Utility of a Bayesian Updating Computer Tool to Monitor Safety Data in Real Time: An Example Evaluating Subacute Stent Thrombosis for the CYPHER Drug Eluting Stent

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Abstract

Background: Low event rates and rapid evolution of technology create challenges for safety monitoring in interventional cardiology. A Bayesian method incorporates previous information (priors) into risk estimates and updates estimates over time as clinical data are accrued, allowing the potential detection of safety issues earlier than a corresponding frequentist analysis. We explore the feasibility of a software monitoring tool that uses the Bayesian method to detect significant changes in event rates

Methods: Our software tool evaluated CYPHER subacute stent thrombosis (SAT) rates at our center. This system includes a web-based user interface and an SQL database to perform the data manipulation and analysis. For any new procedure or product, initial risk estimates (priors) are calculated using the FDA approval data. We used data from the SIRIUS and RAVEL (RCT) trials in this example. The risk stratification model was based on previously published SAT rates for low risk bare metal stent (BMS) data. The system calculates updated risk estimates over time, and displayed tabular and graphical summaries in a web-based interface.

Results: There was 1 SAT event in 653 procedures in the RCT data (prior). The risk stratification model was validated using BMS data available from our center (area under the ROC curve=0.81). Single center SAT rates for 1617 DES cases were evaluated from 4/03 to 7/04 at monthly intervals. The observed SAT rates were 0.23% (2/887) and 1.1% (8/730) for the low risk and high risk groups, respectively. Initial risk estimates for SAT were 0.15% and 0.77%. Final risk estimates were 0.17% (0.04-0.47) and 1.1% (0.5-1.9). Early events in the low risk group caused fluctuations in the risk estimate, but the risk did not exceed 0.23%. Risk estimates in the high risk group did not exceed 1.2%.

Conclusion: The example analysis confirmed that CYPHER SAT rates were within acceptably predicted ranges for low and high risk patients at our center. Our results suggest that it is feasible to use a system based on Bayesian updating to perform real time monitoring of the safety of newly developed technologies. The system is structured to provide flexible monitoring options for any new device or procedure.

Background

Safety monitoring of medical devices, under the auspices of the FDA, has undergone significant change over the last few decades. Post-marketing data is now reviewed by the FDA using data from both required and voluntary sources. However, it is suspected that large numbers of events fail to be reported. Recent FDA actions surrounding suspected CYPHER stent subacute thrombosis rates, and TAXUS stent balloon non-deflations highlight the need for further development of early detection systems. In addition to a clear need for early monitoring systems, interventional cardiology (IC) provides an excellent standardized data dictionary for such a task with the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR).

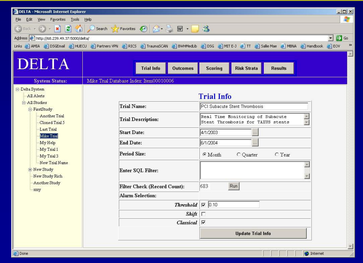
Classical statistical monitoring methods have limitations when the event rate is very low, and when the amount of prior data is limited. Bayesian statistical updating provides an explicit method for incorporating prior study data, and extrapolating reasonable estimates of initial risk profiles based on limited data and therefore, may have advantages compared to classical frequentist methods alone.

We therefore sought to develop a computer application that uses both Bayesian updating and classical frequentist statistical methodology to provide real time safety monitoring that would serve as an early warning system for device related morbidity.

DELTA System

The DELTA (Data Extraction and Longitudinal Time Analysis) system imports a real time data stream in a flat file format from a source outcomes database. It then stores the stream in a Microsoft SQL 2000 server (Redmond, WA). A Microsoft IIS 5.0 web server and a web application developed in the Microsoft .NET environment serve as the user interface, and is shown in Figure 1. This program allows researchers to easily create, modify, monitor, and retrieve results of studies. All study and trial configuration information is stored in the DELTA SQL database and available for concurrent or retrospective analyses.

1. Main Menu of DELTA Showing Overview and the Style of the Tool



2. (Left) A Summary of Risk Factors and Scores Used for Risk Stratification. (Right) Risk Strata with Score Cutoffs

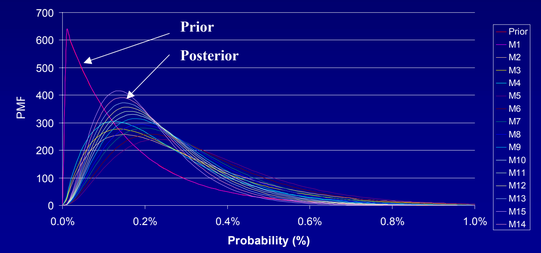
Risk Factors	Score
Final Dissection	6
Stent Length >25mm	1
Final balloon < 3.0mm	4
Age > 60	1
Acute MI in 24 hours	4

Risk Strata	Score Cutoff
Low risk	0-4
High risk	>5

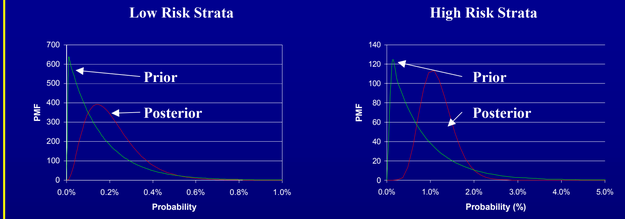
3. Summary of SAT Events and Number of Procedures per Risk Stratification

Risk Strata	SAT Events	Procedures	%
Low Risk	2	883	0.23%
High Risk	8	682	1.17%

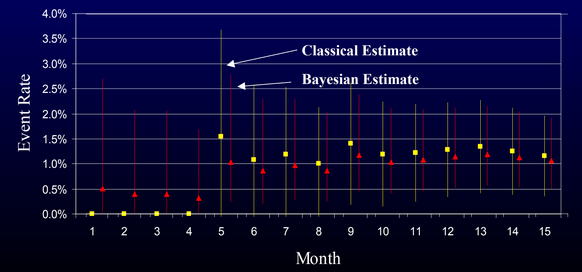
4. Evolution of Risk Estimates Through Each Period for Risk of SAT in the Low Risk Strata



5. Prior and Posterior Probability Distributions in Each Risk Strata for SAT



6. Comparison of Risk Estimates for Bayesian and Classical Methods in High Risk Patients with 95% Confidence Intervals



Methods

To provide an example of the system in operation, a simulation trial was setup to monitor CYPHER drug-eluting stent implantation in percutaneous coronary interventions (PCI) for the outcome of SAT. DELTA was run in simulated monthly increments using data from April 01, 2003 to June 01, 2004 incorporating the first fourteen months of CYPHER use after FDA approval. All data was obtained from the IC database at our center. The data fields collected are based on the ACC-NCDR data dictionary with a variety of additional, detailed elements.

The Bayesian statistical updating methodology requires choosing pertinent risk variables and ascribing each one a weight according to its relevance to the outcome of interest. Those risk factors chosen for this example are shown in Figure 2, and are based on a literature review. These risk factors were validated by using multivariate logistic regression on available BMS data from our center (ROC = 0.81). Phase 3 RCT on CYPHER stents were used to develop the prior event rate for the low risk category, and BMS high risk data was used to estimate the prior event rate for the high risk category with a proportional decrease in statistical confidence.

Results

There was one SAT event in 653 procedures in the low risk RCT data that was used for the prior. The observed SAT rates were 2 of 887 (0.23%) for the low risk group, and 8 of 730 (1.1%) in the high risk group (Figure 3). Early events in the low risk group causes fluctuations in the risk estimate, but the risk did not exceed 0.23% in any period, as shown by the low risk strata period by period breakdown in Figure 4. Risk estimates in the high risk group did not exceed 1.2%. Figure 5 shows a summary of the prior and posterior risk estimates for each risk strata. The low risk estimate had very little variation over the study, and gradually increased its probability density function (PDF), a rough indicator of power. The high risk strata showed a slight increase over the course of the study that was not statistically significant.

The 95% confidence intervals for both the classical and Bayesian methods per period are shown in Figure 6. The first four periods did not have an outcome event, and this is shown in the graph. The Bayesian method, through use of the prior data from pre-marketing clinical trials, shows a narrower confidence interval. In addition, at no point during the study do the two methods disagree in a statistically significant way.

Discussion

This example demonstrates the use of the DELTA system for real time safety monitoring for SAT with respect to implanting a new DES device in PCI. This study confirmed that CYPHER SAT rates were within acceptably predicted ranges for low and high risk patients at our center. Our results suggest that it is feasible to use a system based on Bayesian updating to perform real time monitoring of the safety of newly developed technologies. The system is structured to provide flexible monitoring options for any new device or procedure.

Some of the potential limitations of the Bayesian methodology lies in defining the risk strata and the priors for each risk strata. We used a logistic regression technique on closely related data to validate the risk variables chosen, and that potentially introduces error as well.

Overall, DELTA shows promise as an early warning tool with support for automated alerting based on both Bayesian and classical frequentist statistical methods.

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