

Can a New Interpretation of Survival Data Help Patients Successfully Modify Adverse Risk Profiles?

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ABSTRACT

Background: Adverse risk profiles diminish survival for the approximately 485,000 patients who undergo coronary artery bypass surgery (CABG) in the United States annually. Yet, non-compliance with treatment strategies remains a problem in management of cardiovascular disease. Defining more “user-friendly” mechanisms that convey the messages of clinical trials in familiar terms may favorably impact the attainment of treatment goals.

Methods: Cox proportional hazards regression models were used to assess the relationship between triglycerides and survival following CABG surgery for a cohort of older women (N=1,158). Models were developed using time-on-study (M1) and age (M2) as response variables.

Results: Both approaches yielded similar results with regard to the importance of high triglyceride (hazard ratio(M1)=1.60 (95% CI = 1.26-2.03); hazard ratio(M2)=1.64 (1.29-2.08). The age-based approach showed that the median age of death for high triglyceride patients was approximately nine years younger than for normal triglyceride patients (72 vs. 81 years).

Conclusion: The traditional and age-based approaches produced consistent results. The age-based approach produced an estimate of foreshortened life expectancy for women with high triglycerides. This interpretation may be helpful in conveying the relevance of risk factors as physicians and patients implement treatment strategies.

INTRODUCTION

Approximately 485,000 CABG surgeries are performed in the U.S. each year. Modifiable risk factors such as lipids have been identified as predictors of survival following CABG surgery[1-4]. Nevertheless, the management of modifiable risk factors in the secondary prevention setting often falls short of goals[5-10].

The traditional method for evaluating outcomes after cardiac surgery has been to employ Cox proportional hazards regression models with time-on-study as the time scale[11, 12]. However, it has been suggested that age is an alternative time scale for survival analyses with desirable properties in some settings [13, 14]. Both approaches produce an estimated hazard function and hazard ratio that are used in determining the degree to which the probability of mortality is increased for a given set of risk factors. Using age as the time scale allows the generation of survival estimates that approximate the percentage of patients surviving to a given age, rather than the duration of survival after an event or procedure. Proponents of the age-based approach point to the fact that this methodology is less restrictive than traditional models and produces an easily understood interpretation of the results. The latter point is the focus of this investigation. With better understanding by patients of the implications of increased risk, compliance to indicated treatment strategies may be improved.

METHODS

Subjects

Previous reports suggest that survival post-CABG in women is critically influenced by baseline TG values even after adjustment for other metabolic and surgical variables [15]. A population of women aged 55 or older with baseline TG measurements who had primary isolated CABG surgery at the Cleveland Clinic Foundation between 1982 and 1992 (N=1,158) was chosen as the basis of this example. Patients are followed at five-year intervals post surgery for up to 15 years. Seventy-four percent of patients were alive at last contact. In addition, patients who experienced operative mortality (death within 30 days of surgery) were excluded in order to minimize the impact of intraoperative factors on long-term outcomes. Fasting lipid values were measured prior to surgery, usually the day before. Information for other risk factors was determined through chart review after discharge from the hospital.

Statistical Analyses

Time-to-event data were analyzed according to the primary endpoint of all-cause mortality (overall survival). Survival estimates were generated with the Kaplan-Meier method [15]. Cox proportional hazards modeling (PROC PHREG, SAS Institute, Cary, N.C.) was used to assess the relative importance of baseline risk factors to the endpoints [16]. The traditional models used time-on-study as the time scale. The alternative model used age at surgery as the time scale. Tied event data were handled using Efron's method of approximation for both the traditional and age-based approaches [17]. Overall model significance was assessed with likelihood-ratio tests, and significance of each variable in the model with the Wald test [18]. Hazard ratios are presented (with 95% confidence intervals) to show the risk of an event when the factor is present. TG was categorized as either high (1, greater than 235 mg/dL, which defines the highest quartile) or normal (0, lower three quartiles) to minimize noise within the normal range of TG and to facilitate relevance as a clinical tool. Covariates included in the models (age, DM, HTN, LVF, ITA) were chosen based on previous work [15].

Both the traditional and age-based approaches include patients who were alive at last contact leading to right censoring. Because the age-based approach includes patients who were older than 55 at the time of CABG surgery, the data are also left truncated. Therefore, the standard proportional hazards model must be extended by incorporating the delayed entry of patients older than 55.

The time scale for the traditional approach is simply age at death or censoring minus age at surgery. This yields Y , which is the exposure time in years. For the age-based approach a delayed entry factor, W , is included. This measures the number of years from age 55 until the surgery date. The response in the age-based model, T , measures the sum of W and Y . The censoring indicator, D , is either 1 if the subject died or 0 if the subject was censored. The traditional approach to survival analysis uses the time-on-study (Y) and the vital status (D) as the basis for the survivor function.

$$\hat{s}_1(y) = \prod_{j|y_j \leq y} \left\{ 1 - \frac{d(y_j)}{r(y_j)} \right\}, \text{ where}$$

$d(y_j)$ is the number of deaths at time y_j , and $r(y_j)$ is the number of individuals at risk of dying at time y_j . For example, if one were interested in 10-year survival then y would be 10 and the survivor function would be determined by the number of patients dead ($D = 1$) at 10 years and the number of patients surviving ($D = 0$), $r(y_j)$, at 10 years.

The survivor function for the age-based model is as follows:

$$\hat{s}_2(y) = P(T \geq t) = \prod_{j|t_j \leq t} \left\{ 1 - \frac{d(t_j)}{r(t_j)} \right\}, \text{ where}$$

$P(T > t)$ is the probability of survival past any specific time (t), $T = Y + W$, $d(t_j)$ is the number of deaths at time t_j , and $r(t_j)$ is the same as in (1) except that it includes only those patients who had CABG surgery at an age younger than $t_j + 55$.

A distinguishing feature of the age-based approach is that the number of subjects at risk is variable over time, while the traditional approach yields a monotonically decreasing number of subjects at risk over time. For example, an individual who undergoes surgery at age 65 is not at risk prior to that age. Therefore, that individual would not contribute to estimation or hypothesis testing prior to age 65.

The source code for both the traditional and age-based models follows.

Traditional Model:

```
proc phreg;
  model Y*DEAD(0)=HIGHTG covariates
    / ties=efron rl;
  title 'Overall Survival - Women';
  title2 'Traditional Model';
run;
```

Age-Based Model:

```
proc phreg;
  model (W,T)*DEAD(0)=HIGHTG covariates
    / ties=efron rl;
  title 'Overall Survival - Women';
  title2 'Age-Based Model';
run;
```

RESULTS

The median age at surgery was 67 years. Twenty seven percent (27%) of patients had a history of medically treated diabetes mellitus (DM), and 69% had a positive history of hypertension (HTN). Left ventricular dysfunction (LVF) as determined by cardiac catheterization was defined as none (I, 48% of patients), mild (II, 29%), moderate (III, 15%) or severe (IV, 8%). Internal thoracic arteries (ITA) were used in 74% of surgical procedures. The median TG level was 168 mg/dL with an interquartile range from 121 mg/dL to 235 mg/dL. A description of subjects with high TG compared to those with normal TG is shown in Table 1.

Table 1. Description of population by TG status.

	Normal TG	High T
N	855	303
Age*	68 ± 6	66 ± 6
DM*	23%	38%
HTN	68%	71%
Severe LVF	8%	9%
ITA Used	75%	72%

*p < 0.05

Whether using the traditional or age-based approach we find consistent results with regard to the importance TG as a risk factor for mortality post CABG. The hazard ratio for high TG was 1.60 (95% CI 1.26-2.03, p=0.0001) under the traditional approach and 1.64 (1.29-2.08, p=0.0001) under the age-based approach. Tables 2a and 2b delineate the model results for both approaches.

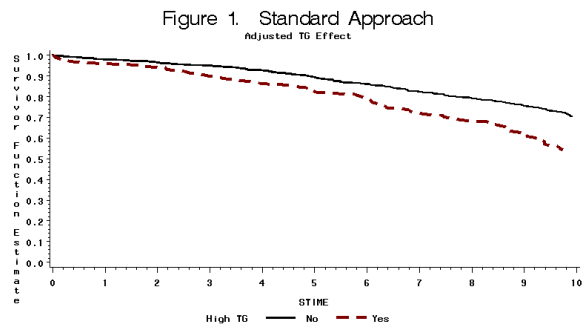
Table 2a. Results of traditional model.

	Hazard Ratio	Confidence Interval	p-value
Age	1.05	1.03-1.07	0.0001
DM	1.55	1.21-1.98	0.0004
HTN	1.84	1.40-2.41	0.0001
LVF	1.27	1.14-1.42	0.0001
ITA used	0.76	0.59-0.97	0.02
High TG	1.60	1.26-2.03	0.0001

Table 2b. Results of age-based model.

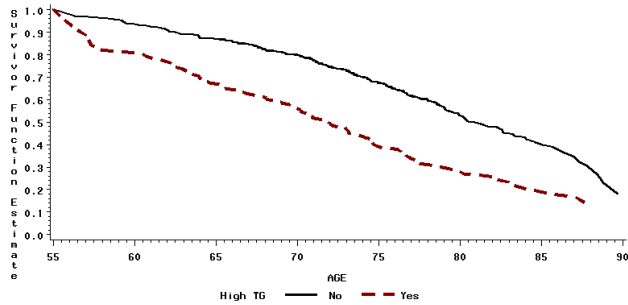
	Hazard Ratio	Confidence Interval	p-value
DM	1.45	1.14-1.86	0.003
HTN	1.68	1.28-2.19	0.0002
LVF	1.27	1.14-1.42	0.0001
ITA used	0.79	0.62-1.01	0.06
High TG	1.64	1.29-2.08	0.0001

Figure 1 shows the adjusted Kaplan-Meier survival curves for patients with high TG versus those with normal TG using the traditional time-on-study approach. The potential confounding effects of aging are incorporated into the model by including age at the time of surgery as a covariate. A significant TG by time interaction is seen (p=0.0001) indicating that the TG effect should be considered the average effect over the course of the study [19].



The Kaplan-Meier curves for the adjusted TG effect under the age-based approach are depicted in Figure 2. With age as the time scale, we can see that the median age of death (50% on the vertical axis) is about nine years later for subjects with normal TG versus those with high TG (81 years and 72 years respectively). This interpretation is not available under the traditional approach.

Figure 2. Age-Based Approach
Adjusted TG Effect



CONCLUSION

This report demonstrates that by producing a result that has equivalent statistical validity but may be more clinically meaningful to both patient and provider, the age-based survival analysis technique complements the traditional time-on-study approach. As chronic care becomes more relevant to the well being of our aging community, and individuals assume more responsibility for their own welfare, the influence of known risk factors must be fully and understandably communicated. The potential loss of nine years of life may be a concept that the provider can incorporate into the critical educational component of treatment plans for management of CAD risk factors. As such, it may be a useful tool for improving compliance with recommended guidelines an increasing attainment of accepted treatment goals.

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**YOUR COMMENTS AND QUESTIONS ARE VALUED AND ENCOURAGED.
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