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Although clinical guidelines may have substantial implications for allocation of health-care resources, these issues typically are not considered in the guideline development process or are only considered informally. This is a particular challenge for guidelines intended to be applicable in a diversity of settings. Based on theoretical and practical issues, we develop and apply a basic strategy for incorporating resource considerations into clinical guidelines. Formal economic assessments, such as cost-effectiveness analyses, provide a powerful tool to account for the health and economic implications of clinical guidelines. An acceptable tradeoff of money for health can depend highly on local considerations, and it is feasible to incorporate resource considerations into clinical guidelines. Although use of a “bright line” criterion for what constitutes an acceptable tradeoff of money for health has some appeal, this approach can lead to guidelines that are sensible in some contexts but unrealistic in others. One way to address this tension is through “resource aware” guidelines in which the recommendations are primarily based on scientific evaluations of efficacy supplemented by a review of evidence about the health and economic tradeoffs associated with various options. This approach limits the possibility that the guideline committee can make a universal recommendation based on resource considerations, but we expect it will encourage more thoughtful discussion of economic issues; greater sensitivity to the diversity of investment in health resource internationally; and, perhaps, innovative ways of overcoming resource barriers to the use of the most effective therapies.

*Key words:* cost analysis; cost-effectiveness analysis; costs; health-care costs; practice guidelines

**Abbreviations:** ACCP = American College of Chest Physicians; CBA = cost-benefit analysis; CURE = clopidogrel in unstable angina to prevent recurrent ischemic events; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; VTE = venous thromboembolism

Clinical guidelines are systematically developed documents whose ultimate goal is to promote high-quality clinical practice by informing decision makers at all levels about what works, how well, and under what circumstances. Increasingly, the accepted foundation for clinical guidelines is high-quality scientific studies (particularly randomized clinical trials) that address the benefits and risks of each relevant decision problem. Such evidence then is used to create actionable if-then statements, such as: “If a patient is found to have X (a specific set of characteristics), then the guideline panel recommends strategy Y (a mix of diagnostic and/or treatment approaches).”

The moment a guideline statement is published, resource considerations become relevant. This is particularly true for clinical situations in which current practice is inconsistent with the guideline and thus requires a change in practice—a deviation from the status quo, a stable situation reflecting a confluence of scientific and resource considerations by the various stakeholders responsible for decision making. Because a new guideline often endorses change from the status quo, it is likely to engender some degree of resistance. One important source of resistance derives from careful assessment of the scientific and clinical merit of a proposed change. Why support the

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recommendation if the foundations of the recommendation may not be true? However, even if the evidence is persuasive, resistance to a new guideline can still emerge when change requires health-care resource reallocation. By health-care resources, we are referring not only to the familiar resources directly involved in the production of health services, but also to the time, political clout, and emotional energy expended by the provider, administrator, or other stakeholder.

By bringing resource issues into a discussion of clinical guidelines, the entire range of factors that make the recommendation the object of controversy come aggressively into the foreground. These factors range from the economic worth of health benefits relative to all other potential use of resources (ie, their “value”) to the question of whether a particular recommendation is feasible in a given local environment or jurisdiction. Given the complexity and controversy engendered by resource use considerations, the majority of guideline development panels explicitly disregard resource use issues, suggesting their charge is limited to purely “scientific issues” and leaving resource considerations for individual decision makers to hash out.

In March 2005, the American College of Chest Physicians (ACCP) convened a task force to address how resource considerations could be incorporated into clinical guidelines. This task force formally rejected the notion that resource considerations be dismissed or treated informally. The group provided suggestions for addressing resource allocation issues directly (Table 1). They recognized that such an effort would face a variety of challenges, including the lack of familiarity of guideline panelists with economic analysis, the dearth of high-quality data regarding resource implications, and the need for a more explicit approach to making the task force’s suggestions operationally useful.

Although it may be premature to establish a unified approach to incorporating resource considerations into clinical guidelines, we agree with the task force that it is imperative to make resource considerations a more explicit element of clinical guidelines. In the spirit of moving this agenda forward, this chapter provides an overview of some key concepts relevant to the task of incorporating resource issues into clinical guidelines. Specifically, we (1) describe key introductory economic concepts; (2) highlight special issues raised by incorporating resource use issues into clinical guidelines, in particular the applicability of traditional societal economic analyses to local contexts; and (3) present a basic framework for incorporating resource considerations into clinical guidelines as well as provide brief illustrations of how this framework was applied to specific recommendations in the Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition).

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**Table 1—Recommendations for Clinical Guideline Developers Considering Resource Allocation Issues**

<table>
<thead>
<tr>
<th>Recommendation No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Guideline panels should be explicit about the extent to which they consider resource allocation issues in their recommendations.</td>
</tr>
<tr>
<td>2</td>
<td>Panels should consider resource allocation issues for a subset of recommendations in keeping with the amount of funding available for this task.</td>
</tr>
<tr>
<td>3</td>
<td>Panels should place a premium on doing a good job with each recommendation in which they consider resource issues and compromise, if necessary, on the number of such recommendations.</td>
</tr>
<tr>
<td>4</td>
<td>Panels should consider resource allocation issues when it is plausible that they will influence the direction or strength of a recommendation.</td>
</tr>
<tr>
<td>5</td>
<td>Panels should conduct a systematic search for economic analyses and should consider the findings in generating each recommendation for which the panel decides to consider resource allocation issues.</td>
</tr>
<tr>
<td>6</td>
<td>Panels should apply clear and consistent criteria to the interpretation of economic analyses.</td>
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<tr>
<td>7</td>
<td>Panels considering resource allocation issues should specify the target audience explicitly.</td>
</tr>
<tr>
<td>8</td>
<td>Panels should explicitly address in the recommendation whether resource allocation issues differ substantially across the target audience and, if necessary, offer differing recommendations across segments of the target audience.</td>
</tr>
<tr>
<td>9</td>
<td>Panels should include one or more members with expertise in economic evaluation and should mandate that those members lead the group in consideration of resource allocation issues.</td>
</tr>
</tbody>
</table>

*From Guyatt et al.*

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in this chapter was applied to a subset of the ACCP recommendations as a “proof of concept.”

**KEY INTRODUCTORY ECONOMIC CONCEPTS**

**Value for Money**

The questions asked in the evaluation of clinical efficacy (Does a new therapy or strategy work in the ideal or best case situation?) and effectiveness (Does the new therapy or strategy work in the usual world of routine medical care?) define the following: (1) that a therapy can work, (2) the magnitude of benefit provided, and (3) the major determinants of that magnitude. Economic questions start with the presumption that the therapy works (and is at least equivalent in effectiveness to established treatment options) for some plausible situations and asks whether it is good value for money (or if equivalent, cost saving). An exception is when a new strategy is marginally less effective but notably cost saving; in practice, such strategies could be considered a reasonable option but face obvious challenges in the medical marketplace.

At one level, whether something is a good value for money is a basic sort of question that every consumer understands. However, in the consumer goods world, where there is free competition and widespread experience with the toasters, cars, and portable media players that people may wish to purchase, the “value” or benefit part of this assessment is made subjectively by each consumer, whereas the price or cost part is set by markets. In medicine, neither of those factors can be relied on. Patients usually do not have experience with the alternative health states that their therapies may provide for them and therefore are unable to assess subjectively how they would value these states. There is little evidence for free market forces in medicine to set prices both because of the absence of true competition among providers on price and because of price setting by payers, particularly in European countries. Health insurance further distorts the picture by disconnecting the consumer from the payer, creating a situation where too much care may be consumed in some cases and too little in others.

One implication of this observation is that although assessments of the value for money are part of the human experience, such assessments in the medical context are especially difficult at the consumer level. Thus, systematic and explicit analysis of the health and economic tradeoffs attributable to a medical intervention typically are performed from the societal perspective rather than from that of the individual patient. The objective in this situation is to maximize the health benefits provided to the population for a given level of health-care spending. As will be described in the following sections, methods have been developed to permit a quantitative assessment of value for money in medical care. Although such methods require some useful simplifications, they also play an important role by requiring the analyst to clearly define what is being added by the new therapy or strategy and what that addition will cost in the long run.

**Assessment of Value**

Large randomized clinical trials are the best sources of unbiased information on what works in medicine. It might be presumed, therefore, that clinical trials define clearly what has been added by a new therapy. In many cases, however, such is not the case. Because of a variety of factors beyond the scope of this chapter, trials select populations that may not reflect the eventual patients who will most commonly receive the therapy; the end point of the trial frequently is chosen to keep sample size and cost at a manageable level rather than because of its clear-cut importance to patients; and follow-up usually is short relative to the time course over which the therapy might have some continuing effects. Whether a clinical study is applicable to a given patient context depends on how well the study addresses outcomes of importance to the patient. What matters to patients is how long they will live and how they will feel while alive (often referred to as their quality of life). Treatments that do not demonstrate improvements in either length or quality of life may not be providing any “value” at all. Based on (oversimplified) pathophysiologic reasoning and “common sense,” clinicians often are willing to conclude that benefit has been delivered through intermediate outcomes, such as changes on an imaging study or a biomarker. The best that can be said of such situations is that the case has not been well made. Many examples exist in medicine where important patient outcomes were disassociated from intermediate outcomes, such as the markers improved, but more patients died.

For this reason, most economists prefer to translate the results of all clinical benefit data into an aggregate effectiveness measure that summarizes all that is known about the health benefits provided. The standard approach is to estimate the number of life years or quality-adjusted life years (QALYs) added by the new therapy relative to the appropriate comparison. QALYs represent the quantity of incremental life expectancy produced weighted by the quality of life for that extra survival. The weights are derived either from patients with experience in the
health states in question or from the general public asked to imagine themselves in these health states and to value them relative to excellent health and death. QALYs are not the only method for combining quantity and quality of life into a single composite measure, and the current methods to develop QALYs are far from perfect, but they are the most common approach to making the tradeoffs between length and quality of life explicit.

The difficulties in making such projections of value, which for chronic diseases may extend across the remaining life expectancy of the study cohort, much longer than the clinical trial follow-up, is the uncertainty in the calculations. No good methods exist to validate life-expectancy estimates. Empirical validation is not feasible in a population with a life expectancy > 5 years. The best that can be done is to use clear, transparent methods for estimation and perform sensitivity analyses that demonstrate the “answer” to be robust to the most plausible variations in methods and assumptions.

A decision made without accounting for resource considerations still has resource implications. Such difficulties might lead the noneconomist to conclude that the whole effort is not worth serious attention. Two important points rebut this skeptical attitude. First, choices must be made regardless of whether the data are robust and pristine or messy and ambiguous. In the real world, even no decision is a decision. The economist is an immensely pragmatic individual willing to make decisions with the best information at hand. Because of their training, clinicians often think of themselves as purists, settling only for high-quality, “statistically significant” results. In reality, clinicians use highly uncertain information to manage patients daily. Second, the process of attempting to translate short-term clinical trial results using composite clinical endpoints into lifetime estimates of added QALYs is instructive in forcing all interested parties to specify exactly what they believe will happen in areas where there are no data but where decisions will still need to be made. The best analyses clarify key pressure points in the decision, areas where more data are needed and where choices may be affected by varying the assumptions being made.

Fortunately, the many details of clinical trials and economic analyses tend to reduce to some common patterns that can be readily understood and communicated to decision makers. Two key items are necessary to keep in mind in this process. First, cost should never be discussed in isolation. Money is always spent to buy something, in this case extra health-care benefits. Whether it is a good investment is a separate question. The key point is that value for money can never be decided by discussing only the money side of the problem. Hospitals and payers tend to make this mistake because from their point of view, the benefits may be invisible. For example, the cost is incurred in the hospital while the benefit occurs long after the patient has gone home or after the patient has shifted to a different insurance or managed care plan. Second, in the majority of medical-value-for-money problems, the magnitude of clinical benefits rather than the cost of therapy determines whether the full analysis shows good value or otherwise. In short, a highly effective therapy that saves lives will support a premium price/long-term cost, but a therapy that is marginally effective on nonfatal endpoints better be inexpensive.

Formal Metrics of Value for Money

As a practical matter, economic questions are asked in medicine when a new therapy becomes available that is both more effective than the alternative and more costly. The task for the economic analyst is to make the long-term stream of costs and health outcomes explicitly clear and, if necessary, to perform formal calculations of value for money in the form of cost-effectiveness analyses or cost-benefit analysis (CBA). (An additional form of analysis, cost-minimization analysis, specifically disregards the health implications of choices and, thus, either implicitly or explicitly assumes that health benefits are equivalent for options under consideration.)

The foundation for cost-effectiveness analyses and CBA is that any assessment of value for money should improve the allocation of resources among possible alternatives and to account for the impacts over all relevant stakeholders. The standard in economic analysis for health care is to perform the exercise from the “societal” perspective, and thus, the analyst starts with an objective (here some mathematical representation of health of a community and its individuals) and the range of resources required by various alternative strategies in terms of their economic cost, specifically, opportunity costs that represent the price in a free market when the resource is applied to its best alternative.

In a case of cost-effectiveness analysis, the analyst calculates a metric of value for money, termed the incremental cost-effectiveness ratio (ICER):

\[(\text{cost}_A - \text{cost}_B)/(\text{effectiveness}_A - \text{effectiveness}_B)\]

where A is the more effective choice and B the less effective. In the case of CBA, the metric is net cost, where health benefits are assigned a monetary value:

\[(\text{cost}_A - \text{cost}_B) - (\text{benefit}_A - \text{benefit}_B)\].

In either case, these metrics can be used to identify relative efficiencies in the allocation of re-
sources, at least theoretically. For cost-effectiveness analyses, the ICER for a particular clinical decision can be compared to the ICER for other decisions. The allocation of resources can be optimized (theoretically) from an efficiency perspective in one of two ways. In the first approach, resources are allocated progressively from interventions with the lowest ICER to the highest, stopping when health-care resources are all allocated. This way might be possible in the case of a fully planned health system. The second approach is to consider new recommendations one at a time; policy recommendations with an “acceptable ICER” are embraced, and interventions with ICERs above that range are rejected.

In CBA, only interventions with a net cost savings are accepted (where net cost incorporates the monetized value of health outcomes). The purported advantage of cost-effectiveness analysis over CBA is that it does not require assigning a monetary value to health benefits because that exercise is particularly controversial in the medical arena.

ICERs usually are compared to other “acceptable” interventions in terms of expenditures for health benefits, using benchmarks such as “league tables,” which list the ICERs for a variety of well-accepted interventions.3 It is common for an analyst or decision maker to conclude that recommending drug Y over drug X in a particular context is likely to be a good value for money in that the ICER for Y vs X is similar or lower than, say, medical treatment for hypertension. This conclusion is possible only when the outcomes are denominated in the same units. When health outcomes are represented as QALYs, a cost-effectiveness analysis is termed a cost utility analysis.2

Special Issues Raised by Incorporating Resource Considerations Into Clinical Guidelines: Beyond Standard Cost-effectiveness Analyses

Cost-effectiveness analysis is a potentially powerful approach in that it provides an explicit accounting of the health and economic implications of health-care decisions. In some countries, such as the United Kingdom, Canada, and Australia, such analyses are key inputs to policy making.4 However, our objective here is to develop guidelines for an international audience, and in this context there are limits to the use of cost-effectiveness analysis as the sole calculus for determining that a particular choice is broadly acceptable.

Several typical features of a cost-effectiveness analysis tend to limit the generalizability of an analysis, particularly for local decision makers. For example, in a cost-effectiveness analysis it is typically assumed that the resources required to produce an outcome are uniform across different practice settings (or at least sufficiently so for practical purposes). In reality, the health-care system is notoriously inefficient both in the delivery and administration of services.5 Moreover, the resource used for health-care production is quite variable from site to site because of differences in both efficiency and resource availability and cost structure (eg, in developed countries, the cost of drugs relative to personnel is lower than in developing countries).

Another limitation in generalizing from a typical cost-effectiveness analysis is that costs are treated as variable; that is, addition or subtraction of one unit of service adds or subtracts one unit of corresponding cost. Long-term costs, such as development of the infrastructure to provide thrombolytic therapy for acute stroke patients (eg, the emergency department, the ICU, the diagnostic imaging and laboratory testing facilities required for care of these patients), tends to be folded into a per-treatment cost through amortization (ie, allocation of the costs of technology over the useful lifetime of that technology). For example, from the long-term societal perspective, the need for CT before treatment with thrombolytic therapy is accounted for in the cost assigned to the CT test. However, from the local hospital perspective, providing this part of the care might require the building of a new CT suite dedicated to the emergency department and 24-hour staffing for that facility. The decision to make this investment requires a host of considerations that are wholly separate from the considerations regarding the cost-effectiveness of thrombolytic therapy for acute stroke.

A third issue relates to the validity for most decision makers of the ICER as a guide to value for money. On theoretical grounds, the ICER could allocate societal health-care resources much more efficiently relative to current practice. However, such a utopian scheme requires national consensus on the maximization of the general societal well-being without regard to specific winners and losers, and it requires detailed, high-quality economic information on all major spending choices, data that do not currently exist. Attempts to use cost-effectiveness criteria to set spending policy in the United States have been limited and generally unsuccessful. Use of these data in other countries to set spending policy has been more successful, particularly in the United Kingdom and Australia, but many countries that require economic analysis as part of the new drug approval and reimbursement process are more interested in the potential impact on overall health-care spending and how this can be controlled.

In developing international guidelines, it must be appreciated that the acceptable level of ICER will vary depending on national wealth. Various benchmarks for this threshold have been cited, ranging from about US $30,000 to US $100,000 per QALY.6,7 However, what
may be an acceptable tradeoff of health for resources in Canada is likely to be unrealistic in Tanzania. The World Health Organization Commission on Macroeconomics and Health has suggested that an acceptable threshold ICER is on the order of three times the gross national income per capita; for sub-Saharan Africa where gross national income is US $470, the threshold ICER might be no higher than US $1,400 per QALY. More fundamentally, whatever is spent for health care is no longer available for use in the production of education, roads, defense, clean water, and other public goods. Economics actually has nothing to say about the correct level of spending on health care. That is a political and, perhaps, ethical question. Economics can help inform the answer by identifying whether additional spending can produce significant extra health. But if there is not ability to shift funding toward health care, the efficiency question referred to above becomes irrelevant.

In spite of the limitations just described, we think that cost-effectiveness analyses can be useful insofar as they help local decision makers to understand the general implications of their choices and to clarify the factors influencing relative value. Thus, in addition to any traditional cost-effectiveness analysis exercise, we suggest that a resource assessment focus on how value is likely to be affected by factors that vary across jurisdictions. This assessment allows local decision makers to be better informed in the exercise of their decisional autonomy—their prerogatives as stewards responsible to their constituents.

Framework for Developing Guidelines Informed by Resource Considerations

In keeping with the suggestions put forth by the ACCP task force, we present a simple framework for a guideline panel to consider when examining resource issues. We start from the proposition that the goal is to provide information to decision makers in a way that is primarily informative rather than prescriptive—what we term resource aware guidelines. The four-step approach described below is intended to offer guidance for the range of realistic situations.

1. Select Target Guideline Recommendations for Resource Use Evaluation: As described by the ACCP task force, not all guideline recommendations raise compelling or controversial resource use issues. Attention, therefore, should focus on interventions for which the panel members believe that some in the guideline’s target audience are likely to resist or experience reluctance to implement on the basis of high costs.

2. Identify the Literature: The focus here are published studies regarding resource use, identified using standard search techniques and reviewed using general criteria for quality. It should be noted that formal methods for the assessment of the quality of economic studies are not as well developed as for the assessment of clinical trials.

3. Evaluate the Evidence With Regard to the Following Questions: What are the resource considerations from a social perspective? These considerations typically are examined through the performance of a “reference case” or “base case” cost-effectiveness analysis, CBA, or cost-minimization analysis. The goal is to estimate the long-run impact of alternative treatments to society as a whole. The reference case refers to the most plausible set of starting assumptions on effectiveness and costs. The product of the reference case analysis is an incremental cost-effectiveness ratio, often with some measure of variability. From this base, the effect of variations in starting parameters can be examined using sensitivity analyses, which provide information about the factors that most strongly affect the ICER calculation. For example, it is crucial to note whether the cost-effectiveness tradeoff is strongly affected by, say, duration of efficacy or the cost of the intervention. In the former case, the analysis speaks to the need for long-term clinical follow-up studies. In the latter case, knowing that a treatment only would be a good value at a lower cost can provide an impetus for considering ways to make the more effective strategy cheaper.

What is the differential impact of resource considerations on various stakeholders in various jurisdictions? An intervention may make “sense” in a theoretical framework of total societal costs and aggregate health benefits, whereas in many particular situations it may not. In particular, gains and losses from implementing a guideline are usually not uniformly distributed within or across practice locations (either within or between countries). Analyses that consider specific stakeholder perspectives can help to identify the “winners and losers.” For example, in stroke treatment, an economic analysis may indicate that improved acute treatment may reduce disability and perhaps nursing home and other long-term-care costs, leading to a cost-effective therapy from a societal perspective. However, a recommendation for acute care hospitals to provide eligible acute stroke patients with tissue plasminogen activator therapy increases the cost of care for the hospital by several thousand dollars. In many cases, such as reimbursement based on a diagnosis-related group, the extra cost of the thrombolytic therapy cannot be passed on by the hospital to the payer. As a consequence, hospitals may be less than enthusiastic about implementing acute stroke reperfusion therapy until the reimbursement issue is addressed. Revealing this
discordance opens an opportunity for such discussions and, perhaps, reimbursement policy change.

4. Incorporate Evidence Into Recommendation Statement: In rare circumstances, an economic evaluation may provide compelling information that will lead a guideline panel to modify a recommendation about an intervention that has been shown to be clinically effective. A more common possibility is that an intervention that was of only modest clinical interest based on considerations of benefit will be given a more favored position in the guideline because of demonstrable cost savings (e.g., treatment is less expensive initially, or initially expensive treatment leads to countervailing cost savings down the line). In the most common situations, the new therapy being considered is both more effective and more expensive than the comparison strategy. In such situations when economic analyses of acceptable quality are available, they will allow identification of circumstances under which the use of the new, more expensive therapy provides reasonable value for money. Here the recommendation may be worded so as to clarify the tradeoff and, in particular, can highlight the circumstances in which resource considerations present opportunities (as for cost saving due to reduction in expensive down-line events) or barriers (as when changes in drug administration procedures might make treatment a good value).

In the ACCP guidelines, the following wording was approved for inclusion in recommendation statements when economic considerations resulted in a decrease in enthusiasm for a therapy: “The grading of this recommendation as weak rather than strong reflects a consideration of not only the tradeoff between the advantages and disadvantages of the intervention as reflected in its effects on clinical outcomes, but also the implications in terms of resource use (costs) in a representative group of countries.”

Illustrative Examples

As a preliminary effort to incorporate resource considerations into the ACCP guideline process, five chapters were selected in which cost issues were considered particularly salient. To illustrate the ways in which economic data can relate to clinical guideline recommendations, we consider two brief examples taken from these other chapters in this supplement: duration of venous thromboembolism (VTE) prophylaxis after hip surgery and clopidogrel use for secondary prevention in patients with atherosclerotic vascular disease.

Duration of VTE Prophylaxis Following Hip Replacement

1. Select Target Guideline Recommendations for Resource Use Evaluation: As reviewed in the “Prevention of VTE” chapter of this supplement, clinical trial data indicate that prolongation of VTE prophylaxis beyond 2 weeks following hip surgery is effective in reducing symptomatic VTE. However, such therapy can be costly, particularly when low-molecular-weight heparin is the treatment used, and the panel was concerned that these issues would create a barrier at some sites.

2. Identify the Literature: A review of the literature revealed seven studies performed in developed countries (France, Sweden, Italy, United States, United Kingdom, Switzerland, and Belgium) that examined the cost implications of shorter vs longer duration of prophylaxis for VTE after hip replacement. These studies were of variable quality based on modeling with minimal empirical cost data.

3. Evaluate the Evidence: What are the resource considerations from a social perspective? Despite different assumptions and methods, prolonged VTE prophylaxis after hip replacement was generally judged to be a good use of resources (either cost saving or had a “reasonable” ICER). Estimates of the ICER of extended VTE prophylaxis ranged from negative (cost saving) to approximately US $35,000. Generally, the most important factor driving these results was the cost offset provided by prophylaxis (from reduced medical costs for deep vein thrombosis and pulmonary embolism) relative to the cost of treatment.

What is the differential impact of resource considerations on various stakeholders, in various jurisdictions? No explicit assessment was made regarding the differential impact of prolonged VTE prophylaxis on various stakeholders. No studies in less-developed countries were identified. However, it was noted that the cost of providing prophylaxis was an important factor in the assessment of cost-effectiveness. In particular, if home care nursing for administering injections could be avoided, then most analyses indicated that prolonged prophylaxis likely would be cost saving. To the extent that cost of drug acquisition, drug administration, and downstream VTE outcomes are borne by different stakeholders, a recommendation of prolonged VTE prophylaxis is likely to have a differential effect on these different stakeholders.

4. Incorporate Evidence Into Recommendation Statement: Based on a clinically important advantage in reducing symptomatic VTE, prolonged prophylaxis following hip replacement was categorized as a Grade 1A recommendation. Favorable evidence regarding cost implications reinforced this recommendation, despite concerns about the potential impact of drug costs on the acceptability of extending VTE prophylaxis beyond...
The rationale for this recommendation and how resources influenced it are described in the text providing the evidence for this recommendation.

**Clopidogrel Use for Secondary Prevention in Patients With Atherosclerotic Vascular Disease**

1. **Select Target Guideline Recommendations for Resource Use Evaluation:** As reviewed in the “Primary and Secondary Prevention of Chronic Coronary Artery Disease” chapter of this supplement, several major clinical trials have examined the prognostic benefits of varying duration of clopidogrel therapy with or without aspirin, compared to aspirin alone, for secondary prevention in coronary artery disease and other vascular diseases (clopidogrel vs aspirin in patients at risk for ischemic events; clopidogrel in unstable angina to prevent recurrent ischemic events [CURE]; clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance). Clopidogrel is relatively expensive, with a retail cost in the United States in 2007 of around $4 per day and no generic formulation expected until 2011. The clinical issues that need to be considered are when to start the drug for secondary prevention purposes, in which patients, and for how long to continue it.

2. **Identify the Literature:** Three major analyses of this therapy have been conducted from the United States perspective since 2002 along with analyses from the United Kingdom, Sweden, Denmark, Australia, and Germany. The economic analyses consider both short-term (30 days, 9 to 12 months) and long-term therapy (years, up to a lifetime).

3. **Evaluate the Evidence:** What are the resource considerations from a social perspective? In prevention, the cost of therapy does not usually depend on the patient’s clinical status. Thus, in the case of antiplatelet therapy for secondary prevention, the cost of 75 mg/d of clopidogrel does not depend on whether the patient has greater or lesser disease severity or on the projected future clinical risk of complications. However, when used in a higher risk population, as reflected in the CURE trial of patients with acute coronary syndrome, clopidogrel treatment reduced in-hospital refractory ischemia and need for revascularization and, as a consequence, had an approximately 50% reduction in the net cost of therapy at 9 to 12 months.

Cost-effectiveness analysis of the limited course of therapy reflected in CURE suggested robust evidence of good value for money, with cost-effectiveness below $10,000 per life year added. However, a model-based analysis considering the same CURE acute coronary syndrome population but extending the treatment out past 1 year showed that each subsequent year of therapy becomes progressively less economically attractive. This result depended on the assumptions about the long-term risk of the population when treated with aspirin alone, the durable effectiveness of clopidogrel therapy, and the long-term risk of bleeding. In CURE, most of the treatment benefit was established by 3 months. As a consequence, the incremental benefit of treating for progressively longer periods must address the same cost per day of therapy but smaller absolute benefits. More recent 28-month data from the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance trial support the reduced reduction of absolute improvement in event rates in the long term. Taken together, the available trial and economic analysis data support the strong case for early secondary prevention therapy with clopidogrel in higher risk patients but suggest that the clinical and economic case is much less persuasive for chronic therapy or therapy in lower risk populations.

What is the differential impact of resource considerations on various stakeholders, in various jurisdictions? The use of clopidogrel for secondary prevention takes place largely in the outpatient setting. The economic impact on stakeholders other than society as a whole depends on who pays the cost of the drug therapy and who bears the cost of care for complications of the disease that are not averted. No economic studies examine the perspective of the developing countries. For lifetime therapy with clopidogrel to reach nominal thresholds of cost-effectiveness, Gaspoz et al estimated that the price would need to be reduced to about $0.60 per day.

4. **Incorporate Evidence Into Recommendation Statement:** In light of the clinical trial data, the committee made several recommendations in support of the use of antiplatelet agents, including clopidogrel. However, based on the economic review in which cost of clopidogrel was a key to its cost-effectiveness, it was acknowledged explicitly that the recommendations place a low value on avoiding high medication costs.

**Conclusions**

The clinician’s (and possibly the patient’s) version of an ideal world is one where all clinical practice (and clinical practice guidelines) are based solely on assessments of which interventions provide the greatest health benefit. For better or worse, however, we are faced with resource constraints that force us to temper our actions. Within this real world, enthusiasm is best reserved for therapies that provide the greatest value for resources consumed. Economic

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**References:**

1. The rationale for this recommendation and how resources influenced it are described in the text providing the evidence for this recommendation.

2. Several major clinical trials have examined the prognostic benefits of varying duration of clopidogrel therapy with or without aspirin, compared to aspirin alone, for secondary prevention in coronary artery disease and other vascular diseases.

3. Clopidogrel is relatively expensive, with a retail cost in the United States in 2007 of around $4 per day and no generic formulation expected until 2011.

4. Clinical issues that need to be considered are when to start the drug for secondary prevention purposes, in which patients, and for how long to continue it.

5. Three major analyses of this therapy have been conducted from the United States perspective since 2002 along with analyses from the United Kingdom, Sweden, Denmark, Australia, and Germany.

6. Economic analyses consider both short-term (30 days, 9 to 12 months) and long-term therapy (years, up to a lifetime).

7. What are the resource considerations from a social perspective? In prevention, the cost of therapy does not usually depend on the patient’s clinical status.

8. In the case of antiplatelet therapy for secondary prevention, the cost of 75 mg/d of clopidogrel does not depend on whether the patient has greater or lesser disease severity or on the projected future clinical risk of complications.

9. However, when used in a higher risk population, as reflected in the CURE trial of patients with acute coronary syndrome, clopidogrel treatment reduced in-hospital refractory ischemia and need for revascularization and, as a consequence, had an approximately 50% reduction in the net cost of therapy at 9 to 12 months.

10. Cost-effectiveness analysis of the limited course of therapy reflected in CURE suggested robust evidence of good value for money, with cost-effectiveness below $10,000 per life year added.

11. However, a model-based analysis considering the same CURE acute coronary syndrome population but extending the treatment out past 1 year showed that each subsequent year of therapy becomes progressively less economically attractive.

12. This result depended on the assumptions about the long-term risk of the population when treated with aspirin alone, the durable effectiveness of clopidogrel therapy, and the long-term risk of bleeding.

13. In CURE, most of the treatment benefit was established by 3 months.

14. As a consequence, the incremental benefit of treating for progressively longer periods must address the same cost per day of therapy but smaller absolute benefits.

15. More recent 28-month data from the clopidogrel for high atherothrombotic risk and ischemic stabilization, management, and avoidance trial support the reduced reduction of absolute improvement in event rates in the long term.

16. Taken together, the available trial and economic analysis data support the strong case for early secondary prevention therapy with clopidogrel in higher risk patients but suggest that the clinical and economic case is much less persuasive for chronic therapy or therapy in lower risk populations.

17. What is the differential impact of resource considerations on various stakeholders, in various jurisdictions? The use of clopidogrel for secondary prevention takes place largely in the outpatient setting.

18. The economic impact on stakeholders other than society as a whole depends on who pays the cost of the drug therapy and who bears the cost of care for complications of the disease that are not averted.

19. No economic studies examine the perspective of the developing countries.

20. For lifetime therapy with clopidogrel to reach nominal thresholds of cost-effectiveness, Gaspoz et al estimated that the price would need to be reduced to about $0.60 per day.

21. In light of the clinical trial data, the committee made several recommendations in support of the use of antiplatelet agents, including clopidogrel.

22. However, based on the economic review in which cost of clopidogrel was a key to its cost-effectiveness, it was acknowledged explicitly that the recommendations place a low value on avoiding high medication costs.

23. The clinician’s (and possibly the patient’s) version of an ideal world is one where all clinical practice (and clinical practice guidelines) are based solely on assessments of which interventions provide the greatest health benefit.

24. However, we are faced with resource constraints that force us to temper our actions. Within this real world, enthusiasm is best reserved for therapies that provide the greatest value for resources consumed.
analysis provides a useful analytic approach to assessing this tradeoff. In addition to offering a basic metric of value for money—the ICER—economic analysis is useful in defining the circumstances in which a particular intervention may be cost saving and, if not, when the tradeoff of health outcomes for resources is particularly favorable or unfavorable.

In the context of developing clinical guidelines intended for an international audience, particular attention to issues of regional variation is important. Rather than promote guidelines that are sensible for some countries but unrealistic in others, the goal is to make recommendations based on scientific evidence of efficacy and to inform decision makers about resource barriers, which they may or may not be equipped to overcome.

Although this approach limits the possibility that the guideline panel can make a firm recommendation based on resource considerations, we expect it will encourage more thoughtful discussion of economic issues; greater sensitivity to the diversity of investment in health resources internationally; and, perhaps, innovative ways of overcoming resource barriers to the use of the most effective therapies.

REFERENCES


