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ORIGINAL ARTICLE

# Certainty ranges facilitated explicit and transparent judgments regarding evidence credibility

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## Abstract

**Objectives:** The Grading of Recommendations Assessment, Development and Evaluation approach to rating certainty of evidence includes five domains of reasons for rating down certainty. Only one of these, precision, is easily amenable—through the confidence interval—to quantitation. The other four (risk of bias, inconsistency, indirectness, and publication bias) are not. Nevertheless, conceptually, one could consider a quantified ''certainty range'' within which the true effect lies. The certainty range would be at least as wide as the confidence interval and would expand with each additional reason for uncertainty.

**Study Design and Setting:** We have applied this concept to rating the certainty of evidence in the baseline risk of venous thromboembolism (VTE) and bleeding in patients undergoing urological surgery. We considered rating up moderate or low quality evidence when the net benefit of VTE prophylaxis was unequivocally positive, that is, when the smallest plausible value of VTE reduction was greater than the largest plausible value of increased bleeding. To establish whether the net benefit was unequivocally positive, we expanded the range of plausible values by 20% for each of the four nonquantitative domains in which there were serious limitations.

**Results:** We present how we applied these methods to examples of open radical cystectomy and laparoscopic partial nephrectomy. In high-VTE risk laparoscopic partial nephrectomy patients and high- and medium-VTE risk open radical cystectomy patients, results proved robust to expanded certainty intervals, justifying rating up quality of evidence. In low-risk patients, the results were not robust, and rating up was therefore not appropriate.

**Conclusion:** This work represents the first empirical application in a decision-making context of the previously suggested concept of certainty ranges and should stimulate further exploration of the associated theoretical and practical issues. © 2018 Elsevier Inc. All rights reserved.

*Keywords:* GRADE; Guidelines; Quality of evidence; Systematic reviews; Thresholds; Thromboprophylaxis

## 1. Introduction

The widely used Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rating certainty in evidence (synonyms quality or confidence in evidence) can be applied to a variety of questions in health care, including to alternative management strategies [1] and prognosis [2]. In evaluating therapy questions, randomized trials start as high quality evidence; for prognosis, observational studies start as high quality evidence. For both sorts of questions, five domains of limitations may result in rating down certainty.

The uncertainty associated with one of these domains of limitations, imprecision, can be quantitated by examining confidence (for frequentist analysis) or credible (for Bayesian analysis) intervals. The extent of uncertainty associated with the other four domains of limitations—risk of bias, inconsistency, indirectness, and publication bias—is, thus far, not fully amenable to quantitation [3]. In this article, we will use the term ''certainty range'' to characterize uncertainty that considers all these domains.

Conceptually, each of the five limitations extend the range of uncertainty—the range of plausible true effect—around the best estimate of effect. One could therefore

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**What is new?**

**Key findings**

- This study represents a first foray into utilizing the concept of the certainty range to place a quantitative estimate on domains of uncertainty (risk of bias, inconsistency, indirectness, and publication bias) that are up to now addressed only qualitatively.
- We applied quantitative estimates to the baseline risks of venous thromboembolism and major bleeding in patients undergoing urological surgery and in doing so established whether inferences regarding the net benefits of pharmacologic prophylaxis were secure.

**What this adds to what was known?**

- The Grading of Recommendations Assessment, Development and Evaluation approach to rating certainty of evidence includes five domains of reasons for rating down certainty. Only one of these, precision, is easily amenable—through the confidence interval—to quantitation. The other four (risk of bias, inconsistency, indirectness, and publication bias) are not.
- This work highlights the concept of the uncertainty range and the potential for ultimate quantitation of all domains of uncertainty.

**What is the implication and what should change now?**

- This is the first empirical application in a decision-making context of the previously suggested concept of certainty ranges.
- This work should stimulate further exploration of the associated theoretical and practical issues to take these concepts forward.

picture the certainty range around that best estimate [3]. The width of the certainty range would depend on the extent of concerns regarding imprecision—captured in the confidence or credible interval—and the extent of concern regarding the other four domains (Fig. 1) [3].

Fig. 1 depicts the certainty range—like the confidence interval—as symmetrical around the point estimate. This need not be the case. For instance, if one knew the likely direction of risk of bias, the certainty range could be asymmetrical, skewed in that direction [3]. Furthermore, for studies of prognosis or baseline risk—the focus of this article—given that values can range only between 0% and 100%, low probabilities or risks are likely to be skewed to the right (e.g., if the point estimate is 1%, the certainty range can only drop by 1% to 0, while it will plausibly rise to substantially more than 1%).

The extent to which concerns regarding the four, as of yet, nonquantitative domains of uncertainty widen the certainty range is highly speculative. As a result, the notion of the certainty range has heretofore been largely theoretical. In the course of a recently completed project [4], we rated the certainty of evidence regarding the likelihood of thrombosis and bleeding following urological surgery. In doing so, we felt that, despite the speculative nature of the certainty range, it would be worth invoking the concept to help in applying the GRADE certainty of evidence rating. We present the work here because it may be the first scientific publication to empirically apply the certainty range to the rating of GRADE quality of evidence.

We have an important disclaimer: although two of the authors are co-chairs of the GRADE working group (H.J.S. and G.H.G.), this work is not a product of, nor has it been endorsed by, the GRADE working group. Moreover, a number of the concepts presented here, and the way the concepts have been incorporated, go considerably beyond current GRADE guidance. Thus, the current work represents an exploration of possible future directions in thinking about and rating certainty of evidence.

## 2. Background of the project

Patients undergoing surgery are at risk of postsurgical deep venous thrombosis or pulmonary embolism (venous thromboembolism [VTE]). VTE can be serious and indeed fatal. Thus, prophylaxis against VTE with anticoagulants, in particular heparinoids, has become popular.

Unfortunately, pharmacologic prophylaxis is associated with an increased risk of bleeding—always a concern after any surgical procedure—which can also be serious (in our definition, requiring reoperation) and even fatal. Thus, the decision regarding prophylaxis involves a tradeoff between reduced risk of VTE and increased risk of bleeding. That trade off depends on both the risk of VTE and bleeding in the absence of prophylaxis (which we will call the baseline risk) and the relative decrease in VTE and increase in bleeding with prophylaxis.

As part of a team charged with developing guidelines for prophylaxis after urological surgery [4], we undertook a series of systematic reviews to estimate the baseline risk of both VTE and bleeding [5–7]. We interpreted our results in the context of its implications for pharmacologic prophylaxis after major urological procedures.

## 3. Methods and results: judging the certainty of baseline risk estimates

Readers will find details of our methods in other articles [4–7]. In brief, we used rigorous systematic review

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