


General concepts and critical appraisal

Salim Yusuf, Editor

COPYRIGHTED MATERIAL

Evidence-based decision making: patient–physician interface

Philip J Devereaux,¹ Marc Pfeffer² and Salim Yusuf¹

¹Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario, Canada

²Brigham and Women's Hospital, Boston, MA, USA

Introduction

In 1836 Elisha Bartlett, the editor of the *American Journal of Medical Sciences*, heralded a study as “one of the most important medical works of the present century, marking the start of a new era in science.”¹ What evoked such praise and suggested a paradigm shift was Dr Pierre Louis’ systematic collection and numerical presentation of data on blood letting. Louis adopted a Baconian approach of collecting vast amounts of data on a large number of patients (by the standards of the early 1800s), which allowed him to systematically evaluate the efficacy of blood letting. Louis argued that large numbers of patients and enumeration were necessary to equalize differences between treatment groups since “by so doing, the errors (which are inevitable), being the same in two groups of patients subjected to different treatment, mutually compensate each other, and they may be disregarded without sensibly affecting the exactness of the results.”² Louis subsequently went on to state: “a therapeutic agent cannot be employed with any discrimination or probability of success in a given case, unless its general efficacy, in analogous cases, has been previously ascertained” and thus, “without the aid of statistics nothing like real medicine is possible.”³

The prevailing concept of illness, at the time, was that the sick were contaminated, whether by some toxin or contagion, or an excess of one humor or another. This understanding of illness contained within it the idea that these states were improved by opening a vein and letting the sickness run out. Louis’ finding that blood letting hastened the death of the ill was a bombshell. George Washington

had 2.4 liters of blood drained from him in the 15 hours prior to his death; he had been suffering from a fever, sore throat, and respiratory difficulties for 24 hours.⁴ Some have suggested that Washington was murdered.^{5–7}

While this is a relatively recent example, the plea for comparative evaluation is mentioned as early as the Old Testament. Throughout history there have been repeated exhortations to quantify medical or health problems and to compare outcomes in patient groups managed differently, with the goal of setting state policy or assisting individual physicians.

In this chapter we will consider what evidence-based medicine is and then discuss an approach to evidence-based decision making. We will use a clinical case to highlight the components of this approach which include: clinical state and circumstances, patient preferences and actions, research evidence, and clinical expertise. At the end of the chapter we will review the application of these components of evidence-based decision making as they apply to our patient and provide a decision aid that clinicians can use in such a case. This chapter is an overview of core concepts and other chapters in this book (e.g. clinical trials and meta-analysis) provide more in-depth coverage of specific topics.

What is evidence-based medicine?

Although the foundations for evidence-based medicine were laid over several centuries, an explicit philosophy with its attendant concepts, definitions, and models has been largely developed as a formal doctrine only during the last few decades. Evidence-based medicine is about solving clinical problems. Initially, the focus of evidence-based medicine was largely on finding the best objective quantifiable research evidence relevant to the particular problem, and applying that evidence in resolving the particular issue.⁸ This early focus de-emphasized “intuition,

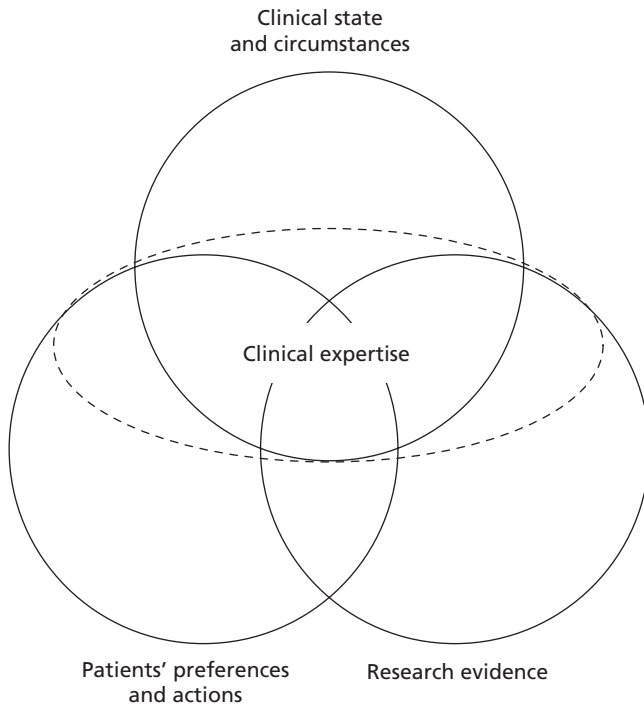


Figure 1.1 Current model of evidence-based clinical decision making.

unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making” and stressed “the examination of evidence from clinical research.”⁹ Subsequent versions of evidence-based decision making have emphasized that research evidence alone is rarely sufficient to make a clinical decision.¹⁰ Research evidence by itself seldom tells us what to do in individual situations, but rather it provides useful information that allows us to make more informed decisions. Clinicians must always view evidence in the context of the individual patient and then weigh the potential benefits versus the risks, costs, and inconveniences of each action. Ideally the patient’s values and preferences affect these issues¹⁰

An initial description of evidence-based medicine from an editorial in 1996 provided the following definition: “Evidence-based medicine is the conscientious and judicious use of current best evidence from clinical care research in the management of individual patients.”¹⁰ The editorial also included the caveat that the definition of evidence-based medicine will evolve as new types of information emerge and therefore will be continuously refined. The concepts of evidence-based medicine have evolved considerably and the current model is outlined in Figure 1.1.⁸ In the next section we use this model of evidence-based clinical decision making to help resolve a common clinical scenario.

Approach to evidence-based clinical decision making

Clinical scenario

A family physician refers a patient who has just moved cities to live with his daughter. The physician is requesting our input on the appropriateness of antithrombotic therapy. The patient is an 80-year-old male with a history of hypertension who 10 months ago, on routine exam, was diagnosed with atrial fibrillation. The patient suffered a major gastrointestinal bleed, requiring hospitalization, urgent endoscopy, and a transfusion 1 month prior to his diagnosis of atrial fibrillation. At the time of his bleed, the patient on endoscopy was diagnosed with a duodenal ulcer and *Helicobacter pylori*. The patient has been free of any gastrointestinal symptoms since his bleed 11 months ago and he received appropriate antibiotic and acid suppression therapy. Within 2 weeks of the patient’s diagnosis of atrial fibrillation he underwent a transesophageal echocardiogram in his former city of residence and this demonstrated normal valvular and left ventricular function and a left atrium measurement of 6.5 cm without evidence of thrombus. An attempt at cardioversion was unsuccessful. The patient is very worried about having a stroke as his wife was left dependent on him for 2 years prior to her death, following a major stroke. The referring physician, who recently had a patient who suffered a serious gastrointestinal bleed while on warfarin, is very concerned about the risk of bleeding given this patient’s age and history of gastrointestinal bleeding.

Model for evidence-based clinical decisions

Figure 1.1 depicts a model for evidence-based clinical decisions,⁸ which has more recently been redefined as “the integration of best research evidence with clinical expertise and patient values.”¹¹ This model represents a desirable approach to how clinical decisions should be made. However, we acknowledge that, at present, many clinical decisions are not made this way. For instance, at present, clinicians’ individual preferences (as distinct from clinical expertise) often play a large role in their actions, leading to large “practice variations” in managing similar cases. For example, when faced with critically ill patients with identical circumstances, different clinicians may, according to their preferences, institute aggressive life-prolonging interventions or withdraw life support.¹² Our model acknowledges that patients’ preferences should be considered first and foremost, rather than clinicians’ preferences, whenever it is possible and appropriate to do so (i.e. the patient wants to be involved in the decision making and they have the capacity to understand the outcomes and their consequences when explained by their physician). Although this model may look static, clinical decision making commonly requires an iterative approach whereby decisions are re-evaluated to ensure that they are still appropriate as evol-

ing information comes to light. Integrating clinical state and circumstances, patient preferences and actions, and research evidence requires judgment and clinical expertise, thus constituting an overarching element. We will describe each of the components of the model, and the role of clinical expertise in integrating them.

Clinical state and circumstances

A patient's clinical state and circumstances often play a dominant role in clinical decisions. Clinical trials provide us with results reflective of the average patient within the treatment groups of the trial. Rarely is a patient in clinical practice the same as the average patient from a clinical trial. Individual patients have unique characteristics that typically put them at lower or higher risk of the outcome or treatment side effect than the average patient in the trial. As such, optimal clinical decisions should be individualized to the patient's clinical state. If a patient is at very high risk of a future vascular event but at low risk of any complication from a drug (e.g. a patient with a low-density lipoprotein value of 8.0 mmol/L post myocardial infarction and no contraindication to statin therapy), or conversely at low risk of the outcome and high risk of a treatment's complications (e.g. a 40-year-old man with atrial fibrillation without any associated stroke risk factors who has experienced a major gastrointestinal bleed 2 weeks ago), the clinical state of the patient may dominate the clinical decision-making process.

It is notable that the circles of clinical state and circumstances and research evidence overlap. Frequently research evidence can inform us about the influence of the clinical state and circumstances. Considering our patient, the pooled data from five randomized controlled trials (RCTs) evaluating the efficacy of warfarin in patients with non-valvular atrial fibrillation (NVAF) demonstrated an average annual stroke rate of 4.5% and major bleeding rate of 1% in patients not receiving antithrombotic therapy.¹³ The investigators who combined the five RCTs used the control patient data to develop a clinical prediction tool to estimate the annual risk of stroke. Independent risk factors that predicted stroke in control patients were increasing age, a history of hypertension, diabetes, and prior stroke or transient ischemic attack (TIA).¹³ These trials likely exclude patients with a history of bleeding 11 months prior to enrollment and as a result we would not want to rely upon these trials to estimate our patient's risk of severe bleeding; however, we believe, and research suggests,¹⁴ that the estimate of stroke from the clinical prediction tool (which takes into account age) is relevant to our patient even though he is older than the average patient in the trials. Using this model, our patient's annual risk of stroke is predicted to be about 8%, which is higher than that of the average control patient in the five RCTs whose annual stroke rate was 4.5%.¹³

A clinical prediction tool has also been developed for predicting the risk of major bleeding (defined as the loss of 2 units of blood within 7 days or life-threatening bleeding) while taking warfarin therapy.¹⁵ Independent risk factors that predict major bleeding in patients taking warfarin include age >65, history of stroke, history of gastrointestinal bleeding, recent myocardial infarction, anemia, renal failure, and diabetes (note that many of the factors that predict a higher risk of stroke also increase the risk of bleeding). Our patient's annual risk of major bleeding of 8% also differs from that of the average patient receiving warfarin in the five RCTs whose annual risk of major bleeding was 1.3%. We are unaware of any clinical prediction tool for predicting major bleeding while taking aspirin and the atrial fibrillation trials had inadequate power to estimate this risk. The results of the meta-analysis by the antithrombotic trialists' collaboration suggest that aspirin increases the risk of major bleeding from 1% to at least 1.3%.¹⁶ This likely is an underestimation in our patient who is older than the average patient who participated in the atrial fibrillation trials, and in this setting of suboptimal information we estimate our patient's annual risk of major bleeding is approximately 2% with aspirin therapy.

The clinical circumstances we find ourselves in (e.g. our ability to administer and monitor a treatment) may be very different from that of an RCT. For example, the patient may not be able to obtain frequent tests of the intensity of anticoagulation. However, for a patient with the same clinical characteristics, we can frequently optimize clinical circumstances to decrease the risk of an outcome or treatment side effect. For example, we can decrease the risk of bleeding due to warfarin therapy by more intensive monitoring to ensure that the international normalized ratio (INR) is maintained in the range of 2–3. Thus, an “evidence-based” decision about anticoagulation for a patient with atrial fibrillation is not only determined by the demonstrated efficacy of anticoagulation and its potential adverse effects,¹⁷ but will vary based on the patient's clinical state and according to individual clinical circumstances.

Patients' preferences and actions

Patients may have no views or, alternatively, unshakable views on their treatment options, depending on their condition, personal values and experiences, degree of aversion to risk, healthcare insurance and resources, family, willingness to take medicines, accurate or misleading information at hand, and so on.⁸ Accordingly, individuals with very similar clinical states and circumstances may choose very different courses of action despite being presented with the same information about the benefits, risks, inconveniences, and costs of an intervention.

For our patient with NVAF, research evidence informs us about the differing preferences of patients and their

physicians for antithrombotic therapy in atrial fibrillation when they weigh the competing risks of stroke and bleeding.¹⁸ In this study,¹⁸ participants (i.e. both physicians and patients) reviewed flipcharts describing in detail the acute and long-term consequences of a major and minor stroke and a major bleeding event. Participants were instructed that the likelihood of a minor or major stroke was equal. The participants then underwent a probability trade-off technique which determined the minimum number of strokes participants needed to be prevented before they felt antithrombotic therapy was justified (this value was determined for both warfarin and aspirin), given the associated increased risk of bleeding, costs and inconveniences. The same technique was also used to determine the maximum number of excess bleeds the participant considered acceptable with antithrombotic therapy (determined both for warfarin and aspirin), given the benefits in terms of stroke reduction with this therapy. This study demonstrates significant variability between physicians and patients in their weighing of the potential outcomes associated with atrial fibrillation and its treatment. Patients required less stroke reduction and were more tolerant of the risk of bleeding than physicians. For example, on average, patients were willing to accept the risk of 17 extra major bleeding events in 100 patients over a 2-year period if warfarin prevented eight strokes among these 100 patients. Physicians, however, were only willing to accept 10 major bleeding events for the same level of benefit. Furthermore, physicians varied significantly among themselves in how much bleeding risk they thought was acceptable for a given stroke reduction associated with an antithrombotic agent. Hence different physicians would make very different recommendations to the same patient with identical risks of bleeding and stroke. This underscores the importance of having patient values and preferences drive clinical decision making. It is the patient who is at risk of the outcome and hence, when willing and able, they should be the one to weigh the potential benefits versus the risks, costs, and inconveniences.

There is debate regarding the optimal way to elicit and incorporate patient preferences into clinical decision making. One method is to discuss the potential benefits and risks with a patient and then qualitatively incorporate your impression of the patient's preferences into the clinical decision. Alternatively, at least two quantitative approaches exist: decision analytic modeling and probability trade-off technique. In a decision analytic model, a standard gamble, time trade-off or visual analog scale technique is used to determine the utility (patient value/preference) for the various outcomes. This information is then fed into a decision tree that includes the probabilities of the outcomes for all clinical decisions being considered. Using the decision tree, calculations are undertaken to determine what course of action optimally fits the patient's prefer-

ences. Probability trade-off technique presents patients with the probabilities for the various interventions being considered and then asks them to make a decision based on this information. This allows a direct and quantitative incorporation of the patient's preferences. The only study we are aware of that has directly compared these two quantitative approaches demonstrated that over twice as many patients stated they would base their preferences on the results of the probability trade-off as opposed to the decision analysis.¹⁹

Regardless of what their preferences may be, patients' actions may differ from both their preferences and their clinicians' advice.²⁰ For example, a patient may prefer to lose weight, quit smoking and take their medications as prescribed, but their actions may fall short of achieving any of these objectives. Alternatively, they may follow the treatment as prescribed, even if they resent its imposition, adverse effects, and costs. Unfortunately, clinicians' estimates of their patients' adherence to prescribed treatments have no better than chance accuracy.²¹ Thus, physicians' decisions for care will better meet the model's specifications if they are able to assess whether their patients will follow, or are following, the agreed-upon decision.²¹

We recognize that at present formal incorporation of patients' preferences is rarely done in clinical practice. This may be related to lack of training of physicians in these approaches, a reluctance to tread unfamiliar ground, and also in many circumstances the lack of accurate quantitative information on risk and benefits as well as clinical risk prediction tools. However, this is likely to change as clinical models can be derived from large databases and hand-held computers can be utilized to quantitate risks and benefits at the bedside.

Research evidence

We support a very broad definition of research evidence, namely "any empirical observation about the apparent relation between events."²² In keeping with this definition research evidence includes everything from the unsystematic observation of a single physician to a systematic review of large RCTs. Not all evidence is created equal and hence there exists a hierarchy of evidence that varies depending on whether one is addressing a diagnostic, prognostic or therapeutic decision. We will focus on the hierarchy of evidence for therapeutic decisions (Box 1.1).

All evidence has value and clinicians should give appropriate consideration to the best evidence available in the hierarchy, even if it is not at the top of the hierarchy. Therefore, the unsystematic observations of colleagues should not be dismissed when no higher level evidence exists. Indeed, unsystematic observations can lead to many important insights and experienced clinicians usually develop a respect for the insights of their astute colleagues.

However, it is equally important to recognize that unsystematic observations commonly are limited by the small number of observations, variability in outcomes, lack of objectivity, and the difficulties in integrating (e.g. taking

into account the natural history of a disorder, placebo effect, and a patient’s desire to please) and drawing inferences from observations.²³ Clinicians should also realize that even for the highly cited animal studies demonstrating a beneficial treatment effect and published in a leading scientific journal, only a minority will be confirmed in human trials.²⁴

All evidence has limitations. Although the majority of advances in medicine are initially uncovered through individual observations, physiologic studies, observational studies or randomized controlled trials evaluating surrogate endpoints, there have also been several extremely misleading findings that have, at times, resulted in harm. It is important to remember that contradictory results across studies on the hierarchy of evidence table are not isolated to one or two instances (Table 1.1).

Perhaps the most powerful example is the story of antiarrhythmic therapy. Despite encouraging evidence that encainide and flecainide could prevent premature ventricular beats after a myocardial infarction, a large RCT demonstrated a higher mortality rate with these drugs compared to placebo, such that these drugs resulted in an extra death for every 20 patients treated with encainide or flecainide.³⁹ It is estimated that more Americans were killed by these drugs than died in the Vietnam War.⁴⁰

Ideally we would have evidence from all levels of the hierarchy and the evidence would be coherent across all levels. This would represent the most persuasive evidence.

BOX 1.1 Hierarchy of evidence for treatment decisions*

Coherence of evidence from multiple sources
Systematic review of several well-designed, large randomized controlled trials
Single large randomized controlled trial
Systematic review of several well-designed small randomized controlled trials
Single small randomized controlled trial
Systematic review of several well-designed observational studies
Single observational study
Physiologic studies
Unsystematic observation from a physician
Animal study

This hierarchy is not meant to represent a rigid structure. At times a single observation may be very powerful (e.g. defibrillation for ventricular fibrillation) or observational studies may provide unequivocal evidence (e.g. smoking cessation and decreased risk of lung cancer). However, in most cases where treatment effects are likely moderate, outcomes variable or the clinical course unpredictable, clinicians may find the hierarchy proposed useful.

Table 1.1 Some examples of contradictory results across studies at various positions in the hierarchy of evidence

Results from lower level evidence	Results from higher level evidence
Milrinone demonstrated improvement in left ventricular function during exercise. ²⁵	A large RCT ²⁶ and meta-analysis of several RCTs ²⁷ demonstrated a 28% relative increase in mortality with milrinone compared to placebo.
An observational study of extracranial to intracranial bypass surgery suggested a “dramatic improvement in the symptomatology of virtually all patients” undergoing the procedure. ²⁸	A large RCT demonstrated a 14% relative increase in the risk of fatal and non-fatal stroke in patients undergoing this procedure compared to medical management. ²⁹
A meta-analysis of 16 cohort studies and three cross-sectional angiographic studies (including studies of women with known coronary artery disease) demonstrated a relative risk of 0.5 (95% CI 0.44–0.57) for coronary artery disease among women taking estrogen. ³⁰	A moderate size secondary prevention RCT did not demonstrate any reduction in coronary heart disease events but did demonstrate an increase in thromboembolic events in patients receiving estrogen. ³¹ A primary prevention RCT (Women’s Health Initiative) of 16,608 women demonstrated that hormone replacement therapy increases the risk of coronary artery disease (hazard ratio (HR) 1.29), stroke (HR 1.41), pulmonary emboli (HR 2.13), and breast cancer (HR 1.26). ³²
A secondary analysis of an RCT suggested that lower doses of ASA were associated with a higher risk of perioperative stroke and death in patients undergoing carotid endarterectomy. ³³	A large prospective RCT showed a higher risk of perioperative stroke, myocardial infarction, or death with high-dose ASA. ³³
A physiologic study demonstrated beta-blockers result in a decline in ejection fraction and increases in end-diastolic volume in patients with prior myocardial infarction. ³⁴	A meta-analysis of 18 RCTs ³⁵ and three large trials (CIBIS-2, ³⁶ MERIT-HF, ³⁷ and COPENICUS ³⁸) in patients with heart failure found a 32% relative risk reduction in death in patients receiving beta-blockers.

However, this rarely happens as even RCTs by chance may frequently demonstrate contradictory findings, especially when they are small. Therefore, physicians should always aim for the highest level of evidence for clinical decision making. Clinicians can still make strong inferences particularly when there is evidence from a systematic review of several well-designed large RCTs or simply a large single pragmatic RCT. The RCT is such a powerful tool because randomization is our only means to reduce bias in treatment comparisons by controlling for unknown prognostic factors.⁴¹ Therefore, RCTs have the potential to provide the most valid (i.e. likelihood that the trial results are unbiased) estimates of treatment effect.⁴² Furthermore, large RCTs with broad eligibility criteria enhance the generalizability of their findings.

A common error in interpreting evidence relates to the confidence clinicians should have in a study based upon statistical significance despite its size and number of events. Consider two hypothetical RCTs that are both evaluating the effect of a new investigational drug versus placebo on patient mortality in patients at risk of a myocardial infarction. Both of these trials use identical methodology (e.g. blinding, complete patient follow-up, intention-to-treat principle). The first trial randomizes 100 patients to receive investigational drug A and 100 patients to receive placebo, and fewer patients assigned the investigational drug die (1 versus 9 patients, $P = 0.02$). The second trial randomizes 4000 patients to receive investigational drug B and 4000 patients to receive placebo, and fewer patients assigned the investigational drug die (200 versus 250 patients, $P = 0.02$). Given that both trials used the same methodology and achieved the same level of statistical significance, some would assume we should view both results with similar confidence. This, however, is not the case.

Although the P values in our hypothetical trials suggest that the results have the same probability of representing a true finding, we propose that there is a substantial difference in the fragility of the demonstrated P values. In the first trial if we were to add two events to the treatment group the P value would become 0.13 whereas adding two events to the treatment group in the second trial would have no meaningful impact on the P value which would remain 0.02. When one considers that there are at least nine independent risk factors associated with myocardial infarction,⁴³ the prevalence of these factors in patients suffering a myocardial infarction varies from 18% to 65%, and many of these risk factors have substantially larger associations with myocardial infarction (e.g. odds ratio 2.87 for current smoker versus never) than the moderate effects that are plausible in interventional trials, it is not difficult to understand how the effect seen in our first hypothetical trial could have easily occurred due to an imbalance in risk factors, whereas the size of our second trial substantially minimizes the likelihood of a meaningful imbalance in prognostic factors that could explain the result of our second trial.

The number of participants and events that represents the transition from a small trial to a large trial is a matter of debate and ongoing investigation. It is important to recognize that the number of both participants and events is relevant. Some have argued that cardiovascular trials with event rates of 10% require at a minimum several thousand participants and at least 350 events and ideally 650 events to provide convincing evidence of a moderate size treatment effect (i.e. a relative risk reduction of 20–30%).⁴⁴ Indeed, if the true effect of size is a 15% relative risk reduction, studies with over 1000 outcome events may be required. In the case of a more prevalent outcome or the rare case of a true large treatment effect, fewer participants and events are required. We encourage clinicians when assessing evidence to not simply assume that a P value <0.05 represents a true finding but to consider the sample size, number of events, and the fragility of the P value and to exercise caution when making clinical decisions based upon data from small trials. Research demonstrates that highly cited studies in leading medical journals are not uncommonly contradicted (16%) or demonstrated to have exaggerated treatment effects (16%) in subsequent studies, and the only identified factor explaining this outcome is that the initial trial had a small sample size.⁴⁵

Another issue clinicians have to consider regarding research evidence is the applicability to their current patient. If a patient fulfills most of the eligibility criteria from a trial then most physicians would view the evidence as applicable to their patient, assuming the trial is high quality. If a patient does not fulfill most of the eligibility criteria, we recommend that physicians ask themselves if there is a strong biologic reason to believe their patient would respond quite differently to the intervention from the patients who participated in the trial. As stated above, it is likely that most of the atrial fibrillation trials excluded patients who had a history of gastrointestinal bleeding within 11 months of randomization. Given this, we think the results from the atrial fibrillation trials regarding bleeding risk are not applicable to our patient, and this is why we used a clinical model based upon a study that included patients with a prior history of gastrointestinal bleeding to estimate our patient's risk of severe bleeding with warfarin. However, we do not have a strong biologic rationale to suspect that the stroke benefit demonstrated in the trials is not applicable to our patient, and research suggests that despite his age we can expect a similar benefit.¹⁴

Considering our case of the patient with NVAE, the highest level of evidence comes from a systematic review of all the RCTs that have evaluated antithrombotic therapy in patients with atrial fibrillation.¹⁷ This systematic review included six warfarin versus placebo RCTs that included a total of 2900 patients and 186 strokes, and six aspirin versus placebo RCTs that included a total of 3337 patients and 376 strokes, and demonstrated that warfarin reduced the rela-

tive risk of stroke (ischemic and hemorrhagic) by 62%, and aspirin by 22%.¹⁷

Considering the risk of bleeding associated with warfarin therapy, there is an RCT of 325 patients with 25 major bleeding events that demonstrates a 50% decrease in the risk of bleeding if a patient is willing to undergo education, training, and self-monitoring of prothrombin time.⁴⁶

Clinical expertise

Evidence-based decision making requires clinical expertise to establish and balance the patient's clinical state and circumstances, preferences and actions, and the best research evidence. Before a therapeutic decision can be considered, clinical expertise is required to get the diagnosis and prognosis right. As shown above, clinical prediction tools can be extremely helpful in determining a patient's prognosis but they are unlikely to eliminate the need for sound clinical judgment acquired through clinical experience.

Sizing up the clinical circumstances has never been more challenging, as commonly there exist several potential interventions, some of which require technical expertise for their effective and safe delivery. Getting the evidence right requires the skill to identify, evaluate, and apply the evidence appropriately. Communicating with patients has always been considered important. This takes on greater importance, given that there is a growing desire on the part of patients to be involved in decisions relating to their health.⁴⁷ Expertise is required to provide patients with the information they need, to elicit their preferences and to incorporate their preferences into the decision.

Currently there is no consensus on how this information should be presented to patients and how their preferences should be incorporated. However, research suggests that information should not be presented to patients in relative terms (e.g. warfarin will decrease your risk of stroke by 62%) because patients assume their baseline risk is 100% even when they are instructed it is not.⁴⁸ A recent systematic review of RCTs compared decision aids (i.e. interventions designed to help people make specific choices among options by providing information on the options and outcomes relevant to the patient's health) to traditional ways of involving/informing patients in decision making and demonstrated that decision aids, compared with usual care, improved average knowledge scores of patients for the options and outcomes by 20% (95% CI 13–25), reduced decisional conflict scores (i.e. patients felt more certain, informed, and clear about values in their decision), and increased patient participation in decision making.⁴⁹ Where available, decision aids provide a potential means to facilitate information presentation, incorporation of preferences, and participation in the decision making process.

The varying roles of the components of evidence-based clinical decisions

Depending on the circumstances, any of the circles in the new model could dominate. Varying the size of the circles to reflect their actual contribution to the clinical decision could visually portray this concept. Sometimes the clinical state or circumstance dominates the clinical decision. For example, a patient who is at very high risk of an outcome and low risk of a complication may have their clinical state dominate the decision-making process. A patient living in a remote area may not have access to anticoagulation monitoring and this would likely dominate the decision-making process. Patients' preferences can be so strong that they act as the driving factor in the decision-making process. For example, some patients will not take blood products regardless of the clinical situation. Research evidence can be the main factor in decision making when the benefit of an intervention is moderate to large in size and the risk of treatment small, as with ACE inhibitors in coronary artery disease or heart failure, or cholesterol lowering with statins. Finally, clinical expertise can dominate especially when it is related to technical capabilities.

Approach to decision making

We advocate a shared decision-making process between the physician and patient with both as active partners.⁴⁷ There is evidence to support better health outcomes when shared decision making occurs.⁵⁰ Considering a therapeutic decision, the physician must incorporate the clinical state and circumstances into the relevant evidence to help inform the patient and then elicit the patient's values regarding the potential benefits, risks, costs, and inconveniences associated with the intervention. If a patient chooses not to take an effective therapy that the physician believes is in the patient's best interest then the physician's role is to ensure that the patient's choice represents a difference in values (e.g. monetary concerns) as opposed to a misunderstanding about the probable benefits, risks, inconveniences, and costs. Regardless of a patient's wishes (e.g. CABG surgery in the setting of extensive coronary artery disease without graftable distal vessels, non-therapeutic use of narcotics) no physician is required to provide an intervention that they feel is unethical, illegal or not in the patient's best interest. Although more patients want shared decision making, some may choose to take a passive role in the decision-making process.⁴⁷ For example, a patient may ask the physician "If it were you or your loved one what would you do?" This question permits the physician to present an evidence-based background, the uniqueness of the clinical state and circumstances, and the doctor's explicit values associated with their recommendation. If a physician does

this they will provide the patient with a helpful understanding of their recommendation, and if a patient disagrees they can then express their perspective. Finally, after making a decision it is important to ensure that the patient understands that even the best evidence-based decision does not guarantee the patient that they will not suffer a negative outcome.

Application to our patient

For our patient the evidence would suggest an annual 8% risk of stroke and 1% risk of major bleeding without any antithrombotic therapy. With warfarin therapy we would expect the annual risk of stroke to decrease to 3% and the risk of major bleeding to increase to 8%. This risk of major

bleeding could potentially be reduced to 4% if the patient was willing to undergo self-monitoring of their prothrombin time and an education program as discussed above; however, it is important to acknowledge that our confidence in this intervention is not strong as the results are based upon one small trial with few events.⁴⁶ With aspirin therapy we would expect the annual risk of stroke to decrease to 6% and the risk of major bleeding to increase to 2%.

As discussed above, there is no consensus on how to present this information to our patient or incorporate his preferences. The patient expresses that he would like to participate in the decision-making process and you then share with him a decision aid for patients with atrial fibrillation that describes atrial fibrillation (Table 1.2), a major and minor stroke (Table 1.3), a severe bleed (Table 1.4), and

Table 1.2 Atrial fibrillation: the most common disorder of the heartbeat

Risk	Chances of developing atrial fibrillation increase with age and it occurs in approximately 10% of all people above the age of 75
Physical Symptoms	Irregular and usually rapid beating of the heart, sensed as a fluttering in the chest. Some patients feel no symptoms and are unaware that they have atrial fibrillation
Complications	Stroke - Atrial fibrillation increases the risk of a clot developing in the heart. This clot can be swept up towards the brain, causing a stroke - The chance of developing a stroke with atrial fibrillation increases with either age greater than 65 years, high blood pressure, diabetes, heart failure, or a history of strokes or "mini-strokes" - The risk of developing a stroke with atrial fibrillation varies, depending on how many of these risk factors you have
Treatment	- There are medications that thin the blood, which help to prevent clots and therefore stroke - Because the blood is thinned there is an increased risk of bleeding

Table 1.3 Strokes can be minor or major in severity. If you have a stroke as a result of atrial fibrillation, your chance of having a minor or major stroke are equal

	Minor stroke	Major stroke
Physical symptoms	You suddenly cannot move or feel one arm and one leg	You suddenly are unable to move one arm and one leg You cannot swallow
Mental symptoms	You are unable to fully understand what is being said to you You have difficulty expressing yourself	You are unable to understand what is being said You are unable to speak
Pain	You feel no physical pain	You feel no physical pain
Recovery	You are admitted to hospital Your weakness, numbness and problem with understanding improve, but you still feel weak or numb in one arm and one leg You are able to do almost all of the activities you did before the stroke You can function independently You leave the hospital after 1 week	You are admitted to hospital You cannot dress The nurses feed you You cannot walk After 1 month of physiotherapy you are able to wiggle your toes and lift your arm off the bed You remain this way for the rest of your life
Further risk	You have an increased risk of having more strokes	Another illness will probably cause your death

Table 1.4 Severe bleeding while taking warfarin or ASA: an example of a stomach bleed

Physical Treatment	You feel unwell for 2 days, then suddenly you vomit blood You are admitted to hospital You stop taking warfarin or ASA A doctor puts a tube down your throat to see where you are bleeding from You receive sedation to ease the discomfort of the test You do not need an operation
Recovery	You receive blood transfusions to replace the blood you lost You stay in hospital for 1 week You feel well at the end of your hospital stay You need to take pills for the next 6 months to prevent further bleeding After that you are back to normal

Bleeding from the stomach is the most common type of serious bleeding while taking warfarin or ASA; however, rarely other serious forms of bleeding can occur, such as bleeding within the head after a fall.

Warfarin or ASA can also cause minor bleeding, including bruising and nose bleeds.

Taking warfarin can mean costs and inconvenience to yourself and family. For example: need for blood tests; parking/transportation; cost of warfarin.

Taking ASA can mean costs to yourself.

For example: cost of ASA.

Without any blood thinning medication

Chance of stroke over next 2 years
is ____ out of 100

Chance of severe bleeding over next 2 years
is ____ out of 100

ASA

Chance of stroke over next 2 years
is ____ out of 100

Chance of severe bleeding over next 2 years
is ____ out of 100

Warfarin

Chance of stroke over next 2 years
is ____ out of 100

Chance of severe bleeding over next 2 years
is ____ out of 100

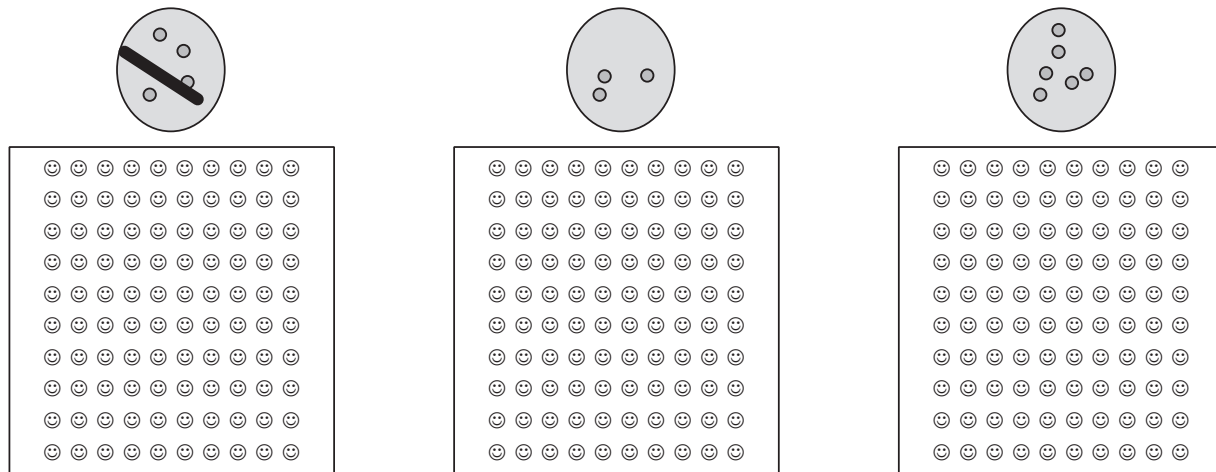


Figure 1.2 Patient decision aid.

a probability trade-off for no treatment, aspirin, and warfarin therapy (Fig. 1.2), which you individualize for him, filling in the specific numbers and coloring the faces relevant to his care. The description of major and minor stroke and a severe bleed are slight modifications of the descriptions developed and tested by Man-Son-Hing and colleagues.⁵¹ After careful consideration of this information, our patient decides he wants to take warfarin therapy. He recognizes his increased risk of bleeding but places sub-

stantially more weight on avoiding a stroke than a severe bleed.

Once this evidence-based clinical decision is reached, our job is not over. The patient will need monitoring to ensure he is able to follow through on his clinical decision. One advantage of the decision aid provided (including his individualized probability trade-off) is that the patient can take the information home and does not have to rely on his memory to recall the facts discussed during your meeting.

Limitations of the evidence-based clinical decision model

This model does not consider the important roles that society, governments or healthcare organizations can play in decision making. We purposely restricted ourselves to decisions made by patients and their healthcare providers to allow a focused exploration of the issues involved in their immediate decision-making process. However, a healthcare organization may pre-empt these decisions. For example, not funding primary percutaneous transluminal coronary angioplasty in acute myocardial infarction can have an impact on health outcomes and will impose a clinical decision on all patients and physicians by eliminating this option. Alternatively, the system may fund preferentially, and at a higher level, a theoretically more attractive but more expensive and in reality no more effective therapy (e.g. dual-chamber pacemaker compared to single-chamber pacemaker for bradyarrhythmia) and this can distort the information presentation to patients, recommendations, and decisions made by physicians and healthcare providers. Physicians will have to factor in such issues when considering their patient's clinical circumstances.

Conclusion

The foundations for evidence-based medicine were established over the centuries but the specific philosophies, concepts, definitions, and models have essentially evolved over the past few decades. Evidence-based medicine is about solving clinical problems. Evidence-based decision making depends upon utilizing clinical expertise to integrate information about a patient's clinical setting and circumstances with the best research evidence while incorporating the patient's preferences and actions. Although there have been substantial advances throughout the last few decades, if evidence-based decision making is to achieve its full potential there is a need for further research to inform both the evidence base and the process of decision making. This chapter has provided an introduction to the concepts of evidence-based decision making, and subsequent chapters expand on the points we have discussed, describing different aspects of evaluating evidence and applying them.

References

- Loius PCA. Researches on the effects of blood-letting in some inflammatory diseases, and on the influence of tartarised antimony and vesication in pneumonitis. *Am J Med Sci* 1836;**18**:102–11.
- Loius PCA. Researches on the Effects of Bloodletting in Some Inflammatory Diseases and on the Influence of Tartarised Antimony and Vesication in Pneumonitis. Boston: Hilliard, Gray, 1836.
- Louis PCA. Medical statistics. *Am J Med Sci* 1837;**21**:525–8.
- Morens DM. Death of a president. *N Engl J Med* 1999;**341**(24):1845–9.
- Lloyd JU. Who killed George Washington? *Eclectic Med J* 1923;**83**:353–6, 403–8, 453–6.
- Marx R. A medical profile of George Washington. *American Heritage* 1955;**6**:43–47:106–7.
- Pirruccello F. How the doctors killed George Washington. *Chicago Tribune Magazine*, 1977.
- Haynes RB, Devereaux PJ, Guyatt GH. Clinical expertise in the era of evidence-based medicine and patient choice. *ACP J Club* 2002;**136**(2):A11–14.
- Evidence-based medicine working group. Evidence-based medicine. A new approach to teaching the practice of medicine. *JAMA* 1992;**268**(17):2420–5.
- Haynes RB, Sackett DL, Gray JM, Cook DJ, Guyatt GH. Transferring evidence from research into practice: 1. The role of clinical care research evidence in clinical decisions. *ACP J Club* 1996;**125**(3):A14–16.
- Sackett DL, Straus S, Richardson SR, Rosenberg W, Haynes RB. Evidence-Based Medicine: How to Practice and Teach EBM, 2nd ed. London: Churchill Livingstone, 2000.
- Cook DJ, Guyatt GH, Jaeschke R, Reeve J, Spanier A, King D *et al.* Determinants in Canadian health care workers of the decision to withdraw life support from the critically ill. Canadian Critical Care Trials Group. *JAMA* 1995;**273**(9):703–8.
- Atrial fibrillation investigators. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;**154**(13):1449–57.
- Evans A, Kalra L. Are the results of randomized controlled trials on anticoagulation in patients with atrial fibrillation generalizable to clinical practice? *Arch Intern Med* 2001;**161**(11):1443–7.
- Beyth RJ, Quinn LM, Landefeld CS. Prospective evaluation of an index for predicting the risk of major bleeding in outpatients treated with warfarin. *Am J Med* 1998;**105**(2):91–9.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* 2002;**324**(7329):71–86.
- Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med* 1999;**131**(7):492–501.
- Devereaux PJ, Anderson DR, Gardner MJ, Putnam W, Flowerdew GJ, Brownell BF *et al.* Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. *BMJ* 2001;**323**(7323):1218–22.
- Man-Son-Hing M, Laupacis A, O'Connor AM, Coyle D, Berquist R, McAlister F. Patient preference-based treatment thresholds and recommendations: a comparison of decision-analytic modeling with the probability-tradeoff technique. *Med Decis Making* 2000;**20**(4):394–403.
- Haynes RB. Improving patient adherence: state of the art, with a special focus on medication taking for cardiovascular disorder.

- ders. In: Burke LE, Okene IS, eds. Patient Compliance in Health-care and Research. American Heart Association Monograph Series. Armonk, NY: Futura Publishing Co., 2001:3–21.
21. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. The rational clinical examination. Is this patient taking the treatment as prescribed? *JAMA* 1993;**269**(21):2779–81.
22. Guyatt G, Haynes B, Jaeschke R *et al.* Introduction: the philosophy of evidence-based medicine. In: Guyatt G, Rennie DR, eds. Users' Guides to the MEDICAL LITERATURE. Chicago: AMA Press, 2002:3–12.
23. Nisbett R, Ross L. Human Inference. Englewood Cliffs, NJ: Prentice-Hall, 1980.
24. Hackam DG, Redelmeier DA. Translation of research evidence from animals to humans. *JAMA* 2006;**296**(14):1731–2.
25. Timmis AD, Smyth P, Jewitt DE. Milrinone in heart failure. Effects on exercise haemodynamics during short term treatment. *Br Heart J* 1985;**54**(1):42–7.
26. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM *et al.* Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. *N Engl J Med* 1991;**325**(21):1468–75.
27. Yusuf S, Teo KK. Inotropic agents increase mortality in patients with congestive heart failure. American Heart Association 63rd Scientific Sessions, November 12–15 1990, Dallas, Texas.
28. Popp AJ, Chater N. Extracranial to intracranial vascular anastomosis for occlusive cerebrovascular disease: experience in 110 patients. *Surgery* 1977;**82**(5):648–54.
29. EC/IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke. Results of an international randomized trial. *N Engl J Med* 1985;**313**(19):1191–200.
30. Stampfer MJ, Colditz GA. Estrogen replacement therapy and coronary heart disease: a quantitative assessment of the epidemiologic evidence. *Prev Med* 1991;**20**(1):47–63.
31. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B *et al.* Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA* 1998;**280**(7):605–13.
32. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML *et al.* Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;**288**(3):321–33.
33. Taylor DW, Barnett HJ, Haynes RB, Ferguson GG, Sackett DL, Thorpe KE *et al.* Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. *Lancet* 1999;**353**(9171):2179–84.
34. Coltart J, Alderman EL, Robison SC, Harrison DC. Effect of propranolol on left ventricular function, segmental wall motion, and diastolic pressure-volume relation in man. *Br Heart J* 1975;**37**(4):357–64.
35. Lechat P, Packer M, Chalon S, Cucherat M, Arab T, Boissel JP. Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;**98**(12):1184–91.
36. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;**353**(9146):9–13.
37. The MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;**353**(9169):2001–7.
38. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P *et al.* Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;**344**(22):1651–8.
39. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH *et al.* Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med* 1991;**324**(12):781–8.
40. Moore TJ. Excess mortality estimates. In: Deadly Medicine: Why Tens of Thousands of Heart Patients Died in America's Worst Drug Disaster. New York: Simon & Schuster, 1995:281–9.
41. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ* 1998;**317**(7167):1185–90.
42. Chalmers I. Unbiased, relevant, and reliable assessments in health care: important progress during the past century, but plenty of scope for doing better. *BMJ* 1998;**317**(7167):1167–8.
43. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004;**364**(9438):937–52.
44. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? *Stat Med* 1984;**3**(4):409–22.
45. Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. *JAMA* 2005;**294**(2):218–28.
46. Beyth RJ, Quinn L, Landefeld CS. A multicomponent intervention to prevent major bleeding complications in older patients receiving warfarin. A randomized, controlled trial. *Ann Intern Med* 2000;**133**(9):687–95.
47. Guyatt G, Montori V, Devereaux PJ, Schunemann H, Bhandari M. Patients at the center: in our practice, and in our use of language. *ACP J Club* 2004;**140**(1):A11–12.
48. Malenka DJ, Baron JA, Johansen S, Wahrenberger JW, Ross JM. The framing effect of relative and absolute risk. *J Gen Intern Med* 1993;**8**(10):543–8.
49. O'Connor AM, Rostom A, Fiset V, Tetroe J, Entwistle V, Llewellyn-Thomas H *et al.* Decision aids for patients facing health treatment or screening decisions: systematic review. *BMJ* 1999;**319**(7212):731–4.
50. Naik AD, Kallen MA, Walder A, Street RL Jr. Improving hypertension control in diabetes mellitus: the effects of collaborative and proactive health communication. *Circulation* 2008;**117**(11):1361–8.
51. Man-Son-Hing M, Laupacis A, O'Connor A, Wells G, Lemelin J, Wood W *et al.* Warfarin for atrial fibrillation. The patient's perspective. *Arch Intern Med* 1996;**156**(16):1841–8.