

Two approaches for non-contextualized ratings of certainty

1. *The true effect lies within the 95% Confidence intervals*

The first non-contextualized option is to rate our certainty that the true effect – presented in either relative or absolute terms - lies within the 95% confidence intervals that emerged from the meta-analysis (Table A1). Imprecision is one of the domains that GRADE considers in rating certainty, but with this approach imprecision is, in most cases, omitted.[§]

Considering mortality in Table 2, there are no serious limitations with respect to risk of bias, consistency, directness or publication bias. We can therefore be confident that the true impact of longer-duration DAPT on death is a relative risk of 1.04 to 1.36 or an absolute increase in 0 to 4 deaths per 1,000 patients per year. This level of certainty is also warranted for effects on serious bleeding and stroke. For myocardial infarction, however, the inconsistency in results could reduce our certainty that the true effect lies in the specified confidence interval (relative effect 0.58 to 0.92; absolute effect 2 to 12 fewer myocardial infarctions per year) (Table A2).

In this example, estimates of effect are quite precise (few events have occurred and over 21,000 patients have participated in randomized trials). In other situations, this first approach could mean that we express high certainty in a very imprecise result. This is potentially confusing. Therefore, in applying this strategy for non-contextualized certainty rating, authors can choose not to provide an overall rating for an outcome (high, moderate, low or very low). Rather, those summarizing the evidence would simply note in an evidence profile or summary of findings table that there are, or are not, issues of risk of bias, inconsistency, indirectness and publication bias that undermine our certainty regarding whether the confidence interval represents the range of plausible truth. If authors choose to make an overall rating of certainty in the confidence interval based on four domains they need to make it clear that, when this is contextualized, the final rating of certainty for this outcome must include precision.

2. *The intervention is effective (i.e., Non-null effect)*

Certainty in this approach reflects our confidence that there is a non-null effect – expressed in either relative or absolute terms – of the intervention for a specific outcome. In Table A1, we would rate certainty following this approach as high for serious bleeding (CI of RR does not include 1), and moderate for death (because the confidence interval includes a RR of 1.0, we cannot exclude a null effect, and thus we rate down for imprecision). For myocardial infarction, the CI does not include 1; therefore, we would not rate down for imprecision and only rate down for inconsistency in results (Table A2). These judgments are not contextualized. The non-null effect approach raises challenges for situations in which we are rating certainty that the truth lies close to a null effect. In this case one should consider assessing a null effect which is described under the paragraph *Partly contextualized ratings of certainty*.

[§] As we have mentioned, it is possible, however, that in the presence of an apparent large treatment effect, a relatively small sample size will reduce the certainty associated with the 95% confidence interval. The standard we suggest for addressing this issue is to assess whether the optimal information size (OIS) is met. When effects are large, and sample sizes appreciably less than the OIS, one would rate down for imprecision (2).

Table A1. Two possible ways of setting non-contextualized thresholds or ranges and what the certainty expressed will represent

Setting	Threshold or range	How it is set	What the certainty rating represents
Primarily for systematic reviews and health technology assessment	Range: 95% Confidence Interval	Using existing limits of the 95% CIs, which implies precision is not routinely part of the rating	Certainty that the effect lies within the confidence interval
	OR ≠ 1, RR ≠ 1, HR≠ 1, RD ≠ 0	Using the threshold of null effect	Certainty that the effect of one treatment differs from another

Table A2. Possible non-contextualized certainty ratings for Myocardial infarction (MI) for longer-duration versus shorter-duration DAPT

Approaches	Examples of set thresholds or ranges	Certainty
Range: 95% Confidence Interval	Decrease of 2-12 per 1000	We have moderate certainty that longer-duration DAPT decreases MI by 2-12 per 1000 patients compared to shorter-duration DAPT (rating down for inconsistency).
OR ≠ 1		We have moderate certainty that longer-duration DAPT decreases the incidence of MI compared to shorter-duration DAPT (rating down for inconsistency).