A computer program for statistically-based decision analysis

A Computer Program for Statistically-Based Decision Analysis

Jeanette X. Polaschek RN[1], Leslie A. Lenert MD[1], Alan M. Garber MD[2]

[1]Section on Medical Informatics
MSOB X-215, Stanford University School of Medicine
Stanford, CA 94305-5479
[2]Department of General Internal Medicine
Stanford University

Abstract

The majority of patients with coronary artery disease do not fall into the well defined populations from randomized clinical trials. Observational databases contain a rich source of information that could be used by practicing physicians to evaluate treatment alternatives for their patients. We describe a computer system, the CABG Kibitzer, which uses an integrated approach to evaluate the treatment alternatives for CAD patients. We combine a statistical multivariate model for calculating survival advantages with DA techniques for assessing patient preferences and sensitivity analysis, to create one tool that physicians find easy to use in daily clinical practice. The development of tools of this kind is a necessary step in making the data of outcome studies accessible to practicing physicians.

1. Introduction

The optimal treatment choice for patients with coronary artery disease (CAD) is highly dependent on individual patient characteristics. Randomized clinical trials of carefully selected patient groups suggest that, for younger patients with stenosis of the left main coronary artery or three-vessel disease combined with left-ventricular dysfunction, coronary artery bypass graft (CABG) surgery increases life expectancy over medical therapy. Further, in cases of moderate to severe angina pectoris, surgery improves quality of life through symptom relief [1]. Application of these results in the form of guidelines for management of patients with comparable characteristics is a relatively straightforward process.

Patients not directly comparable with populations used in randomized trials present difficulty. Conducting additional trials might be considered the optimal solution; however, the delay in obtaining results and the speed with which results become outdated often preclude using this approach. In the absence of relevant data for these patients, physicians rely on personal experience and observational studies to guide their clinical judgment. If not carefully controlled, however, personal experience and observational studies can trigger faulty decision making through selection or availability biases, lack of randomization, and anchoring or adjustment difficulties [2].

Several observational databases have been developed that provide a rich source of nonrandomized data on CAD patients. The Duke Cardiovascular Disease Databank, in existence since 1971, prospectively collects data on all CAD patients seen in Duke clinics [3]. Information on medical history, physical findings, and cardiac-catherization results are included. A Cox proportional hazards model is used to estimate the 1 - , 3 -, and 5 - year survival rates for medical and surgical patients. Several studies using this model and the Duke database have shown that the model is able to predict accurately the outcomes of patients from major randomized clinical trials and to perform with more discrimination than do human experts [3-5]. These studies indicate that with proper statistical procedures, observational data can be used to predict individual patient prognosis reliably [3-5].

Multivariate statistical models, such as the Cox model, are necessary to reduce the effect of selection bias inherent in the nonrandomized approach. These models cancel out the effects of known confounding prognostic factors, isolate the effects of therapy alternatives, and calculate survival advantages for individual patients [6].

Decision-analytic (DA) techniques have also been applied to the evaluation of patient candidacy for bypass surgery. These techniques provide a normative method for including individual patient preferences and lifestyles in the therapy decision. Sensitivity analysis allows the physician to explore how each prognostic factor influences the overall decision. A major problem with using DA techniques in clinical practice has been that performing probability assessments is difficult. For instance, given that a patient will have surgery at the age of 68 years and has a history of diabetes, what is the chance that this patient will develop angina or die after 1, 2, or 3 years? These types of assessments are very impractical to estimate based on subjective experience alone.

This paper describes a computer system, the CABG Kibitzer, which uses an integrated approach to evaluate the treatment alternatives for CAD patients. We combine a statistical multivariate model for calculating survival advantages with DA techniques for assessing patient preferences and sensitivity analysis, to create one tool that physicians find easy to use in daily clinical practice. The development of tools of this kind is a necessary step in making the data of outcome studies accessible to practicing physicians.

2. Background

Early work done by Pliskin and associates illustrates the difficulties of performing individual therapy evaluation in the absence of population based data -- that is, without knowledge of the results of randomized clinical trials and before any large observational databases had been tested [7]. Pliskin modeled the decision problem using a decision tree. To apply the tree to a particular patient, physicians first were required to estimate the probability of eight different events, many with multiple conditional dependencies. The probability of any event in the model depended on patient factors such as age, gender, the presence of other diseases (hypertension, diabetes, or congestive heart failure), the extent of CAD demonstrated on angiography, and the severity of the patient's angina. Second, physicians estimated probabilities that were conditionally

0195-4210/90/0000/0795$01.00 © 1990 SCAMC, Inc.

dependent on other events. In addition to the difficulties with probability assessment, wide variations were seen among physician estimates for the same patient cases. This method for deriving patient-specific probabilities was clearly not feasible for clinical use.

In the years since Pliskin's analysis, data from randomized clinical trials and nonrandomized observational databases have become available for simplifying the task of probability assessment. Two CAD databases, the Duke Databank and the Coronary Artery Surgical Study (CASS) Registry, have been used in conjunction with multivariate statistical models to create an improved methodology for calculating individual prognosis.

CASS was a randomized clinical trial designed to study the efficacy of surgical intervention in selected subgroups of CAD patients [6]. Concurrent with this study, nonrandomized patients not meeting the subgroup criteria under study were entered into an observational database, the CASS Registry. Careful recording of symptoms and events over a 5 - to 8 - year period provided observational data on the outcomes of medical and surgical therapy for these nonrandomized patients. This data has been used in several outcome studies [Gersh, 85].

We have developed a statistical model that replaces the decision-tree approach for a subset of patients who must decide whether to undergo CABG surgery. Our model calculates the probability of individual survival given surgery or medical therapy for geriatric patients over a user-specified number of years. This estimate of the patient's course replaces the decision-tree model. No estimation of probabilities is required; only patient data for prognostic factors -- such as age, gender, and extent of coronary artery disease -- are needed. The advantage of this approach is a rapid and consistent approximate solution to the difficult problem of estimating patient-specific probabilities. The approach is unique in the design of combining statistical models with DA techniques into a package that any physician can feasibly use in clinical practice.

3. Design Considerations

Two goals motivated us to develop the CABG Kibitzer. The first was to create a computer-based tool that assists physicians in evaluating the relative benefits of CABG surgery versus. other treatment alternatives (for example, medical management or angioplasty) in CAD patients. The second was to develop an approach for combining decision-analytic techniques with statistical models for estimating individual outcomes.

4. System Description

The CABG Kibitzer was developed on a MacIntosh II computer; it requires 2 megabytes of RAM and Multifinder to run. The main portion of the CABG Kibitzer is a HyperCard stack; the mathematical model was written in LightSpeed Pascal. The entire system fits on one 800 kilobyte disk. We chose HyperCard because it allows rapid prototyping and is easy to maintain.

Decision analysis has been described as a cyclical process with three stages [8]. In the initial cycle, a decision model is formulated, evaluated, and interpreted. If the result of the first cycle fails to convince the decision maker that a specific course of action is appropriate, the cycle is repeated. The model is expanded and reevaluated, and the results are reinterpreted. Cycling continues until the decision maker feels confident of the decision.

The CABG Kibitzer implements two cycles of the decision-analytic process. In the first cycle, a statistical model calculates the relative advantage of surgical or medical therapy using patient-specific prognostic data and two simplifying assumptions -- smoothing of operative mortality and use of population-based values for the quality of life with angina. These simplifications allow rapid performance of the initial consultation. After the first cycle has been completed, the patient and counseling physician discuss complicating factors and decide whether the advantages seen with the selected therapy hold when risks not represented in the model are considered.

A second cycle is initiated if the physician and patient remain unconvinced. In this cycle, the decision model is expanded to include additional treatment alternatives such as angioplasty, estimation of the effect of living with angina on the patient's quality of life, risk aversion to surgical mortality, and pain and suffering associated with surgery. Probabilities for outcomes are adjusted on an individual basis using the survival and angina-recurrence data from the first cycle. Figure 1 illustrates the decision-analytic cycle and shows how components of the CABG Kibitzer correspond to each stage. We shall discuss each component in detail.

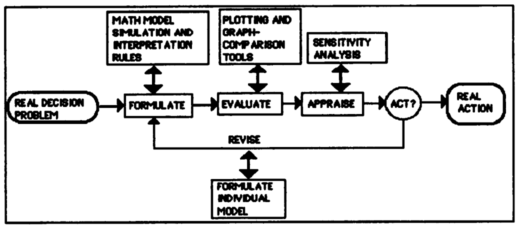

Figure 1. Correspondence between the CABG Kibitzer and the decision-analytic cycle. Double sided arrows indicate components of the CABG Kibitzer; single sided arrows indicate DA cycle components. Input to the DA cycle is a decision problem; output is a commitment to some course of action.

Regardless of the structure used, the decision model must represent survival rate and symptom characteristics of the patient over time. In Pliskin's model, the probability of survival, postoperative survival, and survival to years 1 through 5 with and without angina were represented by probabilities assessed directly by physicians. The CABG Kibitzer replaces this approach with a statistical Markov process model.

The Markov process is a standard model for the dynamic behavior of probabilistic processes [9-11]. Markov models predict state probabilities -- that is, the likelihood that an individual or process will be in a particular state at a given time. Our model includes three mutually exclusive states of health : alive without angina, alive with angina, and death.

The analysis estimates the probability that a patient will be in each of the three states for each month over a user-specified number of months. The expected duration of survival without angina and of survival with angina is calculated from the resulting estimates. The model can predict the likelihood that a patient will be in a given state, as well as the duration of the state, by treating the changes in health states as a Markov process.

We performed a multinomial logit regression on an observational database to determine the contribution of known prognostic variables. We combined these regression parameters with patient-specific variables using a logit function. For each patient consult, estimates of transition probabilities for the Markov process model are calculated for variables such as age, sex, and extent of disease. We combine transition probabilities into a Markov transition matrix. One matrix is calculated for each year in the simulation. The expected probability of survival and of having angina for each year is calculated via multiplication of the matrix generated for a given year by the previous year. These probabilities are compared and expected differences in survival are calculated for the two alternatives. Two additional calculations are then performed using nominal and extreme values for level of patient activity :

1. Differences in expected quality-adjusted life years (QALYs) with class III or IV angina
2. Joint effect of QALY and time discount

Once the calculations are completed, a set of rules is invoked to analyze the results. The differences among the area under the curve of the unadjusted survival curves, the quality-adjusted survival curves, the time-discounted survival curves, and the joint survival curves are used to select recommendations for therapy and to perform more detailed modeling.

The CABG Kibitzer provides two features that allow the user to review the results : a plotting tool and graph-comparison tool. The plotting tool reads in the data from a text file created by the math model and plots the values using a standard survival-curve format (probability of survival versus years of life lived). The graph-comparison tool superimposes graphs that have been created. This feature allows the user immediately to detect stochastic dominance of one alternative if it exists. Figure 2 illustrates these features. The upper panel of this figure shows the plotted medical and surgical survival curves for a 75-year-old female with a moderate degree of CAD and severe angina. The two curves are superimposed in the lower panel; they clearly indicate the overwhelming survival advantage for the surgical outcome.

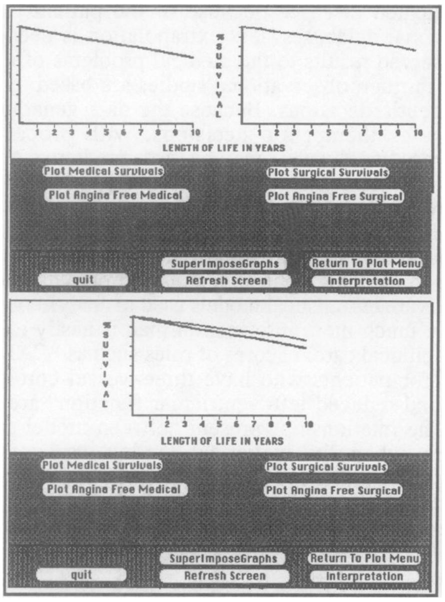

Figure 2. Example of the plotting and graph-comparison tools. The upper panel of the figure shows the graphs for the survival rate for a 75-year-old female with a moderate degree of CAD and severe angina. The bottom panel shows the graph-comparison tool which superimposes the graphs. The top line is the rate for surgery.

Once the graphs have been evaluated, the physician has the option of ending the CABG Kibitzer session or continuing with further model refinement. Sensitivity analysis can be performed on any of the prognostic variables included in the model. Analysis involves repeated calls to the statistical model using incremental values of the chosen variable while holding constant the values of all other variables. Plotting tools similar to the tools described previously are then used to examine the results. An example of the results of sensitivity analysis performed on the number of involved segments is shown in Figure 3. For this patient, no matter how many segments are involved in disease, the decision favors surgery over medical therapy by a comfortable margin.

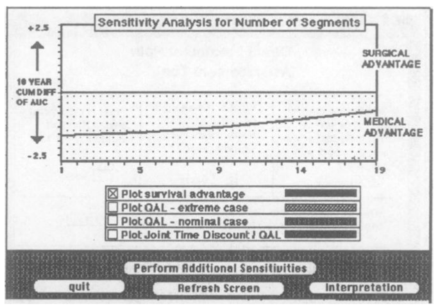

Figure 3. Sensitivity analysis for the number of involved segments. For this patient, no matter how many segments are diseased, medical therapy is the preferred alternative.

If reviewing the population data does not allow the patient and physician to reach a clear decision regarding treatment, a second cycle of decision analysis is performed. In the second cycle, the decision model is refined and expanded to fit that particular patient's clinical scenario and personal preferences.

The physician chooses which therapeutic alternatives to consider in the model by menu selection (surgery, angioplasty, or medical treatment). If angioplasty is considered as an alternative, the physician estimates for each year the probability of survival and of continued angina. Previous model estimates of survival and occurrence of angina are displayed to help anchor physician estimates. Modifications of the model-generated estimates for medical and surgical alternatives can also be made at this time if necessary.

Value-model components are selected by the physician through consultation with the patient. The CABG Kibitzer predefines a set of recommended components based on analysis from cycle 1. For example, if an advantage for one alternative only becomes apparent after several years, consideration of time discount is included. Careful and frank discussion between physician and patient is needed to identify which components are significant. Value-model components are chosen from a menu and include items such as "surgical pain and suffering," and "risk aversion to operative mortality," as well as "effect of pain" and "activity loss due to angina." Value-model components are combined to form a patient-specific utility function. The time-tradeoff approach is used to express the utility of different events.

Because probability and utility assessment of outcomes is one of the most difficult parts of a decision analysis, we have explored designs to facilitate their assessment. Examples of graphical tools to aid in assessments are shown in Figure 4. Once outcome probabilities and time trade-offs have been specified, the model is assessed in the usual manner.

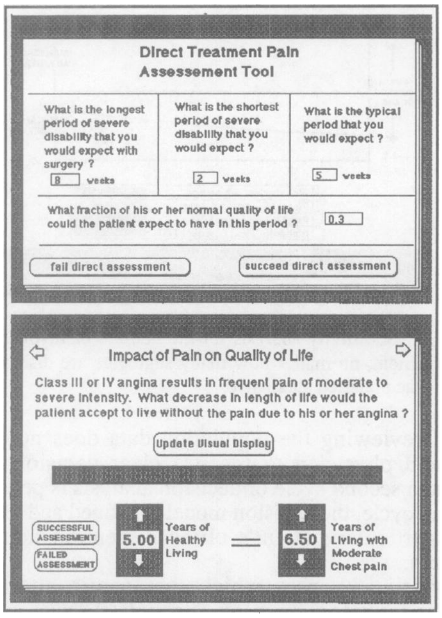

Figure 4. Example of tools for eliciting patient preferences. The left side of the figure is used to assess the effect of pain related to treatment on the decision. The right side of the figure is used to assess the effect of pain on the quality of life.

5. System Status

The current version of the CABG Kibitzer includes an entry form for patient data, a statistical model for calculating patient prognosis and sensitivity analysis, and plotting and graph-comparison tools. Several help features have been designed to assist the user with data entry. Figure 5 shows the help screen developed for entering the number of involved coronary-artery segments. When the user clicks on the location of diseased segments in the diagram, the program automatically tallies the total and stores the information in the proper space on the patient-data entry form.

Verification of the statistical model and evaluation of the system are underway. Verification will be performed using a patient data set that is independent of the observational database used for initial system construction.

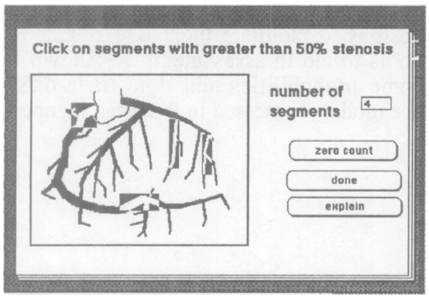

Figure 5. Help screen for the number of involved segments. The user clicks on portions of the diagram corresponding to stenosed segments. The running total is displayed in the box on the right.

6. Discussion

In the CABG Kibitzer, we replace subjective probability estimates for decision models with statistically based estimates. A significant factor in the lack of acceptance of decision analysis in the medical community is this method's reliance on subjective probabilities. Obtaining subjective probability estimates for medical decision models is difficult and time consuming. The variability among different physicians' estimates of outcome probabilities raises doubts for many people about the validity of decision analysis. Believers counter that although decision analysis does not guarantee a good outcome, it does ensure a good decision based on normative application of the information available. To unbelievers, the distinction between decisions and outcomes is artificial. To be tractable, decision models contain significant simplifications. A "good" decision based on seriously flawed probability estimates in a simplified model is not really a good decision. If the probabilities and simplifications in a decision model could be validated objectively, then perhaps the unbelievers could be brought to belief.

In some sense, all probabilities are subjective. Even with frequency data from controlled experiments, a person who uses the data as the basis for a decision must believe that the conditions under which the frequencies were observed still hold. Nonetheless, some probabilities are more subjective than are others. We believe that a sound basis of outcome probability in frequency data and validation in the prediction of independent observations make these probabilities less "subjective".

Disregarding the issues of subjectivity, observational data are particularly well suited for use in estimation of outcomes for decision–analytic models. Observational databases are available on a wide range of patients with varying severity of disease and other concomitant illnesses. RCT's are typically performed on highly similarly patients with uncomplicated disease. Because of the patient diversity in observational databases, less extrapolation is needed to map from observed results to the medical problems of a particular patient. Further, observational studies are based on outcomes of therapeutic decisions. Because the data generated are the *products* of therapeutic decisions, with proper analysis, models based on this data may be more predictive of *outcomes* of decisions than data from RCT's. In contrast, data from RCT's are generated in a unique decision–free context.

Even if the reader remains skeptical of the value of decision–theory, implementing the results of the analysis of outcome studies in graphical computer programs makes sense. The multivariate statistical models used to analyze observational data have much more information than is easily expressed in rules for clinical care. Scores of rules such as "CABG extends survival for patients who have three–vessel coronary artery disease and reduced left–ventricular function" are needed to express the relationships present between model parameters. However, when the statistical models are coupled with graphical tools such as HyperCard, vivid and patient-specific predictions of the consequences of a decision can be generated. The rules can be set aside and the data can speak to the problem at hand.

Acknowledgements

The authors would like to thank Samuel Holtzman, Lyn Dupre, and Lawrence Fagan for their comments on earlier drafts of this paper. This work was supported in part by grant LM05208 from the National Library of Medicine, NCHSR grant H00028-01A1 from the National Center of Health Services Research, and grant AG 07651 from the National Institute of Aging. Dr. Garber is a Henry J. Kaiser Family Foundation Faculty Scholar in General Internal Medicine.

References

[1] Bonow, RO, et al. "Indications for Coronary Artery Bypass Surgery in Patients with Chronic Angina Pectoris: Implications of the Multicenter Randomized Trials." Circulation, 72(supp V), 1985. pp. V23-V30.

[2] Califf, RM, et al. "Beyond Randomized Clinical Trials: Applying Clinical Experience in the Treatment of Patients with

Coronary Artery Disease." Circulation, 74(6), 1986. pp. 1191-1194.

[3] Hlatky, MA, et al. "Comparison of Predictions Based on Observational Data with the Results of Randomized Controlled Trials of Coronary Artery Bypass Surgery." JACC 11(2), 1988. pp. 237-245.

[4] Lee, KL, et al. "Predicting Outcome in Coronary Disease: Statistical Models Versus Expert Clinicians." American Journal of Medicine, 80, 1986. pp. 553-560.

[5] Harrell, FE, et al. "Regression Modelling Strategies for Improved Prognostic Prediction." Statistics in Medicine, 3, 1984. pp. 143-152.

[6] Gersh, BJ, et al. "Comparison of Coronary Artery Bypass Surgery and Medical Therapy in Patients 65 Years of Age or Older." New England Journal of Medicine, 313(4), 1985. pp 217-224.

[7] Pliskin, JS, et al. "Coronary Artery Bypass Graft Surgery: Clinical Decision Making and Cost-Effectiveness Analysis." Medical Decision Making 9(1), 1981. pp 11-28.

[8] Holtzman, S. Intelligent Decision Systems. Addison Wesley, Mass. 1989.

[9] Hoel PG, Port SC, Stone CJ. Introduction to Stochastic Processes. Boston:
Houghton Mifflin Company, 1972.

[10] Luenberger DG. Introduction to Dynamic Systems. New York: John Wiley & Sons,
1979.

[11] Karlin S, Taylor HM. A First Course in Stochastic Processes (2nd ed.). New York: Academic Press, 1975.