Assessing the Value of Newer Pharmacologic Agents in Non-ST Elevation Patients: A Decision Support System Application

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Newer pharmacologic agents have demonstrated significant clinical and economic benefit in high-risk percutaneous transluminal coronary angioplasty (PTCA) patients. However, the higher costs of these agents may prohibit their use in lower-risk coronary artery disease (CAD) populations. We developed a decision support system (DSS) to determine the level of clinical effectiveness these newer agents must exhibit to be either cost-neutral or cost-effective in non-ST elevation patients. Our DSS evaluated six month cumulative costs, increased years of life saved (YOLS), and lifetime cost-effectiveness. We found that these therapies can cost as much as $1500 and be cost-neutral at six months if they reduce the composite endpoint of death, myocardial infarction (MI), or revascularization by 15%, and they may cost as much as $3000 and be cost-effective if they reduce this endpoint by 10%.

INTRODUCTION

Approximately 4,500,000 patients in the U.S. survive an acute ischemic event each year.[1] One-third of these patients present with ST-elevation and are eligible for thrombolytic therapy which greatly reduces their risk of death.[2-4] The remaining two-thirds (non-ST elevation patients) are not eligible for thrombolytic therapy.[5] Glycoprotein IIb/IIIa platelet inhibitor is a new class of pharmacologic agent which has promise for use in acute ischemic syndrome patients; however, its greatest effectiveness has been demonstrated in high-risk patients undergoing PTCA procedures. The Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) multi-center clinical trial demonstrated that a bolus and 12 hour infusion of abciximab (a glycoprotein IIb/IIIa platelet inhibitor) reduced 30-day clinical events related to abrupt closure by 35% and subsequent major ischemic events (death, MI) or the need for revascularization up to six months by 23%.[6, 7] The EPIC Economics and Quality of Life (EQOL) substudy demonstrated a six month cumulative cost savings of $1,114 in the bolus and infusion versus the placebo arm ($16,862 vs. $17,976, respectively) exclusive of the drug cost.[8] Two recent clinical trials of abciximab in PTCA patients were stopped after interim analyses when both demonstrated greater effectiveness than reported in EPIC with less bleeding.[9] Despite these dramatic results, it is uncertain whether the use of glycoprotein IIb/IIIa platelet inhibitors will be cost-neutral or cost-effective in non-ST elevation patients.

METHODS

DSS Design

We developed a DSS to evaluate newer pharmacologic agents in non-ST elevation patients. This system was designed to be used: (1) when planning a phase III clinical trial[10] to evaluate potential results scenarios; (2) after the trial's completion to perform secondary analyses using the trial's actual results; and (3) during post-trial marketing to extrapolate the trial's results to the practices of individual health care providers.

We began by defining general requirements for our information system using the Gorry and Scott-Morton decision support framework[11] which combines Anthony's taxonomy of managerial activities[12] and Simon's stages of human decision making.[13] Our problem fits within Anthony's strategic planning domain which includes managerial decisions related to the long-range goals of the business entity and its policies for resource allocation. In addition, our information system will facilitate semistructured decision making by partially automating the second phase of Simon's human decision making taxonomy: the invention, development, and analysis of possible courses of action.

Decision Model Structure

We implemented our DSS as a 403 node Markov decision model[14, 15] using DATA 3.0 by TreeAge. This software integrates all three DSS subsystems: data, model, and dialogue management.[16] Our decision model simulates clinical trials with two arms (newer

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pharmacologic agent vs. placebo), measures clinical events and costs of care during two intervals (enrollment through 30 days and 31st day through sixth month), and estimates life-time survival with Markov processes.

Table 1: Non-ST Elevation Patients

Characteristic	Percent / Median (25%-75% Range)
Age	64 (54 - 73)
Male Gender	63%
Race	
Black	10%
Hispanic	2%
Other	2%
White	86%
Risk Factors	
Current Smoker	45%
Diabetes Mellitus	24%
Family History of CAD	55%
Hypercholesterolemia	47%
Prior CAD Events	
Chest Pain	84%
Congestive Heart Failure	9%
MI	32%
CABG	19%
PTCA	19%

Several methods have been proposed for managing composite clinical endpoints in clinical trials.[17, 18] We chose the ranked negative outcomes method because it preserves the integrity of the original endpoints. During model development, Duke Clinical Research Institute faculty used this method to identify conditionally independent clinical events for a hypothetical non-ST elevation clinical trial and to order these events according to the severity of adverse outcome. The events selected in ranked order were: death, nonfatal stroke, nonfatal MI, coronary artery bypass graft (CABG) surgery, PTCA procedure, rehospitalization, and no event. Using this method, a patient having an MI and CABG surgery in the same time period would be classified as an MI since this event has greater risk to the patient than CABG surgery.

Event Probabilities

All event probabilities used in this study were derived from U.S. non-ST elevation patients in the GUSTO-IIb clinical trial.[19] GUSTO IIb enrolled 12,142 patients worldwide (4,130 ST elevation and 8,011 non-ST elevation). U.S. patients comprised 2,250 of the non-ST elevation group. Table 1 shows significant characteristics of this population at enrollment with continuous variables represented as medians with interquartile ranges and discrete variables represented as means. Generally, this population is older, predominantly male, non-minority, with CAD risk factors, and previous CAD clinical events.

Table 2 shows the base event rates in this population. As expected, the greatest number of events occur within the first 30 days with a rather dramatic drop-off in months two through six. Using these base rates, we identified 30-day ranked events which were

Table 2: Clinical Event Probabilities

Clinical Event	Event Probabilities Through Day 30	Event Probabilities 31st Day - 6-Months
Death	3.5	2.2
Nonfatal Stroke	1.0	0.3
Nonfatal MI	4.8	1.6
CABG Surgery	19.5	2.6
PTCA Procedure	27.1	3.1
Rehospitalization	5.1	10.4
No Event	39.1	79.9

independent of each other and second- through sixth-month ranked events which were also independent of each other but which were conditioned upon their predecessor events at 30-days. Thus, the nonfatal stroke events in the second- through sixth-month were independent of all other events occurring in that time interval but the probability of their occurring was conditioned upon their predecessor event (e.g., nonfatal stroke, nonfatal MI, etc.) in the first 30 days.

Event Costs

All cost data used in this study came from the GUSTO IIb EQOL substudy.[20] Event costs were estimated using the index hospitalization costs of care in Table 3. These data show that patients undergoing CABG surgery had the highest average costs of care while patients experiencing no other events during their index hospitalization had the lowest average costs of care. We used these index hospitalization costs to estimate follow-up costs for each patient in the GUSTO IIb EQOL substudy. In our costing procedure, each patient had one index hospitalization event, one event between discharge and day 30, and up to three events between day 31 and the end of six months of follow-up. Additionally, costs for follow-up events were adjusted to account for the presence of chest pain or an MI. The average six-month

Table 3: Non-ST Elevation Index Hospitalization Costs of Care	
Clinical Event (By Severity)	**Total In-Hospital Costs of Care**
Death	$17,452
Nonfatal Stroke	$23,674
Nonfatal MI	$26,576
CABG Surgery	$30,556
PTCA Procedure	$15,309
No Other Event	$8,112

cumulative costs of care for our non-ST elevation population was $20,723 with a range from $8112 in patients with no other event in the six months after enrollment to $68,326 in patients with CABG surgery in the first 30 days and a stroke in months two through six.

Life-Time Survival

Our model assumed that the acute episode for non-ST elevation patients lasted for six months and that patients surviving to this point returned to a chronic state with identical life expectancies.[1] We modeled patient survival from six months through a maximum of 38 additional life years using GUSTO I survival estimates for acute MI patients treated with tissue plasminogen activator (Figure 1).[21] This survival curve was constructed by combining 14 years of data on Duke University Medical Center MI survivors with data from a Gompertz parametric survival function for the remaining life years. The average life expectancy in GUSTO 1 was 15.41 years and in our non-ST elevation patient simulation it was 15.471 years. After discounting at an annual rate of 3%, the average discounted life expectancy for our non-ST elevation patients was 11.316 years and the range for patients surviving the first 30 days was from 9.818 years in patients with a nonfatal stroke to 11.850 years in patients undergoing revascularization.

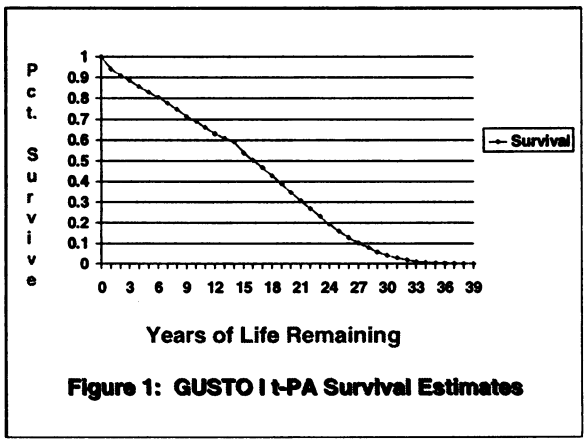

Figure 1: GUSTO I t-PA Survival Estimates

Cost-Effectiveness Criteria

Several studies have proposed rules of thumb for assessing the cost-effectiveness of newer medical technologies. In 1981, Kaplan and Bush found that technologies costing less than $20,000 per quality-adjusted life year (QALY) were cost-effective.[22] However, increases in the consumer price index have made this threshold a moving target. Thus, the original Kaplan and Bush cost-effectiveness threshold, inflated using the medical care component of the consumer price index, is $53,197 in 1995 dollars. We chose $50,000 per QALY as our cost-effectiveness threshold for newer pharmacologic agents in non-ST elevation patients.

RESULTS

Cost and Life Expectancy Simulations

Table 4 shows the incremental six-month costs and incremental life-expectancies resulting from reductions in various events occurring during the two

Table 4: Cost-Savings and Discounted Life Expectancies From Newer Agents			
	Percent Event Reduction		
Clinical Events	**5%**	**15%**	**25%**
Cumulative Cost Savings (in $)			
Death	(2)	(6)	(10)
Nonfatal MI	67	201	336
Revascularization	416	1284	2146
Death and MI	65	197	331
Death, MI, and Rev	483	1456	2437
Cumulative Life Gained (in discounted YOLS)			
Death	0.034	0.101	0.169
Nonfatal MI	0.001	0.002	0.003
Revascularization	0.000	0.000	0.000
Death and MI	0.034	0.103	0.171
Death, MI, and Rev	0.034	0.103	0.171
Note: Negative values are in parentheses.			

time intervals of interest (enrollment through day 30 and day 31 through six months). Clearly, different events affect cost and life-expectancy quite differently. Reducing the mortality rate (Death) increases costs as patients are moved to more costly therapies. However, reducing the mortality rate by 25% increases the entire population's life expectancy by 0.169 discounted life years (approximately two months). Similarly, reducing the revascularization rate by 25% decreases the population's average six-month costs of care by $2146, approximately 10%. However, reducing the revascularization rate has no effect on patient life-expectancies. Reducing the composite endpoint of death, nonfatal MI, or

revascularization has the greatest effect on both costs and life-expectancy as it includes elements which significantly influence both measurements.

Cost-Effectiveness Simulations

Table 5 shows the cost-effectiveness ratios resulting from 5%, 15%, and 25% reductions in non-ST elevation event rates in our two time intervals of interest. These results assume costs of $1500 and $3000 for the pharmacologic agent regardless of the administration regimen. Thus, a drug cost of $1500 could represent a one-time cost for a bolus or a $50 daily cost for 30 days. When drug costs are $1500, even a 5% reduction in mortality is cost-effective using a $50,000 per year of life saved (YOLS) standard, and a 5% reduction in the composite endpoint of death, nonfatal MI, or revascularization is highly cost effective at $29,912 per YOLS. With a $3000 drug cost, a 5% reduction in any of the endpoints is not cost-effective (< $50,000/YOLS), while with a 15% reduction all endpoints are highly cost-effective.

Table 5: Cost-Effectiveness of New Agents

Clinical Endpoints	Percent Event Reductions		
Drug = $1500	**5%**	**15%**	**25%**
Death	44,177	14,911	8,935
Death and MI	42,206	12,651	6,836
Death, MI, and Rev	29,912	427	Dominant
Drug = $3000			
Death	88,294	29,762	17,811
Death and MI	86,324	27,214	15,608
Death, MI, and Rev	74,029	14,990	3,292

Note: Cell values measure $ / YOLS.

DISCUSSION

This study demonstrates that significant economic benefits may be realized in the management of non-ST elevation patients through the use of newer pharmacologic agents such as glycoprotein IIb/IIIa platelet inhibitors. An agent costing $1500 only needs to demonstrate a 15% reduction in the composite endpoint of death, nonfatal MI, or revascularization to be cost-neutral at six months. In addition, an agent costing $3000 only needs to demonstrate a 10% reduction in the same composite endpoint to be cost-effective.

One limitation to this analysis was that we used YOLS rather than QALYs as our effectiveness measure. To assess the potential significance of this difference, we performed a sensitivity analysis and varied the average quality of life in this population from 0.900 to 0.500 (comparable to the quality of life in an acute MI survivor suffering a reinfarction and subsequent stroke). We found that our cost-effectiveness assessments were reasonably insensitive to quality of life adjustments. For example, when the average quality of life was decreased to 0.500, the cost-effectiveness ratio for a 5% reduction in the composite endpoint of death, nonfatal MI, or revascularization with a $1500 drug cost increased to $59,824/QALY, marginally cost-effective. Similarly, when we decreased the quality of life to 0.500, the cost-effectiveness ratio for a 15% reduction in the same composite endpoint with a $3000 drug cost increased to $29,981, still highly cost-effective. Thus, while our cost-effectiveness ratios changed when QOL was modeled, our assessments of the relative cost-effectiveness of these therapies did not.

To date, EPIC is the only glycoprotein IIb/IIIa platelet inhibitor clinical trial with an economic substudy. This trial's composite endpoint reductions (at 30 days and in months two through six) were largely driven by reductions in the rates of MI and revascularization with minimal contribution from reductions in mortality. However, our decision model has demonstrated that reductions in both death and revascularization are required for a new pharmacologic agent costing $1500-$3000 to be cost-effective in a non-ST elevation population. Thus, if current clinical trials fail to achieve significant reductions in mortality, pharmaceutical companies may need to economically justify these newer pharmacologic agents based upon cost-savings from reduced revascularization rates alone.

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