Exploration of a Bayesian Updating Methodology to Monitor the Safety of Interventional Cardiovascular Procedures

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Appropriate methods for monitoring of the safety of medical devices introduced into clinical practice have been elusive to develop and implement. A novel approach is the application of Bayesian updating, which incorporates existing knowledge regarding event rates into the estimation of risk. This framework has been shown in other domains to be data efficient and to address some of the limitations of conventional statistical methods. In this article, the authors propose a methodologic framework for developing initial prior probability distributions in risk-stratified patient groups and a mechanism for incorporating accumulating procedure safety experience. In addition, they use this methodology to retrospectively analyze the clinical outcomes of 309 patients undergoing an infrequent interventional cardiology procedure, rotational atherectomy. These exploratory analyses demonstrate the feasibility of Bayesian updating applied to medical device safety evaluation and indicate that the methodology is capable of generating stable estimates of risk in a variety of patient risk groups. ***Key words:*** *Bayesian statistics; procedural safety; coronary angioplasty.* ***(Med Decis Making 2004;24:399–407)***

The practice of interventional cardiology has experienced remarkable growth in recent years and is constantly evolving as new devices are introduced and higher-acuity patient groups are being treated. New devices and therapies are used to treat subgroups of patients for whom very limited outcome information is available from randomized clinical trials. In addition, randomized clinical trials are typically underpowered to adequately assess the safety of the therapy being evaluated, especially in terms of low-frequency adverse reactions or outcomes. Rarely used techniques such as formal posttrial registries to monitor safety or rigorous case-control studies may be required to evaluate the safety of a device once approved for use.

It is therefore often difficult to assess the relative safety and efficacy of new therapies in clinical practice as compared with existing techniques. Major complications of interventional cardiology procedures generally occur at low frequency but may occur at a higher than expected rate when devices or therapies are used in patients who have not been extensively studied previously. In addition, the population of patients treated in real-life clinical practice may be quite different from the highly selected patients included in randomized clinical trials. For these reasons, a reliable methodology is needed for monitoring the safety of devices and therapies introduced into clinical practice.

One approach to this problem is to use Bayesian updating methods to dynamically monitor the safety of procedures performed within the field of interventional cardiology. Such Bayesian safety monitoring methods have been successfully used in other industries for many years, such as nuclear reactor safety engineering,[1] and have recently been reported in profiling hospital quality.[2] However, the use of this strategy for

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the direct assessment of procedural safety has not been reported. This methodology can formally derive estimates of risk of adverse events following procedures through the combination of prior risk estimates with data from current experience. The potential advantages of the Bayesian approach relative to classical frequentist statistical methods include their efficiency in terms of data usage as well as the explicit incorporation of prior knowledge in the estimate of risk. However, to conduct valid Bayesian analyses, the appropriate estimation of prior probabilities is crucial.

This investigation seeks to explore a Bayesian updating framework for monitoring the safety of medical devices introduced into clinical practice in interventional cardiology and to compare the results of this method to those of classical frequentist statistics.

BACKGROUND

Safety Monitoring in Interventional Cardiology

The field of interventional cardiology is focused on the percutaneous treatment of coronary artery disease with more than 900,000 interventional coronary procedures performed annually in the United States.[3] The field continues to evolve, with more than 25 stent designs having been approved for clinical use in the United States since 1995. In addition, entirely new classes of devices have been recently introduced including vascular closure devices, coronary brachytherapy devices, distal protection devices, and drug-eluting stents. Given the rapid growth of the field coupled with the rate of change of the technology and the expansion of procedures being performed to ever more acutely ill patients, it has been difficult to ascertain the absolute or relative safety of new devices and procedures.

The patient population treated by modern interventional cardiology is at high risk for acute and delayed adverse events, such as postprocedural myocardial infarction (2%–5%) and in-hospital death (1%–2%).[4,5] It is clear, however, that not all patients carry the same risk of subsequent events. Recently published analyses of large clinical registries indicate a wide variation in the rates of adverse events.[6,7] Numerous studies have identified a variety of clinical and demographic predictors associated with relatively higher risks of such events. Clinical factors including the presence of diabetes, advanced age, hemodynamic stability at the time of the procedure, presence of congestive heart failure, and presentation with an acute myocardial infarction have been consistently demonstrated to predict higher rates of adverse events following the procedure. Several authors have developed risk prediction models, typically relying on multiple logistic regression analysis, with varying levels of discriminatory power in predicting the risk of an adverse event.[6–12]

In addition to patient-related factors, the technology used during interventional procedures has occasionally led to adverse events, even after Food and Drug Administration (FDA) approval. One example was the Bard USCI Probe B angioplasty balloon (C. R. Bard, Inc., Murray Hill, NJ, 1989) that suffered mechanical failures leading to device separation in the body and embolization of device components, with subsequent significant clinical complications (*US v. Prigmore*, 243 F.3d 1 [1st Circuit] 2001). Another device, the Nir on Sox™ stent delivery system (Boston Scientific Co., Framingham, MA), suffered balloon rupture at low pressures due to a manufacturing defect. These balloon ruptures were associated with numerous acute clinical complications, and the device was withdrawn 6 months after FDA approval in April 1998.[13] Therefore, continued surveillance of device and procedure safety, even after initial FDA approval, is necessary to detect possible trends in adverse events following interventional cardiology procedures.

Bayesian Methods for Safety Monitoring

Bayesian methods address the fundamental issue of how empirical evidence should change our beliefs about the value of some quantity of interest. Applied to medical device safety monitoring, the quantity of interest may be the underlying risk of an adverse event following the use of the device. Bayesian methods involve the formal combination of a priori beliefs about the risk (before the accumulation of evidence) along with the pilot evidence observed to yield an updated, or posterior, belief ("true" risk) through the application of Bayes's theorem.[14] Bayes's theorem (Equation 1) can be derived directly from the fundamental axioms of probability theory and relates the probability of a proposition (θ) given the observed evidence (x). In the equation below, the notation $f\{\theta \mid x\}$ denotes the conditional probability of a parameter θ given the data (or evidence) that x is true.[15]

$$f\{\theta \mid x\} = \frac{f\{x \mid \theta\} f\{\theta\}}{f\{x\}}. \quad (1)$$

There are several important features of Bayesian updating methods that warrant consideration. The first is that the prior belief ($f\{\theta\}$ in Equation 1) is not restricted

to include only empirical evidence but may include subjective (expert) opinion as well. Although the incorporation of subjective estimates is controversial in the medical device safety domain, formal strategies have been developed and validated in other industries for eliciting and integrating such subjective data with empirical data in the development of the prior estimate.[15] In addition, the theorem can be applied to both discrete as well as continuous probability distributions. For the domain studied here, continuous probability distributions are most appropriate to consider. Finally, it can be shown that as the observed evidence increases, the posterior probability, $f\{\theta \mid x\}$ in Equation 1, converges to the observed event rate (number of adverse events / number of patients at risk).[14] Therefore, as the amount of empiric evidence increases, the Bayesian posterior distribution begins to approach, and eventually converges to, the classical maximum likelihood estimate. Bayesian methods are efficient, allow for hypothesis testing, and are easily extended to a decision-analysis framework. These features make the Bayesian methodology attractive as a candidate framework for analyzing the safety of medical devices and may offer advantages over classical statistical methods in this domain.

In contrast to Bayesian methods, the classical frequentist statistical approach to monitoring medical device safety encompasses sampling from a population and estimating the underlying population event rate from the sample. No information outside of the empirically observed sample is incorporated in the estimation of risk. Typically, the estimate is based on the proportion of observed events to the number of individuals at risk in the sample using the *z* approximation for binomial data. Variance is estimated as a simple function of the estimated proportion, and a confidence interval is used to describe the range of values into which a specified proportion of sample means would lie. Typically, in the frequentist approach, periodically observed mean event rates are compared to acceptable rates of adverse events, which are based on previously published or observed empirical data. A significant limitation of the classical approach is encountered when evaluating observed event rates for which no prior empirical data are available for comparison. Benchmark data from similar patient populations can be used, but there is no clear consensus on what constitutes significant differences in such circumstances. The Bayesian framework seeks to address this limitation directly through the construction and explicit use of a prior probability estimate and with direct comparison of the final posterior distribution (after empirical data observed) to the prior estimate.

METHOD

As described below, the Bayesian updating methodology is composed of 5 distinct steps:

1. risk stratification (i.e., grouping patients into similar risk strata),
2. prior probability estimate development,
3. Bayesian updating process,
4. results interpretation, and
5. sensitivity analysis.

To use Bayesian updating for monitoring procedural safety using our proposed framework, several fundamental assumptions are required. First, we assume that the risk of an adverse event can be modeled as a binomial process within a group of patients with similar preprocedural risks, or risk strata. That is, for each population of patients who have similar clinical risk factors, we assume that the chance of an event is random and can be considered a Bernoulli trial. Second, we assume that steady-state risk has been achieved; we therefore eliminate consideration of possible learning curve effects or systemic factors outside of the patient and the device or procedure being performed. We also assume that the probability of adverse events for the new technology can be modeled as a continuous distribution for each stratum of patient risk. To simplify the calculations required for the Bayesian updating process, we use the conjugate prior distribution of the binomial distribution, which is the beta distribution. The beta distribution has 2 parameters that can represent the shape of the distribution in a flexible way. With appropriate choice of parameters, the beta distribution can have a symmetric shape, or a tail to the left or the right, of arbitrary density. Importantly, as a result of the conjugate relationship of the binomial and beta distributions, the Bayesian updating process yields the posterior distribution that is, itself, another beta distribution, enabling a computational convenient, iterative process.[16]

Initial prior probability distributions for the risk of adverse events for each risk stratum can be developed from published clinical trial information, local experience, expert opinion, or a combination of such sources. As experience is generated for patients within risk strata, the Bayesian process allows us to update these prior distributions to form new, or "posterior" probability distributions, describing our new state of knowledge in light of the experience gained. New empiric data are used to update the prior estimates through a simple process of incrementing the parameters of the

beta distribution. The resulting parameters describe a new beta distribution that is the posterior probability distribution, after combining the empiric evidence with the original prior probability distribution. This distribution can be used to estimate a mean, median, and 2.5th and 97.5th percentile probability interval that is the central posterior interval (also known as a 95% credible interval). We chose to implement these calculations using Microsoft Excel 2000 (Microsoft Corporation, Redmond, WA), although any software that supports the estimation of the beta distribution may be used.

We illustrate how this Bayesian updating process can work in practice with an example using clinical data from our catheterization laboratory.

A Clinical Example

Let us consider the risk of an adverse event after undergoing rotational atherectomy (RA), a relatively infrequently performed procedure representing less than 10% of the percutaneous coronary interventional procedures performed at our institution. Because of the complexity of the procedure and relatively infrequent use, we hypothesized that there may be a higher than usual in-hospital complication event rate following the use of this therapy. To test this hypothesis, we retrospectively reviewed the clinical outcomes of those patients who underwent RA between January 1997 and December 1999 and analyzed the risk of postprocedure death as well as the combined endpoint of death, myocardial infarction, or coronary bypass surgery, using a Bayesian updating framework. Using the methodology outlined above, this example will review the risk stratification, prior probability estimation, Bayesian updating process, and interpretation of results.

Step 1: Risk Stratification

We previously developed and validated risk models for predicting the risk of death as well as the combined endpoint of death, myocardial infarction, or need for urgent coronary bypass surgery (together constituting the major adverse cardiac events [MACE]), using simplified risk-scoring models.[5] From 1 January 1997 through 31 December 1999, data were collected on 4264 consecutive interventional procedures at our catheterization laboratory. Patients could be stratified into low-risk (total risk score <3), moderate-risk (scores 3–4), and high-risk (scores >4) groups; each group had a distinct risk of in-hospital adverse events. The observed mortality rate for these 3 groups increases from 0.39% (95% confidence interval [CI] = 0.2%–0.68%) in the low-risk population, to 2.19% (95% CI = 1.3%–3.4%) in the moderate-risk group, to 16.1% (95% CI = 12.5%–20.1%) in the high-risk group. Of note, although only 9% of patients were classified as high risk, these patients represented 67% of all in-hospital deaths due to the high mortality rate in this risk group.[11]

Table 1 Distribution of Patients and Clinical Events for Rotational Atherectomy Cases, 1997–9

			Death		MACE	
Risk Group	***n***	**%**	***n***	**%**	***n***	**%**
Low	195	63.1	1	0.51	4	2.05
Medium	75	24.3	1	1.33	4	5.33
High	39	12.6	2	5.13	6	15.4
Total	309	100	4	1.29	14	4.53

Note: MACE = major adverse cardiac event (death, coronary artery bypass surgery, or postprocedure myocardial infarction).

From 1 January 1997 through 31 December 1999, 309 patients were treated with RA at our institution. Four patients died prior to discharge (1.29%), whereas 14 (4.53%) suffered a MACE complication. Among the rotational atherectomy patient cohort, there were 195 low-risk patients (63%), 75 moderate-risk patients (24%), and 39 high-risk patients (13%) in the time period sampled. As shown in Table 1, the complications were disproportionately distributed into the high-risk patient group.

Step 2: Development of Prior Probability Estimates

Using a MEDLINE search, 5 studies assessing the outcomes of patients undergoing RA were identified as having been published or presented before 1 January 1997.[17–21] Pooling these results (of similar patients) revealed that 6 out of 709 patients died whereas a total of 10 out of 453 patients studied suffered a MACE. Using a large sample normal distribution, the mean mortality rate was therefore 0.85% (s = 0.30%) and MACE event rate was 2.21% (s = 0.70%) for the 5 studies included. Since all 5 published studies were performed exclusively in low-risk patients, extrapolation of expected risk to the medium- and high-risk groups was required.

For the estimation of the probability of death in low-risk patients, we approximated the binomial distribution with a beta distribution by matching the mean and variance to derive the beta distribution parameters that would best fit a mean of 0.85% with a standard deviation of 0.30%. We characterize the beta distribution

with shape parameters q and r. The mean and variance are shown in Equations 2 and 3, respectively.[22]

$$\text{Mean: } \mu = q/(q + r) \tag{2}$$

$$\text{Variance: } \sigma^2 = qr/[(q + r)^2(q + r + 1)]. \tag{3}$$

Solving for the parameters q and r, we obtain the following equations that can be used to establish the initial prior probability beta distribution on the basis of the prior knowledge from the literature.

$$q = \mu[(\mu(1 - \mu) / \sigma^2) - 1] \tag{4}$$

$$r = (1 - \mu)[(\mu(1 - \mu) / \sigma^2) - 1]. \tag{5}$$

Substituting our values from the literature, of a reported mean of 0.85% and standard deviation of 0.30%, we obtain initial parameters for our prior distribution of

$$q = 6 \text{ and } r = 703.$$

Note that these parameters conveniently equal the number of patients dying and those surviving. In a similar fashion, the parameters for low-risk patients suffering a MACE event were calculated.

Since no data were available in the published literature to guide our estimates of event rates in the moderate- and high-risk groups undergoing RA, we used the relationship of the risk of adverse events in low-, moderate-, and high-risk patients who underwent traditional (non-RA) interventional procedures to estimate prior probability distributions for these patient subsets. Specifically, we assumed that the adverse event rates for the moderate- and high-risk groups were proportional to the rates observed in the non-RA moderate- and high-risk patients studied during the study period. For example, if non-RA patients in the medium-risk group were twice as likely to die as were non-RA patients in the low-risk group, we would estimate that RA patients in the medium-risk group were also twice as likely to die as the RA patients in the low-risk group, for whom we had prior probability estimates derived directly from the literature. In addition, the standard deviation for the moderate- and high-risk prior probability distributions was assumed to be proportional to the ratio of mean to standard deviation in the low-risk patient population. A sensitivity analysis for this extrapolation was performed using diffuse and noninformative prior probability distributions as described below (see Effect of Choice of Prior Probability Distribution below).

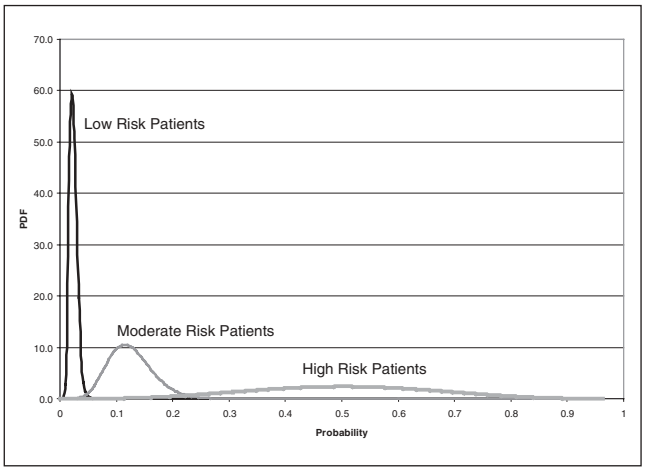

Figure 1 Prior probability distributions for risk of a major adverse cardiac event following rotational atherectomy stratified by patient risk. PDF = probability density function value.

The use of a proportional risk estimate is based on the reasoning that the higher risk patients would be expected, in absence of treatment with RA, to suffer adverse events proportional to the risk ratios calculated in the non-RA population. Since there exist published data regarding the risk of RA in low-risk patients, from a Bayesian perspective it would be incomplete to assert that no information regarding the risk of the RA procedure exists. Extrapolating the known risk of RA in low-risk groups using the proportional risks of moderate- and high-risk populations is therefore necessary so as to incorporate all available knowledge in the development of the initial prior distributions.

The prior probability density functions for the risk of MACE in each risk stratum are plotted in Figure 1. As shown, prior probability distributions demonstrate increasing risk of adverse events within each risk group. In addition, the increasing spread of the distributions demonstrates increasing uncertainty regarding the estimation, such that we are less confident in our risk estimation in the high-risk population, for which we have no prior published data, as compared to the lowest risk group, for which we have published literature from which to formulate our estimate. As a result of such increasing uncertainty with increasing risk, it is implicit that observations in high-risk patients will influence our estimates of risk for this population to a greater extent than the same number observations in the low-risk group.

Table 2 Evolution of Posterior Beta Distribution Using Bayesian Updating for a Major Adverse Cardiac Event in High-Risk Patients

Time Period		Number of Patients	Number of Adverse Events	Parameters of Beta Distribution		Revised Beta Distribution	
Year	Quarter			q	r	$\bar{x}$	s
Prior estimate		(Estimated from low-risk cases)		4.6	4.6	0.500	0.157
1997	1	1	1	5.6	4.6	0.549	0.149
	2	0	0	5.6	4.6	0.549	0.149
	3	1	0	5.6	5.6	0.500	0.143
	4	2	1	6.6	6.6	0.500	0.133
1998	1	3	0	6.6	9.6	0.407	0.118
	2	6	1	7.6	14.6	0.342	0.099
	3	7	0	7.6	21.6	0.260	0.080
	4	6	2	9.6	25.6	0.273	0.074
1999	1	5	1	10.6	29.6	0.264	0.069
	2	4	0	10.6	33.6	0.240	0.064
	3	2	0	10.6	35.6	0.229	0.061
	4	2	0	10.6	37.6	0.220	0.059
Final		39	6	10.6	37.6	0.220	0.059

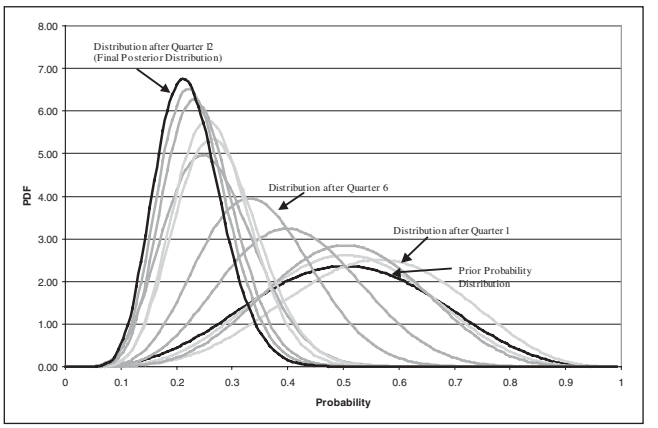

Figure 2 Evolution of risk estimates through 36 mo for risk of major adverse cardiac events in high-risk patients undergoing rotational atherectomy. PDF = probability density function value.

Step 3: Bayesian Updating Procedure

Having estimated prior probability distributions for each patient subgroup, we can now modify these estimates through the Bayesian updating process as empirical data are collected. At the completion of each time interval (3 months), the total number of cases undergoing RA and the number of cases who suffered an adverse event were recorded. This empiric evidence was then combined with the prior evidence by updating our distribution parameters to generate posterior probability distributions of the likelihood of an adverse event. The posterior distribution after updating a beta distribution is itself another beta distribution in which the parameters are as follows:

$$q_{i+1} = q_i + k_i \quad (6)$$

$$r_{i+1} = r_i + n_i - k_i, \quad (7)$$

where n is the number of patients observed and k is the number of adverse events experienced. Subscript i refers to the current time period, and subscript $i + 1$ refers to the subsequent cycle.

Table 2 presents the empiric data for the risk of MACE for the high-risk patients undergoing RA. The first 2 columns indicate the total number of patients treated with the new procedure and number of patients suffering at least 1 adverse event occurring during the quarter, whereas columns 3 and 4 show the updated parameters based on these empiric data. The updated mean and standard deviation for the posterior distribution, calculated using Equations 2 and 3, are shown as well. The calculated mean and standard deviation for the final posterior distribution are highlighted at the bottom of Table 2.

Figure 2 graphically demonstrates the evolution in the posterior distributions for the risk of MACE in high-risk patients as more information was gathered during the study period. The updated beta distributions were plotted sequentially for each of the 12 time periods studied, revealing a qualitative trend toward a decrease in the expected major complication rate in these high-risk patients undergoing rotational atherectomy, as compared with the initial prior estimates. In addition, there is a progressive narrowing of the distribution over time, implying increased confidence around the mean of the distribution.

The initial prior probabilities and final posterior probability distributions are characterized for all risk strata for both death and MACE outcomes in Table 3. In addition, the 2.5th, 97.5th, and 50th (median) percentile calculated probabilities for each estimated probability distribution are shown. For the risk of MACE in high-risk patients, the prior probability median was 0.50, whereas after 12 quarters of experience, the Bayesian model has updated this to a reduced esti-

Table 3 Median (50th Percentile), 2.5th, and 97.5th Percentile Probability Values for Prior and Posterior Probability Distributions

	Death			MACE		
Patient Risk	**2.5th**	**50th**	**97.5th**	**2.5th**	**50th**	**97.5th**
Low risk						
Prior	0.003	0.008	0.016	0.011	0.021	0.037
Posterior	0.003	0.007	0.014	0.012	0.021	0.034
Medium						
Prior	0.017	0.045	0.092	0.059	0.120	0.209
Posterior	0.014	0.033	0.064	0.048	0.086	0.138
High risk						
Prior	0.106	0.339	0.648	0.202	0.500	0.798
Posterior	0.042	0.108	0.215	0.116	0.216	0.346

MACE = major adverse cardiac event.

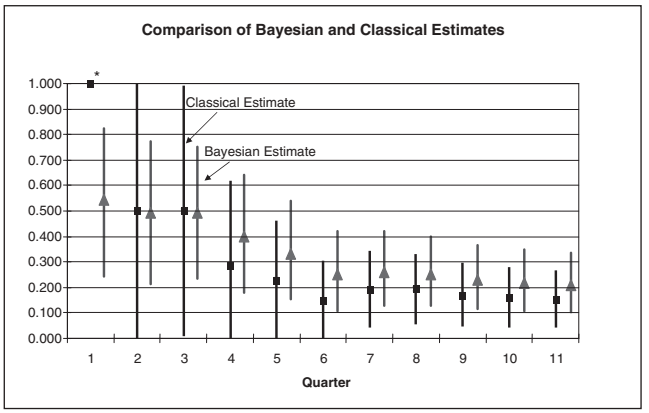

Figure 3 Comparison of risk estimates for Bayesian and classical methods for the risk of a major adverse cardiac event in high-risk patients. Squares represent classical frequentist methods, whereas triangles represent the Bayesian estimate. Means are represented by the symbol (square or triangle) for each quarter, whereas the 95% confidence intervals and the 95% central posterior intervals are shown by solid bars. The asterisk (*) indicates that the 95% confidence interval for the maximum likelihood estimate is undefined, due to exceedingly small sample size.

mated median risk of 0.216. There is an associated substantial shift "to the left" (reduced expected risk) as shown in Figure 2.

Step 4: Interpretation of Results

Based on the results of the analysis presented in Table 3, the principal finding is that the revised estimates of risk tended toward lower probability of the risk of death or MACE in both medium- and high-risk patient groups, whereas there was essentially no change in the estimates of risk in the lowest risk population. In addition the 95% central posterior interval (2.5th to 97.5th percentile, also known as the 95% credible interval) of the posterior distribution, decreases in width compared with the prior distribution for each analysis, as should be expected with increasing and consistent evidence. Furthermore, each subset analysis yielded a posterior distribution that stabilized over the period studied.

We also compared the results of the Bayesian analysis to the normal approximation (the *z* approximation) of the binomial distribution to represent the proportion of events observed (without including prior data). In all cases, the 95% confidence interval of the normal approximation for the proportion of empiric data extensively overlapped with the 95% central posterior intervals of the beta distribution. The frequentist and Bayesian results seemed to be generally comparable in this particular case. Figure 3 illustrates the change in risk estimate (and 95% posterior intervals) for MACE in high-risk patients for both classical methods and the Bayesian methodology. However, if the prior assumptions are valid, the Bayesian inference provides more efficient analysis with narrower lengths of the central posterior interval as has been demonstrated previously.[23] In Figure 3, quarters 2 and 3 illustrate a potential benefit of the Bayesian methodology, as the Bayesian estimate of risk yielded a 95% central posterior interval that is finite, whereas the frequentist estimate yielded 95% CIs spanning a range as to make them noninterpretable. Over time, and with increasing empiric evidence, the classical and Bayesian methods converge, as expected.

Although the results from the RA example did not suggest that this higher risk technique resulted in a higher risk of adverse events in the sickest patients than was expected, the finding that there was a trend toward reduced risk in moderate- and high-risk patients is potentially informative. It is likely that the moderate- and high-risk patients undergoing RA were selected from among the population of moderate- and high-risk patients based on some unmodeled factors that predict better outcomes, for example, no recent evidence of congestive heart failure on presentation. Alternatively, it is possible that RA itself is somewhat protective in higher risk subsets of patients, although this is highly speculative and clinically counterintuitive.

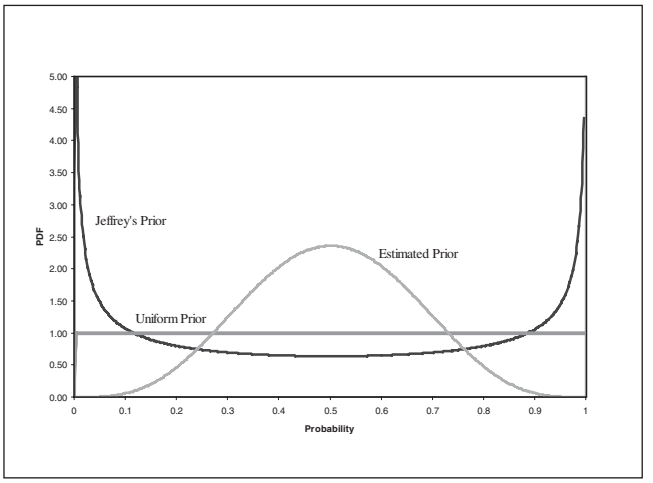

Figure 4 Uniform, Jeffrey's, and extrapolated prior probability distributions for risk of major adverse cardiac events in high-risk patients. PDF = probability density function value.

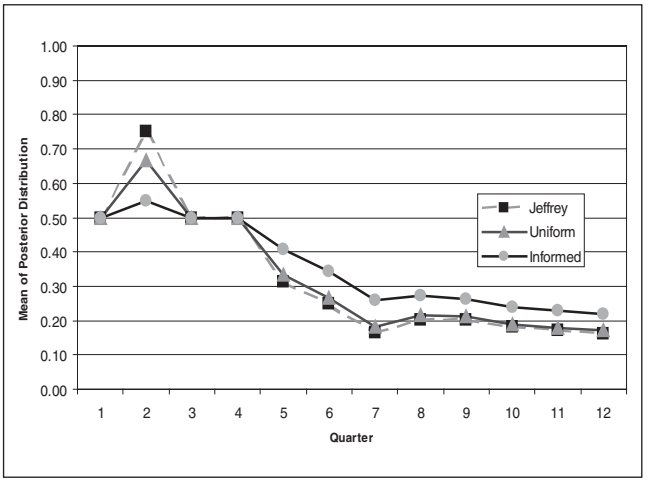

Figure 5 Trends over time of the means of posterior distributions for each of the candidate prior distributions—uniform prior, Jeffrey's prior, and extrapolated prior—for the risk of major adverse cardiac events in high-risk patients.

Step 5: Sensitivity Analysis—Effect of Choice of Prior Probability Distribution

The choice of initial prior probability distributions can be controversial, as there are limited accepted principles to guide this selection. As such, in any Bayesian updating review, a sensitivity analysis is warranted to confirm that the results obtained were not due to the choice of the initial prior alone. In this example, we chose a proportional risk model, assuming that the risks of adverse events in moderate- and high-risk RA groups were proportional to the risks in lower risk groups. An alternative approach would have been to use a noninformative prior probability distribution, indicating no expectation regarding the final probability distribution. Two such noninformative distributions include the uniform prior [$\beta(1,1)$], which has a constant value of 1.0 over the interval of 0 to 1, as well as Jeffrey's prior [$\beta(0.5,0.5)$], which has 2 peaks, one near the value of 0 and the other at 1. Figure 4 illustrates the uniform prior, Jeffrey's prior, and the estimated prior probability distribution used in this analysis for the risk of MACE in high-risk patients.

Although the 2 noninformative prior distributions have quite different shapes than our estimated prior distribution, their impact was small after the accumulation of only a few quarters of empiric data. As can be seen in Figure 5, the means of the posterior distributions tend to quickly converge regardless of the choice of the prior. Similarly, the variance of the posterior distributions was only minimally affected by the choice of prior (data not shown). Therefore, we conclude that the choice of prior, in this example, did not significantly affect the results of the analysis.

DISCUSSION

This exploratory study used the Bayesian updating methodology to efficiently incorporate prior knowledge and accumulating clinical experience into refined estimates of risk for particular procedures used in interventional cardiology. There are several potential advantages of this method over non-Bayesian frequentist methods for monitoring procedural and device safety. These include an analysis based on a formalized theoretic foundation that maximizes the use of information available to assess safety. In addition, prior estimates are not restricted to include only empiric evidence but may include subjective (expert) opinion as well. This approach can be used prospectively, and results are available nearly in real-time, conveying significant advantages over retrospective analyses.

A significant challenge in interpreting the results of the Bayesian updating process is to assess the relative differences between the posterior and prior distributions. One methodology to consider is to compare overlap of the distributions through comparison of 95% intervals for each, as illustrated in the example presented above. Using a frequentist statistical framework, if the 95% intervals for 2 distributions do not overlap, then there is at least a 95% likelihood that the distributions are distinct. Similarly, in the Bayesian framework, we would conclude that the posterior distribution showed a significant reduction in expected risk if the 97.5th

percentile of the posterior distribution was less than the 2.5th percentile of the prior distribution. This level of separation is unlikely without a great deal of experience (data) to move the probability distribution far to the left and was not achieved by the RA example (see Table 3). However, less stringent requirements for supporting a substantial change from the prior to the posterior distributions may warrant consideration.

The examples presented are intended primarily to illustrate the methodology and are based on a retrospective analysis from a single center, and therefore the clinical results may not be generalizable to other environments. The risk stratification models used have acceptable but limited discriminatory power, and incorporation of advances in observational statistical methods, such as propensity score modeling, may improve their reliability by accounting for heterogeneity in treatment allocation.[24] The initial assumptions of the models used for generating the prior probability estimates influence the results to a great extent. Specifically, the assumption that the uncertainty of the initial estimates (the standard deviation of the prior probability distribution) should be proportional to the estimated mean probability of adverse outcome may be overly conservative. However, the sensitivity analyses, described above, did not significantly alter the results of this study.

Future Directions

This exploratory analysis demonstrates the feasibility of Bayesian updating applied to the domain of medical device safety evaluation and indicates that the methodology is capable of generating stable estimates of risk in a variety of patient risk groups. Further study is needed to assess the tradeoffs of Bayesian over classical statistical methods and to evaluate this methodology prospectively and in automated data acquisition environments.

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