Improving GRADE 'Summary of Findings' tables for Cochrane reviews: detailed guidance for the calculation of absolute effects from time-to-event data

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Programme

1. **Calculation of absolute effects:**

- Introduction
- How to estimate baseline risk in the control arm
- GRADEpro software

2. **GRADEing time-to-event outcomes:**

- Censoring

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Poll #1

Have you ever dealt with time-to-event data while working on a systematic review (for example as a reviewer or an editor)?

1. Yes
2. No

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Poll #2

Have you ever prepared a Summary of Findings table including time-to-event data?

1. Yes
2. No

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Introduction

Time-to-event data:

Measure the length of time until an event occurs

Different events:

Death, duration of hospitalisation, tumor recurrence etc

Different starting points:

Date of randomisation, date of diagnosis, date of start therapy etc

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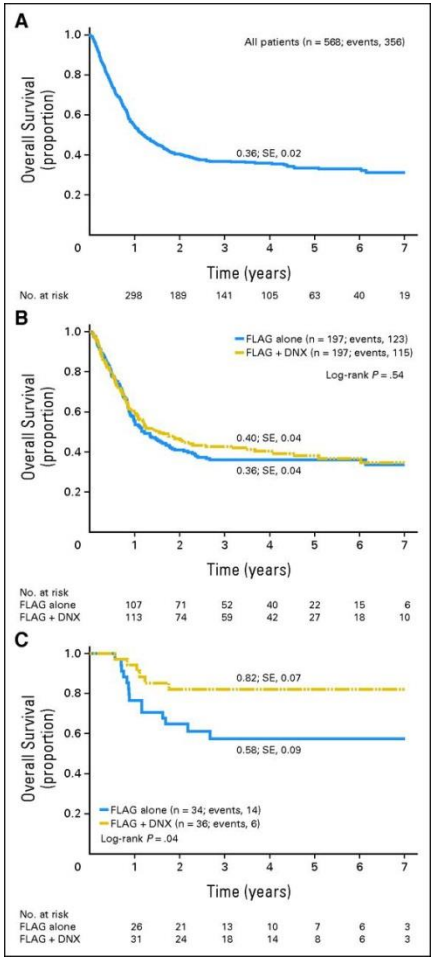
Introduction

Graphical display in survival curves:

(Example from Kaspers GJ et al. JCO 2013; 31: 599-607)

Hazard ratio:

- Ratio of hazard for one group compared to hazard for another group
- What is the meaning of HR<1/HR>1: which group is favored?



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Introduction

- Mandatory to include ‘Summary of Findings’ (SoF) tables in Cochrane intervention reviews
- Absolute effects should be included in SoF tables
- To calculate absolute effects a baseline risk in the control arm should be established and then the HR is used to calculate the event rate in the intervention arm
- But clear guidance on how to do this for time-to-event data is lacking
- Often no absolute effects for HRs calculated at all*
- If absolute effects are calculated mistakes frequently occur*

* Skoetz et al. Absolute effect measures in ‘Summary of Findings’ tables for time-to-event data in cancer-related Cochrane reviews: a methodological systematic review (submitted)

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Introduction

Challenge:

What definition for time-to-event outcomes is used?

- Event (e.g. death/mortality; people dead at a specific time point)
- Event-free survival (e.g. overall survival; people alive at a specific time point)

Should be explained in a footnote in the SoF tables

Implications for the calculation and presentation of corresponding absolute effect estimates

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Introduction

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control					
Mortality (instead of OS) Follow up: median 60 months	**Moderate risk**		**HR 1.01** (0.79 to 1.30)	411 (1 study)	⊕⊕⊕◯ **moderate**[1]	Instead of overall survival, mortality is reported in this table, for methodological reasons
	750 per 1000	**753 per 1000** (666 to 835)				
Relapses/death (instead of PFS) Follow up: median 60 months	**Moderate risk**		**HR 0.79** (0.63 to 0.99)	411 (1 study)	⊕⊕◯◯ **low**[1,2]	Instead of PFS, relapses and deaths are reported in this table, for methodological reasons
	820 per 1000	**742 per 1000** (661 to 817)				

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Poll #3

What do you think was used to calculate absolute effects?

1. Event
2. Event-free survival
3. Not sure

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Introduction

Tricks to assess if ‘event’ or ‘event-free survival’ has been used when not explained in a footnote:

- Assumed risk control group at overall survival < assumed risk at event-free/progression-free survival: number of people with event is used

- Assumed risk control group at overall survival > assumed risk at event-free/progression-free survival: number of people being event-free is used

Unfortunately not always helpful…

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Introduction

Absolute effects correctly calculated (for events); consistent labelling of outcomes throughout the review:

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control					
Mortality (instead of OS) Follow up: median 60 months	**Moderate risk** **750 per 1000**	**753 per 1000** (666 to 835)	**HR 1.01** (0.79 to 1.30)	411 (1 study)	⊕⊕⊕◯ **moderate**[1]	Instead of overall survival, mortality is reported in this table, for method-ological reasons
Relapses/death (instead of PFS) Follow up: median 60 months	**Moderate risk** **820 per 1000**	**742 per 1000** (661 to 817)	**HR 0.79** (0.63 to 0.99)	411 (1 study)	⊕⊕◯◯ **low**[1,2]	Instead of PFS, relapses and deaths are reported in this table, for method-ological reasons

Introduction

Absolute effects correctly calculated (for events); inconsistent presentation of outcomes in SoF table and other parts of the review:

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control					
Overall survival (median 2 years)	**Moderate risk**		**HR 0.65** (0.45 to 0.94)	335 (1 study)	⊕⊕⊕○ **moderate**[1]	
	250 per 1000	**171 per 1000** (121 to 237)				
Progression free survival (median 2 years)	**Moderate risk**		**HR 0.61** (0.47 to 0.81)	356 (2 studies)	⊕⊕○○ **low**[2,3]	
	500 per 1000	**345 per 1000** (278 to 430)				

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Introduction

Incorrect calculation of absolute effects: using the positive event (e.g. event-free survival) control risk, but less instead of more people alive in the favored arm (wrong direction of effects):

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
OS (at 3 years)	Study population		**HR 0.78** (0.62 to 0.98)	1421 (3)	⊕⊕⊕⊕ **high**	
	830 per 1000	749 per 1000 (667 to 824)				
PFS (at 3 years)	Study population		**HR 0.64** (0.55 to 0.74)	1421 (3)	⊕⊕⊕◯ **moderate**[1]	
	450 per 1000	318 per 1000 (280 to 358)				

Introduction

Completely unclear how control risk was assumed (same for OS and PFS) and thus whether directions of results are correct:

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
OS	Low risk population[1]		HR 0.80 [0.59 to 1.09]	2586 (4 studies)	+++O moderate[4]	
	100 deaths per 1000	81 per 1000 (60 to 108)				
PFS	Low risk population[3]		HR 0.53 [0.44 to 0.64]	2586 (4 studies)	+++O moderate[5]	
	100 progressions or relapses per 1000	54 per 1000 (45 to 65)				

[3]The risk was taken from trial X

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