Copyright Warning & Restrictions

The copyright law of the United States (Title 17, United States Code) governs the making of photocopies or other reproductions of copyrighted material.

Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be "used for any purpose other than private study, scholarship, or research." If a, user makes a request for, or later uses, a photocopy or reproduction for purposes in excess of "fair use" that user may be liable for copyright infringement,

This institution reserves the right to refuse to accept a copying order if, in its judgment, fulfillment of the order would involve violation of copyright law.

Please Note: The author retains the copyright while the New Jersey Institute of Technology reserves the right to distribute this thesis or dissertation

Printing note: If you do not wish to print this page, then select "Pages from: first page # to: last page #" on the print dialog screen

ABSTRACT

Bayesian Methods in

Preoperative Risk Assessment for Cardiac Surgery

by

Huey-chung Teng

Many strides have been made in the last decade to improve the accuracy of preoperative risk estimation, particular for cardiovascular surgery. It is our goal to estimate the preoperative risk associated with cardiac bypass surgery for patients in different risk categories. These risk categories are determined by the Parsonett model.

The Parsonett model assigns a risk value to a range of risk factors consisting of patient attributes and disease parameters. Logistic modeling is applied to generate a comprehensive risk function. The database being utilized contains over 3,000 patients who have had cardiovascular surgery within the last 5 years.

This thesis will utilize a database comprised of preoperative risk categories and their respective surgical outcomes in order to uniformly rate institutional and surgical performance.

BAYESIAN METHODS IN
PREOPERATIVE RISK ASSESSMENT FOR CARDIAC SURGERY

by

Huey-chung Teng

A Thesis
Submitted to the Faculty of
New Jersey Institute of Technology
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Applied Mathematics

Department of Mathematics

May 1993

APPROVAL PAGE

Bayesian Methods in

Preoperative Risk Assessment for Cardiac Surgery

Huey-chung Teng

Dr. Rose Ann Dios, Thesis Adviser
Associate Professor of Mathematics, NJIT

Date

Dr. Manish C. Bhattacharjee, Committee Member
Associate Professor of Mathematics, NJIT

Date

Dr. Bonnie Ray, Committee Member
Assistant Professor of Mathematics, NJIT

Date

BIOGRAPHICAL SKETCH

Author: Huey-chung Teng

Degree: Master of Science in Applied Mathematics

Date: May 1993

Date of Birth:

Place of Birth:

Undergraduate and Graduate Education:

- Master of Science in Applied Mathematics,
  New Jersey Institute of Technology, Newark, NJ, 1993
- Bachelor of Science in Appplied Mathematics,
  Providence University, Taichung, Taiwan, 1991

Major: Applied Mathematics

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACHD	atherosclerotic coronary heart disease
ANOVA	analysis of variance
AVR	aortic valve replacement
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CASS	the collaborative study in coronary artery surgery
CMM	complete predictor/maximum information model
CNM	complete predictor/no information model
d.f.	degree of freedom
Dr.	doctor
DRG	diagnosis related group
et al.	*et alii* (= and others)
MS	mean square
MVR	mitral valve replacement
OM	operative mortality
PA.	Pennsylvania
POSCH	the program on the surgical control of the hyperlipidemias
Prob.	probability
RMM	reduced predictor/maximum information model
RNM	reduced predictor/no information model
SS	sum of squares
US	United States

CHAPTER 1

INTRODUCTION AND LITERATURE SURVEY

1.1 Problem Statement

Preoperative risk is dependent upon a wide range of patient attributes and disease parameters which are viewed as "risk factors". It is our goal to estimate the preoperative risk associated with cardiac bypass surgery for patients in different "overall risk" categories. The categories are identified by the Parsonett model, which serves as the source of the prior subjective probabilities of expiration for individual patients as shown in Table 1.1. (See appendix)

Table 1.1 Prior Subjective Probabilities of Expiration (Risk)

Risk Factors	Coefficient of Risk	Prior Subjective Probability (% of Risk)
sexriskn (gender) (male,female)	1	(0,1)
obesity (no,yes)	1	(0,3)
diabetic (no,yes)	1	(0,3)
hyperten (hypertension) (no,yes)	1	(0,3)
efriskno (ejection fraction) (good,fair,poor)	1	(0,2,4)
ageriskn (age) (0-69,70-74,75-79,80+)	1	(0,7,12,20)
reoperat (repoperation) (no,first,second,third)	1	(0,5,10,10)
preopiab (intra aorta balloon) (no,yes)	1	(0,2)
lva (no,yes)	1	(0,5)
crashptc (no,yes)	1	(0,10)
dialdepe (dialysis dependent) (no,yes)	1	(0,10)
avr (no,gradient≥120,gradient<120)	1	(0,7,5)
mvr (no,pressure≥60,pressure<60)	1	(0,8,5)
tvr (no,yes)	1	(0,3)
addedcab (no,yes)	1	(0,2)
smoker (no,yes)	1	(0,1)
heredity (no,yes)	1	(0,1)
hicholes (high cholesterol) (no,yes)	1	(0,1)

1.2 Methodology

Table 1.1 has shown the prior subjective probabilities of expiration. These prior probabilities are transformed into posterior risk values by utilizing a range of regression procedures. This Parsonett model can be viewed as a step function which absorbs risk contributions from the presence or absence of a risk factor.

$$R = b_0 + b_1 x_1 + b_2 x_x + \cdots + b_k x_k$$

b_0 = intercept (minimum risk)

b_i = coefficient for risk factor x_i

For example: Let x_4 denote hypertension risk number then

$x_4 = 0$ if patient is not hypertense

$x_4 = 3$ if patient is hypertense

So $0 \leq b_4 x_4 \leq 3b_4$. Hence, the patient's risk is increased by $3b_4$% if he (or she) is hypertense and is not increased at all if he (or she) is not hypertense. Then b_4 is the adjustment factor which transforms a prior risk value to a posterior risk value. This is repeated for all remaining risk factors.

1.3 Literature survey

1.3.1 Preoperative Risk Assessment in Cardiac Surgery:

Dose the Model Predict Risk Accurately?

–A summary of the research by Dr. F.L. Junod, et al. (1).

This risk assessment model focuses upon assessing the probability of mortality due to a given surgical procedure as a function of:

CABG = coronary artery bypass grafting

AVR = aortic valve replacement

MVR = mitral valve replacement

as well as other patient history information.

For cardiac surgery, CABG, AVR and MVR are high risk factors. Changing methods of surgical management are probably altering risk but identifying areas for further improvement.

A model was constructed as follows:

1. The patients were isolated into groups (severity of risk).
2. The groups were compared using a χ^2 test for significant difference.
3 Once the groups were determined to be significantly different from the others, the risk was assigned to future patients who fell into a specified risk category.

Data was then gathered on patients not previously utilized to determine the original risk model in order to check model validity. The results of the study showed that patients rated as high priority were indeed of higher risk.

For the surgical population reported, emergency surgical priority had a highly significantly different risk from elective priority ($p < 0.01$). Operative deaths by surgical priority are shown in Table 1.2.

Table 1.2 Operative Mortality by Surgical Priority for Patients Having Isolated Primary CABG

Group	All Patients	Patients with Isolated Primary CABG
Elective	11/533 (2.1)*	2/329 (0.6)
Urgent	15/580 (2.6)	5/450 (1.1)
Emergent	26/190 (13.7)	7/134 (5.2)

*Numbers in parentheses are percents.

Table 1.2 shows that patients were not given an erroneously low risk. Therefore, preoperative risk assignments is an effective method of quality assurance. Results of a further study are given in Table 1.3.

Table 1.3 Operative Mortality by Age and Sex for Patients Having Isolated Primary CABG

Age(yr)	All patients	Male	Female
<50	0/84	0/70	0/14
50-59	2/249(0.8)*	2/213(0.9)	0/36
60-69	7/348(2.0)NS**	6/250(2.4)NS	1/98(1.0)
≥70	5/232(2.2)NS	1/148(0.7)	4/84(4.8)p<0.05
Total	14/913(1.5)	9/681(1.3)	5/232(2.2)NS

*Numbers in parentheses are percents.
**NS = not significant to $p < 0.05$.

There was no increased risk associated with increased age. The only subset of patients with higher risk was for women over 70 years old. So the CASS researchers concluded that an age greater than 60 years and female sex affected operative mortality. However, Dr. F.L. Junod and co-workers (1) support the decreased importance of age as a determinant in the seventh and eighth decades. Only the class of women showed a statistically significant difference in patients older than 79 years. Overall, there was no difference in risk between men and women.

This paper devoted a great deal of time to discussing high risk factors in surgical outcome risk. Frequently, high risk patients are all grouped together regardless of why they are considered to be high risk. High risk patients are usually compared to low risk

ones. But this paper compared one high risk class to another one and so on. For this reason, it is interesting and useful for our future work.

1.3.2 Analysis of Operative Mortality in Coronary Artery Surgery

1.3.2.1 Difference in Mortality from Coronary Artery Bypass Graft Surgery at Five Teaching Hospitals

There are some possible reasons for differences in mortality from coronary artery surgery at different hospitals. Dr. S.V. Williams and co-workers (2) use hospital discharge abstracts and itemized bills at five hospitals in Philadelphia, PA. to measure hospital and surgeon-specific mortality rates for patients with coronary artery bypass graft surgery and to examine possible reasons for any differences.

Dr. S.V. Williams (2) observed differences in hospital mortality rates for 4,613 patients categorized into two groups:

1. Diagnosis related group 106 (DRG 106) :

   Patients underwent coronary artery catheterization and CABG surgery during the same admission .

2. Diagnosis related group 107 (DRG 107):

   Patients underwent only CABG.

The hospital-to-hospital differences in mortality rates for DRG 107 were small and not statistically significant ($p = 0.572$). In contrast, there were substantial differences in hospital mortality rates for DRG 106 ($p = 0.0004$). Although illness severity did identify patients who were more likely to expire, differences in severity of illness did not explain differences in hospital- or surgeon-specific mortality rates. Dr. S.V. Williams (2) found inconclusive evidence for patient mortality rates associated with a surgeon's clinical skills, and, to a lesser extent, with the hospital's volume of procedures and the hospital's organization and staffing.

This encourages us to pursue the study of preoperative surgical risk for patients in different " overall risk " categories. A " prior probability of mortality " may be used to identify the primary risk groups. Hence, our work focuses upon the use of the " Parsonett Model ". (See chapter 2)

1.3.2.2 Multivariate Discriminant Analysis of Operative Mortality From the Collaborative Study in Coronary Artery Surgery (CASS)

The Collaborative Study in Coronary Artery Surgery (CASS) is a large multi-institutional study of the medical and surgical treatment of coronary artery disease (CAD). In an effort to better understand the clinical and angiographic characteristics predictive of OM, Dr. J.W. Kennedy and associates (3) have done a multivariate discriminant analysis of variables associated with OM.

The data file of CASS (3) contains detailed information about the clinical, angiographic, and surgical characteristics of patients enrolled in the study. The baseline data were controlled by physicians and trained data technicians at the time the patient was hospitalized for coronary arteriography.

The results of this multivariate discriminant analysis of the predictors of OM are presented for several clinical groups as shown below.

Table 1.4 Clinical Groups.

Group I	All operated patients
Group II	All CABG operations
Group III	Elective CABG operations
Group IV	Urgent or emergent CABG operations
Group V	Patients in group II divided by age
Group VI	Patients in groups II, III, and IV divided by sex

The operative mortality for the total groups of patients and various subgroups is given in Table 1.5.

Table 1.5 Operative mortality for groups

Groups	No. of pts*	Description	OM(%)
I	6,652	All operated pts	2.9
II	6,176	All CABG pts	2.3
III	4,913	Elective CABG pts	1.7
IV	1,263	Urgent - emergent CABG pts	4.4
V	4,303	CABG only, < 60 years	1.4
	1,873	CABG only, ≥ 60 years	4.2
VI	5,197	Men CABG only	1.8
	979	Women CABG only	4.5

*No. of pts = Number of patients.

Clinical variables of most predictive value were age, female sex, increased heart size, and congestive heart failure. Angiographic variables of importance included left ventricular wall motion abnormalities, and left main coronary disease. There were six variables that contained the most predictive information by analysis for a group of 6,176 patients who had isolated bypass operations. They are age, left main coronary artery stenosis ≥ 90%, female sex, left ventricular wall motion score, left ventricular end-diastolic pressure, and râles. The risk of OM for an individual patient may be estimated with the use of these clinical and angiographic characteristics.

1.3.3 Further Issues in Cardiac Risk Assessment for Specific Population Groups

1.3.3.1 Exclusion of the Elderly and Women From Coronary Trials. Is Their Quality of Care Compromised ?

–Equal Access to Cardiac Treatment

Currently, 13% of the population is older than age 65 years; this percentage is expected to increase to 21%, or 35 million people, by the year 2030 (4). The majority of US patients with clinical manifestations of coronary heart disease are older than 65 years; more than half of all myocardial infractions now occur in this elderly age group. Therefore, increasing numbers of elderly individuals have changed not only the profile of the US population, but also the demography of cardiovascular disease.

The clinical presentation, symptoms, disease severity, clinical course, and prognosis of the more than 3.6 million elderly patients with coronary heart disease differ substantially from those encountered at younger age and likely necessitate differences in assessment and therapy. The mean ages of study patients in the clinical trials with and without age exclusionary criteria were comparable, indicating potential investigator, treating physician, societal, cultural, and elderly patient bias regarding enrollment in clinical trials of therapies for acute myocardial infarction. Furthermore, two thirds of the US expenditures for the care of cardiovascular illness involves patients older than 65 years of age.

Any age-based rationing of clinical care disproportionately disadvantages women because more women than men survive to older age, and women more frequently develop cardiovascular illness at an older age. The prognosis for women with coronary heart disease is more ominous than that for men for both medical and surgical therapies; women's subsequent symptomatic and functional limitations are greater. In addition, rates of invasive cardiovascular procedures differ between the sexes, although it is not clear whether gender differences in the use of medical care affect the outcome or prognosis of coronary disease in women.

The high incidence of recurrent coronary events in elderly and women patients increases the likelihood of detecting benefit (or risk) of an intervention, because of the frequent occurrence of designated clinical trial end points. The incorporation of elderly and women patients in clinical trials of diagnostic and management strategies has substantial potential to define age- and gender-based differences and improve their responses to therapies for coronary disease.

1.3.3.2 The Exclusion of the Elderly and Women From Clinical Trials in Acute Myocardial Infarction

This paper focuses upon a range of goals: to determine the extent to which the elderly have been excluded from trials of drug therapies used in the treatment of acute myocardial

infarction, to identify factors associated with such exclusions, and to explore the relationship between the exclusion of elderly and the representation of women.

Patients 65 years of age and older comprise over 60% of those discharged from the hospital with a diagnosis of acute myocardial infarction, although they constitute only 13% of the US population. Because of the demographic shifts taking place in the US population, the numbers of older patients suffering an acute myocardial infarction will only continue to increase. Since women outlive men by an average of 7.5 years, they are disproportionately represented in an elderly population. While women comprise only 24% of those younger than age 65 years who die of acute myocardial infarction, they constitute 64% of those who die at age 85 years or older.

Dr. J.H. Gurwitz and associates (5) conducted a systematic search of the English-language literature from January 1960 through September 1991 to identify all relevant studies of specific pharmacotherapies employed in the treatment of acute myocardial infarction. Only trials in which patients were randomly allocated to receive a specific therapeutic regimen or a placebo or nonplacebo control regimen were included in the present review.

Studies were abstracted for year of publication, source of support, performance location, drug therapies to which patients were randomized, use of invasive diagnostic tests or therapeutic procedures, exclusion criteria, size and demographic characteristics of the randomized study population, and principle outcome measures.

A total of 150,920 study subjects were randomized in the 214 clinical trials. The median number of subjects for all studies was 145 (mean: 705; range: 14 to 20,768). Information regarding the mean age of study participants was available for 75% of the trials (n = 160) and was 57.5 $\pm$ 2.8 years. Information on the gender characteristics of study participants was available for 89% of studies (n = 191) involving 145,388 participants, of whom 20% were female.

Age-based exclusions are frequently used in clinical trials of medications used in the treatment of acute myocardial infarction. Such exclusions limit the ability to generalize findings to the patient population that experiences the most morbidity and mortality from acute myocardial infarction.

1.3.3.3 Incidence of Silent Ischemia After Acute Myocardial Infarction

-Further Issues in Cardiac Risk Assessment

Dr. G.J. Taylor and associates (6) tested the hypothesis that silent ischemia is more common in patients treated with thrombolytic therapy for acute myocardial infarction. This paper focuses on determining the incidence of angina pectoris during induced myocardial ischemia in patients who have had thrombolytic therapy for acute myocardial infarction in comparison with angina pectoris.

Twenty-five patients with angina pectoris who were undergoing angioplasty were compared with 30 patients having angioplasty 2 days after thrombolytic therapy for acute myocardial infarction. During pertaneous transluminal coronary angioplasty, both study groups had coronary artery occlusion by the balloon dilatation cather for 5 minutes.

During balloon occlusion 16 (64%) of 25 patients in the angina pectoris group developed angina. In contrast, 9 (30%) of 30 patients in the thrombolysis group had angina pectoris during balloon occlusion of the infarct artery ($p < 0.01$). The electrocardiographic response to ischemia and changes in pulmonary wedge pressure were similar in the two study groups.

These results are consistent with other studies reporting that spontaneously occurring or exercise-induced ischemia after coronary thrombolysis did not provoke symptoms in 48% to 83% of patients. Furthermore, their suggestion that there is cardiac sensory dysfunction after coronary thrombolysis should focus greater attention on a symptomatic coronary artery reocclusion after thrombolytic therapy.

1.3.4 Cardiac Risk for Specific Treatment Protocols

1.3.4.1 A Study of In-Hospital Mortality Associated With Coronary Artery Bypass Grafting

The use of mortality rates as an indicator of the quality of medical care has raised concerns that observed differences in mortality rates by institution may be the result of confounding by characteristics of patient case mix, which may distort apparent rates of in-hospital mortality and lead to false conclusions about the quality of medical care provided. Then, a prospective regional study by Dr. G.T. O'Connor and associates (7) was conducted to determine if the observed differences in-hospital mortality rates associated with coronary bypass grafting are solely the result of difference in patient case mix.

This study (7) includes data from all surgeons performing cardiothoracic surgery in Maine, New Hampshire, and Vermont. The data were collected from five regional medical centers and from all consecutive isolated CABG surgery patients during the study period. Data included patient demographic and historical data, body surface area, cardiac catheterization results, priority of surgery, comorbidity, and status at hospital discharge. This study (7) presents data for 3,055 CABG patients between July 1, 1987, and April 15, 1989.

Most of these patients (73.2%) were male. The mean age was 63 years, with a range from 25 to 89 years. With regard to priority of surgery, 202 (6.6%) of the CABG procedures were classified as emergent, 1,287 (42.1%) were classified as urgent, and the remaining 1,566 (51.3%) were elective. The overall crude in-hospital mortality rate for isolated CABG was 4.3%. The rate varied among centers (range, 3.1% to 6.3%) and among surgeons (range, 1.9% to 9.2%). Predictors of in-hospital mortality included increasing age, female gender, small body surface area, greater comorbidity, reoperation, poorer cardiac function as indicated by a lower ejection fraction, increased left ventricular end diastolic pressure, and emergent or urgent surgery. Logistic regression analysis was

used to adjust crude in-hospital mortality rates for variation in predictors of in-hospital mortality.

After adjusting for the effects of potentially confounding variables, substantial and statistically significant variability was observed among medical centers ($p=0.021$) and among surgeons ($p = 0.025$). Dr. G.T. O'Connor et al. (7) concluded that the observed differences in-hospital mortality rates among institutions and among surgeons in northern New England are not solely the result of differences in case mix as described by these variables and may reflect differences which are currently unknown.

1.3.4.2 Changes in Coronary Arteriograms and Coronary Events

The Program on the Surgical Control of the Hyperlipidemias (POSCH) (8) was designed to ascertain whether the lipid modification induced by the partial ileal bypass operation affects the clinical course and the sequential coronary arteriograms of patients with documented atherosclerotic coronary heart disease (ACHD). A specific design objective of POSCH (8) was to examine the validity of the use of changes observed on sequential coronary arteriograms as a surrogate end point for clinical coronary events.

A total of 838 patients were studied, with 417 patients randomized to the control group and 421 to the intervention group. Of all patients, 695 had baseline and 3-year arteriograms. The control group received American Heart Association Phase II diet instruction and the intervention group received identical dietary instruction plus a partial ileal bypass operation.

The Program on the Surgical Control of the Hyperlipidemias, a randomized secondary atherosclerosis intervention trial, obtained coronary arteriograms at baseline, 3, 5, and 7 or 10 years of follow-up. Assessments of changes between pairs of coronary arteriograms were made by two-member panels blinded to the patients' assigned treatment and to the temporal sequence of the films. The relationship of changes between the baseline and the 3-year follow-up arteriograms and subsequent clinical coronary events was examined.

Changes between the baseline and the 3-year coronary arteriographic overall disease assessment were significantly associated with subsequent overall and atherosclerotic coronary heart disease mortality ($p < 0.01$). For the combined end point of atherosclerotic coronary heart disease mortality or confirmed nonfatal myocardial infarction, a significant relationship between the overall disease assessment and subsequent clinical events was found in the control group ($p < 0.0001$) and in the surgery group ($p = 0.04$). For this combined end point, however, the control and the surgery groups were different with respect to clinical coronary event after 3 years, stratified by the baseline to 3-year overall disease assessment.

Coronary arteriographic changes can be used in atherosclerosis intervention trials as a limited surrogate end point for certain clinical coronary events. This relationship is statistically compelling for overall mortality and atherosclerotic coronary heart disease mortality. For an individual patient, changes in the severity of coronary atherosclerosis seen on sequential coronary arteriograms can serve as prognostic indicators for subsequent overall or atherosclerotic coronary heart disease mortality.

CHAPTER 2

MATHEMATICAL MODELS FOR RISK ESTIMATION

2.1 Linear Regression

We wish to establish a model that estimates the risk of cardiovascular surgery (as a percentage likelihood of fatality due to the surgical procedure). The initial model will utilize the available data for 1,021 patients. The data is organized so that each input variable identifies key risk contributors and quantifies their values in the form of percentages of risk. The risk contributions are modeled to be additive and mutually independent in the calculation of overall risk. Hence, we select a linear regression model to estimate overall risk as shown.

$$\hat{y} = b_0 + b_1 x_1 + b_2 x_2 + \cdots + b_k x_k$$

where $x_1, x_2, \cdots x_k$ denote k independent variables. This is a form of linearly combining contribution to surgical risk in order to obtain an aggregate risk value. In this model, the goodness of fit is determined by the F statistic. The ANOVA table associated with this multivariate regression process is shown in Table 2.1.

Table 2.1 Analysis of Variance (ANOVA)

Source	SS	d.f.	MS	F ratio
Regression	SS_{reg}*	k	SS_{reg} / k	$F = \frac{MS_{reg}}{MS_{res}}$
Residual	SS_{res}**	n-k-1	$SS_{res} /(n-k-1)$	
Totals Corrected	$SS_{total\ corrected}$	n-1		

*reg=regression
**res=residual

The correlation coefficient is R as shown

$$R = \sqrt{\frac{SS_{reg}}{SS_{total\,corrected}}} \tag{2.1}$$

where

$$SS_{regression} = \sum (\hat{y} - \bar{y})^2 \tag{2.2}$$

$$SS_{residual} = \sum (y - \hat{y})^2 \tag{2.3}$$

$$SS_{total\,corrected} = \sum (y - \bar{y})^2 \tag{2.4}$$

The data is $(x_{1i}, x_{2i}, \cdots x_{ki}, y_i)$. We utilize the fundamental partition equation

$$SS_{total\,corrected} = S_{reg} + SS_{res} \tag{2.5}$$

$$\hat{y} = b_0 + \sum_{i=1}^{k} b_i x_i \tag{2.6}$$

$$\bar{y} = \frac{\sum_{i=1}^{N} y_i}{N} \tag{2.7}$$

The following models which are initially proposed:

Mortality number. $= \sum_{m=0}^{k} b_m x_m$; where $x_0 = 1$ and k=15 or k=18

Discharge status $= \sum_{m=0}^{k} b_m x_m$; where $x_0 = 1$ and k=15 or k=18

Mortality number and discharge status are quantitative measures of overall risk: the former is a subjective probability assignment by the physician or surgeon; the latter is a discrete code for the outcomes of the surgical procedure. The mortality number is a weighted sum of risk contributions. The pre-established weights are the physician's subjective contribution to this measure. The discharge status incorporates the discrete nature of the dependent variable data which may be viewed as a step function (see Figure

2.1). Therefore, logistic modeling may be useful in smoothing the risk values into a continuous equation.

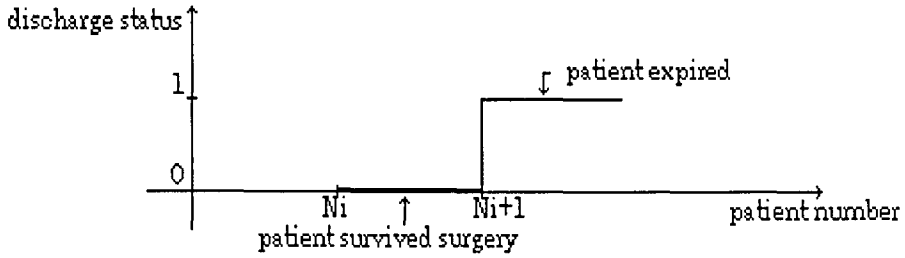

Figure 2.1 A step function for discharge status and patient number.

2.2 General Model

Frequently, one wishes to pose a model which possesses some specific asymptotic trends. In particular, when we wish to "smooth" out a step function, we recognize the need to incorporate the following conditions:

$$\lim_{x\to-\infty} f(x) = 0 \qquad \text{and} \qquad \lim_{x\to+\infty} f(x) = B \tag{2.8}$$

where B is a constant, usually equal to 1. If we further require that f(x) be monotone increasing, then we establish two key features in the model: (1) f(x) satisfies the conditions of a distribution function (e.g., a probability distribution for $0 < B \leq 1$). (2) f(x) possesses attributes of a function, y, which satisfies the following initial value problem.

$$\frac{dy}{dx} = Ay(B-y) \qquad \text{with} \qquad y(0) = B_0 \tag{2.9}$$

We want a function whose rate of change is (a) proportional to the dependent variable value, and (b) proportional to a constant minus the dependent value. That is

$$y' \propto y \qquad \text{and} \qquad y' \propto (B-y) \tag{2.10}$$

Historically, $y' \propto y$ leads us to a well known model in population dynamics [The Malthusian Linear Model]. Demographically, we expect however that the population growth will level off as the maximum available space and resources are depleted. Hence $y' \propto (B-y)$ represents a leveling off of the growth function which leads us to the previously outlined initial value problem referred to as the logistic model. This approach allows us to smooth a step function to a differentiable probability distribution which will model the cumulative risk and utilize the database variable.

2.3 Logistic Modeling

Dr. Parlar and collaborators (9) have employed a logistic model to estimate the probability, P, of lesions in some defined region, S, of the brainstem. This estimate is obtained from an "implication factor", M, which represents a measure of malfunctioning neural pathways in this region based upon neurological test outcomes. A region, S, is made up of elements (voxels), allowing each neural pathway to be representable as a set of voxels contained in S. An implication factor M for a region S then reflects summation of individual "malfunction factors" defined for each voxel.

A sigmoid logistic model for the lesion probability, P, in region S has previously been introduced as:

$$P = P(M) = \frac{A}{1 + Be^{-\alpha M}} \tag{2.11}$$

where A, B, and α are patient and disease parameters, with A as the maximum possible lesion probability. Equation 2.11 is the solution of the initial value problem.

$$\frac{dP}{dM} = P' = \alpha A(\frac{P}{A})(1 - \frac{P}{A}) \tag{2.12a}$$

$$P(M = 0) = \frac{A}{1 + B} \tag{2.12b}$$

This model is plausible because it contains intrinsic and necessary patterns in the rate of change of lesion probability with respect to a positive net malfunction factor (i.e., the slope of the tangent to the curve). These patterns are clear by inspection of the curve's convexity. There is a change when $M = \ln B/\alpha$. This point is an inflection point because P" change sign (from positive values when $M < \ln B/\alpha$ to negative when $M > \ln B/\alpha$). It is clear that since P" is negative, and hence, P' is a decreasing function for $M > \ln B/\alpha$. We see that P is a monotone increasing function of M.

Let us discuss this rate of change condition in the Equation (2.11) above. The curve approaches horizontal asymptotes: P=0 and P=A. Also observe that P and P' are well defined for all values of M. The function P is bounded, and in fact the derivative is bounded since, first of all,

$$\begin{matrix} \alpha > 0 \\ A > 0 \end{matrix} \qquad \text{and} \qquad 0 \le P \le A \Rightarrow P' \ge 0 \tag{2.13}$$

and further, by deriving all possible inflection points, the slope of the tangent, P' achieves its maximum value for $P = A/2$ (i.e., $M = \ln B/\alpha$). By computation, we see this value to be,

$$P'_{max} = \frac{\alpha A}{4} \qquad \text{for} \qquad P = \frac{A}{2} \tag{2.14}$$

Thus

$$0 < P' < \frac{\alpha A}{4} \tag{2.15}$$

2.4 Logistic Regression

If we allow

$$y = \beta e^{-\gamma z} \tag{2.16}$$

where

$$z = b_0 + \sum_{i=1}^{k} b_i x_i \tag{2.17}$$

then

$$\ln y = \ln \beta - \gamma z \tag{2.18}$$

$$\ln y = \ln \beta - \gamma (b_0 + \sum_{i=1}^{k} b_i x_i) \tag{2.19}$$

or

$$\hat{w} = A + \gamma \sum_{i=1}^{k} b_i x_i \tag{2.20}$$

Thus, we fit $\ln y$ with the previous independent variables and compute A and b_i for each x_i. We may then compute R^2 as:

$$R^2 = \frac{SS_{reg}}{SS_{total}} = \frac{\sum(\hat{w}-\overline{w})^2}{\sum(w-\overline{w})^2}$$
$$= \frac{\sum(A+\gamma\sum b_i x_i - \frac{\sum \ln y_i}{N})^2}{\sum(\ln y_i - \frac{\sum \ln y_i}{N})^2} \qquad (2.21)$$

CHAPTER 3

COMPUTATION AND SUMMARY OF STATISTICAL RESULTS

3.1 Conversion of Prior Risk Values to Posterior Risk Values

We wish to determine the posterior probability of expiration due to cardiovascular surgery, based upon a prior "cardiac risk distribution" provided by the "Parsonett Model". These initial risk values will be adjusted so as to estimate an overall risk function (at first, by linear approximation). This adjustment is twofold. We seek a linear combination of "independent" risk factors as an average computation of risk. Further, since we are utilizing regression analysis, we are minimizing the sum of squares of the errors as shown.

$$\sum_{\text{over all patients}} [\text{ final risk } - \text{ initial risk }]^2 \text{ is a minimum}$$

3.2 Comparison of Risk Values

The adjusted risk values incorporate actual patient survival rates for improved accuracy. A common problem with prior estimates is that they are too conservative: actual survival rates indicate that risk is being overpredicted for most patients, especially those in high risk categories. Our revised estimates tend to more accurately predict risk for high risk patients, but are not sufficiently accurate for patients where the aggregate risk value is less than 4%. In these cases, the prior estimates should be utilized.

3.3 Tabulated Results

We have four distinct regression models:

Model(I) Reduced Predictor/Maximum Information Model (RMM):

$$\text{(Parsonett risk value)} = b_0 + \sum_{i=1}^{15} b_i r_i$$

where r_i = i th risk factor (total of 15 of them).

Model(II) Reduced Predictor/No Information Model (RNM):

$$\text{(Survival state)} = b_0 + \sum_{i=1}^{15} b_i r_i$$

where r_i = i th risk factor (total of 15 of them) and 0 for survival; 1 for expiration.

Model(III) Complete Predictor/Maximum Information Model (CMM):

$$\text{(Parsonett risk value)} = b_0 + \sum_{i=1}^{18} b_i r_i$$

where r_i is the same as (1) except that 3 additional risk factors (smoker, heredity, high cholesterol) are included.

Model(IV) Complete Predictor/No Information Model (CNM):

$$\text{(Survival state)} = b_0 + \sum_{i=1}^{18} b_i r_i$$

The Complete Predictor Model includes 3 additional risk factors (smoker, heredity, and high cholesterol). The tabulated posterior risk values are shown below:

Table 3.1 Reduced Predictor/Maximum Information Model (RMM).

Risk Factors	Initial Weight	Final Weight	Initial Risk Contribution (Maximum Parsonett Number) (Prior Prob.)	Final Risk Contribution (Posterior Probability)
intercep	1	0.896634	0	0.896634
sexriskn (male,female)	1	1.196721	(0,1)	(0,1.196721)
obesity (no,yes)	1	0.876160	(0,3)	(0,2.62848)
diabetic (no,yes)	1	1.203874	(0,3)	(0,3.611622)
hyperten (no,yes)	1	0.968884	(0,3)	(0,2.906652)
efriskno (good,fair,poor)	1	1.451194	(0,2,4)	(0,2.902388,5.804776)
agerisk (0-69,70-74,75-79,80+)	1	1.045009	(0,7,12,20)	(0,7.315063 ,12.540108,20.90018)
reoperat (no,first,second,third)	1	1.086016	(0,5,10,10)	(0,5.43008,10.86016 ,10.86016)
preopiab (no,yes)	1	2.846297	(0,2)	(0,5.692594)
lva (no,yes)	1	1.431998	(0,5)	(0,5.187995)
crashptc (no,yes)	1	1.037599	(0,10)	(0,10.37599)
dialdepe (no,yes)	1	1.052031	(0,10)	(0,10.52031)
avr (no,gradient≥120 ,gradient<120)	1	1.107784	(0,7,5)	(0,7.754488,5.53892)
mvr (no,pressure≥60 ,pressure<60)	1	1.498085	(0,8,5)	(0,11.98468,7.490425)
tvr (no,yes)	1	2.947985	(0,3)	(0,8.843955)
addedcab (no,yes)	1	0.777405	(0,1)	(0,0.777405)

Table 3.2 Reduced Predictor/No Information Model (RNM).

Risk Factors	Initial Weight	Final Weight	Initial Risk Contribution (Maximum Parsonett Number) (Prior Prob.)	Final Risk Contribution (Posterior Probability)
intercep	1	-0.018019	0	-0.018019
sexriskn (male,female)	1	0.051789	(0,1)	(0,0.051789)
obesity (no,yes)	1	0.011205	(0,3)	(0,0.033615)
diabetic (no,yes)	1	0.016343	(0,3)	(0,0.049029)
hyperten (no,yes)	1	0.002456	(0,3)	(0,0.007368)
efriskno (good, fair, poor)	1	0.015496	(0,2,4)	(0,0.02992,0.05984)
ageriskn (0-69,70-74,75-79,80+)	1	0.005076	(0,7,12,20)	(0,0.035532,0.060912,0.10152)
reoperat (no,first,second,third)	1	0.036479	(0,5,10,10)	(0,0.182395,0.36479)
preopiab (no,yes)	1	0.048045	(0,2)	(0,0.09609)
lva (no,yes)	1	0.031283	(0,5)	(0,0.156415)
crashptc (no,yes)	1	0.004150	(0,10)	(0,0.0415)
dialdepe (no,yes)	1	0.010785	(0,10)	(0,0.10785)
avr (no,gradient≥120 ,gradient<120)	1	-0.002090	(0,7,5)	(0,-0.01463,-0.01045)
mvr (no,pressure≥60 ,pressure<60)	1	0.010462	(0,8,5)	(0,0.083696,0.05231)
tvr (no,yes)	1	0.057859	(0,3)	(0,0.173577)
addedcab (no,yes)	1	0.009134	(0,1)	(0,0.009134)

Table 3.3 Complete Predictor/Maximum Information Model (CMM).

Risk Factors	Initial Weight	Final Weight	Initial Risk Contribution (Maximum Parsonett Number) (Prior Prob.)	Final Risk Contribution (Posterior Probability)
intercep	1	1.142688	0	1.142688
sexriskn (male,female)	1	1.191676	(0,1)	(0,1.191676)
obesity (no,yes)	1	0.876011	(0,3)	(0,2.628033)
diabetic (no,yes)	1	1.205170	(0,3)	(0,3.61551)
hyperten (no,yes)	1	0.970243	(0,3)	(0,2.910729)
efriskno (good,fair,poor)	1	1.451066	(0,2,4)	(0,2.902132,5.804264)
agerisk (0-69,70-74,75-79,80+)	1	1.039467	(0,7,12,20)	(0,7.276269 ,12.473604,20.78934)
reoperat (no,first,second,third)	1	1.087440	(0,5,10,10)	(0,5.4372,10.87440 ,10.87440)
preopiab (no,yes)	1	2.875147	(0,2)	(0,5.750294)
lva (no,yes)	1	1.424371	(0,5)	(0,70121855)
crashptc (no,yes)	1	1.035834	(0,10)	(0,10.35834)
dialdepe (no,yes)	1	1.049197	(0,10)	(0,10.49197)
avr (no,gradient≥120 ,gradient<120)	1	1.094140	(0,7,5)	(0,7.65898,1.1971423)
mvr (no,pressure≥60 ,pressure<60)	1	1.488098	(0,8,5)	(0,11.904784,7.44049)
tvr (no,yes)	1	2.957870	(0,3)	(0,8.87361)
addedcab (no,yes)	1	0.789381	(0,1)	(0,0.789381)
smoker (no,yes)	1	-0.068366	(0,1)	(0,-0.068366)
heredity (no,yes)	1	-0.417990	(0,1)	(0,-0.417990)
hicholes (no,yes)	1	-0.160634	(0,1)	(0,-0.160634)

Table 3.4 Complete Predictor/No Information Model (CNM).

Risk Factors	Initial Weight	Final Weight	Initial Risk Contribution (Maximum Parsonett Number) (Prior Prob.)	Final Risk Contribution (Posterior Probability)
intercep	1	-0.016471	0	(0,-0.016471)
sexriskn (male,female)	1	0.051700	(0,1)	(0,0.051700)
obesity (no,yes)	1	0.011161	(0,3)	(0,0.033483)
diabetic (no,yes)	1	0.016024	(0,3)	(0,0.048072)
hyperten (no,yes)	1	0.002874	(0,3)	(0,0.048072)
efriskno (good,fair,poor)	1	0.015180	(0,2,4)	(0,0.03038,0.06072)
ageriskn (0-69,70-74,75-79,80+)	1	0.005003	(0,7,12,20)	(0,0.035021,0.060036 ,0.10006)
reoperat (no,first,second,third)	1	0.036322	(0,5,10,10)	(0,0.18161)
preopiab (no,yes)	1	0.048239	(0,2)	(0,0.096478)
lva (no,yes)	1	0.030954	(0,5)	(0,0.15477)
crashptc (no,yes)	1	0.004120	(0,10)	(0,0.04120)
dialdepe (no,yes)	1	0.010793	(0,10)	(0,0.10793)
avr (no,gradient≥120 ,gradietn<120)	1	-0.002410	(0,7,5)	(0,-0.01687,-0.01205)
mvr (no,pressure≥60 ,pressure<60)	1	0.010108	(0,8,5)	(0,0.080864,0.05054)
tvr (no,yes)	1	0.057633	(0,3)	(0,0.172899)
addedcab (no,yes)	1	0.010065	(0,1)	(0,0.010065)
smoker (no,yes)	1	-0.002494	(0,1)	(0,-0.002494)
heredity (no,yes)	1	0.012017	(0,1)	(0,0.012017)
hicholes (no,yes)	1	-0.020797	(0,1)	(0,-0.020797)

3.4 Motivation

The reasons for considering 4 distinct models are as follows:

(1) Recognizing the improved estimates obtained by utilizing Parsonett risk values as opposed to survival rates allow us to (a) assess the overall information which is present or absent in a prior "probability of expiration" distributions; (b) determine the usefulness and validity of the Parsonett risk model as an initial condition for future risk estimation; (c) estimate risk values that utilize the intuition of experienced physicians as well as a database of surgical outcomes.

(2) The risk factors denoted by smoker, heredity, high cholesterol are tested for importance and relevance to best determine whether or not to they should be included in future models. All 18 risk factors were chosen for specific evaluation by the consulting physicians.

3.5 Summary of Multivariate Models

Below are the inferential statistics associated with the 4 different multivariate models.

Table 3.5 Results of All Models

Model	R^2	R	F	P
I RMM	0.729	0.854	180.245	0.0001
II RNM	0.093	0.305	6.86696	0.0001
III CMM	0.729	0.854	150.0853	0.0001
IV CNM	0.094	0.306	5.7642	0.0001

We see that the Parsonett model dramatically improves preoperative risk estimation and is rich in medical information which is consistent with the information contained in the patient database.

3.6 Analyzing the Impact of the Parsonett Model as a Prior Probability Distribution

We would like to identify the relation between the Parsonett number (as a percentage of risk) and the surgical outcome (survival or expiration). We fit the Parsonett number with this outcome (refereed to as "Discharge Status") in a linear model to determine the regression and correlation coefficients.

$$\text{Discharge status} = b_0 + b_1 \cdot (\text{Parsonett risk number}) \tag{3.1}$$

We find

$$\hat{z} = -0.04 + 0.10408y \tag{3.2}$$

where $\hat{z}$ is posterior risk and y is prior risk. From ANOVA Table 3.6 we get R=0.3489. This is a measure of the improvement of the risk estimation provided by the Parsonett prior probability function. Hence, we see the reason for having derived better models when the Parsonett number was used in place of discharge status in the preceding multivariate models.

Table 3.6 ANOVA for Dependent Variable = Discharge Status

Variable	d.f.	estimate	R^2	F	P
Intercep	1	-0.040037	0.1217279	141.233	0.0001
Mortalno	1	0.010408			

z = Discharge status = 0 for survival; 1 for expiration

y = Mortality number (Parsonett number = Prior risk value)

$\hat{z}$ = -0.040037 + 0.010408y (Posterior risk value) is shown in Figure 3.1.

Figure 3.1 Risk transformation

Table 3.7 ANOVA for Dependent Variable = Mortality number

Variable	d.f.	estimate	R^2	F	P
Intercep	1	13.269019	0.1217279	141.233	0.0001
Dischsta	1	11.695894			

y = Mortality number (Parsonett number = Prior risk value)

z = Discharge status = 0 for survival; 1 for expiration

$\hat{y}$ = 13.269019 + 11.695894z (Posterior risk value) is shown in Figure 3.2.

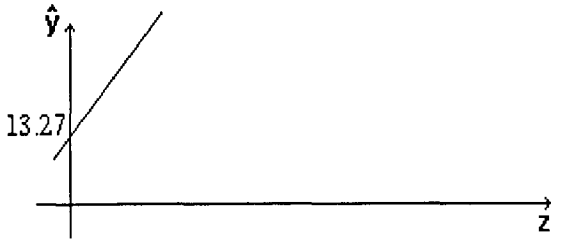

Figure 3.2 Risk transformation (inverse function)

3.7 Risk Category Histogram

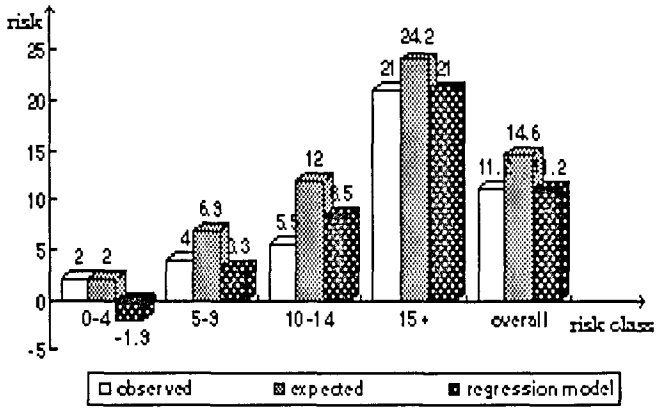

Figure 3.3 Risk category histogram

In Figure 3.3: observed = average Parsonett number for a given risk class

expected = actual % of mortality for a given risk class

regression model = posterior risk value from Equation 3.2

CHAPTER 4

CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH

4.1 Conclusions

In this work we have utilized linear modeling and Bayesian methods to transform prior cardiac surgery risk values into more reliable posterior risk estimates. The models which incorporate both the experience of physicians and an extensive patient database have been seen to be superior in both accuracy and determination of a patient's overall risk category. The information contained in the Parsonett prior probability distribution has been shown to be significant and very valuable to this process.

4.2 Suggestions for Future Research

Much future work is possible and promises to be quite valuable:

(1)The Parsonett model assigns a risk value to a range of "risk factors" consisting of patient attributes and disease parameters. Testing individual factors for relative importance should be explored.

(2)Piecewise linear models should be utilized to combine prior risk information provided by experienced surgeons.

(3)Logistic modeling may be applied to generate a comprehensive risk function which is compatible with the piecewise linear functions for each of the different risk categories.

(4)A time series model should then incorporate the impact of improved technology and evolution of surgical procedures in an effort to further improve the accuracy of risk and performance estimation.

APPENDIX

Risk Factor	Weight
Age at operation	
0-69	0
70-74	7
75-79	12
80+	20
Sex	
Male	0
Female	1
Ejection Fraction	
Good or 50%+	0
Fair or 30%-49%	2
Poor or 1%-29%	4
Morbid Obesity	
No	0
Yes	3
Diabetes	
No	0
Yes	3
Hypertension	
No	0
Yes	3
Reoperation	
No	0
First	5
Second	10
Third	10
Preoperative IABP	
No	0
Yes	2
LV Aneurysm	
No	0
Yes	5
Dialysis-dependent	
No	0
Yes	10

Disasters and Rare Conditions	Weight
0. None	0
CARDIAC CONDITIONS	
1. Left Main Disease, Unstable Angina	3
2. Ventricular Tachycardia / Ventricular Fibrillation (VT/VF), aborted sudden death	5
3. Shock/Cardiogenic (urinary output <10 cc/hr, mean BP 40 without vasopressors)	25
4. Transmural Acute MI within 48 hrs	7
5. CHF, chronic (with peripheral edema, plural effusion)	5
6. Pacemaker Dependent	2
7. AR, acute (endocarditis)	10
8. MR, Acute (endocarditis, papillary muscle rupture, etc.	10
9. VSD, Acute	20
10. Constrictive Pericarditis	5
11. Congenital Heart Disease in adult, cyanotic	10
HEPATO-RENAL CONDITIONS	
12.Renal Failure, Chronic(CR>2,w/out dialysis)	5
13.Renal Failure, Acute	25
14. Cirrhosis of liver, (serum bilirubin > 5)	10
PULMONARY CONDITIONS	
15. COPD, severe	5
16. Pulmonary Hypertension (mean pressure > 30)	10
17. Idiopathic Thrombocytopenci Purpura (ITP)	10
18. Endotrachial Tube, pre-operation	5
19. Asthma (peak expiratory flow rate <100)	20
20. Asthma (peak expiratory flow rate < 200)	10
VASCULAR CONDITIONS	
21. PVD, severe	2
22. Carotid Disease, unilateral occlusion	5

Risk Factor	Weight
PTCA or Catherization "crash"	
No	0
Yes	10
MV procedure	
No	0
Yes	
PA pressure>=60	8
PA pressure<60	5
AV procedure	
No	0
Yes	
Gradient>=120	7
Gradient<120	5
TV procedure	
No	0
Yes	3
Added CABG	
No	0
Yes	2

Disasters and Rare Conditions	Weight
23. Carotid Disease, bilateral	10
24. AAA, Asymptomatic	5
25. Dissecting Thoracic Aneurysm	10
MISCELLANEOUS CONDITIONS	
26. Severe neurologic disorder (healed CVA, paraplegia, muscular dystrophy, hemoparesis)	5
27. Diabetes, Juvenile	5
28. Hyperlipidemia (cholesterol > 300, HDL < 30)	3
29. Jehovah's Witness	10
30. Cold Agglutinins	5
31. Aspirin Rx (ASA Rx)	2
32. Substance abuse (alcohol, drugs), severe	3
33. AIDS, active disease (HIV positive excluded)	10
34. Active Neoplasm (leukemia, lymphoma, etc.)	5
35. High-dose steroids, active	2

REFERENCES

1. Forrest L. Junod, Bradley J. Harlan, Janie Payne, et al. "Preoperative Risk Assessment in Cardiac Surgery: Comparison of Predicted and Observed Results." *The Annals of Thoracic Surgery.* 43 (January, 1987):59-64.

2. Sankey V. Williams, David B. Nash, Neil Goldfarb. "Differences in Mortality From Coronary Artery Bypass Graft Surgery at Five Teaching Hospitals." *Journal of the American Medical Association.* 266 (August 14, 1991):810-815.

3. J. Ward Kennedy, George C. Kaiser, Lloyd D. Fisher, et al. "Multivariate Discriminant Analysis of the Clinical and Angiographic Predictors of Operative Mortality From the Collaborative Study in Coronary Artery Surgery (CASS)." *The Journal of Thoracis and Cardiovascular Surgery.* 80 (December, 1980):876-887.

4. Nanette K. Wenger. "Exclusion of the Elderly and Women From Coronary Trials: Is Their Quality of Care Compromised?" *Journal of the American Medical Association.* 268 (September 16, 1992):1460-1461.

5. Jerry H. Gurwitz, Nananda F. Col, Jerry Avorn. "The Exclusion of the Elderly and Women From Clinical Trials in Acute Myocardial Infarction." *Journal of the American Medical Association.* 268 (September 16, 1992):1417-1422.

6. George J. Taylor, Richard E. Katholi, Kelly Womack, et al. "Increased Incidence of Silent Ischemia After Acute Myocardial Infarction." *Journal of the American Medical Association.* 268 (September 16, 1992):1448-1450.

7. Gerald T. O'Connor, Stephen K. Plume, Elaine M. Olmstead, et al. "A Regional Prospective Study of In-Hospital Mortality Associated With Coronary Artery Bypass Grafting." *Journal of the American Medical Association.* 266 (August 14, 1991):803-809.

8. Henry Buchward, John P. Matts, Laurie L. Fitch, et al. "Changes in Sequential Coronary Arteriograms and Subsequent Coronary Events." *Journal of the American Medical Association.* 268 (September 16, 1992):1429-1433.

9. Yusuf Parlar, Rose A. Dios, Andrew U. Meyer. "The Logistic Model in Lesion Localization for Neurological Diseases." *Annual International Conference of the IEEE Engineering in Medicine and Biology Society.* 13 (1991):1076-1077.