Cost-Effectiveness of Targeting Patients Undergoing Percutaneous Coronary Intervention for Therapy With Bivalirudin Versus Heparin Monotherapy According to Predicted Risk of Bleeding

Amit P. Amin, MD; Steven P. Marso, MD; Sunil V. Rao, MD, FSCAI; John Messenger, MD; Paul S. Chan, MD, MSc; John House, MS; Kevin Kennedy, MS; Katherine Robertus, MPH; David J. Cohen, MD, MSc; Elizabeth M. Mahoney, ScD

Background—Although bivalirudin compared with unfractionated heparin with glycoprotein IIb/IIIa inhibitors reduces bleeding and hospitalization costs in patients undergoing percutaneous coronary intervention (PCI), little is known about the economic impact of bivalirudin versus heparin alone and at what threshold of procedural bleeding risk bivalirudin would be considered cost-effective.

Methods and Results—A validated model was used to predict risk of major bleeding for 81,628 National Cardiovascular Data Registry (NCDR) CathPCI Registry patients from 2004 to 2006 who received unfractionated heparin only. Costs were derived from multiple sources including wholesale acquisition costs (for drugs) and single-center data (for PCI-related complications). Based on ISAR-REACT 3, we assumed that bivalirudin would reduce the risk of major bleeding by 33% compared with unfractionated heparin alone. A Markov model was used to estimate lost life expectancy associated with a major bleed. Major bleeding was predicted to occur in 2.2% of patients. Bivalirudin for all patients was estimated to increase costs by $571 per patient, yielding cost-effectiveness ratios of $287,473 per bleeding event averted and $1,173,360 per quality-adjusted life-year gained. Bivalirudin was cost saving for patients with a predicted bleeding risk \( \leq 10\% \) (0.16% of CathPCI population). At willingness-to-pay thresholds of $50K and $100K per quality-adjusted life-year gained, bivalirudin was cost-effective for patients with a bleeding risk \( \geq 8\% \) (2.5% patients) and \( \geq 5\% \) (7.9% patients), respectively.

Conclusions—This decision-analytic modeling study demonstrates that for patients undergoing PCI, substitution of bivalirudin for unfractionated heparin monotherapy is projected to increase costs for virtually all patients and would be considered cost-effective for only a minority of patients with a high bleeding risk. From a policy standpoint, studies such as this, aimed at identifying the appropriate risk threshold for initiating treatment, may help in the development of informed guidelines for the use of expensive therapies. (Circ Cardiovasc Qual Outcomes. 2010;3:00-00.)

Key Words: cost-effectiveness analysis • bivalirudin • unfractionated heparin • percutaneous coronary intervention • bleeding • Markov model

Major bleeding occurs in 0% to 10% of patients undergoing percutaneous coronary intervention (PCI) and is associated with increased morbidity, mortality, prolonged hospital stay, and increased costs.1–3 Bivalirudin, a direct thrombin inhibitor, reduces major bleeding in patients undergoing PCI.4–7 Although bivalirudin has been shown to be a safe and effective adjunctive antithrombin during PCI, its high cost may prevent its use in all eligible patients. Nevertheless, use of bivalirudin has been reported by Blue Cross/Blue Shield to be as high as 50% of all PCI procedures.8 There are limited cost-effectiveness data to guide the optimal use of bivalirudin versus other available antithrombotic therapies in patients undergoing PCI.9,10

Although bivalirudin compared with unfractionated heparin (UFH)+glycoprotein IIb/IIIa inhibitor therapy is associated with reduced bleeding and lower costs in patients undergoing PCI,9,10 little is known about the economic attractiveness of bivalirudin versus UFH alone—a more clinically relevant question because UFH alone has negligible costs and is associated with a lower risk of periprocedural bleeding than...
UFH + glycoprotein IIb/IIIa inhibitor therapy. We therefore developed a decision-analytic model using results from published studies as well as external data sources to evaluate the cost-effectiveness of substituting bivalirudin for UFH alone in subgroups of patients undergoing PCI who are identified according to their predicted risk of a major bleeding event.

WHAT IS KNOWN

- Bivalirudin is cost-saving (economically “dominant”) when compared with unfractionated heparin + glycoprotein IIb/IIIa inhibitors in patients undergoing PCI.

WHAT THE STUDY ADDS

- This decision-analytic modeling study fills a critical gap in the literature by examining the cost-effectiveness of bivalirudin versus unfractionated heparin alone and how that cost-effectiveness varies according to patients’ risk of having a periprocedural bleed.
- Results from this study demonstrate quantitatively how bivalirudin becomes more cost-effective when “targeted” to patients at higher levels of risk.
- Substitution of bivalirudin for unfractionated heparin monotherapy is projected to increase costs for virtually all patients, and, based on commonly used benchmarks, would be considered cost-effective for only a minority of patients with a high bleeding risk.
- Although application of these results to decision-making for individual patients must be undertaken with some caution, from a policy standpoint, studies such as this, aimed at identifying the appropriate risk threshold for initiating treatment, may help in the development of informed guidelines for the use of expensive therapies.

Methods

Overview of the Decision-Analytic Model: Model Assumptions and Data Sources

We developed a decision analytic model (Figure 1) to examine the cost-effectiveness of targeting bivalirudin therapy to PCI patients according to incrementally lower thresholds of bleeding risk. According to the model, patients would receive bivalirudin therapy if their predicted risk of bleeding was above a specified treatment threshold. Patients treated with bivalirudin were assumed to have a 10% reduction in the risk of major bleeding, based on results from the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT 3) Trial, a contemporary trial of patients randomized to bivalirudin versus UFH alone. Inputs into the model also included bivalirudin acquisition costs and estimates of the effect of a major bleeding event on hospitalization costs, life expectancy, and quality-adjusted life expectancy. We used the American College of Cardiology (ACC) National Cardiovascular Data Registry (NCDR) CathPCI Registry to implement the model. The CathPCI Registry is a partnership between the ACC and the Society for Cardiovascular Angiography and Interventions.

Patient Population

We identified PCI procedures in the CathPCI Registry that occurred from 2004 to 2006, when bivalirudin use was relatively infrequent, and further excluded centers that used bivalirudin in >10% of PCI procedures during that time period to avoid potential contamination, as well as those that were performed via radial access site. From this sample, we further excluded 791 (0.97%) procedures who had actually received bivalirudin and another 3516 (4.31%) procedures with incomplete data to obtain the bivalirudin-naïve procedures on which the model would be applied. This strategy of including procedures from centers not using bivalirudin, at a time when bivalirudin use was less prevalent, and excluding only a very small (<1%) proportion of procedures who received bivalirudin at sites with low overall bivalirudin use rates, was chosen to minimize selection bias with respect to the identification of bivalirudin-naïve procedures while maintaining as large and nationally-representative a sample as possible (Figure 2).

Definitions

The CathPCI Registry defines major periprocedural bleeding as major percutaneous entry site bleeding—external or a hematoma >10 cm for femoral access, >5 cm for brachial access, or >2 cm for radial access, retroperitoneal bleed, gastrointestinal bleed, genitourinary bleed and other/unknown origin—all occurring between catheterization laboratory visit and discharge and requiring transfusion, and/or resulting in prolonged hospital stay, and/or a drop in hemoglobin >3.0 g/dL.

Prediction of Bleeding Risk

A published CathPCI Registry bleeding risk model (online supplemental material) was used to predict the risk of major bleeding in our “bivalirudin-naïve” sample. This model includes as covariates only variables that are available before the PCI procedure.

Cost of Major Bleeding

Costs associated with major bleeding events were estimated from the United States provider’s (ie, hospital) perspective. Data from 1364 PCI patients from the Mid-America Heart Institute (MAHI) from 2004 to 2006, which share identical variables and data definitions as the CathPCI data, were obtained and linked to patient-level hospitalization cost data. Total hospital costs, including anticoagulation, from date of PCI procedure to discharge, were obtained from the MAHI hospital cost accounting system. Actual catheterization lab-

![Figure 1. Decision-analytic model framework.](image)

![Figure 2. Study population inclusion and exclusion criteria.](image)
oratory costs were used in place of hospital estimates for procedural supplies and devices. Procedural supply costs, including balloons, stents, atherectomy devices, contrast dye, and guide wires were provided directly from the hospital’s catheterization laboratory cost accounting system. From this hospitalization cost data set, a multiple linear regression model was developed to estimate the independent effect of a major bleeding event on total hospitalization costs after adjusting for clinical and demographic variables and other complications. Covariates included in this model included major bleeding (the main exposure variable of interest) along with emergent coronary artery bypass grafting, periprocedural myocardial infarction, [included as 3 dummy categorical variables: creatine kinase-MB level 3 to 5 ng/mL, creatine kinase-MB level 5 to 10 ng/mL and creatine kinase-MB level >10 ng/mL, with creatine kinase-MB <3 ng/mL as the reference category], multivessel PCI, and presentation with an acute coronary syndrome event (unstable angina, non–ST-elevation myocardial infarction, or ST-elevation myocardial infarction) and mirrored those used in a prior published model developed as part of the economic study for the REPLACE-2 trial, for which the incremental cost of a major bleeding event was derived.9 Because the goal of this analysis was explanatory rather than predictive, length of stay variables were not considered. Untransformed cost was used as the dependent variable in the model for ease of interpretation; the extreme 1% of observations was trimmed from the sample to limit the impact of outliers on the stability of the estimated regression coefficients. Based on this analysis, we estimated the incremental cost of a major bleeding event as $8920 (95% confidence interval, $5508 to $12 333).

Cost-Effectiveness Analysis
Cost-effectiveness was assessed using the methods of Weinstein and Fineberg13 and was evaluated comparing progressively lower treatment thresholds in terms of incremental cost per major bleeding event avoided and incremental cost per life-year and quality-adjusted life year (QALY) gained. These incremental (or marginal) cost-effectiveness ratios are most appropriate for identifying the optimal bleeding risk threshold for implementing treatment, as the therapeutic decision is optimally informed by examining the impact of treating the “next most appropriate” (ie, marginal) patient. We also calculated average cost-effectiveness ratios, which represent the cost-effectiveness of treating patients at or above a certain threshold of bleeding risk, compared with the strategy of not treating anyone. The model was specified by a set of definitions and equations that are available on request. Sensitivity analyses were carried out to assess the influence of varying the unit cost and efficacy of bivalirudin therapy on the model results.

Long-Term Cost-Effectiveness
For the long-term cost-effectiveness analysis, a Markov model was used to project life expectancy for patients with and without a major periprocedural bleeding event, contingent on age, sex, and type of presentation (acute coronary syndrome, stable coronary artery disease). For patients without a major bleed, annual mortality rates were based on US life tables; for patients with a major bleed, a relative mortality risk of 2.96 was applied during the first year after the PCI procedure, based on pooled data from the medical literature.14,15 Further details regarding this model are available on request (Figure 3). Projected life expectancy was discounted at an annual rate of 3% consistent with currently guidelines for cost-effectiveness analysis.16,17 A disutility “toll” of 0.015 years for each major bleeding event was subtracted from the patient’s total life expectancy for the derivation of QALY.18

Results
Among all CathPCI Registry patients, 81 628 were identified based on the inclusion and exclusion criteria. These patients underwent PCI between 2004 and 2006 at 178 centers and received UFH alone. This sample represented 51% of all patients (n=160 167) who underwent PCI with UFH alone of UFH + glycoprotein IIb/IIIa inhibitors at these centers from 2004 to 2006 (Figure 1). Clinical, demographic, and angiographic characteristics of the NCDR-derived study population are presented in Table 1. The mean predicted risk of bleeding (as predicted by the CathPCI Registry bleeding risk model) was 2.18%, and its distribution is shown in Figure 4. The ability of the model to discriminate patients with respect to bleeding outcomes was moderate, with a c-index of 0.6875 (95% confidence interval, 0.6731 to 0.7019). Average (±SD) estimated bivalirudin dose for the overall cohort was 138.2±72.1 mg, which rounded up to 1.1±0.27 vials, with associated costs of $637±158. UFH costs were considered negligible ($4) and were not included in the analysis.

Table 2 presents the results of cost-effectiveness analyses. The column to the far left (column 1) presents the treatment threshold in terms of the predicted probability of major bleeding above which therapy with bivalirudin would be substituted for UFH. Assuming a 0% threshold, all 81 628 (100%) of the patients would be treated (column 2), and the risk of major bleeding would be reduced from 2.18% (predicted bleeding risk in the overall population; last row in column 3) to 1.44% (first row of column 3), representing an absolute risk difference of 0.74% or 7.4 major bleeds prevented per 1000 patients treated (column 4). The mean in-hospital cost per patient would also change, from $19 125 (last row of column 5) to $19 696 (first row of column 5), a difference of $571 per patient when treating all versus no patients with bivalirudin.

The average cost per major bleeding episode prevented (column 6) for the strategy of treating all patients versus no patients is derived by dividing the difference in average costs of the 2 strategies by the difference in major bleeding rates,
The incremental cost per major bleeding episode prevented for strategies of treating patients at progressively lower cutoff points with respect to predicted probability of bleeding are presented in Table 2, column 7. Progressing from the bottom of column 7 to the top, values in column 7 describe the additional cost associated with preventing a bleeding event for patients at the next lower level of risk. For example, the cost per major bleeding event prevented, moving from a 9% bleeding risk threshold for treatment to an 8% threshold (ie, treating patients whose predicted risk of a periprocedural bleed is less than 9% but greater than or equal to 8%) is $11,857. Because of the competition for limited healthcare resources, the consideration of additional healthcare expenditures should be based on the evaluation of whether the additional expense is worthwhile given the benefits accrued; therefore, it is the incremental cost-effectiveness ratios that must be evaluated with respect to their acceptability, in establishing the threshold for treatment.

There was marked variation in the incremental cost-effectiveness ratios across the spectrum of risk of major bleeding. As the threshold probability of a major bleed above which patients are treated with bivalirudin increased (fewer patients are treated with bivalirudin), the risk of major bleeding in the treated population increased, and the cost-effectiveness ratios became more favorable. The incremental cost per major bleed prevented ranged from a cost-saving (dominant) strategy when treating the highest risk patients (≥20% predicted probability of a major
bleeding) to $287,473 for the treatment of the lowest-risk (<1% predicted probability of a major bleed) patients.

Two-way sensitivity analyses were carried out, varying both the bleeding risk threshold and each of cost and efficacy of therapy with bivalirudin, respectively (Figure 5A and B). Varying the cost of bivalirudin between $400 and $1000 per vial did not alter the cost-effectiveness ratios appreciably, whereas cost-effectiveness varied greatly when efficacy was varied between a relative risk of 0.5 to 0.8. As expected, with increasing efficacy, it became more cost-effective to treat patients with bivalirudin at lower bleeding risk thresholds. Conversely, when the efficacy of bivalirudin was decreased from a relative risk of 0.66 to a relative risk of 0.8, the cost-effectiveness ratios were higher.

The Markov model used to project life expectancy for PCI patients with and without major bleeding events yielded life expectancy estimates of 11.10 years and 11.33 years, respectively, and thus a decrement of 0.23 years of life expectancy (2.76 months) for patients who have a major bleeding event. Results from the long-term cost-effectiveness analysis, based on these projections (column 8 of Table 2), reveal that at a willingness-to-pay threshold of $50,000 per life-year gained, changing the threshold for treatment from 9% to 8% would be economically attractive (incremental cost-effectiveness ratio = $51,551/life-year gained), whereas changing the treatment threshold from 6% to 5% would be economically (incremental cost-effectiveness ratio = $101,675/life-year gained) at a willingness-to-pay threshold $100,000 per life-year gained. These treatment thresholds would remain similar, based on the same magnitude of willingness-to-pay thresholds in terms of QALYs gained (column 9 of Table 2). Of note, the proportion of patients that would be treated using these 2 willingness-to-pay thresholds is quite small: 2.52% and 7.86% for the $50,000 and $100,000 thresholds, respectively.

**Discussion**

In the present study, we used a decision-analytic model to estimate the cost-effectiveness of targeting patients for bivalirudin anticoagulation at the time of PCI according to the level of predicted bleeding risk within a nationally representative, bivalirudin-naive PCI population. For patients who would otherwise have received UFH alone, our results suggest that it is not economically attractive to substitute bivalirudin for UFH in the vast majority of patients who are at low and intermediate risk of major bleeding, though it appears to be reasonably cost-effective in patients with a high bleeding risk.
We developed this model to answer a clinically relevant question in a cohort for which the cost-effectiveness of bivalirudin has not been examined previously. Although several previous clinical trials have evaluated the cost-effectiveness of bivalirudin versus UFH/glycoprotein IIb/IIIa inhibitors, no prior cost-effectiveness analyses has been carried out comparing bivalirudin to the alternative of UFH alone, and there is only 1 large-scale randomized trial comparing the clinical effectiveness of bivalirudin with UFH alone (the ISAR-REACT 3 trial) and 2 older, smaller trials, which may not be applicable to the contemporary practice of PCI. Despite this lack of evidence, use of UFH alone during PCI is an important alternative anticoagulant use and is fairly common. As seen during our exclusion process, more than half of patients in the CathPCI Registry underwent PCI with UFH alone from 2004 to 2006. Thus, our model fills an important gap in the literature.

It is appropriate to use incremental (or marginal) rather than average cost-effectiveness ratios for decision-making about the appropriate treatment threshold, as it is the additional cost associated with treating the next patient (in order of increasing cost-effectiveness ratios) that should drive the therapeutic decision. However, the average cost-effectiveness ratios represent the cost-effectiveness for the overall population to be treated once the predicted probability threshold for treatment is chosen. For a hypothetical center performing 1000 PCI per year using UFH alone, assuming a bleeding rate of 2.18% (22 major bleeds per year), use of bivalirudin instead of heparin in all patients would prevent 7 to 8 major bleeds at an incremental cost of roughly $571 000 (incremental cost of $571 per patient), or roughly $80 000 per bleeding event avoided. Alternatively, using a threshold of 5%, fewer than 8% of patients would receive bivalirudin, whereas approximately 2 to 3 bleeding events would be prevented at an incremental cost of $28 000 (incremental cost of $28 per patient), or roughly $13 000 per bleeding event avoided. These data allow providers to make informed decisions on the amount they are willing to spend to avoid periprocedural bleeding.

Although disease-specific cost-effectiveness ratios such as incremental cost per bleed prevented are useful, use of a uniform metric such as cost per life years gained or cost per QALY gained enables benchmarking against estimates pertaining to other interventions that might be competing for the same pool of limited health care funds. An acceptable upper limit of cost per episode of major bleeding prevented or life-year or QALY gained were known, then patients in predicted bleeding risk strata for which the incremental cost of preventing a bleeding event is less than this upper limit, would be considered appropriate patients to receive bivalirudin, with the caveat associated with the assumptions underlying our model. For example, at a benchmark threshold of $50 000 as the maximum amount that society would be willing to pay per life-year or QALY gained, then treatment of only a small fraction of patients, roughly 2.5%, with predicted bleeding risks of around 8% or higher would be appropriate. There are no benchmarks for an acceptable average cost per bleed prevented; for patients with a bleeding risk of 8% or greater, the incremental cost-effectiveness ratio, compared with a 9% bleeding risk threshold for treatment...
cutoff, yields an estimate of $5864 per bleed prevented. Whether a higher or lower amount is reasonable in terms of an individual’s or society’s willingness to pay to prevent a bleeding episode is a matter of debate.

Because the bleeding risk estimates on which this decision model is based are derived from easily ascertainable variables before PCI, the results may offer a practical tool for identifying patients for whom bivalirudin during PCI procedures is an efficient use of resources. The modeling approach taken here, which utilizes empirical data to evaluate cost-effectiveness according to level of predicted risk, has been used before in other settings,\textsuperscript{21,22} though it has not been applied to the evaluation of the cost-effectiveness of bivalirudin versus UFH. Results from this model may be of particular value to physicians and hospitals who aim to minimize bleeding complications for patients undergoing PCI while avoiding expenditures that provide little additional benefit. Given the relatively small fraction of patients with a bleeding risk above most thresholds for which this model suggests bivalirudin would be cost-effective, hospitals that use bivalirudin for all patients who would otherwise receive UFH alone would stand to save considerable amounts of money through the adoption of a bleeding risk threshold approach to using bivalirudin, based on results from this cost-effectiveness model (or a similar model adapted to their own hospital setting and costs).

Our cost-effectiveness results were most sensitive to the efficacy of bivalirudin in preventing bleeding. This finding underscores the critical impact of the efficacy of any bleeding avoidance therapy in general that also seems to be driving the cost-effectiveness results in our study. One may further hypothesize that highly effective alternatives such as radial access to prevent bleeding in high-risk patients may prove to be even more cost-effective than bivalirudin, whereas use of other effective therapies such as vascular closure devices or fondaparinux may need to be explicitly tested in separate economic analyses.

Study Limitations
As with any modeling study, this study has limitations. First, the present study was limited by the moderate ability of the CathPCI Registry bleeding risk model to predict major bleeding. An improved ability to predict major bleeding events may improve the accuracy of these cost-effectiveness analyses. Second, in the long-term analyses, we have made the conservative assumption that costs beyond the initial hospitalization period are equivalent in patients who do and do not bleed. However, it is conceivable that patients who have a major periprocedural bleed have higher treatment costs after discharge, which would only serve to improve the cost-effectiveness of bivalirudin therapy, at all levels of risk. Third, the extension of the in-hospital cost-effectiveness analysis to a long-term cost-effectiveness analysis involved multiple additional assumptions in the Markov model, some of which are not verifiable. Recent literature from multiple trials, registries, and pooled studies has suggested that major bleeding during PCI is independently associated with and possibly causally linked with increased mortality over the long term. Data from randomized controlled trials of anti-thrombotic therapies shown to be associated with a significant reduction in bleeding, such as HORIZONS-AMI\textsuperscript{7} and OASIS 5,\textsuperscript{23} have demonstrated a decline in long-term mortality that cannot be explained by revascularization or other comorbidities, lending support to the notion of a potential causal link between bleeding and mortality. However, no data exist regarding the impact of major bleeding events on long-term mortality. We have attempted to use the most conservative estimates, from the best possible data sources, have modeled the hazard up to 1-year after PCI in only the first cycle of the Markov model because that is the time frame supported by the literature, and have not made any assumptions about the impact of major bleeds on risk of death beyond the first year. Fourth, the incremental costs of major bleeding were derived from a smaller subset of NCDR data, combined with hospitalization costs data, from 1 center. It is reassuring, however, that large, multicenter randomized trials that have estimated the cost of major bleeding have been consistent with the present estimate of $8920. The REPLACE-2 trial estimated that a major bleed cost $6300,\textsuperscript{9} whereas in the ACUITY trial a major bleed cost $8658.\textsuperscript{10} Fifth, another potential limitation is the assumption that the efficacy of the drug is independent of the bleeding risk. Perhaps in low-risk patients, bivalirudin is less efficacious, whereas in higher-risk patients, it is more efficacious than a relative risk of 0.66. There are no data available that demonstrate this. Another corollary of this assumption is that the cost of a major bleeding event in high-risk patients is assumed to be equal to that in low-risk patients. Finally, efficacy estimates for bivalirudin used in this study come from the ISAR-REACT 3 Trial, which enrolled low risk patients undergoing elective PCI, despite the prevalence of 57% of patients with acute coronary syndrome among our NCDR-derived population. We believe that our assumption that the relative risk of bleeding associated with bivalirudin is stable across clinical syndromes is a reasonable one; however, because previous studies comparing bivalirudin with UFH+GPIIb/IIIa inhibition have demonstrated consistent relative risk reductions across the full clinical spectrum,\textsuperscript{4,7} Despite these assumptions, most of our analyses were data-driven, and bleeding event rates and associated costs were based on actual patient-level data. Bivalirudin costs were derived estimated from patient-level data, whereas bivalirudin efficacy was used from published sources. Thus drug efficacy and drug costs were the 2 primary variables examined by sensitivity analysis.

Conclusions
By examining patient level data and creating a bleeding risk profile, we demonstrate the ability to examine cost-effectiveness according to predicted level of bleeding risk. This is the first study, to the best of our knowledge, of the cost-effectiveness of bivalirudin that evaluates the strategy of “targeting” PCI patients for bivalirudin treatment according to their predicted “bleeding risk” before PCI. As the level of risk rises, therapy to decrease events can become more cost-effective. From a societal or policy standpoint, studies such as this may help in the development of informed guidelines for the use of expensive therapies. Although application of these results to decision-making for individual patients must be undertaken with some caution, this study shows that substituting bivalirudin for UFH alone may be not be cost-effective in the vast majority (>90%) of patients at low-
and moderate-risk of bleeding when undergoing PCI, whereas bivalirudin is reasonably cost-effective for only a small proportion of the higher risk patients in the prevention of major bleeding.

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Appendix 1: The NCDR® bleeding risk model.  

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