaches to browsing have major limitations of inefficiency and resulting frustration. Picture a clinician with a number of subscriptions placing journals in a pile on her desk awaiting browsing review. She may even be aware that less than 10% of articles that are published in the core medical journals are both high quality and clinically useful. Unable to spend sufficient time to browse, she finds the pile growing until it becomes intimidating. At this point, she tosses the whole pile and starts the process again.

Although it is somewhat of a parody, most experienced clinicians can relate easily to this scenario. Physicians at every stage of training often feel overwhelmed by the magnitude of the medical literature. Evidence-based medicine offers some solutions to this problem.

Browse Secondary Journals. Perhaps the most efficient strategy is to restrict your browsing to secondary journals. For internal and general medicine, ACP Journal Club (www.acponline.org/journals/acpjc/jcmenu.htm) publishes synopses of articles that meet criteria of both clinical relevance and methodologic quality. We describe such secondary journals in more detail later in this section.
Many specialties and subspecialties do not yet have devoted secondary journals. This is likely to be a temporary phenomenon, at least for the major specialties. In the meantime, you can apply your own relevance and methodologic screen to articles in your target journals. Most clinical publications serve a dual purpose: as a forum for both investigator-to-investigator communication and investigator-to-clinician communication. However, only the latter articles will be directly relevant to your practice. Part 1 of this book is devoted to providing the tools that will allow you to screen journals for high-quality, relevant evidence. When you have learned the skills, you will be surprised both at the small proportion of studies to which you need to attend—and at the efficiency with which you can identify them.

Operate in a Problem-Solving Mode. Another part of the solution to the overwhelming-amount-of-literature problem is for clinicians to spend more of the time they have available for consulting the literature in what we call a problem-solving mode. Here, questions raised in caring for patients are defined and then the literature is consulted to resolve these questions. Whether you are operating in the browsing mode or problem-solving mode, this book can help you to judge the validity of the information in the articles you are examining, gain a clear understanding of their results, and apply them to patients.

The remainder of this section focuses on skills you will need to use the literature effectively when you are in the problem-solving mode.

Framing the Question

Clinical questions often spring to practitioners’ minds in a form that makes finding answers in the medical literature a challenge. Dissecting the question into its component parts to facilitate finding the best evidence is a fundamental EBM skill. Most questions can be divided into three parts.

1. **The population.** Who are the relevant patients?

2. **The interventions or exposures** (diagnostic tests, foods, drugs, surgical procedures, etc). What are the management strategies we are interested in comparing, or the potentially harmful exposure about which we are concerned? For issues of therapy or harm, there will always be two or more parts to this: the intervention or exposure and a control or alternative intervention(s) or exposure(s).

3. **The outcome.** What are the patient-relevant consequences of the exposure in which we are interested?

We will now provide examples of the transformation of unstructured clinical questions into the structured questions that facilitate use of the medical literature.
Example 1: Diabetes and Target Blood Pressure

A 55-year-old white woman presents with type 2 diabetes mellitus and hypertension. Her glycemic control is excellent on metformin and she has no history of complications. To manage her hypertension, she takes a small daily dose of a thiazide diuretic. Over a 6-month period, her blood pressure hovers around a value of 155/88 mm Hg.

Initial Question: When treating hypertension, at what target blood pressure should we aim?

Digging Deeper: One limitation of this formulation of the question is that it fails to specify the population in adequate detail. The benefits of tight control of blood pressure may differ in diabetic patients vs nondiabetic patients, in type 1 vs type 2 diabetes mellitus, as well as in those with and without diabetic complications. We may wish to specify that we are interested in the addition of a specific antihypertensive agent. Alternatively, the intervention of interest may be any antihypertensive treatment. Furthermore, a key part of the intervention will be the target for blood pressure control. For instance, we might be interested in knowing whether it makes any difference if our target diastolic blood pressure is < 80 mm Hg vs < 90 mm Hg. The major limitation of the initial question formulation is that it fails to specify the criteria by which we will judge the appropriate target for our hypertensive treatment. The target outcomes of interest would include stroke, myocardial infarction, cardiovascular death, and total mortality.

Improved (Searchable) Question: A searchable question would specify the relevant patient population, the management strategy and exposure, and the patient-relevant consequences of that exposure as follows:

- Patients: Hypertensive type 2 diabetic patients without diabetic complications
- Intervention: Any antihypertensive agent aiming at a target diastolic blood pressure of 90 mm Hg vs a target of 80 mm Hg
- Outcomes: Stroke, myocardial infarction, cardiovascular death, total mortality

Example 2: Suspected Unstable Angina

A 39-year-old man without previous chest discomfort presented to the emergency department at the end of his working day. Early that day he had felt unwell and nauseated; he had had a vague sensation of chest discomfort and had begun to sweat profusely. The unpleasant experience lasted for about 2 hours, after which the patient felt tired but otherwise normal. At the end of his work day, feeling rather nervous about the episode, he came to the emergency department. The patient has no family history of coronary artery disease. He has had hypertension for 5 years that is controlled with a thiazide, has a 15-pack-year smoking history,
and has a normal lipid profile. His physical examination, electrocardiogram (ECG), creatine kinase level, and troponin I level are all normal.

Initial Question: Can I send this man home or should I admit him to a monitored hospital bed?

Digging Deeper: The initial question gives us little idea of where to look in the literature for an answer. We can break down the issue by noting that the patient has suspected unstable angina. However, a number of distinguishing features differentiate him from other patients with possible unstable angina. He is relatively young, he has some risk factors for coronary artery disease, his presentation is atypical, he is now pain free, there is no sign of heart failure, and his ECG and cardiac enzymes are unremarkable.

The management strategies we are considering include admitting him to a hospital for overnight monitoring or sending him home with the appropriate follow-up, including an exercise test. Another way of thinking about the issue, however, is that we need to know the consequences of sending him home. Would discharge be a safe course of action, with an acceptably low likelihood of adverse events? Thinking of our question that way, the exposure of interest is time. Time is usually the exposure of interest in studies about patients' prognosis.

What would be our objective in admitting the patient to a coronary care unit? By doing this, we will not be able to prevent more distant events (such as a myocardial infarction a month later). We are interested primarily in events that might occur during the next 72 hours, the maximum time the patient is likely to be monitored in the absence of complications. What adverse events might we prevent if the patient is in a hospital bed with cardiac monitoring? Should he develop severe chest pain, cardiac failure, or myocardial infarction, we would be able to treat him immediately. Most important, should he develop ventricular fibrillation or another life-threatening arrhythmia we would be able to administer cardioversion and save his life.

Improved (Searchable) Question: A searchable question would specify the relevant patient population, the management strategy and exposure, and the patient-relevant consequences of that exposure as follows:

- Patients: Young men with atypical symptoms and normal ECG and cardiac enzymes presenting with possible unstable angina
- Intervention/Exposure: Either admission to a monitored bed vs discharge home, or time
- Outcomes: Severe angina, myocardial infarction, heart failure, or arrhythmia, all within the next 72 hours
Example 3: Squamous Cell Carcinoma

A 60-year-old, 40-pack-year smoker presents with hemoptysis. A chest radiograph shows a parenchymal mass with a normal mediastinum, and a fine needle aspiration of the mass shows squamous cell carcinoma. Aside from the hemoptysis, the patient is asymptomatic and physical examination is entirely normal.

Initial Question: What investigations should we undertake before deciding whether to offer this patient surgery?

Digging Deeper: The key defining features of this patient are his non-small-cell carcinoma and the fact that his history, physical examination, and chest radiograph show no evidence of intrathoracic or extrathoracic metastatic disease. Alternative investigational strategies address two separate issues: Does the patient have occult mediastinal disease, and does he have occult extrathoracic metastatic disease? For this discussion, we will focus on the former issue. Investigational strategies for addressing the possibility of occult mediastinal disease include undertaking a mediastinoscopy or performing a computed tomographic (CT) scan of the chest and proceeding according to the results of this investigation.

What outcomes are we trying to influence in our choice of investigational approach? We would like to prolong the patient’s life, but the extent of his underlying tumor is likely to be the major determinant of survival and our investigations cannot change that. The reason we wish to detect occult mediastinal metastases if they are present is that if the cancer has spread to the mediastinum, resectional surgery is very unlikely to benefit the patient. Thus, in the presence of mediastinal disease, patients will usually receive palliative approaches and avoid an unnecessary thoracotomy. Thus, the primary outcome of interest is an unnecessary thoracotomy.

Improved (Searchable) Question: A searchable question would specify the relevant patient population, the management strategy and exposure, and the patient-relevant consequences of that exposure as follows:

- Patients: Newly diagnosed non-small-cell lung cancer with no evidence of extrapulmonary metastases
- Intervention: Mediastinoscopy for all or chest CT-directed management
- Outcome: Unnecessary thoracotomy

Another way of structuring this question is as an examination of the test properties of the chest CT scan. Looking at the problem this way, the patient population is the same, but the exposure is the CT scan and the outcome is the presence or absence of the target condition, mediastinal metastatic disease. As we will subsequently discuss (see Part 1C2, “Diagnostic Tests”), this latter way of structuring the question is less likely to provide strong guidance about optimal management.

These examples illustrate that constructing a searchable question that allows you to use the medical literature to generate an answer is often no simple matter.
It requires an in-depth understanding of the clinical issues involved in patient management. The three examples above illustrate that each patient may trigger a large number of clinical questions, and that clinicians must give careful thought to what they really want to know. Bearing the structure of the question in mind—patient, intervention or exposure, and outcome—is extremely helpful in arriving at an answerable question.

Once the question is posed, the next step in the process is translating the question into an effective search strategy. By first looking at the components of the question, putting the search strategy together is easier.

SEARCHING FOR THE ANSWER

In this section, we will introduce you to the electronic resources available for quickly finding the answers to your clinical questions. We will demonstrate how the careful definition of the question, including specification of the population, the intervention, and the outcome, can help you develop a workable search strategy. However, you must also consider a fourth component. What sort of study do you hope to find? By sort of study, we mean the way the study is organized or constructed—the study design.

Determining Question Type

To fully understand issues of study design, we suggest that you read the entire Part 1 of this book. Following is a brief introduction.

There are four fundamental types of clinical questions. They involve:

- **Therapy**: determining the effect of different treatments on improving patient function or avoiding adverse events
- **Harm**: ascertaining the effects of potentially harmful agents (including the very therapies we would be interested in examining in the first type of question) on patient function, morbidity, and mortality
- **Diagnosis**: establishing the power of an intervention to differentiate between those with and without a target condition or disease
- **Prognosis**: estimating the future course of a patient’s disease

To answer questions about a therapeutic issue, we identify studies in which a process analogous to flipping a coin determines participants’ receipt of an experimental treatment or a control or standard treatment, the so-called randomized controlled trial or RCT (see Part 1B1, “Therapy”). Once the investigator allocates participants to treatment or control groups, he or she follows them forward in time looking for whether they have, for instance, a stroke or heart attack—what we call the outcome of interest (Figure 1A-2).
Ideally, we would also look to randomized trials to address issues of harm. However, for many potentially harmful exposures, randomly allocating patients is neither practical nor ethical. For instance, one could not suggest to potential study participants that an investigator will decide by the flip of a coin whether or not they smoke during the next 20 years or whether they will be exposed to potentially harmful ionizing radiation. For exposures like smoking and radiation, the best one can do is identify studies in which personal choice, or happenstance, determines whether people are exposed or not exposed. These observational studies provide weaker evidence than randomized trials.

Figure 1A-3 depicts a common observational study design in which patients with and without the exposure of interest are followed forward in time to determine whether they experience the outcome of interest. For smoking or radiation exposure, one important outcome would likely be the development of cancer.

For establishing how well a diagnostic test works (what we call its properties or operating characteristics) we need yet another study design. In diagnostic test studies, investigators identify a group of patients who may or may not have the
disease or condition of interest (such as tuberculosis, lung cancer, or iron-deficiency anemia), which we will call the target condition. Investigators begin by collecting a group of patients whom they suspect may have the target condition. These patients undergo both the new diagnostic test and a gold standard (that is, the test considered to be the diagnostic standard for a particular disease of condition; synonyms include criterion standard, diagnostic standard, or reference standard). Investigators evaluate the diagnostic test by comparing its classification of patients with that of the gold standard (Figure 1A-4).

**FIGURE 1A-4**

**Study Design to Assess a Diagnostic Test**

A final type of study examines patients' prognosis and may identify factors that modify that prognosis. Here, investigators identify patients who belong to a particular group (such as pregnant women, patients undergoing surgery, or patients with cancer) with or without factors that may modify their prognosis (such as age or comorbidity). The exposure here is time, and investigators follow patients to determine if they experience the target outcome, such as a problem birth at the end of a pregnancy, a myocardial infarction after surgery, or survival in cancer (Figure 1A-5).

**FIGURE 1A-5**

**Observational Study Assessing Prognosis**
One of the clinician's tasks in searching the medical literature is to correctly identify the category of study that will address her question. For example, if you look for a randomized trial to inform you of the properties of a diagnostic test (as opposed to whether patients benefit from its application), you are unlikely to find the answer you seek.

Think back to the questions we identified in the previous section. Determining the best strategy for managing hypertension is clearly a treatment issue. However, we may also be interested in rare and delayed adverse effects of the medications we use to lower blood pressure, which is an issue of harm.

Considering the second scenario we presented, we can formulate the question in two ways. If we ask, How likely is myocardial infarction or death among young men with symptoms suggestive but atypical of unstable angina? the issue is one of prognosis. If we ask, What is the impact of alternative management strategies, such as admission to a coronary care unit or discharge? we are interested in treatment and would look for a randomized trial that allocated patients to the alternative approaches.

We can also formulate the question from the third scenario in two ways. If we ask, How well does CT scanning of the chest distinguish between non-small-cell lung cancer patients with and without mediastinal metastases? we would look for a study design that can gauge the power of a diagnostic test (see Figure 1A-4). We might also ask, “What is the rate of unnecessary thoracotomy in non-small-cell lung cancer patients who go straight to mediastinoscopy vs those who have CT scan-directed management?” For this treatment issue, we will seek a randomized trial (see Figure 1A-2).

Is Searching the Medical Literature Worthwhile?
Because our time for searching is limited, we would like to ensure that there is a good chance that our search will be productive. Consider the following clinical questions:

Example: In patients with pulmonary embolism, to what extent do those with pulmonary infarction have a poorer outcome than those without pulmonary infarction?

Before formulating our search strategy and beginning our literature search to answer this question, we should think about how investigators would differentiate between those with and without infarction. Since there is no reliable way, short of autopsy, of making this differentiation, our literature search is doomed before we even begin.

Example: Consider also a 50-year-old woman who has suffered an uncomplicated myocardial infarction 4 days previously and who asks, before discharge home, when she can resume sexual intercourse.
Were we to formulate a question that would allow us to address her inquiry, its components would look something like this:

- Patients: Women after uncomplicated myocardial infarction
- Intervention: Advice to resume intercourse as soon as so inclined vs waiting, say, 8 weeks
- Outcomes: Recurrent infarction, unstable angina, cardiovascular and total mortality, health-related quality of life
- Type of question: Therapy, therefore we would look for a randomized trial.

How likely is it that investigators have conducted a randomized trial of this question? Highly improbable. It is slightly less implausible that investigators have conducted an observational study of timing of return to sexual intercourse (here, patients would report when they had returned to sexual intercourse and investigators would compare outcomes in those who had started early vs those who had waited until later).

These two examples illustrate situations in which you will not want to use the medical literature to solve your patient management problems. The medical literature will not help you when there is no feasible study design that investigators could use to resolve the issue. Your search will also be fruitless if there is a feasible design, but it is very unlikely that anyone has taken the time and effort to carry out the necessary study. Before embarking on a search, carefully consider whether the yield is likely to be worth the time expenditure.

**Sources of Evidence**

You can look to local specialists, subspecialists, and more experienced clinical colleagues not only for opinion, but also for evidence to address your clinical problem (see Part 1A, “The Philosophy of Evidence-Based Medicine”). Their experience and advice are particularly crucial when the medical literature is unlikely to be helpful. Furthermore, experts who stay current on the latest evidence in their field may be able to quickly provide you with the most relevant citations.

Clinicians will not need this book to advise them to consult respected colleagues—they do not neglect this source of data. Where clinicians might need help is in the use of online resources. We focus on online rather than print products because they are generally easier to search and more current than print products (Table 1A-3). With the relatively recent appearance of many of the resources we recommend, however, little research specifically addresses their relative merits. The approaches we describe reflect our own experiences and those of our colleagues working individually or with medical trainees.
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* Costs as of 2000
Selecting the Best Medical Information Resource

What is the optimal medical information resource? To a large extent, it depends on the type of question that you have and the time you have available. During the late 1980s, observational studies suggested that clinicians could identify one to two unanswered questions per patient in an outpatient setting and up to five per patient in a hospital setting. More recent studies in family practice in the United Kingdom and the United States have found the rate of questions arising in patient care to be 0.32 question per patient.

Be sure to match your question to the source of information that could likely provide the most appropriate answer. To take extreme examples, MEDLINE is not the best source of information on gross anatomy, and the hospital information system is the best place to provide laboratory data for a specific patient. Table 1A-4 summarizes the types of questions that clinicians ask, along with the optimal study designs, online sources of data, and MEDLINE searching terms to match the methodologic type.

### TABLE 1A-4

<table>
<thead>
<tr>
<th>Question Type</th>
<th>Population</th>
<th>Intervention/Exposure</th>
<th>Outcome</th>
<th>Best Feasible Study Designs</th>
<th>Suitable Databases</th>
<th>Best Single MEDLINE Search Term for Appropriate Study Type</th>
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<td>In patients with lung cancer</td>
<td>What is the test performance of CT scan</td>
<td>For detecting mediastinal metastatic disease</td>
<td>Cross-sectional analytic study</td>
<td>Best Evidence, UpToDate, MEDLINE</td>
<td>Sensitivity.tw</td>
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<td>Harm</td>
<td>In men</td>
<td>Does vasectomy</td>
<td>Cause testicular cancer</td>
<td>Cohort study, population-based case-control study</td>
<td>Best Evidence, UpToDate, MEDLINE</td>
<td>Risk.tw</td>
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<tr>
<td>Prognosis</td>
<td>In young men with atypical chest pain</td>
<td>Sent home from the emergency department, in the next 72 hours</td>
<td>Suffer appreciable rates of unstable angina, heart failure, arrhythmia, myocardial infarction, or sudden death</td>
<td>Cohort study</td>
<td>Best Evidence, UpToDate, MEDLINE</td>
<td>Explode cohort studies</td>
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<td>Treatment</td>
<td>In patients with hypertension and type 2 diabetes mellitus</td>
<td>Does a target DBP of 80 compared with DBP of 90 mm Hg</td>
<td>Lower risk of stroke, MI, cardiovascular death, and all-cause mortality</td>
<td>RCT or systematic review of RCTs</td>
<td>Cochrane Library, Best Evidence, UpToDate, MEDLINE</td>
<td>Meta-analysis.pt (for systematic reviews) or Clinical trial.pt (for RCTs)</td>
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CT indicates computed tomographic; DBP, diastolic blood pressure; MI, myocardial infarction; RCT, randomized controlled trial.
To answer focused foreground clinical questions, the most efficient approach is to begin with a prefiltered evidence-based medicine resource such as Best Evidence, the Cochrane Library, or Clinical Evidence (see Table 1A-3). By prefiltered, we mean that someone has reviewed the literature and chosen only the methodologically strongest studies. The authors of these products have designed them in such a way as to make searching easy. The sources are updated regularly—from months to a couple of years—with methodologically sound and clinically important studies.

**Textbooks.** To find answers to general background medical questions, prefiltered evidence-based medicine resources are unlikely to be helpful. Referring to a textbook that is well referenced and updated frequently is likely to be faster and more rewarding. UpToDate and Scientific American Medicine are updated regularly—from months to years, depending on the rapidity with which important new evidence is accumulating; they are heavily referenced so that you can assess how current the material is and you can even read the original articles. Other textbooks available in electronic formats, such as Harrison's Principles of Internal Medicine, can also provide valuable general background information. Additionally, new textbooks that are entirely Internet based, such as emedicine, are now available. As texts become more evidence based and routinely are updated as new evidence is published, they will provide an increasingly important source of answers to foreground as well as background questions. Our own experience suggests that UpToDate and Clinical Evidence are already well along the path to becoming evidence-based sources to answer foreground questions.

**MEDLINE.** MEDLINE, the bibliographic database maintained by the US National Library of Medicine, is useful primarily to answer focused foreground questions. The size and complexity of this database, however, make searching somewhat more difficult and time consuming. As a result, we recommend using MEDLINE only when searching prefiltered sources has proved fruitless (or when prior knowledge suggests, before beginning the search, that prefiltered sources will prove barren).

We will now review the databases suitable for answering a specific clinical question, illustrating their use with the example of the optimal blood pressure target level in patients with diabetes.

**Using Prefiltered Medical Information Resources**

A good starting point in the evidence-seeking process is to look for a systematic review article on your topic. A systematic review addresses a targeted clinical question using strategies that decrease the likelihood of bias. The authors of a rigorous systematic review will have already done the work of accumulating and summarizing the best of the published (and ideally unpublished) evidence. You will find both Best Evidence and the Cochrane Library useful for finding high-quality systematic reviews quickly and effectively. Both are also good sources to consult for original studies.
Best Evidence

Best Evidence is one of the quickest available routes to systematic reviews and original studies that address focused clinical questions. Available in CD-ROM format or on the Internet through OVID Technology's Evidence-Based Medicine Reviews, Best Evidence is the cumulative electronic version of two paper-based secondary journals: ACP Journal Club and Evidence-Based Medicine. (These journals were combined into one journal, ACP Journal Club, in North, South, and Central America in January 2000. Evidence-Based Medicine is available only outside the United States.) The editorial team for these journals systematically searches 170 medical journals on a regular basis to identify original studies and systematic reviews that are both methodologically sound and clinically relevant, especially for the more common diseases and conditions. By methodologically sound, we mean that they meet validity criteria (see Part 1B1, “Therapy”; Part 1B2, “Harm”; Part 1C, “The Process of Diagnosis”; Part 1C1, “Differential Diagnosis”; Part 1C2, “Diagnostic Tests”; and Part 1D, “Prognosis”). For example, the treatment section includes only randomized trials with 80% follow-up, and the diagnosis section includes only studies that make an independent, blind comparison of a test with a gold standard.

ACP Journal Club and Evidence-Based Medicine present structured abstracts of studies that meet these criteria, along with an accompanying commentary by an expert who offers a clinical perspective on the study results. In a section of Best Evidence entitled “Other Articles Noted,” clinicians can find other studies that meet methodologic criteria but have been judged less relevant. Best Evidence is updated annually and now includes over 2000 abstracted articles that relate to general internal medicine, dating back to 1991. The editors review each article every 5 years to make sure that it has not become dated in view of more recent evidence. In addition to general internal medicine, Best Evidence includes a broader range of articles since 1995 that encompass obstetrics and gynecology, family medicine, pediatrics, psychiatry, and surgery.

Because Best Evidence includes only articles that reviewers have decided meet basic standards of methodologic quality, it is substantially smaller than many other medical literature databases, and thus is easier to search. The downside of this small size is that it is not comprehensive; a search restricted to Best Evidence will not be complete and will put you at risk for receiving a biased selection of articles. However, we believe that the uniformly relatively high methodologic quality of the articles, and the very quick searches that Best Evidence allows, compensate for this limitation.

Example of Best Evidence Search. To locate information on blood pressure control in people with type 2 diabetes mellitus, we used the “Search” option in Best Evidence 4 (Figure 1A-6). We entered the phrase representing the question aspects, “hypertension AND diabetes AND mortality” resulting in a list of 109 articles. Many of these citations, however, dealt with the prognosis of patients with diabetes and were not directly relevant to our question.
Therefore, we returned to the search option, entered the same terms but changed the search strategy from “All topics” to “Selected topics,” and clicked on the “Therapeutics” option before completing the search. This yielded a shorter list of 27 articles, all pertaining to therapy (Figure 1A-7). Five were review articles but none of these addressed our topic. Of the 22 original studies, the first was entitled “Tight Blood Pressure Control Reduced Diabetes Mellitus-Related Death and Complications and Was Cost-effective in Diabetes” (Figure 1A-8). Double-clicking on this title produced a structured abstract describing a randomized trial that enrolled persons with type 2 diabetes mellitus and hypertension and evaluated the effect of aiming for either a blood pressure of less than 150/85 mm Hg or a blood pressure of less than 180/105 mm Hg (Figure 1A-9). After an average of 9 years of follow-up, the tight blood pressure control arm had a 32% reduction in the risk of death related to diabetes (95% confidence interval, 8%-50%; P = .019) (Figure 1A-10).

FIGURE 1A–6
Best Evidence—Title Page (CD-ROM version)
FIGURE 1A–7

Best Evidence—Selected Topic Search

Reproduced with permission from the American College of Physicians-Society of Internal Medicine.

FIGURE 1A–8

Best Evidence—Search Result

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FIGURE 1A-9

Best Evidence—Abstract

Main outcomes were a first diabetes-related morbidity or fatal prediabetic clinical and point, death related to diabetes, and all-cause mortality. Secondary outcomes were myocardial infarction, stroke, amputation or death from peripheral vascular disease, and microvascular disease.

Main results

Analysis was by intention to treat. Patients allocated to tight control had lower mean blood pressure over 6 years of follow-up than those allocated to less tight control (144/82 vs 154/87 mm Hg, P < 0.001). During follow-up, patients allocated to tight control had reduced risks for developing a diabetes-related clinical endpoint (P = 0.045), diabetes-related death (P = 0.039), stroke (P = 0.013), and microvascular disease (P = 0.006) than patients allocated to less tight control (Table). No differences existed for all-cause mortality, myocardial infarction, and amputations or deaths from peripheral vascular disease (Table).

Based on the use of resources associated with the trial protocol, over the median follow-up period tight control increased the total cost of treatment by $740/patient compared with less tight control but reduced the total cost of complications by $840/patient (a net savings of $720/patient, and discounted values). By the simulation model, tight control increased the withdrawal years free from and points by 0.23 years discounted at 6%/yr but did not increase life expectancy. Based on estimates of the cost of resources in standard clinical practice, the incremental cost per extra year free from and points was $1045 (costs and health effects discounted at 6%/yr) and $638 (costs discounted at 6% per year, and health effects not discounted), and the incremental cost per life-year gained was $720 (costs and health effects discounted at 6%/yr) and $291 (costs discounted at 6%/yr and health effects not discounted).

Conclusions

In hypertensive patients with type 2 diabetes mellitus, tight control of blood pressure target blood pressure <150/85 mm Hg using rosiglitazone or carvedilol reduced the risk for diabetes-related complications or death, stroke, and microvascular disease. Tight control was cost-effective, had favorable cost-effectiveness ratios, and reduced the cost of complications.

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FIGURE 1A-10

Best Evidence—Results Table

<table>
<thead>
<tr>
<th>Outcomes over 6.3 y of follow-up</th>
<th>Tight control</th>
<th>Less tight control</th>
<th>RRR (95% CI)</th>
<th>NNT (CD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes-related clinical endpoint</td>
<td>24%</td>
<td>44%</td>
<td>23% (8% to 32)</td>
<td>11 (6 to 25)</td>
</tr>
<tr>
<td>Diabetes-related death</td>
<td>11%</td>
<td>16%</td>
<td>36% (8% to 50)</td>
<td>20 (10 to 100)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>16%</td>
<td>21%</td>
<td>47% (8% to 75)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>14%</td>
<td>18%</td>
<td>24% (5% to 48)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Stroke</td>
<td>5%</td>
<td>9%</td>
<td>42% (16% to 67)</td>
<td>27 (9 to 81)</td>
</tr>
<tr>
<td>Peripheral vascular stroke</td>
<td>1%</td>
<td>2%</td>
<td>30% (10% to 50)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>9%</td>
<td>14%</td>
<td>26% (8% to 54)</td>
<td>21 (11 to 34)</td>
</tr>
</tbody>
</table>

*Abbreviations defined in Glossary, RRR, NNT, and CI calculated from data in article.

Commentary

The UKPDS shows that meticulous blood pressure reduction is important in patients with type 2 diabetes. This finding has major implications for health care because of the projected dramatic increase in diabetes in the future and the clear relation between diabetes and hypertension. The Systolic Hypertension in the Elderly Program (SHEP) has shown that antihypertensive treatment reduces cardiovascular events in elderly patients with and without diabetes (1). The present trial corroborates this information and extends the findings to younger patients and to patients with newly diagnosed diabetes. The results are consistent with the recently published Hypertension Optimal Treatment (HOT) study, in which intensive blood
Searching Best Evidence will not always provide an article that answers your question. High-quality evidence is not available or may not have been published in one of the 170 Best Evidence target journals. A relevant trial may have been published after the most recent edition of Best Evidence was released, or before 1991. Rigorous studies published since 1991 will not appear in Best Evidence if the editors believe that they pertain more to subspecialty care than to general internal medicine. Despite these limitations, searching Best Evidence will often be rewarding, especially if you are searching for one of the more common diseases and conditions. And if your search is not rewarding, Best Evidence searches occur so quickly that you will have plenty of time to look elsewhere.

Cochrane Library
The Cochrane Collaboration, an international organization that prepares, maintains, and disseminates systematic reviews of health care interventions, offers another electronic resource for locating high-quality information quickly. They publish the Cochrane Library, which focuses primarily on systematic reviews of controlled trials of therapeutic interventions. It provides little help in addressing other aspects of medical care, such as the value of a new diagnostic test or a patient’s prognosis.

Updated quarterly, the Cochrane Library is available in CD-ROM format or over the Internet. It contains three main sections. The first of these, the Cochrane Database of Systematic Reviews (CDSR), includes the complete reports for all of the systematic reviews that have been prepared by members of the Cochrane Collaboration (716 were in the first issue for 2000) and the protocols for Cochrane systematic reviews that are under way. A second part of the Cochrane Library, the Database of Reviews of Effectiveness (DARE), includes systematic reviews that have been published outside of the collaboration; the first issue for 2000 included 2565 such reviews. Database of Reviews of Effectiveness is searchable outside the Cochrane Library (at http://nhscrd.york.ac.uk); this site also includes access to a database of economic evaluations and health technology assessments.

The third section of the Library, the Cochrane Controlled Trials Registry (CCTR), contains a growing list of over 268,000 references to clinical trials that Cochrane investigators have found by searching a wide range of sources. The sources include the MEDLINE and EMBASE (Excerpta Medica) bibliographic databases, hand searches, and the reference lists of potentially relevant original studies and reviews. Although most citations refer to randomized trials, the database also includes a small number of observational studies. Studies of diagnostic tests will likely be included soon. In addition to the three main sections, the Cochrane Library also includes information about the Cochrane Collaboration and information on how to conduct a systematic review and related methodologic issues.

To search the Cochrane Library, you can enter terms in the first screen that appears after selecting “Search” (Figure 1A-11). If you have access to the CD-ROM version, using the Advanced Search option you can create more complex search strategies that include Medical Subject Headings and logical operators (see the
Example of Cochrane Library Search. To find information about blood pressure control in people with diabetes, we entered the search terms

“diabetes AND hypertension AND mortality”

using the 2000 version of the Cochrane Library (Issue 1) (Figure 1A-12). This yielded 36 reports in the CDSR, six citations in the DARE, and 130 citations in the CCTR (Figure 1A-13). A Cochrane review entitled “Antihypertensive therapy in diabetes mellitus” appeared promising (Figure 1A-14). Double-clicking on this item, we found an entire Cochrane Collaboration systematic review, including information on the methodology for the review, the inclusion and exclusion criteria, the results, and a discussion (Figure 1A-15). The results presented the findings in both textual and graphical forms. As was the case with the review article found in Best Evidence, however, this review did not help to resolve the issue of the optimal blood pressure goal for people with diabetes mellitus.
FIGURE 1A–12
The Cochrane Database of Systematic Reviews—Search Strategy

Instructions
Enter the term you are looking for in the window above, combining words with the Boolean AND, OR, or NOT operators. Use the keyword NEAR to search for words near each other, or enclose phrases in quotes to search for words next to each other.

Click the "Search" button above, or press RETURN to have the number of hits your search returned displayed in the index window, then double-click the database that contains the hits you want to see. The number of hits is printed in red after each database entry, together with the total number of items in that database.

Click New Items or Updated Items (below) to find items new or updated in this issue.

For more sophisticated search options, choose "Advanced Search" from this page.

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FIGURE 1A–13
The Cochrane Database of Systematic Reviews—Search Results

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**FIGURE 1A-14**

The Cochrane Database of Systematic Reviews—Article

![Diagram of Cochrane Library 2000 Issue 1](image1)

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**FIGURE 1A-15**

The Cochrane Database of Systematic Reviews—Review Article

![Diagram of Cochrane Library 2000 Issue 1](image2)

**Antihypertensive therapy in diabetes mellitus**


A substantial amendment to this systematic review was last made on 28 August 1997. Cochrane reviews are regularly checked and updated as necessary.

**Objectives:** To assess the effects of interventions, both pharmacological and non-pharmacological, to reduce blood pressure in people with diabetes mellitus on all-cause mortality, specific causes of death, including cardiovascular disease, stroke, ischemic heart disease, and renal disease, and their complications associated with micro- and macrovascular complications of diabetes mellitus and also side effects of the interventions and their influence on quality of life and wellbeing.

**Search strategy:** The search strategy included a search of the Cochrane Library database, MEDLINE, EMBASE, and other electronic databases such as AMED and CRD, and also searching specialist journals in the fields of cardiovascular disease, stroke, hypertension and renal disease.

**Selection criteria:** All trials were considered independently and then discussed by the reviewers to determine ineligibility for inclusion in the review. Methodological quality was assessed from details of the randomization methods, blinding, and whether the intention-to-treat method of analysis was used. Trials included in the review were all randomized controlled trials of the treatment for antihypertensive therapy for the specified indications which included subjects with diabetes mellitus.

**Data collection and analysis:** Data was sought on the number of patients with diabetes mellitus with each outcome measure by allocated treatment group. Data from previous publications or trials not possible, the raw data was obtained and analyzed using the intention to treat methodology. If these data were not available, the results from the published trials were used. To ensure the treatment effect of the intervention, with that of duration...
Turning to the CCTR (we double-clicked on the CCTR option to make the citation titles appear), we found both the United Kingdom Prospective Diabetes Study Group (UKPDS)10 and the Hypertension Optimal Treatment (HOT) trial12 within the first 26 citations. The HOT trial was a randomized trial that compared three different blood pressure management strategies in persons with hypertension. Subgroup analyses showed that patients with diabetes who reduced their blood pressure to 81.1 mm Hg vs 85.2 mm Hg because of being in the groups randomized to lower target blood pressures had lower rates of cardiovascular events and cardiovascular death.

A second search further illustrates the usefulness of the CCTR database. Recall the patient with non-small-cell lung cancer for whom we were considering alternative investigational strategies of mediastinoscopy for all, or a selective approach based on the results of CT scanning. Using the search term “mediastinoscopy,” we found that the clinical trials database yielded 20 citations, of which the fourth and fifth were MEDLINE and EMBASE records of a study a randomized trial in 685 patients with apparently operable non-small-cell carcinoma of the lung. The investigators randomized patients to an arm in which all patients underwent mediastinoscopy or an arm in which all patients underwent CT scanning, with patients with small nodes going straight to thoracotomy and those with larger nodes undergoing mediastinoscopy. The relative risk of an unnecessary thoracotomy in patients in the CT scanning arm was 0.88 (95% confidence interval, 0.71-1.10). The mediastinoscopy strategy cost $708 more per patient (95% confidence interval, $723-$2140). The authors concluded that “the computed tomography strategy is likely to produce the same number of or fewer unnecessary thoracotomies in comparison with doing mediastinoscopy on all patients and is also likely to be as or less expensive.”13

UpToDate
UpToDate is a well-referenced online textbook that is carefully updated every 4 months. It exists in digital format because it is too large to print. Although UpToDate, unlike Best Evidence and the Cochrane Database of Systematic Reviews, does not have a set of explicit methodologic quality criteria that included articles must meet, it does reference many high-quality studies chosen by its section authors.

Example of UpToDate Search. To locate information on blood pressure control in people with type 2 diabetes mellitus, we entered the term “diabetes” in the search window for version 8.3 (Figure 1A-16). This resulted in a list of 21 key word options and we selected “diabetes mellitus, type 2.” This yielded 64 articles, including one entitled “Treatment of Hypertension in Diabetes” that reviewed pathogenesis and included a section on the goal of blood pressure reduction (Figures 1A-17 and 1A-18). This section provided a detailed description of the two large randomized trials, the HOT12 and UKPDS10 trials, that specifically addressed the clinical outcomes associated with more aggressive compared with less aggressive blood pressure management strategies. The text summarized the design and findings, and we were able to retrieve the study abstracts by clicking on the references.
FIGURE 1A-16

UpToDate

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FIGURE 1A-17

UpToDate—Search Results

Reproduced with permission from UpToDate.
Clinical Evidence

Clinical Evidence, published by the BMJ Publishing Group and American College of Physicians/American Society of Internal Medicine, is similar to UpToDate, although less oriented to provide bottom-line clinical advice from experts. Clinical Evidence is text based and available online. By design the producers have not written a textbook; instead, they aim to provide a concise account of the current state of knowledge, ignorance, and uncertainty about the prevention and treatment of common and important clinical conditions. It is published biannually and online products are now available (www.evidence.org).

Example of Clinical Evidence Search. For the question of target blood pressure in people with diabetes, a search using the terms

“target blood pressure AND diabetes”

took us directly to the section entitled “Which interventions improve cardiovascular outcomes in patients with diabetes?” (Figure 1A-19). A subsection on treatment of hypertension includes a discussion of target levels backed up by evidence from the trials we have found in the other resources (HOT and UKPDS trials).
Using Unfiltered Medical Information Sources

MEDLINE

If a search of Best Evidence, the Cochrane Library, UpToDate, and Clinical Evidence does not provide a satisfactory answer to a focused clinical question, it is time to turn to MEDLINE. The US National Library of Medicine maintains this impressive bibliographic database, which includes over 11,000,000 citations of both clinical and preclinical studies. A complementary database known as PreMEDLINE includes citations and abstracts for studies that have been published recently but not yet indexed. MEDLINE is an attractive database for finding medical information because of its relatively comprehensive coverage of medical journals and because it is readily accessible. Anyone with Internet access can search MEDLINE free of charge using PubMed or Internet Grateful Med. In addition, most health sciences or hospital libraries provide access to MEDLINE through a commercial vendor such as OVID, Knowledge Finder, or Silver Platter.

These positive features are balanced with a disadvantage that relates to MEDLINE’s size and to the range of publications that it encompasses. Searching MEDLINE effectively often requires careful thought, along with a thorough knowledge of how the database is structured and how publications are indexed. Understanding how to use Medical Subject Headings is essential, as is text word searching and exploding and use of the logical operators AND and OR to combine different search results.
If you are unfamiliar with MEDLINE searching techniques, an article by Greenhalgh\textsuperscript{14} presents a good introduction. If you suspect that you may have gaps in your searching skills, strongly consider spending some time with an experienced medical librarian or taking a course on MEDLINE searching. Another potential source for information on searching techniques is to visit an Internet Web site designed to introduce the topic. A listing of tutorials designed to assist users of different MEDLINE systems and at different experience levels is available (www.docnet.org.uk/dfrelx/medtut.html). More detailed information on searching MEDLINE and a number of other large bibliographic databases, including EMBASE (Excerpta Medica), is also available in a reference book.\textsuperscript{15} In this section, we present only the most crucial and basic MEDLINE searching advice.

The MEDLINE indexers choose Medical Subject Headings (MeSH) for each article. These headings provide one strategy for searching. Note, however, that indexers reference articles under the most specific subject heading available (for example, “ventricular dysfunction, left” rather than the more general term “ventricular dysfunction”). As a result, if you choose the more general heading (“ventricular dysfunction”) you risk missing out on many articles of interest. To deal with this problem, use a command known as \textit{explode}. This command identifies all articles that have been indexed using a given MeSH term, as well as articles indexed using more specific terms. For example, in the PubMed MEDLINE system for the 1966 to 2000 file, the MeSH heading “sports” contains 10,806 indexed articles, whereas “explode sports,” which picks up more than 20 specific sports from baseball and basketball through weight lifting and wrestling, contains 37,043 indexed articles.

Another fundamental search strategy substitutes reliance on the decisions made by MEDLINE indexers with the choices of study authors regarding terminology. Using “text word” searching makes it possible to identify all articles in which either the study title or abstract includes a certain term. Experience with MEDLINE allows a clinician to develop preferred search strategies. Comprehensive searches will usually utilize both MeSH headings and text words.

\textbf{Example of MEDLINE Search.} To search for information pertaining to blood pressure control targets in people with type 2 diabetes mellitus, we used the National Library of Medicine’s PubMed MEDLINE searching system. We began by entering the term “diabetes mellitus” and clicking the “Go” button. This yielded a total of 143,691 citations dating back to 1966 (Figure 1A-20). Notice that before searching MEDLINE and PreMEDLINE, the PubMed system processed our request. Rather than simply completing a text word search, PubMed developed a more comprehensive strategy that also included the most appropriate MeSH term. To further increase the yield of citations, PubMed also automatically exploded the MeSH term. PubMed searched MEDLINE and PreMEDLINE using the strategy:

\textit{diabetes mellitus} (text word) OR explode diabetes mellitus (MeSH term).
The “OR” in the strategy is called a logical operator. It asks MEDLINE to combine the publications found using either the first search term or the second search term to make a more comprehensive list of publications in which diabetes is a topic of discussion.

**FIGURE 1A-20**

**PubMed—Diabetes Mellitus Search**

![PubMed search interface](image)

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We then searched using the term “hypertension” (180,333 references) and the term “mortality” (320,133 references). To combine these three searches, we initially clicked on the “History” button, which showed us a summary. By entering the phrase

```
#1 AND #2 AND #3
```

into the search window, we were able to ask PubMed to locate only those citations that addressed all of diabetes mellitus, hypertension, and mortality (Figure 1A-21).
Unfortunately, the list of publications that concern all of diabetes, hypertension, and mortality still included 1965 references (Figure 1A-22), prompting us to take advantage of another searching technique designed to help identify particular types of clinical studies. Search hedges or search filters are systematically tested search strategies that help identify methodologically sound studies pertaining to questions of therapy, diagnosis, prognosis, or harm (Figure 1A-23). For example, to retrieve studies related to prognosis, the sensitive search strategy is

incidence (MeSH) OR explode mortality (MeSH) OR follow-up studies (MeSH) OR mortality (subheading) OR prognos: (text word) OR predict: (text word) OR course (text word)

and the specific search strategy is

prognosis (MeSH) OR survival analysis (MeSH).

Sensitive search strategies have comprehensive retrieval with some irrelevant citations, whereas a specific search strategy is not as comprehensive but is less likely to retrieve irrelevant citations. A complete listing of the strategies is available, along with the sensitivities and specificities for each of the different approaches. Although the strategies tend to be complex, many MEDLINE searching systems now have them automatically available for use. The PubMed system has a special section with these strategies entitled “Clinical Queries.” Access to this option is on the left side of the main searching screen.
FIGURE 1A-22
PubMed—Combining Search Terms (Results)

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FIGURE 1A-23
PubMed—Clinical Queries Search

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As an alternative to the hedges, clinicians can use “single best terms” for finding higher-quality studies. These terms include “clinical trial” (publication type) for treatment; “sensitivity” (text word) for diagnosis; “explode cohort studies” (MeSH) for prognosis; and “risk” (text word) for harm (see Table 1A-4).

Combining our previous strategy with the term “clinical trial” (publication type) yielded a list of 117 publications (Figure 1A-24). Once again, we found references to the UKPDS trial and the HOT trial in the citation list.

**FIGURE 1A–24**

*PubMed— Single Best Search Term*

One other useful feature of PubMed is its easy-to-use searching system, which makes knowledge of how to use the various subject heading features and logical operators described above less crucial. The searcher can enter a set of words or phrases into the first window. For example, thinking back to our young man with atypical—possible unstable—angina, we could type

“unstable angina monitor* discharg*”

in the first searching window, and would find 26 citations. The “*” indicates truncation to pick up similar words with varying endings: monitor* picks up “monitor,” monitoring, and monitored. The 11th article is a narrative review.\(^9\) By clicking on the “See related” button, the searcher finds another 238 related citations presented in order from the most to least relevant (according to the computer algorithm).

**The World Wide Web**

The World Wide Web is rapidly becoming an important source of medical information. A vast number of resources can now be accessed using the Internet—some for a fee, others free of charge. To make these resources more accessible,
certain Web sites have been designed specifically to provide links to medical information locations or to facilitate searching for medical information on the Internet. Examples of such Web sites include Medical Matrix, Medscape, ScHARR, and Medical World Search. Clinicians can also use the Internet to access medical journals and clinical practice guidelines.

We must, however, issue a user beware caveat: some of these guidelines may fail to meet Users’ Guides criteria for evidence-based guidelines (see Part 1F, “Moving From Evidence to Action”). An example of a site that provides access to many resources, including journals, textbooks, and guidelines, albeit for a fee, is MD Consult.

Finally, Web sites produced and maintained by reputable organizations such as the American Cancer Society (www.cancer.org) or the American Diabetes Association (www.diabetes.org) provide another approach for finding information.

**CLINICAL APPLICATION**

The health sciences literature is enormous and continues to expand rapidly. To the extent that this reflects ongoing research and the identification of potential improvements for patient care, this is very promising. At the same time, however, it makes the task of locating the best and most current therapy or diagnostic test more challenging. The emergence of new information products specifically designed to provide ready access to high-quality, clinically relevant, and current information is timely and encouraging.

Finding the articles that address your clinical question requires 5 to 30 minutes, depending on the resource you use or your experience with systematic searching. A full assessment of the validity and applicability requires an additional half-hour. The UKPDS study and the HOT study are the closest matches to your patient and the clinical situation. The studies show a clear reduction of diabetes-related mortality with tight blood pressure control in persons with type 2 diabetes mellitus and hypertension. You decide to set target systolic blood pressure at < 150 mm Hg and target diastolic blood pressure at < 80 mm Hg.
References


