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# Non-inferiority Trial

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# Introduction

- In medical research, randomized clinical trials (RCTs) are the gold standard for establishing efficacy of a newly developed drug/treatment method

# Introduction

- **Non-Inferiority clinical trial** have become a major tool for the evaluation of drugs, devices, biologics and other medical treatment
- **Treatment with placebo or with a no-treatment** control in a study **is not ethical** when the effective treatment has already been established.

# Introduction

- Effective medical treatments exist for many medical conditions and are the relevant bar to be surpassed by a new treatment.
- Although some new treatments offer greater efficacy, others may promise greater safety or convenience, or less expense, while providing similar efficacy.

# Introduction

- The concept of good substitution was original rationale for the design of non-inferiority trials.
- These trials span multiple medical and surgical disciplines and diverse treatment strategies.

# Non-inferiority Trial

- To evaluate whether a new treatment is **non-inferior to or as effective as** the standard treatment for a particular endpoint.
- Often because standard treatment is associated with **greater adverse events or costs** compared to the new treatment being studied.
- It is not importance to establish that the new treatment is more effective or has similar effects, **only that it is adequate to determine that it is not inferior to the standard treatment.**

## Table 1. Comparisons between superiority and non-inferiority trials

| | Superiority trails | Non-inferiority trails |
|---|---|---|
| **Null hypothesis ($H_0$)** | New treatment not superior to standard treatment/ placebo | New treatment inferior to standard treatment |
| **Alternate hypothesis ($H_A$)** | New treatment is better than standard treatment/ placebo | New treatment non-inferior to standard treatment |
| **Type 1 error** | Deciding new treatment is better When it is not superior | Deciding new treatment non-inferior when it is inferior |
| **Type 2 error** | Deciding new treatment not superior when it it is better | Deciding treatment inferior when it is non-inferior |
| **Type 1 error rate** | $\alpha$ (significance cut-off) | $\alpha$ (significance cut-off) |
| **Type 2 error rate** | $\beta$ (1-power) | $\beta$ (1-power) |
| **Significant level** | P-value < 0.05 (two-sided) | P-value < 0.025 (one-side) |
| **Non-inferior margin** | Not applicable | Predetermined |

# Necessary features of non-inferiority study

1. Active control
2. End-point selection
3. Choice of non-inferiority margin
4. Assay sensitivity
5. Constancy and metrics
6. Execution
7. Analysis

# Necessary features of non-inferiority study

1. Active control
    - One or more prior randomized trials evaluating the superiority of the active control over placebo.
    - Active control represents the current standard of care.

# Necessary features of non-inferiority study

2. End-point selection

- End point is selected, and on the basis of prior experience.
- The expected performance of the active control is derived.

# Necessary features of non-inferiority study

3. Choice of non-inferiority margin

- This margin cannot be greater than the smallest effect size for the active treatment that would be expected in a placebo-controlled trial.

# Necessary features of non-inferiority study

A variety of statistical methods are used to derive the margin

3.1. Fixed margin:

- Estimates of the effect of the active comparator with placebo in previous studies
- Lower bound of 95% CI

# Necessary features of non-inferiority study

3.2. The synthesis method (uses the same approach as the fixed method):

- Accounts for the variability of the treatment effect of active control versus placebo in determining the margin.

# Necessary features of non-inferiority study

4. Assay sensitivity

- The study must be designed to adequately distinguish between effective and ineffective therapies.
- The study design and conduct would have allowed the active control to be shown to be superior to the placebo.

# Necessary features of non-inferiority study

5. Constancy and metrics

- The design of the new trial preserves the conditions of the trial in which the active control was shown to be effective.
- This is called the “constancy assumption”

# Necessary features of non-inferiority study

5. Constancy and metrics

- An appropriate metric must be used in the non-inferiority trial.
- Because the choice between **relative and absolute effects** can affect both power and validity, this choice must be carefully considered in the design phase of the study.

# Necessary features of non-inferiority study

6. Execution

- Adequate execution of the trial and ascertainment of outcomes.
- Incomplete or inaccurate ascertainment of outcomes, as a result of **loss to follow-up, treatment crossover or nonadherence, or outcomes that are difficult to measure or subjective**, may cause the treatments being compared to falsely appear similar.

# Necessary features of non-inferiority study

7. Analysis

If some patients did not receive the full course of the assigned treatment.

- **Intention to treat (ITT) analysis**: in which all patients who received the experimental treatment, even if only one dose, are included in the statistical tests.
  - May produce a bias toward a false positive conclusion.
  - Narrowing the difference between the treatments.

# Necessary features of non-inferiority study

7. Analysis

- **Per-protocol (PP) analysis**: excludes patients who did not meet the inclusion criteria or did not receive the randomized.
  - Preferable in a non-inferiority trial.
  - May include fewer participants and introduce post randomization bias.

# Necessary features of non-inferiority study

7. Analysis

- Suggest analyzing **both ITT and PP.**
- Examining the results for consistency.
- **Sensitivity analyses** may be needed before drawing conclusions about non-inferiority.

# Non-Inferiority margin

# Non-Inferiority margin

- It is recommended that the margin should be pre-specified based on statistical considerations and clinical judgment.
- The fixed-margin method is the method preferred by regulatory authorities.
- It is considered the most straightforward and readily understood approach.

# Non-inferiority margin

- The method starts by identifying two different measures ($M_1$ and $M_2$).
- $M_1$ is the effect of the active control compared with placebo.
- $M_1$ can be determined based on
  - One or more placebo-controlled trials of the active comparator that have a design similar to the current non-inferiority trial or
  - A meta-analysis of several placebo controlled trials.
  - The latter approach is encouraged because it will result in a pooled, more precise effect estimate of the active comparator

# Non-inferiority margin

- Thus, $M_1$ is chosen as a conservative estimate (smallest effect size) of the effect of the active comparator.
- Which is the upper bound of the 95% CI of the pooled effect size, rather than the point estimate.

# Non-inferiority margin

- Example, the minimum non-inferiority threshold was selected **using data from the meta-analysis by Hart and co-workers.**
- Quantifying the effect of warfarin on the prevention of thromboembolic events vs placebo or the absence of treatment, at a **RR of 0.38 (95% CI 0.28–0.52).**

# Non-inferiority margin

The procedure for computing the threshold is as follows:

- The reference category is changed, as if the **effect of the "placebo or absence of treatment" was being calculated with respect to that of warfarin.**
- This effect is the **inverse of 0.38**, which corresponds to an **RR of 2.63 (95% CI 1.92–3.57); according to the lower 95% CI (1.92**), placebo or absence of treatment shows a **92% increase in the risk of stroke** $(\mathbf{M_1})$
- The **lower margin of this CI (1.92)** is considered the minimum non-inferiority threshold for dabigatran.

# Non-inferiority margin

- Calculate $M_2$ from $M_1$ by choosing how much of the treatment effect is judged necessary to be preserved.
- **$M_2$ = (1-%) × $M_1$** represents the largest clinically acceptable difference (degree of inferiority) of the test drug compared with the active control
- A consideration that may reflect the seriousness of the outcome, the benefit of the active comparator, and the relative safety profiles of the test drug and the comparator.

# Non-inferiority margin

- Choosing a **higher percentage to be preserved** (**e.g., 67%, where $M_2$ is 33% of $M_1$** ) results in a stricter or more conservative non-inferiority margin, meaning it is more difficult to conclude non-inferiority.
- A non-inferiority threshold that assumes that warfarin has a hypothetical effect that is just **50%** of its real effect is chosen.
- **$M_2$ = (1-%) × $M_1$ ; = (1-0.5) × 0.92 = 0.46 = 46%**
- The minimum non-inferiority threshold is set at 1.46 (a 46% increase in the risk of stroke when moving from warfarin to dabigatran).

# Non-inferiority margin

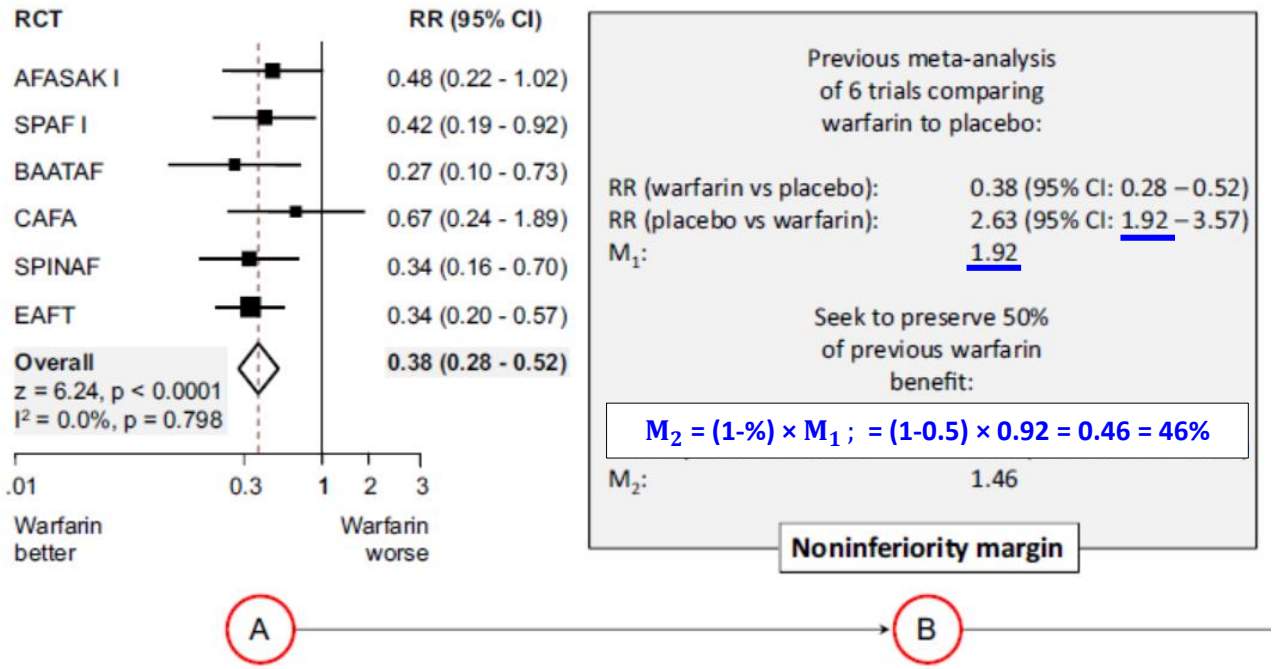



**Figure 1. Steps in evaluating a non-inferiority trial comparing a direct oral anticoagulant (dabigatran) to warfarin**.

**A** Results of the meta-analysis used to compute the minimum non-inferiority threshold

**B** computation of the non-inferiority margin according to the fixed margin method

# How to interpretation of non-inferiority study

# Outcome of Non-inferiority Trial

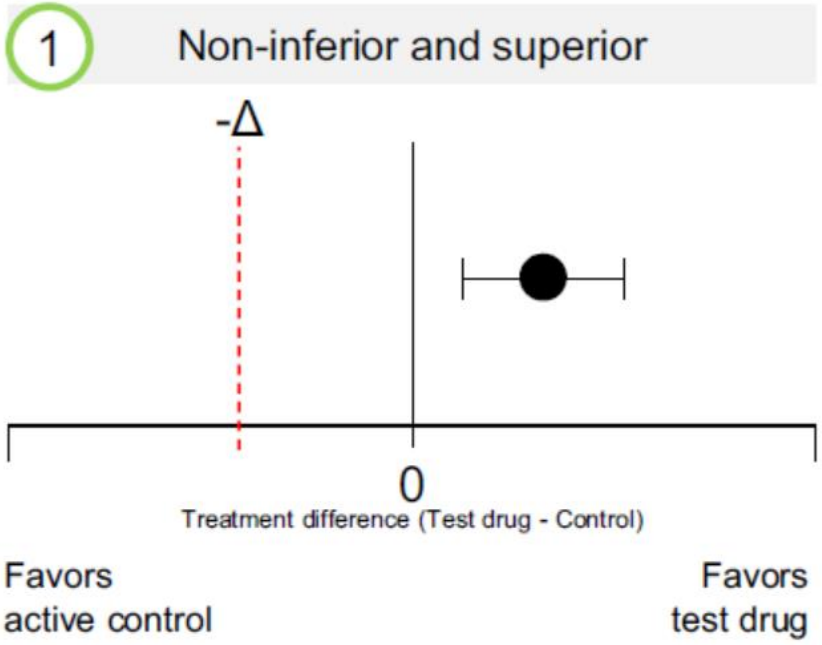
A non-inferiority trial can have several types of outcomes:

1. Non-inferior and superior
2. Non-inferior and not superior
3. Non-inferiority unproven (Inconclusive)
4. Non inferior and inferior
5. Inferior and not non-inferior

# Outcome of Non-inferiority Trial

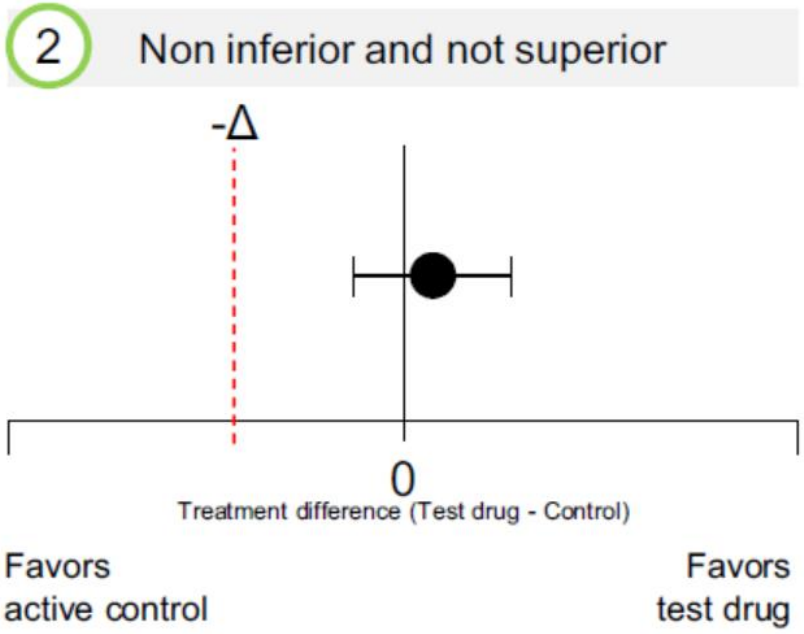
- The results of the non-inferiority trial are **compared with the prespecified non-inferiority margin.**
- If the bound of the 95% CI for the effect estimate is **smaller than the non-inferiority margin, non-inferiority is concluded**

# Outcome of Non-inferiority Trial



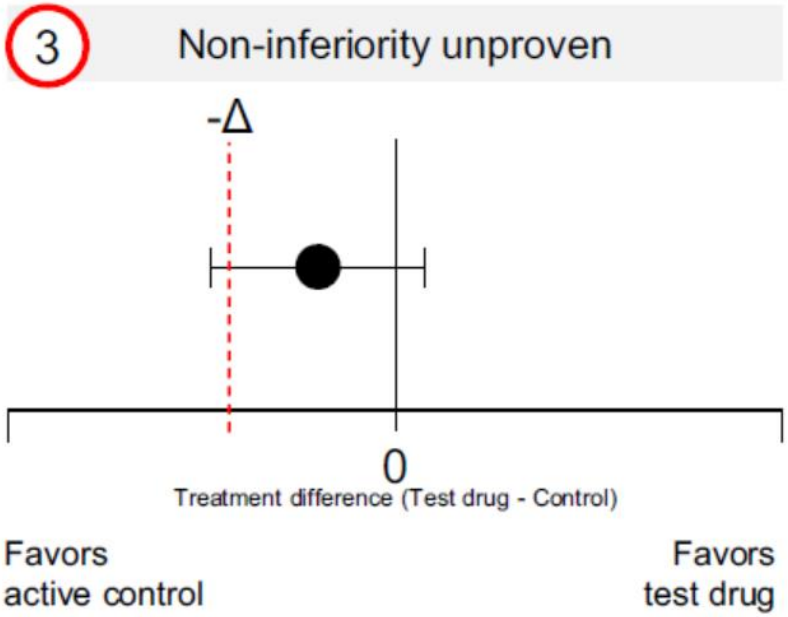

- The new treatment is **non-inferior and also superior** to the control
- When the **CI sits wholly above zero**

# Outcome of Non-inferiority Trial



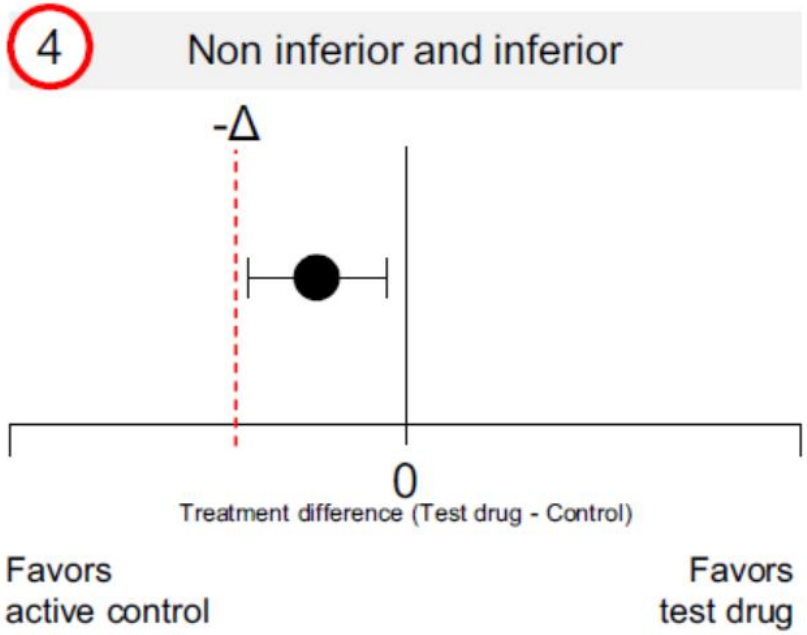

- The new treatment is **non-inferior, but not superior**, to the control
- When the **CI spans zero but lies wholly above – Δ**

# Outcome of Non-inferiority Trial



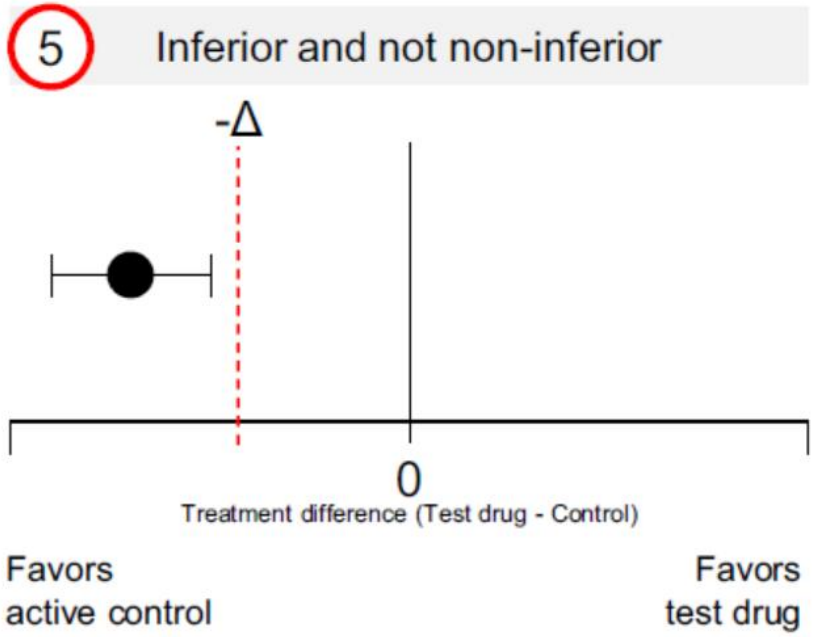

- The new treatment is **neither non-inferior nor superior**
- When the **CI straddles both zero and – Δ**

# Outcome of Non-inferiority Trial




- The new treatment has **the CI tucking between zero and – Δ**
- It illustrates the case of **both non-inferiority and inferiority**

# Outcome of Non-inferiority Trial




- The **new treatment shows inferiority**

# Example

# Example

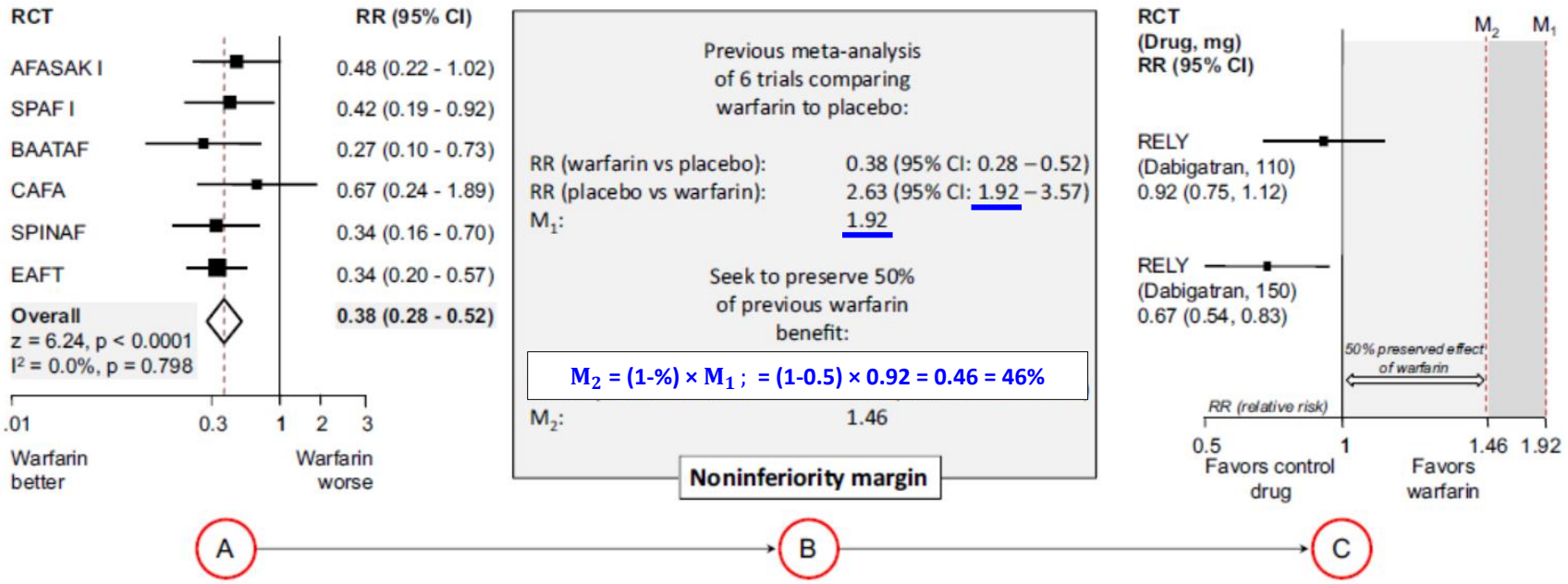
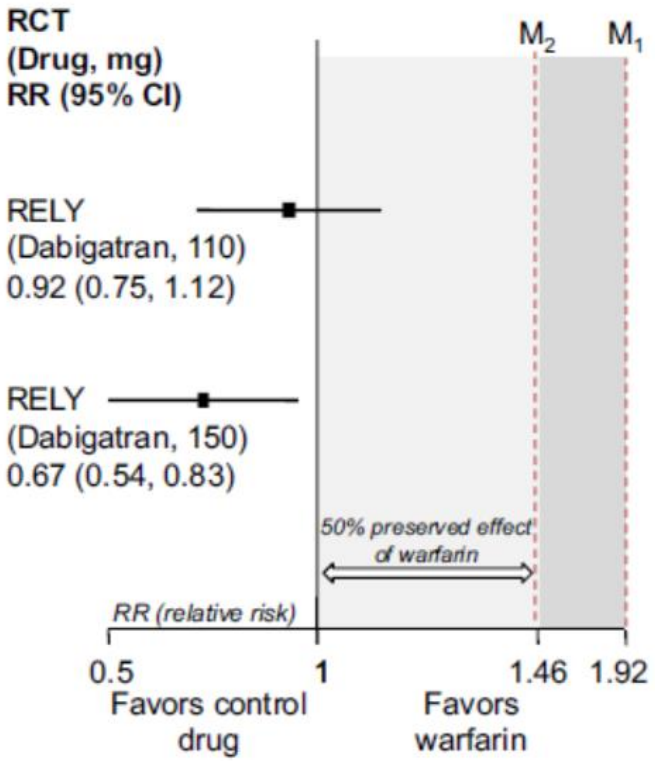



**Figure 2. Steps in evaluating a non-inferiority trial comparing a direct oral anticoagulant (dabigatran) to warfarin**.
**A** Results of the meta-analysis used to compute the minimum non-inferiority threshold
**B** computation of the non-inferiority margin according to the fixed margin method
**C** results of the RE-LY trial proving non-inferiority of dabigatran vs warfarin

# Example




- To conclude that **dabigatran is not inferior to warfarin**, the **upper limit of the 95% CI** of the effect of treatment **should not exceed 1.46 ($M_2$).**
- The effect of treatment show that non-inferiority margins are **below the 50% preserved effects** reference non-inferiority margin.
- Thus, the conclusion of **non-inferiority is established.**
- The **RR and CI for this treatment arm sit wholly below 1**
- **Dabigatran 150 mg superior to warfarin** at reducing stroke or systemic embolism.

# Choosing the non-inferior margins

- Two methods of choosing the non-inferior margin statistically can be used:
  - Relative risk difference
  - Absolute risk difference

# Choosing the non-inferior margins

- **Relative risk difference**
  - A ratio of end point events on the new treatment to that on standard treatment is given as the non-inferior margin.
  - The advantage of this method is that the event rate of the standard treatment does not need to be assumed.
  - Non-inferiority is declared if the upper boundary of the 95% CI of the trial does not exceed that margin.

# Choosing the non-inferior margins

- **Absolute risk difference**
  - Non-inferiority can be declared if the absolute difference in end points between the new and standard treatment is less than a predefined value.
  - This method entails an assumption on the event rate on standard treatment.

# Choosing the non-inferior margins

- **Absolute risk difference**
  - The actual event rate during the trial of the standard treatment is often lower than the assumed event rate.
  - This will lead to a higher relative difference as the non-inferior margin and an underpowered trial, favouring non-inferiority.

# Choosing the non-inferior margins

- Using relative risk difference has the advantage of guarding against unrealistically optimistic claims of non-inferior if the standard treatment event rate is lower than expected.

# Sample size for non-inferiority

# Test for non-inferiority

$H_0$: The new treatment is **inferior** to the standard treatment

$$H_0: \mu_T - \mu_C \leq -d \qquad H_0: P_T - P_C \leq -d$$

$H_A$: : The new treatment is **non-inferior to** the standard treatment

$$H_A: \mu_T - \mu_C > -d \qquad H_A: P_T - P_C > -d$$

-d is a non-inferior margin which indicates how much new treatment can be inferior to standard treatment, but it is still considered non-inferior

# Test for non-inferiority

- Two independent means
- Cross-over design
- Two independent proportion

# Conclusion

- **Noninferiority trials** evaluate a new treatment against standard treatment to demonstrate that the **new treatment is no worse than standard treatment.**
- Interpretation of noninferiority trials requires consideration of the **choice of the non-inferiority margin and deficiencies in trial design** that may diminish the estimated difference between the new treatment and standard treatment.
- Clinicians **should also be careful to draw appropriate** inferences from noninferiority trials

# Thank you